HETEROCYCLIC α-OXOESTERS (HETARYL GLYOXYLATES): SYNTHESIS AND CHEMICAL TRANSFORMATIONS. Part 1.

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Abstract. *In this review, synthesis and chemical properties of pyrrolyl, furyl, thienyl glyoxylates, and their fused derivatives are surveyed. Depending on the nature of the heterocyclic substituent and the position of the ketoester moiety, direct Friedel-Crafts acylation, metalation-glyoxylation, or heterocyclization can be the method of choice to prepare the title compounds. The chemical behavior of hetaryl glyoxylates correlates with their electronic properties as highly electrophilic ketones. Indeed, the ketone functional groups participates in most chemical transformations, often chemoselectively (e.g. reduction, formation of oximes, imines, and hydrazones, addition of organometallic reagents, condensations, olefination, or deoxofluorination). Of particular interest are heterocyclizations of the title compounds, which can occur at the ketone, ester, and both moieties (i.e. as 1,2-CC-bis-electrophiles).*

Contents

1. Introduction

This review covers synthesis and chemical transformations of heterocyclic α-oxoesters, also known as heterocyclic α-ketoesters, hetaryl-2-oxoacetates, or hetaryl glyoxylates. These derivatives are valuable representatives of 1,2-dicarbonyl compounds and bis-electrophiles that provide numerous possibilities for the synthesis of functionalized heterocycles. Common transformations of hetaryl glyoxylates reported in the literature include (Figure 1): a) *ketone reactivity:* selective reduction, formation of oximes and imines, condensations, addition of Grignard reagents, alkenylation, deoxofluorination, heterocyclizations. The result of heterocyclizations: one carbon atom of the α-oxoester becomes a part of heterocycle bearing an ester functional group; b) *oxoester reactivity:* reduction, heterocyclizations. The result of heterocyclizations: both carbon atoms of the α-oxoester become a part of the heterocycle, *i.e.* [4+2]-cyclization in reactions with binucleophiles (for example, 1,2-diamines), condensations with amides, three-component condensations with amines and aldehydes; c) *ester reactivity:* hydrolysis, amination, heterocyclizations. The result of heterocyclizations: one carbon atom of the α-oxoester becomes a part of heterocycle bearing an acyl substituent.

Due to the increased reactivity of their carbonyl group, heterocyclic α-oxoesters can undergo many important transformations, *e.g.* Paal-Knorr synthesis, Dieckmann cyclization, Fischer indole synthesis, Friedlander and Pfitzinger reactions, Pictet-Spengler reaction, aldol condensation, reductive aza-Wittig

cyclization, Bayliss-Hillman cyclization, [2+2]-, [3+2]-, and [4+2]-cycloadditions *etc*.[1] For example, synthetic utility of the dicarbonyl compounds was demonstrated by the preparation of substituted quinoxalines that are widely used as photoinitiators and fluorescence sensors.[2-5] Such transformations of hetaryl glyoxylates allow the construction of organic molecules bearing two or more heterocyclic fragments (Scheme 1).

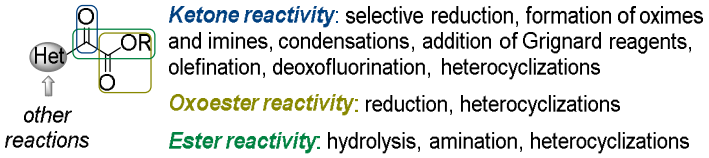
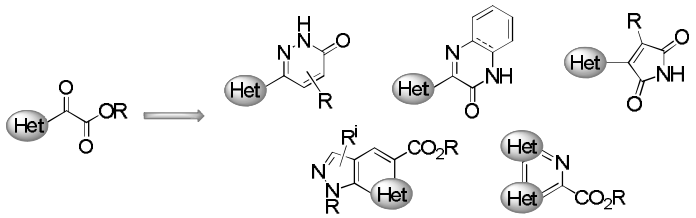


Figure 1. Synthetic potential of heterocyclic α-oxoesters.



Scheme 1. Heterocyclizations of hetaryl glyoxylates: an approach to compounds with two or more heterocyclic fragments.

Derivatives of heterocyclic α-ketocarboxylates are found among biologically and medicinally important compounds since they can act as reversible covalent binders. Examples include antithrombotic agent Tiplasinin **1**,[6,7] agent for treatment of Alzheimer's disease Aleplasinin **2**,[8] antitumor agents Indibulin **3**[9-12] and Rosabulin **4**,[13] as well as drug for septic shock treatment Varespladib **5**[14,15] (Figure 2). In 2020, Aleplasinin was also studied for activity against SARS-CoV-2 as an inhibitor of plasminogen activator 1 (PAI-1) with an α-ketocarboxylate group that covalently binds to threonine residues.[16,17]

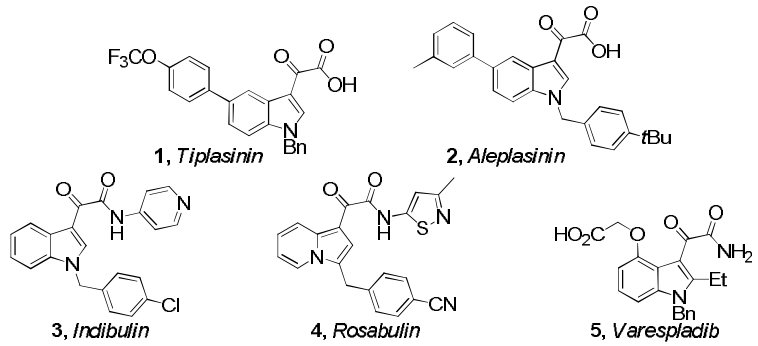


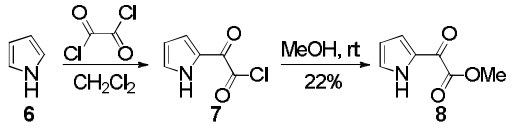
Figure 2. Pharmaceutically important derivatives of heterocyclic α-ketocarboxylates.

2. Synthesis of pyrrolyl, furyl, thienyl glyoxylates and their fused analogs

2.1. Pyrrolyl glyoxylates

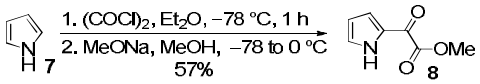
The Friedel-Crafts acylation of pyrroles are most often used for the synthesis of pyrrol-2-ylglyoxylates **6**.[18-21] The parent pyrrole **6** slowly reacts with oxalyl dichloride, but the use of acidic activators for the electrophilic substitution is not suitable since they cause polymerization of the substrate.

The reported procedure included dropwise addition of pyrrole to oxalyl chloride in a low-boiling solvent, *i.e.* CH_2Cl_2, with immediate removal of the formed HCl from the reaction mixture. In contrast, pyrroles bearing one or two methyl groups (*e.g. N*-methylpyrrole) underwent acylation already at –50 °C giving 1,2-di(1*H*-pyrrol-2-yl)ethane-1,2-diones (*i.e.* 2:1 adducts). In turn, glyoxalyl chlorides of type **7** thus formed could be converted into the corresponding glyoxalic acids by the reaction with methanolic KOH or methyl glyoxylate **8** by direct reaction with MeOH (22% yield, Scheme 2).[22]



Scheme 2. Synthesis of methyl pyrrol-2-ylglyoxylate **8**.

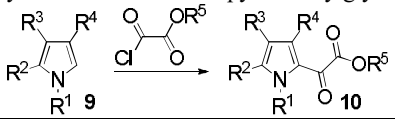
An improved synthesis of pyrrol-2-ylglyoxylate **8** providing the target product in 57% yield included the reaction of pyrrole with oxalyl chloride at –78 °C, followed by treatment with MeONa in MeOH (Scheme 3).[23] Other alcohols could be easily introduced into the reaction in analogous manner to give *t*-Bu,[24] *i*-Bu,[25] Bn,[26] *n*-octyl[27] esters *etc*.



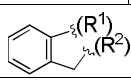
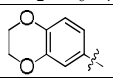
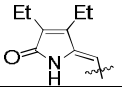
Scheme 3. Optimized method for the synthesis of methyl pyrrol-2-ylglyoxylate **8**.

Numerous examples of the Friedel-Crafts acylation of *N*- and/or *C*-substituted pyrroles **9** with at least one free α-position with alkyl oxalyl chlorides have been reported to date. In most cases, the reaction has been performed under basic conditions with the formation of **10** (common conditions: pyridine in CH_2Cl_2 or other base) (Table 1, Entries 1-13) or upon base-free conditions (Entry 14, 15).[28] As mentioned above, the use of acidic catalysts is less common due to the possible electrophilic polymerization of pyrroles. However, some reports included the use of BF_3-Et_2O (Entries 16, 17), $AlCl_3$ (Entry 18), or $SnCl_4$ (Entries 19, 20).

Table 1. Synthesis of substituted pyrrole-2-ylglyoxylates **10**.

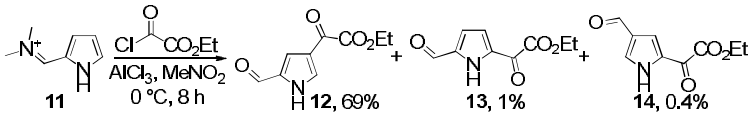


n.	R^1	R^2	R^3	R^4	R^5	Conditions	Yield %	Ref.
1	Me	H	H	H	Et	Pyridine, CH_2Cl_2, –78 °C to rt, 48 h	65	29
2							83	28
3	Me	H	H	OMe	Et	Pyridine, CH_2Cl_2, rt, 48 h	N.A.	28
4	Me	Me	OMe	H	Et		N.A.	28
5	Boc	Me	OMe	H	Me		N.A.	28
6	CH_2CH_2OAc	H	H	H	Et	Pyridine, CH_2Cl_2, –25 °C to rt, 18 h	71	30
7	CH_2CH_2OTHP	H	H	H	Et	Pyridine, CH_2Cl_2, –20 to 0 °C, 24 h	86	30
8	CH_2CH_2Cl	H	H	H	Et	NaH, DMF, –20 °C to rt, 20 h	74	30
9	$(CH_2)_4$		OMe	H	Me	Pyridine, CH_2Cl_2, rt, 48 h	N.A.	28
10	$(CH_2)_4$		OMe	H	Et		N.A.	28
11	Bn	$(CH_2)_3$		H	Et	Pyridine, CH_2Cl_2, –78 °C to rt, 48 h	69	31

12	TIPS[a]	H	H	H	Et	Pyridine, CH_2Cl_2, –20 °C to rt, 48 h	9	32
13			H	H	Me	Na_2CO_3, CH_2Cl_2, rt, 2.5 h, then reflux, 2 min	34	33
14	$(CH_2)_3$		Ph	4-ClC_6H_4	Et	Benzene, 0 °C, 3 h, then 50 °C, 1 h	N.A.	21
15	2-BnC_6H_4	H	H	H	Et	Benzene, reflux, 4 h	69	34
16	*o*-$O_2NC_6H_4$	H	H	H	Et	BF_3-Et_2O, CH_2Cl_2	N.A.	35
17		H	H	H	Et		N.A.	36
18	H	H	Ac	*n*-pentyl	Me	$AlCl_3$, CH_2Cl_2, 0 °C, 3 h, then reflux	30	37
19	H	H	Et	Et	Et	$SnCl_4$, CH_2Cl_2, rt, 18.5 h	67	38
20		H	Et	Et	Et	$SnCl_4$, CH_2Cl_2, rt, 17.5 h	69	38,39

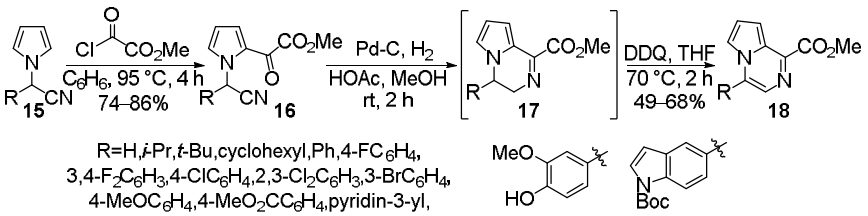
[a]The corresponding *N*-unsubstituted product was formed in 9% yield, while the major product was *N*-TIPS-protected pyrrole-3-ylglyoxylate (79% yield).

The reaction of iminium salt **11** with ethyl oxalyl chloride resulted in the formation of three compounds: formyl-substituted pyrrol-3-yl-glyoxylate **12** (69% yield) and two minor by-products **13** and **14** (1% and 0.4% yield, respectively) (Scheme 4).[40]



Scheme 4. Acylation of iminium salt **11** with ethyl oxalyl chloride.

The preparation of 1,4-disubstituted pyrrolo[1,2-*a*]pyrazine derivatives **18** included acylation of pyrrole-derived nitriles **15** with methyl oxalyl chloride (Scheme 5). The Friedel-Crafts acylation step was followed by palladium-catalyzed reduction of the nitrile group in compounds **16** and further aromatization of the intermediates **17** upon the action of DDQ. The method was suitable for both (het)aryl- and alkyl-substituted substrates **15** for the synthesis of products **18** in moderate yields (51-68%).[41]



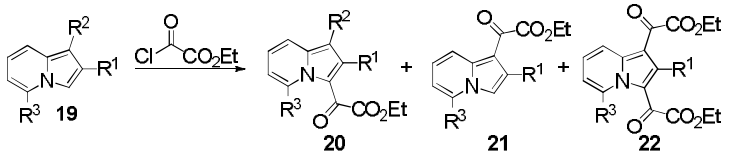
Scheme 5. Synthesis of pyrrolo[1,2-*a*]pyrazine derivatives **18**.

