HETEROCYCLIC α-OXOESTERS (HETARYL GLYOXYLATES): SYNTHESIS AND CHEMICAL TRANSFORMATIONS. Part 2.

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Abstract. *In this review, the synthesis and chemical properties of 1,2- and 1,3-azolyl, triazolyl, azinyl glyoxylates, and their fused derivatives are surveyed. Common synthetic approaches rely on the direct Friedel-Crafts acylation, metalation-glyoxylation, or heterocyclization reactions, and the choice of the most appropriate method depends on the nature of the heterocyclic substituent and the position of the ketoester moiety. The chemical behavior of hetaryl glyoxylates is mainly defined on the highly electrophilic properties of the ketone fragment that can participate in most typical chemical transformations, often chemoselectively (e.g. reduction, formation of oximes, imines, and hydrazones, addition of organometallic reagents, condensations, olefination, or deoxofluorination). Heterocyclizations of hetaryl glyoxylates is also outlined, which can occur at the ketone, ester, or both moieties (i.e. as 1,2-CC-bis-electrophiles) providing important heterocyclic chemotypes.*

Contents

1. Introduction

This review covers the synthesis and chemical transformations of 1,2- and 1,3-azolyl, triazolyl, and azinyl α-oxoesters, also known as α-ketoesters, 2-oxoacetates, or glyoxylates. The presence of 1,2-dicarbonyl bis-electrophilic moiety enables a wide scope of mostly selective reactions and numerous possibilities for the preparation of functionalized heterocycles. The most common transformations of hetaryl glyoxylates are related to the *ketone reactivity:* reductions, condensations, preparation of imines and oximes, addition of Grignard reagents, alkenylations, deoxofluorinations, and heterocyclization reactions, where one carbon atom of the glyoxylate moiety becomes a part of the resulting heterocycle bearing an ester functional group (Figure 1). The *oxoester reactivity* includes reductions and heterocyclizations when both carbon atoms become a part of the heterocycle, which is represented by formal [4+2] cyclization with binucleophiles (*e.g.* 1,2-diamines), condensations with amides, three-component condensations with amines and aldehydes, *etc.* The least common type of chemo- and regioselective reactions relies on the *ester reactivity*, which is represented by hydrolysis, amination, and heterocyclizations, where one carbon atom of the α-oxoester becomes a part of heterocycle bearing an acyl substituent.

Heterocyclizations of hetaryl glyoxylates are of special interest since they allow the construction of organic molecules bearing two or more heterocyclic fragments (Scheme 1). For example, this transformation was implemented into the preparation of hetaryl-substituted quinoxalines used as photoinitiators and fluorescence sensors.[1-4]

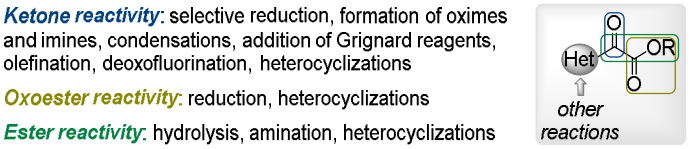
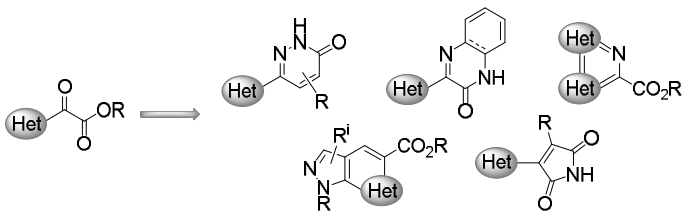


Figure 1. Synthetic potential of heterocyclic α-oxoesters.

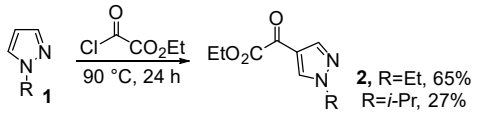


Scheme 1. Heterocyclizations of hetaryl glyoxylates: an approach to compounds with two or more heterocyclic fragments.