The Friedel-Crafts acylation with alkyl oxalyl chlorides was also reported for indolizine derivatives **19**. (Indolizin-3-yl)-2-oxoacetates **20** were formed as the major products in most cases. With C5-substituted derivatives, regioisomers **21** and/or bis-acylated products **22** were observed (Table 2).[28,42,43]

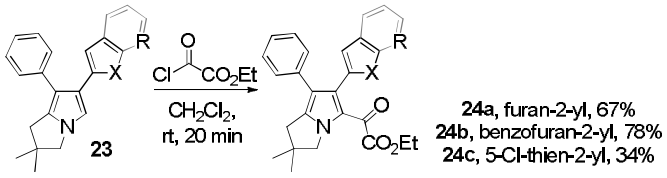
An interesting example demonstrating the reaction chemoselectivity included the Friedel-Crafts acylation of fused pyrroles **23** bearing furan-2-yl, (benzo)furan-2-yl, and thien-2-yl substituents (Scheme

6).[19] In these cases, the electrophilic substitution proceeded exclusively at the free C2-position of the pyrrole ring to give products **24**.

Table 2. Synthesis of indolizinyl-2-oxoacetates **20-22**.

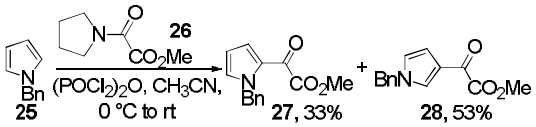


n.	R^1	R^2	R^3	Conditions	Yield % **20**	Yield % **21**	Yield % **22**	Ref.
1	Me	H	H	Benzene, rt, overnight or reflux, 30 min	67	0	0	43
2	Me	H	Me	CH_2Cl_2, 0 °C, 4.5 h	0	0	40	42
3	Ph	H	Me	CH_2Cl_2, 0 °C, 24 h	37	6.4	22	28
4	H	TBDMSO	H	Pyridine, CH_2Cl_2, rt, 48 h	63	0	0	28



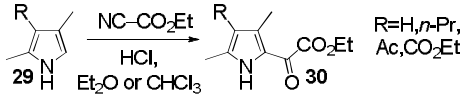
Scheme 6. Synthesis of fused pyrrolyl glyoxylates **24a-c**.

A modified approach included the Vilsmeier-type reaction of *N*-benzylpyrrole **25** with 2-oxo-2-(pyrrolidin-1-yl)acetate **26** as the acylating agent in the presence of pyrophosphoryl chloride. This transformation led to the formation of two α- and β-isomeric glyoxylates **27** and **28** in 33% and 53% yields, respectively (Scheme 7).



Scheme 7. The use of 2-oxo-2-(pyrrolidin-1-yl)acetate **26** as the acylating agent.

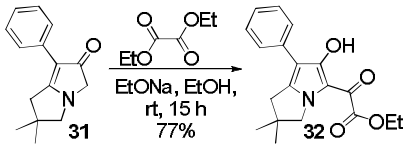
Ethyl carbonocyanidate was one more reagent used to introduce the glyoxylate moiety into the pyrrole **29** to give products **30** (Scheme 8).[44-47]



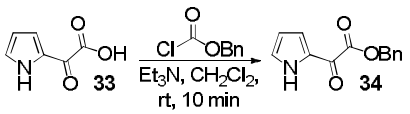
Scheme 8. Acylation of pyrroles **29** with ethyl carbonocyanidate.

Acylation with diethyl oxalate have been reported for 1,2-dihydro-3*H*-pyrrol-3-one derivative **31** that can be considered as a tautomer of the corresponding 3-hydroxypyrrole **32**. In this case, the classical Claisen condensation was involved to give derivative **32** (Scheme 9).[48,49]

Esterification of glyoxylic acids can be in principle used for the preparation of the corresponding esters. In particular, reaction of glyoxylic acid **33** with alkyl chloroformates in the presence of Et_3N in CH_2Cl_2 proceeded in 10 min to give alkyl glyoxylates **34** (Scheme 10).[50]

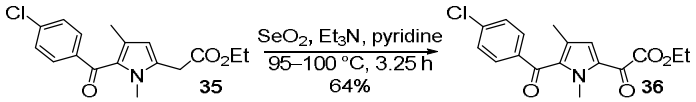


Scheme 9. Acylation of 1,2-dihydro-3*H*-pyrrol-3-one **31**.



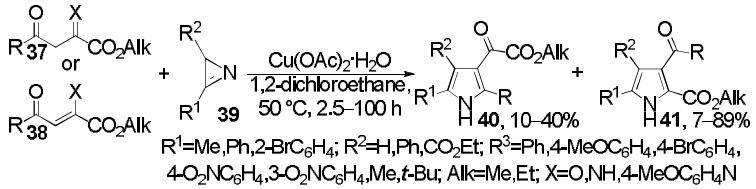
Scheme 10. Alkylation of glyoxylic acids **33** with alkyl chloroformate.

Oxidation of the methylene group of 2-(1*H*-pyrrol-2-yl)acetates **35** with SeO_2 in the presence of Et_3N in pyridine served as an approach for the preparation of pyrrole-2-ylglyoxylate **36** (64% yield, Scheme 11).[51]



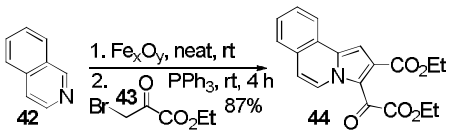
Scheme 11. Oxidation of pyrrole-2-yl acetate **35** with SeO_2.

All the above methods relied on the incorporation of the glyoxylate moiety into already available pyrrole ring. An alternative strategy is based on the construction of the heterocyclic fragment. An interesting study in this direction included the reaction of 1,3-dicarbonyl compounds **37** (or their synthetic equivalents **38**) and 2*H*-azirines **39** resulting in the formation of pyrrol-3-yl oxoesters **40**. Glyoxylates **40** and regioisomeric 3-acyl-1*H*-pyrrole-2-carboxylates **41** (major products in most cases) could be obtained upon action of CuOAc in 1,2-dichloroethane at 50 °C (Scheme 12).[52] Notably, *N*-unsubstituted pyrrol-2-ylgluoxylates are themselves reactive towards azirines through addition to the C=N bond.[53]



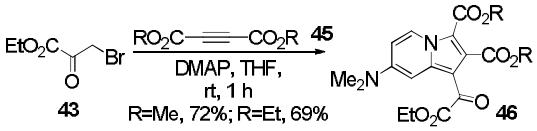
Scheme 12. Reaction of 2*H*-azirines **39** and 1,3-dicarbonyl compounds or their synthetic equivalents.

Construction of fused pyrroles with an α-glyoxylate fragment is exemplified by the synthesis of 2-oxo-2-(pyrrolo[2,1-*a*]isoquinolin-3-yl)acetate **32**. The reaction involves isoquinoline **42** and bromopyruvate **43** as the starting materials forming the pyrrole ring of **44** (Scheme 13).[54] The method was also used for the preparation of the corresponding benzo analogs.[55]



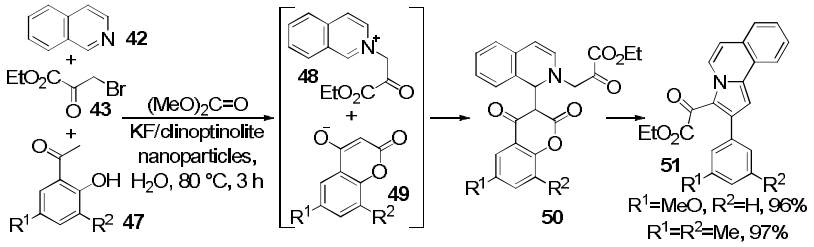
Scheme 13. Synthesis of 2-oxo-2-(pyrrolo[2,1-*a*]isoquinolin-3-yl)acetate **44**.

Another example using bromopyruvate **43** to construct the heterocyclic scaffold of hetaryl glyoxylates included condensation with acetylene dicarboxylates **45** in the presence of DMAP in THF at rt, which resulted in the formation of (2-ethoxy-2-oxoacetyl)indolizine-2,3-dicarboxylates **46** (Scheme 14).[56] Phenanthridine could be also used as the reaction promotor instead of DMAP.[55]



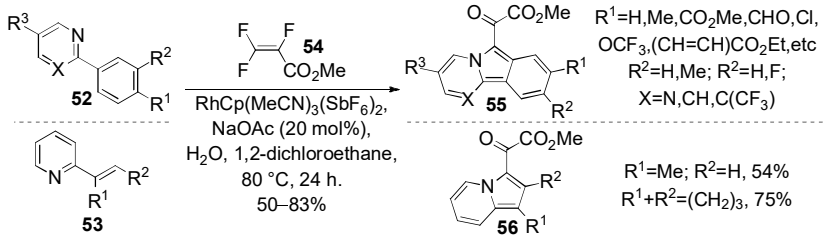
Scheme 14. Synthesis of 2-oxo-2-(pyrrolo[2,1-*a*]isoquinolin-3-yl)acetate **46**.

A multicomponent reaction leading to hetaryl glyoxylates **34** involved condensation of isoquinoline **42**, bromopyruvate **43**, 2-hydroxyacetophenones **47**, and dimethyl carbonate (Scheme 15). Initially, intermediates **48** and **49** were formed; their condensation resulted in derivatives **50**, which led to pyrrolo[2,1-*a*]isoquinoline glyoxylates **51** in excellent yield.[57] These conditions have been also applied to benzene-1,2-carbaldehyde and aminopropionitrile.[58] Bromoacetophenones could be used instead of 2-hydroxyacetophenones in the presence of iron oxide and PPh_3 to give the same type of heterocyclic glyoxylates.[54]



Scheme 15. A four-component reaction in the synthesis of hetaryl glyoxylates **51**.

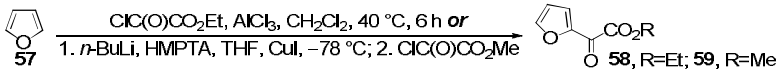
A novel approach to the synthesis of hetaryl glyoxylates includes the rhodium(III)-catalyzed C−H activation of 2-aryl- **52** or 2-alkenylpyridines **53** (and other azines) in the reaction with 2,3,3-trifluoracrylate **54**, which can be considered as a method for fusing two isolated (hetero)aromatic rings **55** and **56** (Scheme 16).[59]



Scheme 16. Rhodium(III)-catalyzed C−H coupling of 2-arylpyridines **55** and **56**.

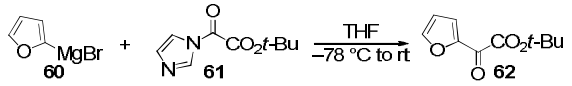
2.2. Furyl glyoxylates

Synthesis of the parent representatives of furan-2-ylglyoxylates included the reaction of furan **57** with ethyl oxalyl chloride in the presence of $AlCl_3$ as a Lewis acid (for the synthesis of **58**),[60] or the metalation-acylation sequence upon action of *n*-BuLi in the presence of HMPTA and CuI at –78 °C (to obtain **59**) (Scheme 17).[61]

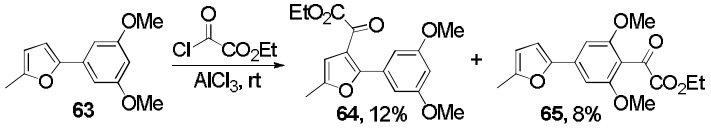


Scheme 17. Synthesis of furan-2-ylglyoxylates **58** and **59**.

A related approach involved the acylation of the Grignard reagent, *e.g.* furan-2-ylmagnesium bromide **60**, with *t*-butyl-2-(1*H*-imidazol-1-yl)-2-oxoacetate **61**, which resulted in the formation of furan-containing glyoxylate **62** (Scheme 18).[62] Acylation of 2,5-disubstituted furan **63** proceeded with low selectivity to give two products **64** and **65** due to the comparable electron density of the dimethoxybenzene ring (Scheme 19).[63]

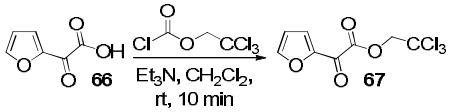


Scheme 18. Synthesis of *t*-butyl-2-(furan-2-yl)-2-oxoacetate **62**.



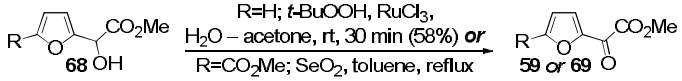
Scheme 19. Selectivity of acylation of electron-rich 2-arylfuran **63**.

As in the case of pyrrole derivatives, esterification of the corresponding glyoxylic acids (*e.g.* **66**) with alkyl chloroformates in the presence of Et_3N in CH_2Cl_2 can be used for the preparation of the corresponding esters, *e.g.* **67** (Scheme 20).[50]



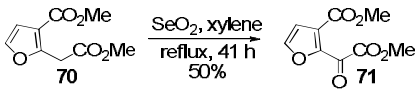
Scheme 20. Esterification of glyoxylic acid **66** with alkyl chloroformate.

Oxidation of the hydroxyacetate fragment in compounds **68** has been realized with *t*-BuOOH and $RuCl_3$ in H_2O-acetone (for the synthesis of compound **59**, 58% yield)[64] or in refluxing toluene in the presence of SeO_2 (for the synthesis of compound **69**) (Scheme 21).[65]



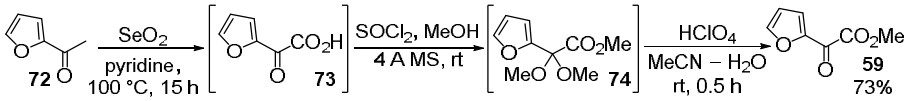
Scheme 21. Oxidation of hydroxyacetates for the synthesis of oxoacetates **59** and **69**.

Another example of the use of selenium dioxide is oxidation of the methylene group in the molecule of bifunctional furan-2-yl acetate **70** in refluxing xylene, which resulted in the formation of glyoxylate **71** bearing an additional ester group (Scheme 22).[60]



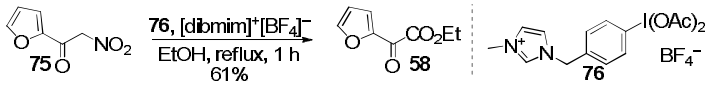
Scheme 22. Preparation of furan-2-ylglyoxylate **71**.

Preparative oxidation of 1-(furan-2-yl)ethan-1-one **72** with selenium dioxide, followed by the esterification of resulting furylglyoxalic acid **73** accompanied by the formation of ketal **74** and, finally, deprotection, provided compound **59** in 73% overall yield (Scheme 23).[66]



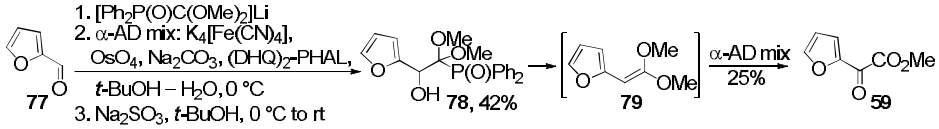
Scheme 23. Synthesis of furan-2-ylglyoxylate **59** from 2-acetylfuran **72**.

Compound **58** was formed in 61% yield by sp^3–C–H oxidation of nitro ketone **75** with 1-[4-(diacetoxyiodo)benzyl]-3-methyl imidazole tetrafluoroborate **76** in ionic liquid (Scheme 24).[67]



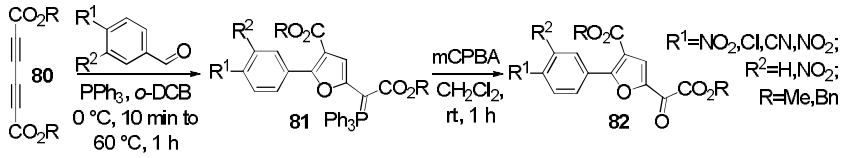
Scheme 24. Preparation of furan-2-ylglyoxylate **58**.

Sharpless-type dihydroxylation of a derivative generated from furfural **77** using α-AD mix ($K_4[Fe(CN)_6]$, OsO_4, Na_2CO_3, $(DHQ)_2$-PHAL) led to the formation of product **78** in 42% yield. Over-oxidation of compound **78** gave glyoxylate **59** through elimination-oxidation of intermediate **79** (Scheme 25).[68]



Scheme 25. Synthesis of furan-2-ylglyoxylate **59** from furfural.

Multicomponent reactions of phosphines, diyndioates **80**, and aromatic aldehydes proceed through the initial α(δ′)-addition of phosphines to **80** followed by addition of the formed trienoates to aldehydes at the key step giving furan derivatives **81**. Intermediates **81** can be easily oxidized to the corresponding α-ketoesters **82** (Scheme 26).[69]

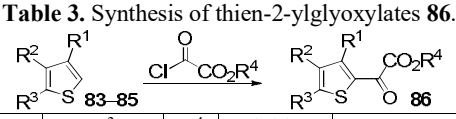


Scheme 26. Synthesis of glyoxylates **82** through α(δ′)-addition of PPh_3 to diyndioates **80**.

2.3. Thienyl glyoxylates

Thiophene derivatives easily undergo electrophilic acylation with the formation of thien-2-ylglyoxylates, similarly to pyrroles and furans. A notable difference is that in most cases the reaction requires the presence of Lewis acids. It is worth noting that for thiophenes it is possible to perform the acylation selectively in both α- and β-positions. Typically, the substitution reaction proceeds at the C2 atom of the parent thiophene (as with derivatives **83** bearing alkyl and aryl groups, α-halo- and β-halothiophenes **84** and **85**, respectively) to give products **86** (Table 3).[70-82] If both α-positions are occupied by substituents (as in the case of **87**), thien-3-ylglyoxylates **88** are obtained (Table 4).[73,83-91]

Table 3. Synthesis of thien-2-ylglyoxylates **86**.



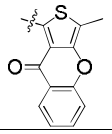
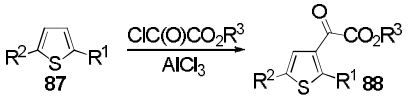
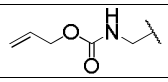
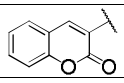
n.	R^1	R^2	R^3	R^4	Yield %	Conditions	Ref.
1	H	H	H	Et	50	$AlCl_3$, CCl_4, rt 3 h	70
2	H	H	H	Et	N.A.	$AlCl_3$, CH_2Cl_2, 40 C, 6 h	71
3	H	H	H	Et	84	$AlCl_3$, CH_2Cl_2, rt, 1 h	72,73
4	H	H	Bn	Et	17	$TiCl_4$, C_6H_6, 27° C, 3 h	74
5	H	H	4-ClC_6H_4	Et	N.A.		
6	4-FC_6H_4	4-MsC_6H_4	H	Et			75
7	4-FC_6H_4	4-$MeSC_6H_4$	H	Et			
8	H	H	Me	Et	64	$AlCl_3$, CH_3NO_2, 10 °C, 1 h, then rt, 1 h	76
9	Me	H	H	Et	61		
10	Br	H	H	Et	79		
11	H	H	Br	Et	51		
12	Cl	H	H	Et	68		
13	H	H	Cl	Et	61		
14	H	H	Br	Et	30	$AlCl_3$, CCl_4, –5 °C to rt, 4 h	77
15	H	H	Br	Et	N.A.	$AlCl_3$, CH_2Cl_2, 0 °C to rt, 5 h	78
16	Br	H	H	Et			
17	H	H	H	Et			
18	H	H	Me	Et	61	$AlCl_3$, CH_2Cl_2, 0 °C, 50 min	79
19	H	H	H	Et	N.A.	$AlCl_3$, CH_2Cl_2, rt, 12 h	80
20	H	$(CH_2)_4$		Et	7		80
21	4-$O_2NC_6H_4$	H	H	Et	N.A.	$AlCl_3$, $CHCl_3$, rt, 24 h	81
22		H	H	Et	65	$AlCl_3$, CH_2Cl_2, 0 °C to rt 1.5 h	82

Table 4. Synthesis of thien-3-ylglyoxylates **88** by electrophilic acylation.

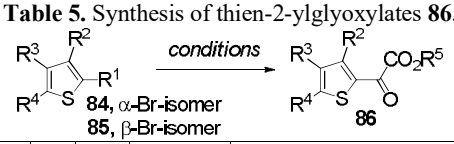


n.	R^1	R^2	R^3	Conditions	Yield %	Ref
1	Me	Me	Et	$MeNO_2$	89	87
2	Me	Me	Et	$MeNO_2$, 10 °C, 1 h to rt	82	83
3	Me	Me	Et	CH_2Cl_2, –5 °C, 2 h	79	84
4	Me	Me	Et	$MeNO_2$, 0 °C to rt, 2 h	70	88
5	Me	Me	Me	$MeNO_2$, 10 °C, 1 h	70	73
6	Me	Cl	Me	CH_2Cl_2, 0 °C, 2 h	73	89
7	Me	Br	Me	CH_2Cl_2, 0 °C, 3 h	68	90
8	Cl	Cl	Et	$MeNO_2$, 10 °C, 1 h to rt	77	83
9	Cl	Cl	Et	$MeNO_2$, 10 °C, 1 h	82	73
10	Me		Me	CH_2Cl_2, –5 °C, 20 h	49	91

11	Me		Et	CH_2Cl_2, –5 °C, 2 h	95	84

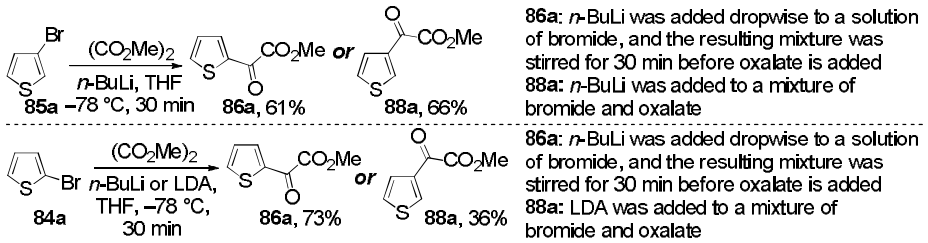
Metalation-acylation of isomeric bromides **84** and **85** with dialkyl oxalates is another important approach to the synthesis of 2-oxo-2-(thiophen-2-yl)acetates **86** (Table 5).[72,85,92-96] In the case of 3-halothiophenes **85** as the starting compounds (instead of 2-isomers **84**), the thien-3-yl anions initially formed during the metalation can rearrange into more stable α-isomeric anions. Thus, 2-oxo-2-(thiophen-2-yl)acetates **86** were obtained with both substrate types.[85] Meanwhile, 2,3,4,5-tetrabromothiophene gave 2,5-bis-glyoxylates under similar conditions.[86]

Table 5. Synthesis of thien-2-ylglyoxylates **86**.



n.	R^1	R^2	R^3	R^4	R^5	Yield %	Conditions	Ref.
1	H	H	H	H	Et	84	1. *n*-BuLi, –60 °C, 0.5 h 2. $(CO_2Et)_2$, –60 °C	72
2	H	Br	H	Br	Et	75		
3	Br	H	H	H	Me	75	1. *n*-BuLi, –80 °C, 0.5 h 2. $(CO_2Me)_2$	85
4	MgBr	H	H	H	Et	54	$(CO_2Et)_2$, –78 °C to rt, 2 h	92
5						86	$(CO_2Et)_2$, Et_2O, –78 °C to 10 °C	93
6						72	$(CO_2Et)_2$, THF, –78 °C, 1 h	94,95
7						39	$(CO_2Et)_2$, THF, –10 °C, 1 h	96

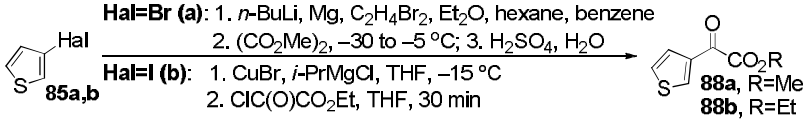
The above regioselectivity can be altered by varying the reaction conditions (metalation agent, solvent) or the order of the reagent addition. In particular, when *n*-BuLi was added to a solution of 3-bromothiophene **85a** and dimethyl oxalate in THF at –78 °C, only β-glyoxylate **88a** was obtained in 66% yield (analogous transformation in Et_2O resulted in 35% yield) (Scheme 27).[85] Metalation of 2-bromothiophene **84a** with LDA was accompanied by the halogen dance reaction providing 3-bromothien-2-yl anion as the major intermediate, which also led to the formation of the β-isomer **88a**.



Scheme 27. Synthesis of isomeric thienyl glyoxylates **86** and **88**.

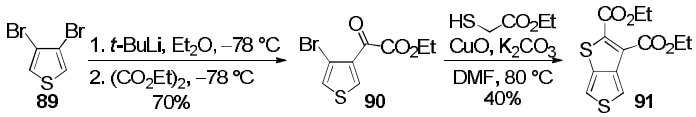
The highest yield of compound **88a** (76%) was achieved when 3-thienyllithium was obtained from 3-bromothiophene **84a**, followed by the preparation of Grignard reagent at –70 °C (*via* transmetalation) with subsequent addition of ethyl oxalate solution at the same temperature.[97] Another technique leading to thien-3-ylglyoxylate **88a** in 57% yield involved a direct formation of the Grignard reagent using magnesium and ethylene dibromide (Scheme 28).[98] In the case of 3-iodothiophene, an alternative approach was tested: *i*-PrMgCl was added to a solution of 3-iodothiophene with CuBr in THF at –15°C, the mixture was stirred, and a solution of ethyloxalyl chloride in THF was added dropwise to form **88b**.[99] It is worth mentioning that

acylation of bromothiophenes with retention of the bromine atom is possible by using the Lewis acids-promoted reaction.



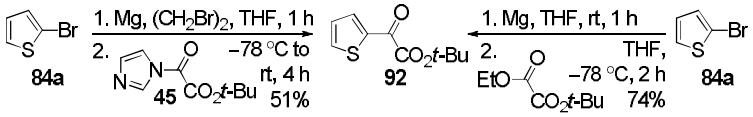
Scheme 28. Synthesis of thien-3-ylglyoxylates **88a,b**.

Selective monometalation of 3,4-dibromothiophene **89** can be achieved by the addition of *t*-BuLi to a solution of dibromothiophene in Et_2O at –78 °C. After the subsequent addition of diethyl oxalate, bifunctional derivative **90** was obtained in 70% yield (Scheme 29).[100] Further reaction of compound **90** with mercaptoacetic ester in the presence of CuO and K_2CO_3 was used for the synthesis of thieno[3,4-*b*]thiophene-2,3-dicarboxylate **91** (40% yield).