Moreover, heterocyclic α-oxoesters can be used in a range of other important reactions, *e.g.* aldol condensation, Paal-Knorr and Fischer indole syntheses, Friedlander, Pfitzinger, and Pictet-Spengler reactions, Dieckmann, reductive aza-Wittig, and Baylis-Hillman cyclizations, as well as [2+2]-, [3+2]-, and [4+2]-cycloadditions, *etc*.[5]

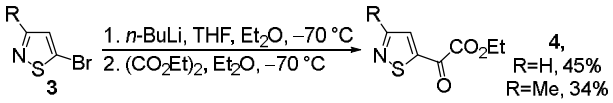
2. Synthesis of 1,2-azolyl glyoxylates and their fused analogs

Examples of direct acylation of 1,2-azoles **1** with oxalic acid derivatives are limited in the literature. Thus, the synthesis of ethyl 2-(1-alkyl-1*H*-pyrazol-4-yl)-2-oxoacetates **2** by electrophilic acylation with ethyl oxalyl chloride at the C4-position was described (Scheme 2).[6,7]



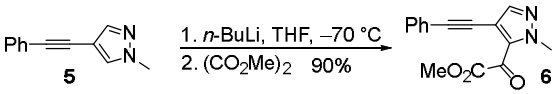
Scheme 2. Synthesis of ethyl 2-(1-isopropyl-1*H*-pyrazol-4-yl)-2-oxoacetates **2**.

2-(Isothiazol-5-yl)-2-oxoacetates **4** were obtained from 5-bromoisothiazoles **3** *via* metalation followed by acylation with diethyl oxalate in 34-45% yield (Scheme 3).[8]



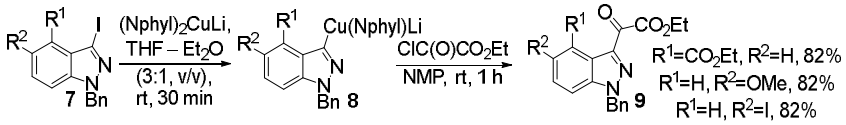
Scheme 3. Synthesis and reactions of 2-(isothiazol-5-yl)-2-oxoacetates **4**.

The sequence of metalation-acylation was also successfully applied to the synthesis of pyrazole-5-yl glyoxylates **6** from 1-methyl-4-(phenylethynyl)-1*H*-pyrazole **5** (Scheme 4).[9]



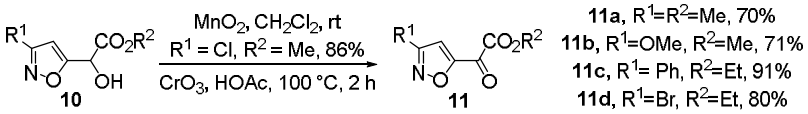
Scheme 4. Preparation of (pyrazol-5-yl)oxoester **6**.

The corresponding benzo analogs have been scarcely reported in the literature. In particular, they were obtained by acylation of 1-benzyl-3-iodo-1*H*-indazoles **7** at the C3-position *via* metalation with di(2,2-dimethyl-2-phenylethyl)lithium cuprate [(Nphyl)$_2$CuLi] and subsequent reaction of **8** with ethyl oxalyl chloride to give indazolyl glyoxylates **9** (Scheme 5).[10]

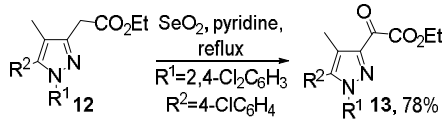


Scheme 5. Synthesis of ethyl 2-(1-benzyl-1*H*-indazol-3-yl)-2-oxoacetates **9**.

One of the most often-used methods for the synthesis of 1,2-azol-5-yl glyoxylates rely on the oxidation of side chains. For example, oxidation of α-hydroxyesters **10** with MnO_2[11] or CrO_3[12] was applied for the synthesis of isoxazol-5-ylglyoxylates **11** (Scheme 6). Oxidation of 2-(1*H*-pyrazol-3-yl)acetates **12** with selenium dioxide gave glyoxylates **13** (Scheme 7).[13]

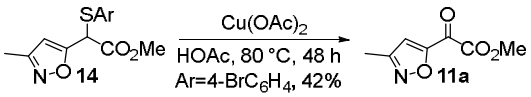


Scheme 6. Synthesis of 3-substituted isoxazole-5-ylglyoxylates **11**.