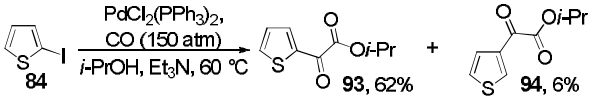
Scheme 29. Synthesis of **90** and **91** from 3,4-dibromothiophene **89**.

Similar synthetic approach includes acylation of Grignard reagents initially generated from **84a** (thien-2-ylmagnesium bromide and its derivatives)[101,102] with *t*-butyl-2-(1*H*-imidazol-1-yl)-2-oxoacetate **61** (51% yield of **92**)[103] or *t*-butyl ethyl oxalate (74% yield of **92**) (Scheme 30).[104]



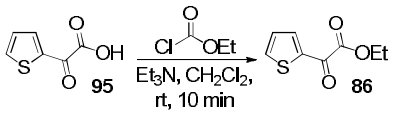
Scheme 30. Synthesis of furan-2-ylglyoxylate **92**.

Palladium-catalyzed double alkoxycarbonylation in the presence of alcohol can also be used for the synthesis of ketoesters. Following this approach, compound **93** was obtained in 62% yield (Scheme 31).[105,106] It is worth noting that the corresponding β-glyoxylate **94** was formed as a side product (6% yield).[107]



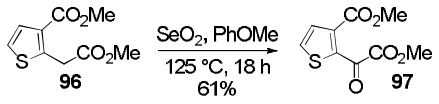
Scheme 31. Double alkoxycarbonylation reaction for the synthesis of glyoxylates **93** and **94**.

As in the case of pyrrole and furan derivatives, esterification of the corresponding glyoxylic acids (*e.g.* **95**) with alkyl chloroformates in the presence of Et_3N in CH_2Cl_2 can be used for the preparation of the esters **86** (Scheme 32).[50]

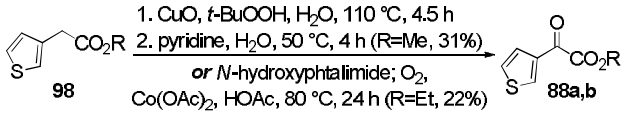


Scheme 32. Alkylation of glyoxylic acids with ethyl chloroformate.

It is possible to form the ketoester moiety by oxidation of thien-2-yl acetate **96** with selenium dioxide in anisole, as shown by the synthesis of compound **97** in 61% yield (Scheme 33).[65] Oxidation of the methylene unit of derivative **98** by the action of CuO and *t*-butylhydroperoxide at 110 °C[108] or oxygen in the presence of $Co(OAc)_2$ and hydroxyphthalimide[109] was used for the synthesis of thien-3-ylglyoxylate **88a,b** (R=Me, Et, 31% and 22% yield, respectively) (Scheme 34).

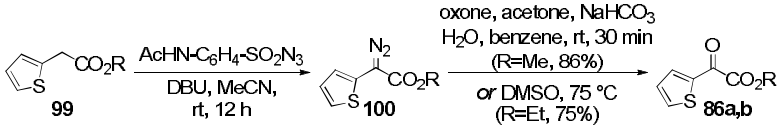


Scheme 33. Preparation of thien-2-ylglyoxylate **97**.



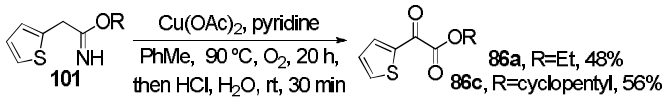
Scheme 34. Synthesis of glyoxylates by oxidation of thien-3-yl acetates **98**.

Another synthetic sequence for the transformation of hetaryl acetates **99** into glyoxylates **86a,b** includes the Regits diazo transfer reaction with 4-acetamidobenzene sulfonyl azide, followed by oxidation of diazo compound **100** thus obtained with oxone (86% yield)[110] or heating in DMSO at 75 °C[111] (Scheme 35).



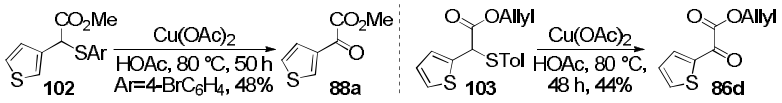
Scheme 35. Synthesis of glyoxylates from diazoacetates **100**.

Thienyl glyoxylates **86a,c** could be also obtained from the corresponding imidates **101**, which occurred in the presence of O_2, $Cu(OAc)_2$, and pyridine in toluene (Scheme 36).[112] An alternative approach included oxidation of α-hydroxyesters.[113]

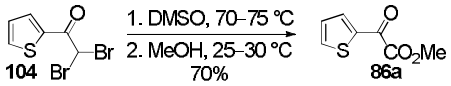


Scheme 36. Synthesis of thien-2-yl acetates from imidates **101**.

One more oxidative method for the preparation of thienyl glyoxilates included treatment of 2-(4-arylthio)-2-(thiophen-3-yl)acetate **102** with $Cu(OAc)_2$ in acetic acid, which resulted in the formation of compound **88a** in 48% yield (Scheme 37).[114] A similar approach was described for the α-isomer **103** that was oxidized to glyoxylate **86d** in 44% yield.[115] It was also found that 2,2-dibromo-1-(thiophen-2-yl)ethan-1-one **104** reacted with DMSO at the sulfur atom when heated, so that derivative **86a** was formed after the subsequent methanolysis in 70% yield (Scheme 38).[116]

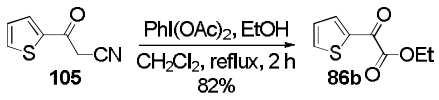


Scheme 37. Oxidation of 2-(4-arylthio)-2-(thiophen-3-yl)acetates **102** and **103**.

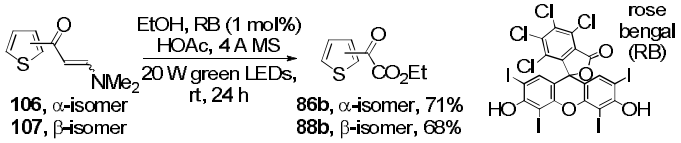


Scheme 38. Synthesis of **86a** from 2,2-dibromo-1-(thiophen-2-yl)ethan-1-one **104**.

The list of oxidative methods for the synthesis of glyoxylates also includes the reaction of 3-oxo-3-(thiophen-2-yl)propanenitrile **105** with bis(acetoxy)iodobenzene for the synthesis of compound **86b** in 82% yield (Scheme 39).[117] Photolysis of β-enaminones **106** and **107** in the presence of rose Bengal in EtOH was also used for the preparation of isomeric thienyl glyoxylates (Scheme 40).[118]

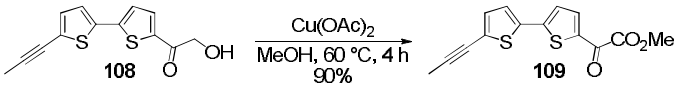


Scheme 39. Oxidation of cyanoketone **105** to derivative **86b**.

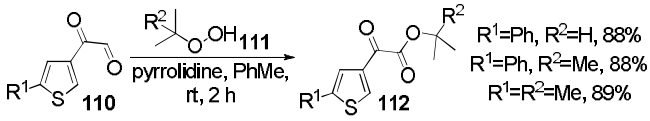


Scheme 40. Photolysis of β-enaminones **106** and **107**.

It was found that α-hydroxy ketones could be oxidized to glyoxylates. Examples include the transformation of compound **108** into product **109** upon the action of $Cu(OAc)_2$ in MeOH (Scheme 41).[119] In turn, 2-oxo-2-(thiophen-3-yl)acetaldehydes **110** were oxidized with hydroperoxides **111** in the presence of pyrrolidine to form oxoesters **112** in high yields (Scheme 42).[120]

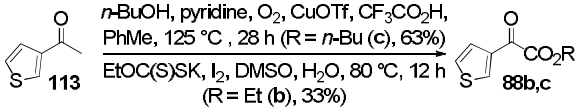


Scheme 41. Oxidation of 2-hydroxy-1-(thiophen-2-yl)ethanone **108**.



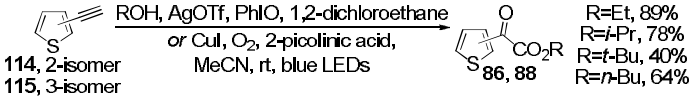
Scheme 42. Synthesis of thien-3-ylglyoxylates **112**.

1-(Thien-3-yl)ethan-1-one **113** could be used as the starting compound to obtain hetaryl glyoxylates **88** (Scheme 43). Oxidation of acyl derivative **113** proceeded upon the action oxygen in the presence of copper triflate in TFA 125 °C (63% yield)[121] or with potassium *O*-ethylcarbonodithioate and I_2 in DMSO/H_2O at 80 °C (33% yield).[122] In addition to that, copper-catalyzed oxidative coupling of 1,3-diketones upon the action of CuBr and oxygen have been also described for the synthesis of glyoxylates.[123]



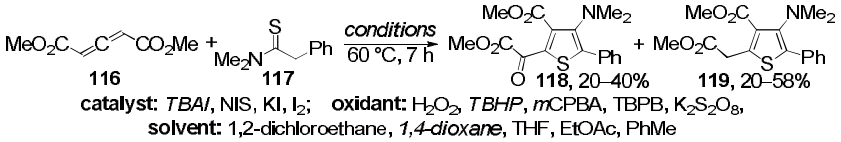
Scheme 43. Oxidation of acetyl-3-thiophene **113**.

Another synthetic approach includes reactions of isomeric ethynylthiophenes **114** and **115** with alcohols in the presence of CuI and O_2[124] or AgOTf and PhIO,[125] which served as a method for the synthesis of both isomeric thienyl glyoxylates of type **86** and **88** in 40-89% yield (Scheme 44). Other related methods involved rearrangements of thienyl acetate-derived arylhydrazones.[81]



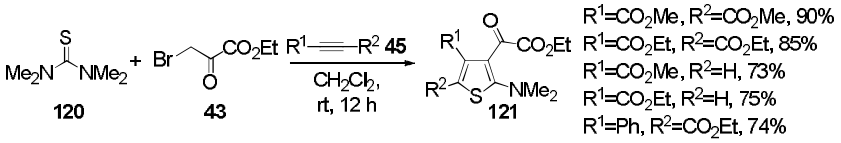
Scheme 44. Ethynylthiophenes **114** and **115** in the synthesis of thienyl glyoxylates.

Some methods for the preparation of thienyl glyoxylates relied on the construction of the thiophene ring. Thus, Michael addition of thioamides **117** to allenes **116** with subsequent oxidative annulation and 1,2-migration of the sulfur atom upon TBAI catalysis gave mixtures of glyoxylates **118** or acetates **119**. Variation of the reaction conditions provided a possibility to shift the reaction regioselectivity towards either glyoxylates **118** (*t*-BuOOH, 1,4-dioxane) or acetates **119** (H_2O_2, 1,2-dichloroethane) (Scheme 45).[126]

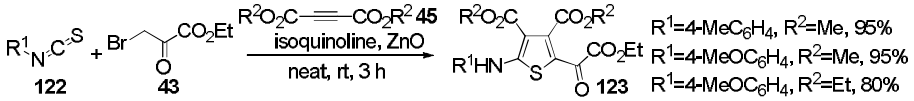


Scheme 45. Synthesis of glyoxylates **118** *via* Michael addition of thioamides.

The three-component condensation of tetramethylthiourea **120**, bromopyruvate **43**, and acetylene mono- and dicarboxylates **45** was reported for the preparation of glyoxylates **121** in good to high yields under mild reaction conditions (Scheme 46).[127] A similar approach was based on the condensation of arylisothiocyanates **122** instead of thioureas, which was used for the synthesis of α-glyoxylates **123** (Scheme 47).[128]



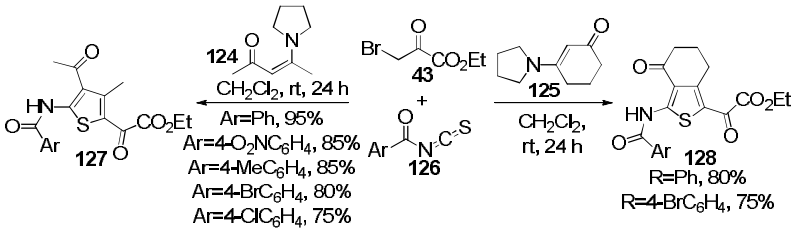
Scheme 46. Synthesis of thien-3-ylglyoxylates **121** *via* the thiophene-forming three-component condensation.



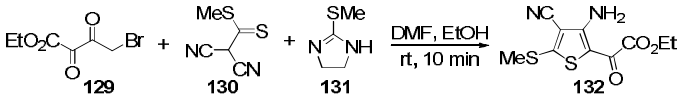
Scheme 47. Synthesis of thien-2-ylglyoxylates **123** by construction of the thiophene ring.

Another application of bromopyruvate in the synthesis of thienyl glyoxylates included condensation with isothiocyanates and 1,3-diketones (or the corresponding enaminones). In particular, acyclic and cyclic enones **124** and **125** reacted with benzoyl isothiocyanates **126** to form tetrasubstituted mono- and bicyclic thien-2-ylglyoxylates **127** and **128**, respectively (Scheme 48).[129]

Dithioester **130** and cyclic thiourea, *e.g.* 2-(methylthio)-4,5-dihydro-1*H*-imidazole **131**, reacted with bromopyruvate analog **129** in a similar way, which was demonstrated by the preparation of thiophene **132** (Scheme 49).[130]

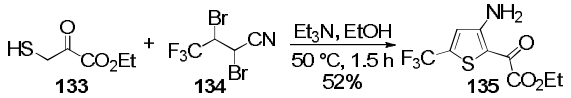


Scheme 48. Condensation of enones **124** and **125** with isothiocyanates **126** and bromopyruvate **43**.



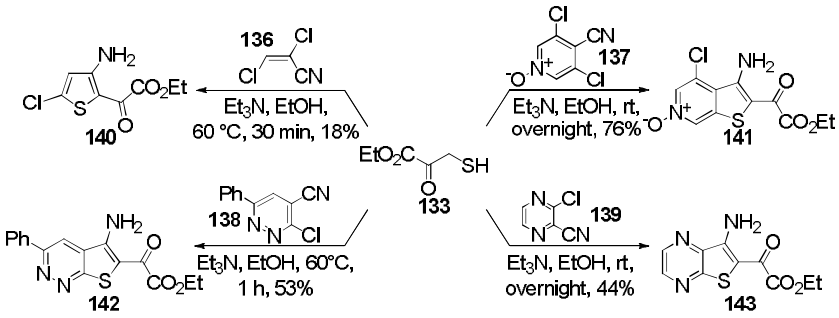
Scheme 49. Condensation of thiourea **131** with dithioester **130**.

Ethyl mercaptopyruvate **133** served as another reagent for the simultaneous introduction of sulfur and carbon atoms, as well as the glyoxylate fragment into the target thiophene ring. In particular, the reaction of compound **133** with 2,3-dibromo-3-trifluoromethylacrylonitrile **134** gave thien-2-ylglyoxylate **135** in 52% yield (Scheme 50).[131]



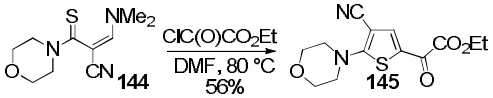
Scheme 50. Reaction of ethyl mercaptopyruvate **133** with 2,3-dibromoacrylonitrile **134**.

Other functionalized nitriles, in particular, 2,3-dichloroacrylonitrile **136**, 3,5-dichloro-4-cyanopyridine-*N*-oxide **137**, 3-chloro-6-phenylpyridazine-4-carbonitrile **138**, and 2-chloro-3-cyanopyrazine **139**, were also suitable for the synthesis of thienyl-2-glyoxylates **140**-**143** in a similar way starting from **133** (Scheme 51).[131]



Scheme 51. Other uses of ethyl mercaptopyruvate **133** in the synthesis of thienyl glyoxylates **140**-**143**.

An interesting approach included the construction of the thiophene ring *via* *S*-acylation of aminothioacrylamide **144** with ethyloxalyl chloride and further cyclization to give derivative **145** in 52% yield (Scheme 52).[132]

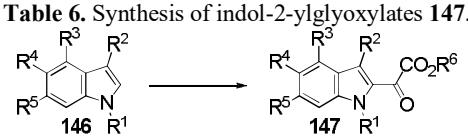


Scheme 52. *S*-Acylation of aminothioacrylamide **144** followed by cyclization.

2.4. Indolyl glyoxylates

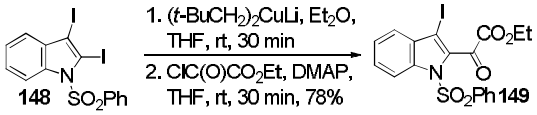
Most known methods for the preparation of (indol-2-yl)oxoacetates **147** include metalation of C2-unsubstituted or C2-halogenated *N*-substituted indoles **146** followed by acylation with dialkyl oxalates (Table 6).

Table 6. Synthesis of indol-2-ylglyoxylates **147**.



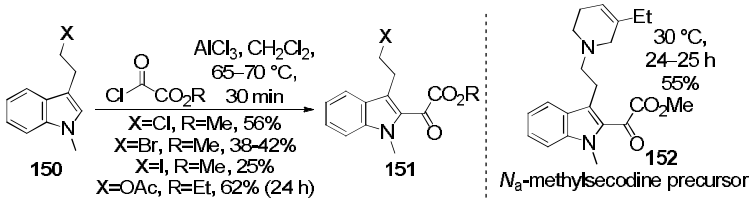
n.	R^1	R^2	R^3	R^4	R^5	Conditions	Yield %	Ref.
1	Me	H	H	H	Et	1. *n*-BuLi, Et_2O, hexane, reflux, 5 h 2. $(CO_2Et)_2$, 0 °C	N.A.	133,134
2	Me	H	H	H	Me	1. *n*-BuLi, THF, –78 °C; 2. $(CO_2Et)_2$, 0 °C	N.A.	135
3	Boc	H	H	H	Me	1. *t*-BuLi, THF, –78 °C; 2. $(CO_2Me)_2$	71	136
4	Boc	H	H	H	Me	1. *t*-BuLi, THF, pentane, –78 °C, 40 min 2. $(CO_2Me)_2$, THF, 1 h	66	137
5	Boc	H	H	H	Et	1. LDA, THF, –78 °C, 1 h; 2. $(CO_2Et)_2$, –78 °C to rt, 4 h	67	138
6	Boc	Me	H	H	Me	1. *t*-BuLi, THF, pentane, –78 °C, 1 h 2. $(CO_2Me)_2$, THF, –78 °C to rt, 1 h	21	139
7	$PhSO_2$	H	H	H	H	1. LDA, THF, hexane, –78 to 15 °C, 2.5 h 2. $(CO_2Me)_2$, THF, –50 °C to rt, 2.5 h	61	140
8						1. MeLi, THF, 0 °C, 1.5 h to rt, 1.5 h 2. $(CO_2Me)_2$, 0 °C, 55 min.	45	137
9						1. *t*-BuLi, THF, pentane, –65 to 0 °C, 1 h 2. $(CO_2Me)_2$, THF, 0 °C, 4 h	34	141
10	$PhSO_2$	Me	H	H	Et	1. *sec*-BuLi, –78 °C to rt; 2. $ClC(O)CO_2Et$, –78 °C to rt	31	142
11	$PhSO_2$	H	H	OMe	Me	1. *t*-BuLi, THF, pentane, –5 °C, 20 min to rt, 20 min 2. $(CO_2Me)_2$, THF, rt, 20 min.	54	143
12	Ts	H	H	H	Et	1. *n*-BuLi, THF, –78 °C; 2 h. $(CO_2Et)_2$	58	144

An important example of the metalation-acylation sequence involved 2,3-diiodoindole **148** that was subjected to the reaction with lithium dineopentylcuprate, and then treated with ethyloxalyl chloride in the presence of 4-dimethylaminopyridine (DMAP) to give the 2-indolyl derivative **149** as the sole product (Scheme 53).[145]



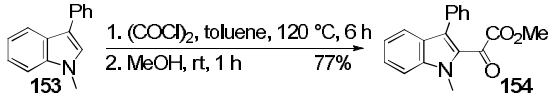
Scheme 53. Preparation of indol-2-ylglyoxylate **149** from 2,3-diiodoindole **148**.

It is worth noting that the use of Friedel-Crafts acylation is also possible for the preparation of indol-2-yl glyoxylates. Typically, the electrophilic acylation proceeds at the free C3-position; the regioselectivity could be altered for the case of C3-substituted indoles, *e.g.* **150**, for the preparation of **151** (Scheme 54).[146,147] This method was used for the synthesis of the tetrahydropyridine precursor **152** of N_a-methylsecodine.[147,148]



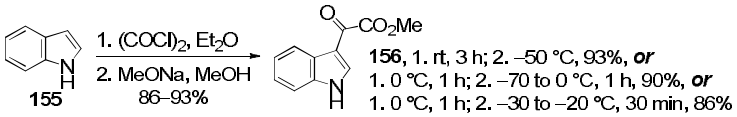
Scheme 54. Friedel-Crafts reaction of C3-substituted indoles **150**.

The synthesis of 3-aryl-substituted indol-2-ylglyoxylates can be performed by acylation of the corresponding indoles **153** with oxalyl chloride followed by treatment with alcohols, which was illustrated by the synthesis of compound **154** (Scheme 55).[149-152] In the case of the presence of two methoxyl groups in the benzene ring of indole , acylation can take place in the C7-position.[153]



Scheme 55. Synthesis of 3-phenylindol-2-ylglyoxylate **154**.

On the contrary, synthesis of isomeric 2-(1*H*-indol-3-yl)-2-oxoacetates typically relied on the straightforward electrophilic acylation at the C3-position.[154-171] Thus, unsubstituted indole **155** could be acylated with oxalyl chloride; further treatment with MeONa finalized the synthesis of glyoxylate **156** (Scheme 56). The yield of the product could be improved by varying the reaction temperature.[160-163] The scope of other electrophilic acylations of C3-unsubstituted indoles **157** for the synthesis of glyoxylates of the general formula **158** is summarized in Table 7.



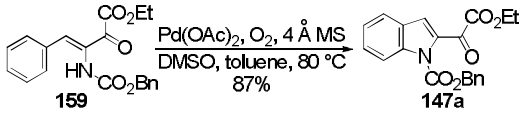
Scheme 56. Synthesis of methyl-2-(1*H*-indol-3-yl)-2-oxoacetate **156**.

Table 7. Synthesis of indol-3-ylglyoxylates **158**.

n.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	Conditions	Yield %	Ref.
1	H	H	H	H	H	H	Et	$ClC(O)CO_2Et$, pyridine, Et_2O, 0 °C, 2 h	81	162
2	H	H	H	H	H	H	Et	$ClC(O)CO_2Et$, pyridine, Et_2O, 0 °C, 1 h to rt, 5 h	74	163
3	H	H	H	Cl	H	H	Et		49	
4	H	H	H	H	H	H	Me	$ClC(O)CO_2Et$, pyridine, Et_2O,	62	164,165

								5 °C, 1.5 h		
5	H	H	H	H	H	Br	Me	$ClC(O)CO_2Et$, THF, pyridine, reflux, 48 h	70	166
6	H	H	H	H	H	OBn	Me		77	
7	H	H	H	H	H	$OCHPh_2$	Me		78	
8	H	H	H	H	H	$NHCO_2Bn$	Me		55	
9	H	H	H	H	H	H	Et	1. Et_2AlCl, hexane, CH_2Cl_2, 0 °C, 30 min 2. $ClC(O)CO_2Me$, CH_2Cl_2, 0 °C, 3 h	72	167
10									55	168
11	H	H	H	H	H	H	Me	1. Et_2AlCl, hexane, CH_2Cl_2, 0 °C, 30 min 2. $ClC(O)CO_2Me$, 0 °C, 2 h	66	169,170
12	H	H	H	F	H	H	Me/Et		N.A.	
13	H	H	H	H	F	H	Me/Et		50 (Et)	
14	H	H	H	H	OMe	H	Me/Et		N.A.	
15	H	H	H	H	H	H	Et	$PhNHCH_2CO_2Et$, $CuCl_2$, O_2 (air), *t*-BuOOH, CH_2Cl_2, H_2O, rt, 24 h	60	171
16	H	H	H	H	H	H	Et	$PhNHCH_2CO_2Et$, $Fe(OTf)_3$, *t*-BuOOH, pivalic acid, 50 °C, 15 h	54	172
17	H	Me	H	H	H	H	Me	1. $(COCl)_2$, Et_2O, 0 °C 2. MeOH, Et_2O	85	156
18									80	173
19									60	156

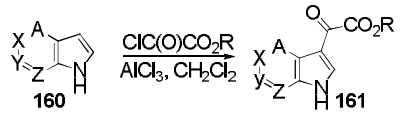
Notably, only a few examples of the synthesis of indolyl glyoxylates *via* the construction of the indole fragment have been disclosed in the literature, being limited by cyclizations of 2-oxo-3-arylbut-3-enoates.[174,175] For example, it was possible to synthesize indole-2-yl glyoxylates **147a** by palladium-catalyzed intramolecular amination-cyclization of *N*-protected α-aminocinnamic ester **159** (87% yield) (Scheme 57).[176]



Scheme 57. Cyclization of *N*-Cbz-*α*-aminocinnamic ester **159**.

Aza-substituted indolyl glyoxylates **161** were synthesized by the Friedel-Crafts acylation of the simplest isomeric azaindoles **160**[177-179] and their substituted derivatives (Table 8).[180]

Table 8. Acylation of compounds **160** for the synthesis of azaindol-3-ylglyoxylates **161**.

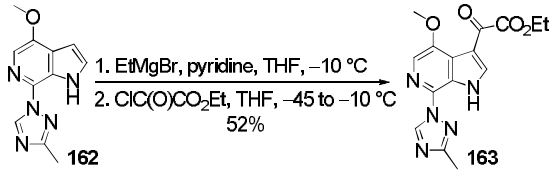


n.	A	X	Y	Z	R	Temperature	Yield %	Ref
1	N	H	H	H	Me	rt	42	177
2					Et	0 °C	50	178
3	H	N	H	H	Me	rt	70	177
4					Et	0 °C	45	178
5	H	H	N	H	Me	rt	42	177
6					Et	0 °C	42	178

7	H	H	H	N	Me	rt	76[a]	177
8					Et	0 °C	51	178
9						rt	53	181,182

[a]EtMgBr, THF, –65 °C, then MeO_2CCOCl, –78 °C, 24%

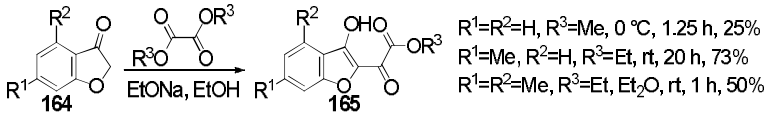
Acylation of (1,2,4-triazol-1-yl)-pyrrolo[2,3-*c*]pyridine **162** (and related derivatives) requires the initial treatment with the Grignard reagent (*e.g.* EtMgBr) and subsequent reaction with ethyloxalyl chloride to give glyoxylate **163** (Scheme 58).[183-186] Other protocols involved the use of other Grignard reagents (*e.g.* *i*-PrMgCl)[187] or Lewis acid (*e.g.* $AlCl_3$)[188] to promote the formation of compound **163**, however, in a lower yield (23%).[185]



Scheme 58. Acylation of (1,2,4-triazol-1-yl)-pyrrolo[2,3-*c*]pyridine **162**.

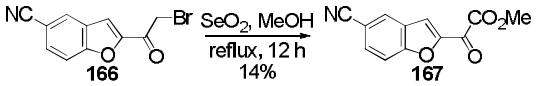
2.5. Benzofuryl and benzothienyl glyoxylates

Claisen-type acylation of benzofuran-3(2*H*)-ones **164** with dimethyl oxalate was used to synthesize benzofuryl glyoxylates **165** in 25% yield (Scheme 59).[189] Similar transformations were described for the methyl-substituted derivative (73% yield)[190] and the dimethylated homolog (50% yield).[191]

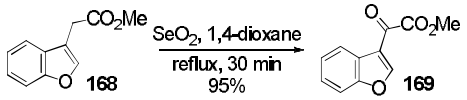


Scheme 59. Acylation of benzofuran-3(2*H*)-ones **164**.

An alternative approach to 2-(benzofuran-2-yl)-2-oxoacetates involves oxidation of α-bromoketone **166** with selenium dioxide, giving derivative **167** in 14% yield (Scheme 60).[192] At the same time, oxidation of the methylene unit in 2-(benzofuran-3-yl)acetate **168** provided C3-glyoxylate **169** in high yield of 95% (Scheme 61).[193]



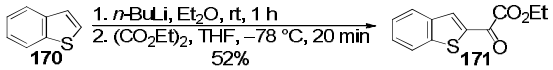
Scheme 60. Synthesis of (benzofuran-2-yl)oxoacetate **167** by oxidation of bromoketone **166**.



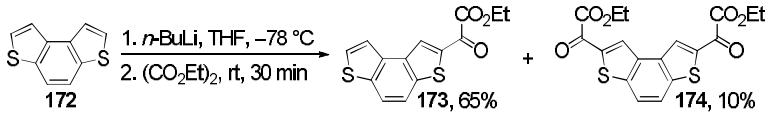
Scheme 61. Synthesis of (benzofuran-3-yl)oxoacetate **169** by oxidation of acetate **168**.

Limited examples of the synthesis of benzothiophene-2-ylglyoxylates include metalation of benzothiophene **170** followed by treatment with ethyl oxalate, which was used for the synthesis of derivative **171** (Scheme 62).[80,194]

In a similar way, metalation-acylation of benzo[1,2-*b*:4,3-*b*']dithiophene **172** results in the formation of mono- and bisglyoxylate **173** and **174** in 65% and 10% yields, respectively (Scheme 63).[195]

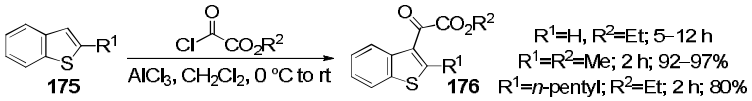


Scheme 62. Synthesis of ethyl 2-(benzo[*b*]thiophen-2-yl)-2-oxoacetate **171**.



Scheme 63. Synthesis of benzo[1,2-*b*:4,3-*b*']dithiophenyl glyoxylates **173** and **174**.

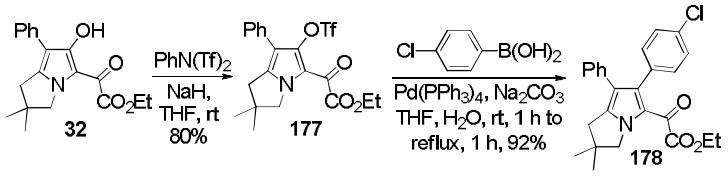
Electrophilic acylation of C3-unsubstituted benzo[*b*]thiophenes **175** is possible,[78,80,196] as shown by the synthesis of 2-methyl (92% and 97% yields)[197] and 2-*n*-pentyl derivatives **176** (80% yield)[197] (Scheme 64).



Scheme 64. Synthesis of 2-(benzo[*b*]thiophen-3-yl)-2-oxoacetates **176**.

3. Chemical transformations of pyrrolyl, furyl, thienyl glyoxylates and their fused analogs

The glyoxylate fragment is tolerant to a certain range of reaction conditions. It remains intact in formylations,[30] halogenation of alkyl side chains[51] and the heterocyclic core,[30] additions to C=C double bonds,[30] oxidation of (halo-)alkyl groups,[198] nucleophilic substitutions at the haloalkyl moieties,[51] acid-mediated cleavage of *N*-carbamate[28] or *O*-THP[30] protecting groups, the addition of the pyrrole nitrogen atom to the triple bond of acetylene dicarboxylate,[199] the Stille coupling[28] *etc*. Thus, *O*-triflylation of 3-hydroxypyrrole **32** was used for the preparation of precursor **177** for the Suzuki coupling with arylboronic acid. All steps proceeded with the retention of glyoxylate fragment, and the derivative **178** was obtained in high yield (Scheme 65).[48,49]



Scheme 65. Synthesis of pyrrole-derived triflate **177** bearing additional glyoxylate fragment and its Suzuki cross-coupling.

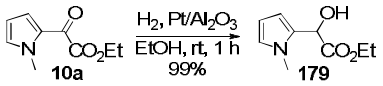
The range of possible synthetic transformations of hetaryl glyoxylates as ketones, esters, or ketoesters is summarized in Figure 1. Below, only selected known examples of the most common and representative reactions involving the discussed subcategory of hetaryl glyoxylates are disclosed.

3.1. Reduction reactions

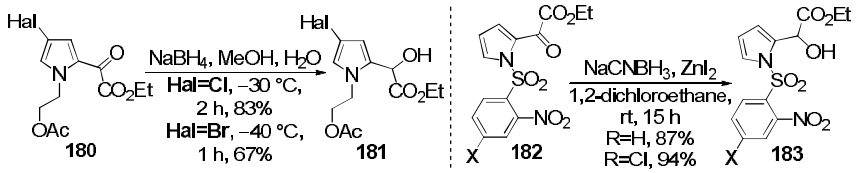
Selective catalytic hydrogenation of pyrrole-2-ylglyoxylate **10a** in the presence of Pt on Al_2O_3 in ethanol served as a method for the synthesis of (pyrrole-2-yl)hydroxyacetate **179** in excellent yield (Scheme 66). Other methods for the synthesis of hydroxyesters include the use of borohydride reducing agents, which was applied for glyoxylates **180** (for the synthesis of compounds **181** using $NaBH_4$[30]) and **182** (for the preparation of **183** upon the action of $NaBH_3CN$[200]) (Scheme 67).

Catalytic hydrogenation of **10** under pressure (10 atm) in the presence of a more active catalyst, *i.e.* Rh on Al_2O_3, was accompanied by the reduction of the heterocyclic fragment, and ended up with the formation of 2-hydroxy-2-(pyrrolidin-2-yl)acetates **184** (Table 9). A similar trend was observed for the indolizine

derivatives **10** and **20** that were selectively reduced to 2-hydroxy-2-(octahydroindolizin-3-yl)acetates **185** and **186** (Scheme 68).[28]

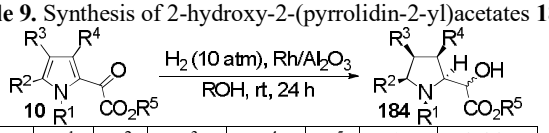


Scheme 66. Hydrogenation of pyrrole-2-ylglyoxylate to hydroxyacetate **179**.



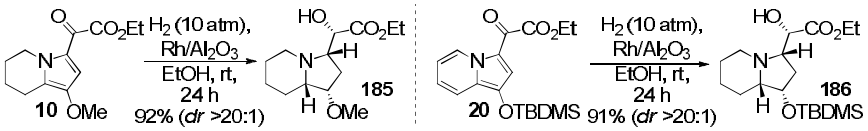
Scheme 67. Reduction of (pyrrol-2-yl)glyoxylates **180** and **182** with borohydride reducing agents.

Table 9. Synthesis of 2-hydroxy-2-(pyrrolidin-2-yl)acetates **184**.



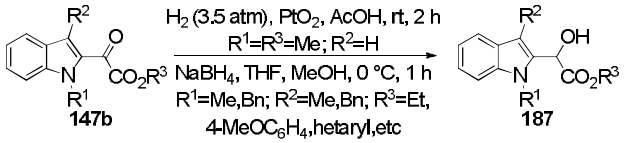
n.	R^1	R^2	R^3	R^4	R^5	*dr*[a]	Yield %
1	Me	H	H	H	Et	1:1	93
2	Me	H	H	OMe	Et	>20:1	91
3	Me	Me	OMe	H	Et	>20:1	90
4	H	Me	OMe	H	Me	3:1	90
5	Boc	Me	OMe	H	Me	2:1	95
6	Me	H	H	vinyl[b]	Me	>20:1	92
7	Me	H	vinyl[b]	H	Et	>20:1	92

[a]Ratio of diastereomers that differ by the relative configuration at the OH group.
[b]Reduction of the vinyl fragment to the ethyl group was observed.



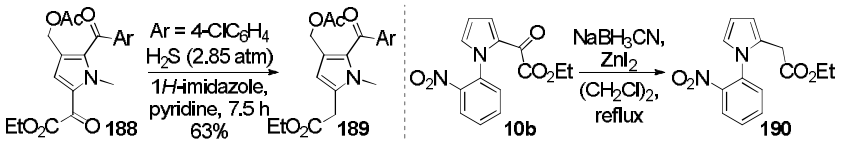
Scheme 68. Synthesis of 2-hydroxy-2-(octahydroindolizin-3-yl)acetates **185** and **186**.

Reduction of indolyl glyoxylates **147** to the corresponding hydroxyesters **187** is possible by using either $NaBH_4$[149] or catalytic hydrogenation in the presence of PtO_2[135] (Scheme 69). It is worth noting that reduction of the carbonyl group with Zn/HOAc, H_2/Pd-C/HOAc, $NaBH_3CN$/HOAc/MeOH, BH_3 THF, or H_2/Pd-C/HCl/EtOH was inefficient.

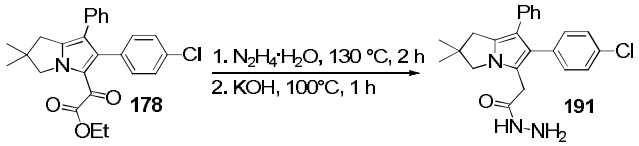


Scheme 69. Synthesis of 2-hydroxy-2-(1*H*-indol-2-yl)acetates **187**

On the other hand, it was possible to completely remove the ketone fragment of hetaryl glyoxylates for the synthesis of hetaryl acetates.[48,49] For example, the use hydrogen sulfide in the presence of imidazole turned out to be a mild, chemo- and regioselective method for the reduction of **188** (derived from **36**) into the derivative **189** in 63% yield (Scheme 70).[51] Another example is the use of $NaBH_3CN$ and ZnI_2 for the synthesis of acetate **190** from **10b**.[35] An example of the Wolff-Kizhner reduction of the carbonyl group of **178** was described, which was accompanied by the formation of corresponding hydrazide to give product **191** (Scheme 71).[21]

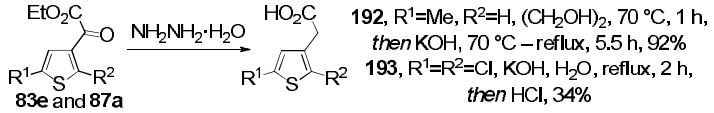


Scheme 70. Synthesis of 2-hydroxy-2-(1*H*-indol-2-yl)acetates **189** and **190**.



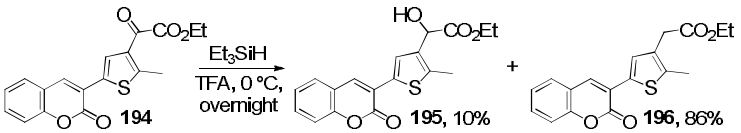
Scheme 71. The Wolff-Kishner reduction of pyrrolyl glyoxylate **178**.

The Wolff-Kishner reduction of the ketone fragment of thienyl glyoxylates **83** and **87** with subsequent hydrolysis for the synthesis of compounds **192** and **193**, respectively, has been described (Scheme 72).[88,201]

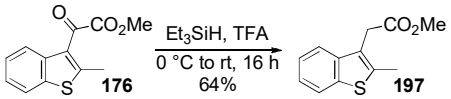


Scheme 72. The Wolff-Kishner reduction of thien-3-yloxoacetates **83** and **87**.

Other examples include reduction of thienyl glyoxylates **194** with triethylsilane in TFA to give a mixture of hydroxyacetate **195** and dehydroxylated derivative **196** as the major product (Scheme 73).[84] Complete reduction of the carbonyl group with triethylsilane is also known for the benzo analogue **176** (64% yield of product **197**) (Scheme 74).[197] A similar transformation was described for the corresponding ethyl ester.[202]

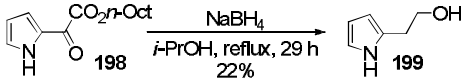


Scheme 73. Reduction of thien-3-ylglyoxylate **194** with formation of compounds **195** and **196**.



Scheme 74. Reduction of 2-(benzo[*b*]thiophen-3-yl)-2-oxoacetate **176**.

The ketoester fragment can be also fully reduced to hydroxyethyl moiety with sodium borohydride under harsh conditions, *i.e.* prolonged reflux in isopropanol (Scheme 75).[27] Compound **199** was obtained in 22% yield from the corresponding *n*-octyl glyoxylate **198**.

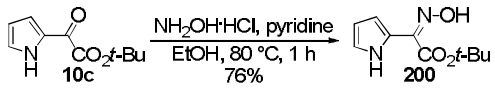


Scheme 75. Synthesis of 2-(1*H*-pyrrol-2-yl)ethan-1-ol **199**.

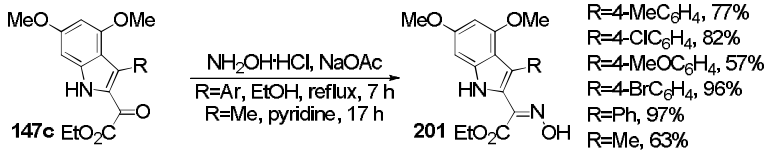
3.2. Reactions with heteroatom nucleophiles

The most straightforward transformation of hetaryl glyoxylates is hydrolysis into the corresponding glyoxylic acids, which can be performed with NaOH in THF,[38,39] KOH[59] or K_2CO_3[30] in MeOH-H_2O.

Oxime formation is a typical reaction of hetaryl glyoxylates which can be performed with hydroxylamine hydrochloride and pyridine upon reflux in EtOH. For example, glyoxylate **10c** could be converted into oxime **200** in 76% yield (Scheme 76).[24] Oxime formation was also described for the indoles **147c** with the representative synthesis of compounds **201** (Scheme 77).[150]

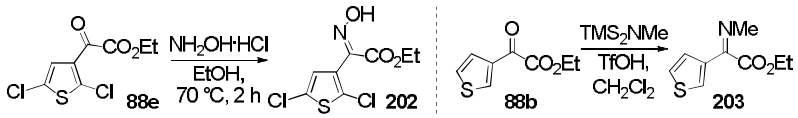


Scheme 76. Synthesis of 2-(hydroxyimino)-2-(1*H*-pyrrol-2-yl)acetate **200**.

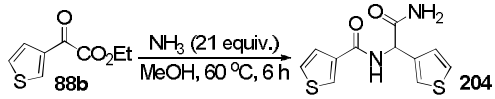


Scheme 77. Transformation of indol-2-ylglyoxylates **147c** into corresponding oximes **201**.

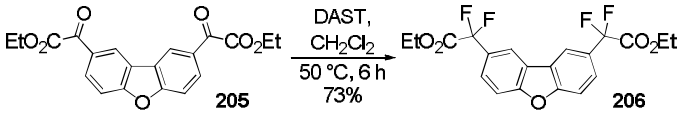
The scope of other related transformations includes the formation of oxime **202** as a 4:1 mixture of *E*/*Z* isomers,[203] as well as imination of glyoxylate with TMS_2NMe and TfOH to give **203** in 68% yield, which could be reduced into the corresponding aminoester (Scheme 78).[204] Formation of *N*-(2-amino-2-oxo-1-(thiophen-3-ylethyl)thiophene-3-carboxamide **204** was observed when the amination of thienyl glyoxylate **88e** was performed with ammonia in alcohol (Scheme 79).[205] *gem*-Difluorination of the discussed hetaryl glyoxylates can be performed in a straightforward manner with standard deoxofluorinating agents like DAST, which can be illustrated by deoxofluorination of dibenzo[*b*,*d*]furyl bis-glyoxylate **205**[206] for the preparation of the corresponding α,α-difluoroacetate **206** (Scheme 80).



Scheme 78. Synthesis of oxime **202** and imine **203** from thien-3-ylglyoxylates.



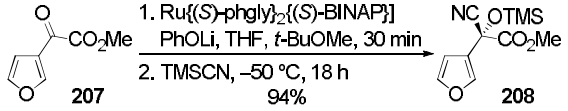
Scheme 79. Synthesis of *N*-(2-amino-2-oxo-1-(thiophen-3-ylethyl)thiophene-3-carboxamide **204**.



Scheme 80. Synthesis of hetaryl α,α-difluoroacetate **206** from glyoxylate **205**.

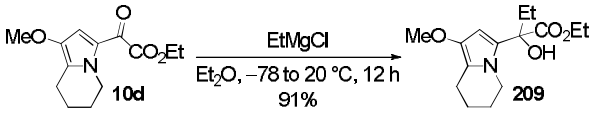
3.3. Reactions with C-nucleophiles

Hetaryl glyoxylates of the discussed series are capable of the classical cyanohydrin synthesis. In particular, the asymmetric synthesis of TMS-protected cyanohydrin **208** from furan-3-yl glyoxylate **207**[207] was described (Scheme 81).



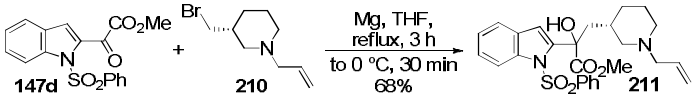
Scheme 81. Asymmetric synthesis of methyl-2-cyano-2-(furan-3-yl)-2-((trimethylsilyl)oxy)acetate **208**.

Other examples of the chemoselective carbonyl group reactivity include the nucleophilic additions of Grignard reagents. Ethyl magnesium chloride reacts with fused pyrrole-2-ylglyoxylate **10d** to form hydroxy ester **209** (Scheme 82).[28,150,152] Using of arylmagnesium bromides is also known in the literature.[208]



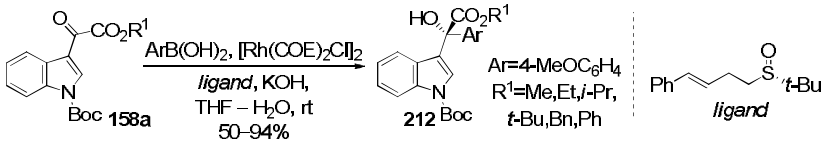
Scheme 82. Reaction of pyrrole-2-glyoxylate **10** with Grignard reagent.

In situ generation of the Grignard reagent from functionalized halides, *e.g.* allyl-3-bromomethylpiperidine **210**, was possible. The corresponding organometallic intermediate reacted with indolyl glyoxylate **147d** for the synthesis of adduct **211** (Scheme 83).[141]



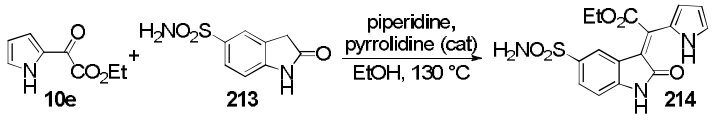
Scheme 83. Reaction of indole-2-glyoxylate **147d** with Grignard reagent obtained from **210**.

An interesting transformation is the rhodium-catalyzed enantioselective 1,2-addition of arylboronic acids to the carbonyl group of hetaryl glyoxylates **158a** for the synthesis of α-hydroxyesters **212** (Scheme 84).[209] Optimization of the reaction conditions was carried out for the case of *p*-methoxyphenylboronic acid as the nucleophilic agent.



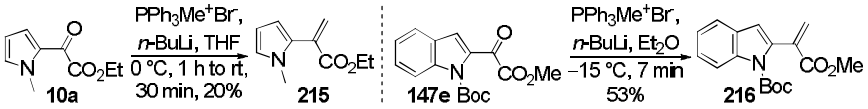
Scheme 84. Enantioselective 1,2-addition of arylboronic acids for the preparation of **212**.

An example of Knoevenagel condensation at the carbonyl group[42] includes the reaction of pyrrol-2-yl glyoxylate **10e** with indolin-2-one **213**, which led to derivative **214** (Scheme 85).[210]



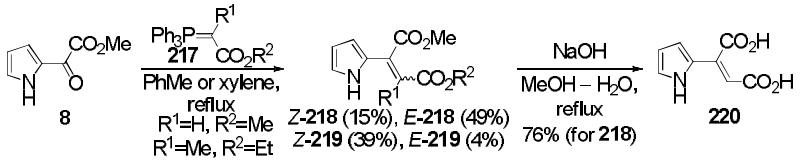
Scheme 85. Condensation of pyrrole-2-ylglyoxylate **10e** with indolin-2-one **213**.

Wittig olefination of the discussed hetaryl glyoxylates also proceeds selectively at the ketone moiety. For example, pyrrolyl-[29] and *N*-Boc-indolyl-glyoxylates[137] **10a** and **147e**, respectively, reacted with the ylide generated from triphenylmethylphosphonium bromide *via* deprotonation with *n*-BuLi. This reaction led to 2-(azol-2-yl)acrylates **215** and **216** in 20% and 53% yield, respectively (Scheme 86). A similar transformation was described for compound **115**,[147,148] as well as for *N*-$PhSO_2$[137] and *N*-tosylindoles,[144] which proceeded in 45%, 41%, and 56% yield, respectively.

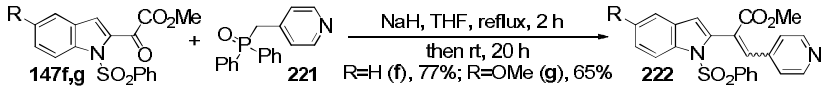


Scheme 86. Wittig olefination of glyoxylates for the synthesis of 2-(azol-2-yl)acrylates **215** and **216**.

Pyrrol-2-yl glyoxylate **8** can undergo olefination with substituted ylides **217** under reflux in xylene or toluene to form compounds **218** and **219** as mixtures of *Z*- and *E*-isomers. Further alkaline hydrolysis of diester **218** was applied for the synthesis of 2-(1*H*-pyrrol-2-yl)maleic acid **220** in 76% yield (Scheme 87).[136] Another example of Wittig olefination involves diphenyl(4-pyridylmethyl)phosphine oxide **221** in reactions with glyoxylates **147f** to give derivatives **222** (Scheme 88).[143] Allylic and benzylic phosphonium ylides have been also introduced in such transformations.

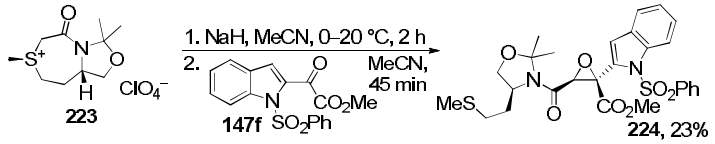


Scheme 87. Alkynylation of pyrrole-2-ylglyoxylate **8** with substituted phosphonium ylides **217**.



Scheme 88. Olefination of indol-2-ylglyoxylate **147**.

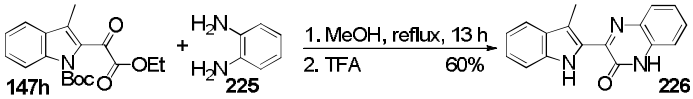
An interesting example includes Corey-Chaikowsky-type epoxidation of indol-2-yl glyoxylate **147f** with chiral sulfonium salt **223** used for the synthesis of compound **224** (Scheme 89).[211]



Scheme 89. Corey-Chaikowsky-type epoxidation of indol-2-ylglyoxylate **147f** with reagent **223**.

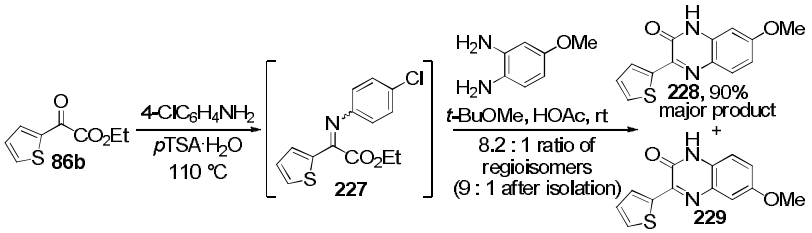
3.4. Heterocyclizations

As mentioned above, heterocyclizations of hetaryl glyoxylates are of particular interest since they provide important bis-heterocyclic scaffolds widely used in synthetic and medicinal chemistry. Hetaryl glyoxylates are commonly used as the 1,2-*CC*-bis-electrophiles in these reactions. For example, indol-2-yl derivative **147h** reacted with *o*-phenylenediamine **225** *via* *CC+NCCN* cyclization to give quinoxalin-2(1*H*)-one **226** in 60% yield (Scheme 90).[139]



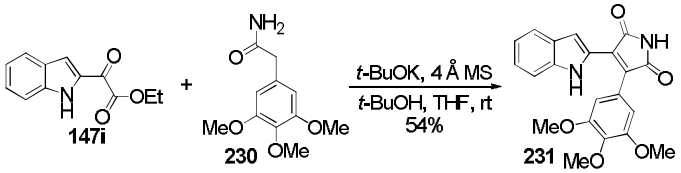
Scheme 90. Synthesis of 3-(3-methyl-1*H*-indol-2-yl)quinoxalin-2(1*H*)-one **226**.

A related transformation included the synthesis of 7-methoxy-3-(2-thienyl)quinoxalin-2-one **228** based on the condensation of the Schiff base **227** (formed in the first step from the glyoxylate and 4-chloroaniline) with 4-methoxybenzene-1,2-diamine (Scheme 91).[212] The formation of 7-methoxy-regioisomer **229** as a minor by-product was also observed.



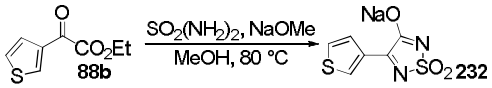
Scheme 91. Synthesis of quinoxalin-2-one **228**.

An example of CC+CCN cyclization was provided by the preparation of diarylmaleimide **231** by condensation of indolyl glyoxylate **147i** and 2-arylacetamide **230** in the presence of *t*-BuOK and molecular sieves (54% yield, Scheme 92).[213]



Scheme 92. Synthesis of arylindolylmaleimide **231**.

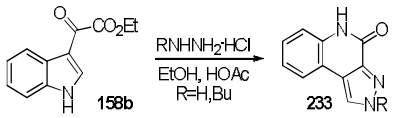
Also, CC+NCN heterocyclization of thien-3-yl glyoxylate **88b** with sulfuric diamide [$SO_2(NH_2)_2$] was used to obtain (thien-3-yl)-1,2,5-thiadiazole **232** (Scheme 93).[214-216]



Scheme 93. Synthesis of sodium 4-(thiophen-3-yl)-1,2,5-thiadiaz-3-olate-1,1-dioxide **232**.

Many examples of heterocyclizations with hydrazines have been described, where one or two additional atoms were introduced from either a third reaction component or other parts of the reacting molecules. In particular, the synthesis of 2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-ones **233** included

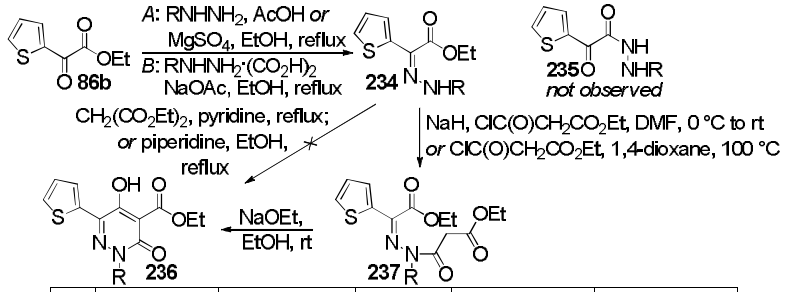
recyclization of indol-3-yl glyoxylate **158b**, which occurred upon treatment with hydrazines ($NH_2NH_2 \cdot HCl$[163] or $BuNHNH_2 \cdot HCl$[162]) (Scheme 94).

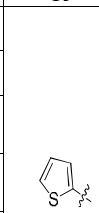
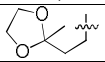
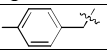
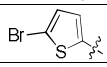
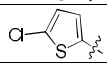


Scheme 94. Synthesis of 2,5-dihydro-4*H*-pyrazolo[3,4-*c*]quinolin-4-ones **233**.

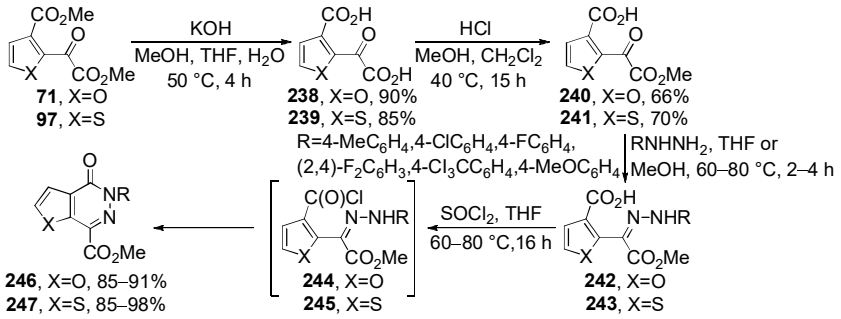
Reaction of thienyl glyoxylates **86b** with hydrazines proceeded through the selective formation of hydrazones **234** (acyl hydrazide **235** was not observed). Attempted heterocyclizations of compounds **234** with diethylmalonate was not effective for obtaining 5-hydroxy-3-oxo-6-(thiophenyl)-2,3-dihydropyridazines **236**. Nevertheless, the synthesis of heterocycles **236** was possible by the reaction of hydrazones **234** with ethyl-3-chloro-3-oxopropanoate due to the formation of intermediate acylhydrazones **237** (Table 10).[216-219]

Table 10. Heterocyclization of thienyl glyoxylates **86b** with hydrazines.



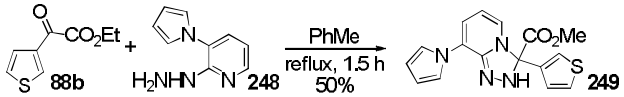
n.	R^1	R^2	Method	Yield % **234**	Yield % **236**
1			*B*	80	80
2			*B*	85	63
3			*B*	57	82
4			*B*	75	62
5			*B*	53	72
6			*A*	45	65
7			*A*	92	74
8			*B*	60	41
9			*B*	53	77
10			*B*	70	71
11			*B*	81	65
12			*B*	84	90

Another example involving the discussed hetaryl glyoxylate for the synthesis of pyridazine derivatives involved a four-step reaction sequence to obtain fused pyridazinones **246** and **247** (Scheme 95).[65] In this case, glyoxylates **71** and **97** acted as 1,4-CCCC-bis-electrophiles due to the presence of an additional ester group. The synthetic scheme included: a) alkaline hydrolysis to give **238** and **239**; b) selective monoesterification of glyoxylic acid moiety for the preparation of **240** and **241**; c) reactions with aryl hydrazines resulted in formation of **242** and **243**; d) treatment with $SOCl_2$, which resulted in pyridazinones **246** and **247** *via* formation of acid chlorides **244** and **245**.



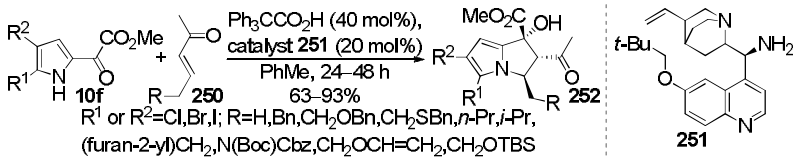
Scheme 95. Synthesis of fused pyridazinones **246** and **247**.

The heterocyclization of 2-hydrazinyl-3-(1*H*-pyrrol-1-yl)pyridine **248** with thien-3-yl glyoxylate **88b** was developed for the synthesis of 2,3-dihydro[1,2,4]triazolo[4,3-*a*]pyridine **249** (Scheme 96).[218] In this case, 2-hydrazinylpyridine served as the NCNN binucleophile, while the glyoxylate reacted only at the more active ketone carbonyl group.



Scheme 96. Synthesis of 2,3-dihydro-1,2,4-triazolo[4,3-*a*]pyridine **249**.

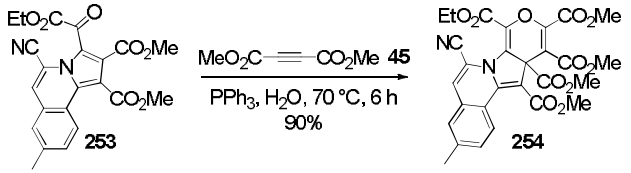
The interaction of pyrrol-2-yl glyoxylates **10f** with α,β-unsaturated ketones **250** proceeded as an NCC+CC cyclization including aza-Michael and aldol reactions in the presence of a quinine-derived catalyst **251**, and serves as a method for obtaining chiral pyrrolizines **252** (Scheme 97).[219] In this case, the pyrrole nitrogen atom and the ketone carbonyl group of the glyoxylate participated in the heterocyclization.



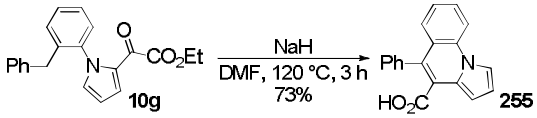
Scheme 97. Asymmetric synthesis of pyrrolizines **252** by cascade aza-Michael and aldol reactions.

The Diels-Alder reaction of glyoxylate **253** with dimethyl acetylene dicarboxylate **45** in the presence of triphenylphosphine provided the formation of tetracyclic compound **254** (Scheme 98).[59] In this case, glyoxylate **253** acted as a hetero-diene.

A number of examples included various intramolecular heterocyclizations where all atoms of the formed heterocycle originated from hetaryl glyoxylate. For example, intramolecular condensation at the diarylmethane fragment present in the molecule of pyrrole derivative **10g** gave fused tricyclic product **255** (Scheme 99).[34]

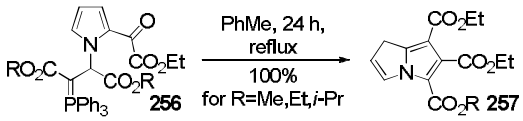


Scheme 98. The Diels-Alder reaction of glyoxylate **253**.



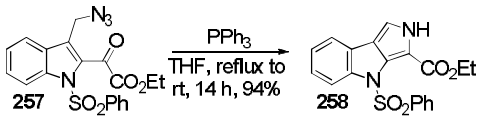
Scheme 99. Intramolecular condensation of 2-(1-(2-benzylphenyl)-1*H*-pyrrol-2-yl)-2-oxoacetate **255**.

Intramolecular Wittig reaction of pyrrol-2-yl glyoxylate **256** was disclosed in the literature for the preparation of fused derivative **257** (Scheme 100).[199]

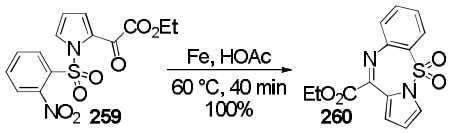


Scheme 100. The intramolecular Wittig reaction of glyoxylate **256**.

Intramolecular cyclization of 2-(3-(azidomethyl)-1*H*-indol-2-yl)-2-oxoacetate **257** *via* the Staudinger-aza-Wittig reaction sequence was used as a method for the annulation of the pyrrole fragment and led to derivative **258** with a yield of 94% (Scheme 101). A related example included the intramolecular reductive cyclization of ethyl 2-(1-((2-nitrophenyl)sulfonyl)-1*H*-pyrrol-2-yl)-2-oxoacetate **259**. The process involved reduction of the nitro group followed by reductive amination at the ketone moiety with the formation of tricyclic azasultam **260** in an excellent yield (Scheme 102).[200]

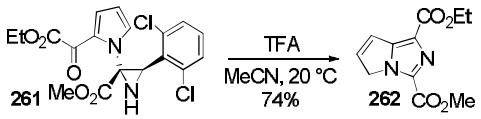


Scheme 101. Synthesis of 2,4-dihydropyrrolo[3,4-*b*]indole-3-carboxylate **258**.



Scheme 102. Synthesis of benzo[*f*]pyrrolo[1,2-*b*][1,2,5]thiadiazepine-11-carboxylate-5,5-dioxide **260**.

One more related example relied on the acid-promoted recyclization of diarylaziridine carboxylate **261** to give pyrroloimidazole derivative **262** (Scheme 103).[220]



Scheme 103. Synthesis of 1-ethyl-3-methyl-5*H*-pyrrolo[1,2-*c*]imidazole-1,3-dicarboxylate **262**.

4. Conclusions

Heterocyclic α-oxoesters, also known as heterocyclic α-ketoesters, hetaryl-2-oxoacetates, or hetaryl glyoxylates, are important polyfunctional substrates for synthetic and medicinal chemistry;[221] their representation in the literature depends significantly on the nature of the heterocyclic substituent. Thus, the synthesis of the simplest five-membered hetaryl glyoxylates has been well-documented. The preparation of pyrrolyl, furyl, and thienyl glyoxylates typically relies on the straightforward and (in most cases) regioselective electrophilic Friedel-Crafts acylation of the corresponding C2-unsubstituted heterocycles with oxalic acid derivatives (the presence of Lewis acids is required only for thiophenes). In the case of 2,5-disubstituted derivatives, the electrophilic reactions take place at the β-position. The metalation-glyoxylation sequence has been widely used for the selective preparation of monocyclic azol-3-yl glyoxylates. On the contrary, the corresponding C2-substituted benzo-fused glyoxylates were typically obtained *via* the metalation, whereas the C3-isomers *via* electrophilic acylation.

Typically, the chemical behavior of hetaryl glyoxylates corresponds to their electronic properties of highly electrophilic ketones. In other words, selective reactions at the ketone moiety are prevalent, *e.g.* reduction, formation of oximes, imines, and hydrazones, organometallic reagent addition, various condensations, olefination, or deoxofluorination. Selective reactions at the ester group are less common and are represented by hydrolysis and amide formation. Many reactions occur at both functional groups and may even involve atoms of the heterocyclic ring or side chains present. In this view, heterocyclizations with hetaryl glyoxylates are especially interesting, particularly when the title compounds act as the 1,2-*CC*-bis-electrophiles. In this role, the hetaryl glyoxylates were used to obtain derivatives of pyrazine, quinoxaline, benzo[*b*][1,4]oxazine, and other heterocycles. Of different reactivity types, heterocyclizations of the title compounds bearing an additional ester moiety (1,4-CCCC-bis-electrophiles) can be outlined, *e.g.* for the synthesis of functionalized pyridazines.

Acknowledgements

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