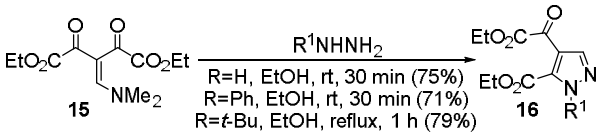
Scheme 7. Synthesis of glyoxylates **13**.

Similarly to the case of thiophene derivatives, oxidation of 2-(4-arylthio)-2-(isoxazol-5-yl)acetate **14** by treatment with $Cu(OAc)_2$ was carried out to obtain glyoxylate **11a** in 42% yield (Scheme 8).[14]



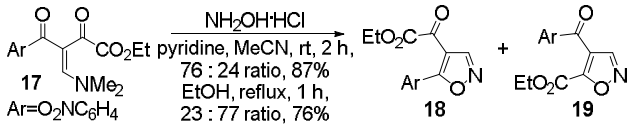
Scheme 8. Synthesis of methyl-2-(3-methylisoxazol-5-yl)-2-oxoacetate **11a**.

An important synthetic approach to pyrazol-4-yl glyoxylates **16** included the condensation reaction of appropriate *CCC*-bis-electrophiles (for example β-aminovinylglyoxylate **15**) with hydrazine hydrate,[15] phenylhydrazine,[16,17] or *t*-butylhydrazine hydrochloride (*t*-BuNHNH$_2$·HCl)[17] (Scheme 9). The formation of the corresponding hydrazones from the target glyoxylates has also been described under the reaction conditions in the case phenylhydrazine.[15,18] A similar approach was used to synthesize isoxazolyl glyoxylates.



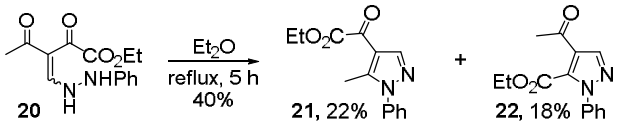
Scheme 9. Synthesis of pyrazole-4-yl glyoxylates **16**.

When non-symmetric *CCC*-bis-electrophile **17** was used, it was possible to adjust the regioselectivity of condensation depending on the reaction conditions, which was shown by the synthesis of glyoxylate **18** and regioisomeric ketone **19** (Scheme 10).[19] The method was also extended to aromatic ketones of benzene series.



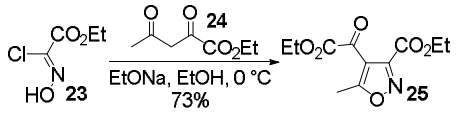
Scheme 10. Condensations of non-symmetric *CCC*-bis-electrophile **17** for the synthesis of isoxazolyl glyoxylate **18** and regioisomeric ketone **19**.

β-Hydrazinoenaminone **20** can undergo intramolecular cyclization at either of the two carbonyl groups with the formation of glyoxylate **21** and its regioisomer **22** (Scheme 11).[18]



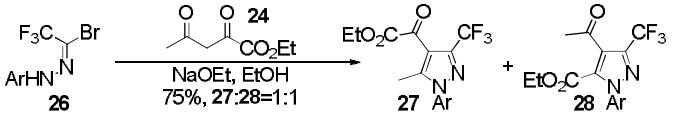
Scheme 11. Non-selective cyclization of β-hydrazinoenaminone **20**.

A method for the synthesis of isoxazole-4-yl glyoxylates includes the condensation of chloroxime **23** and acetylpyruvate **24** resulting in the formation of trisubstituted isoxazole **25** in 73% yield (Scheme 12).[20]



Scheme 12. Synthesis of isoxazol-4-ylglyoxylate **25** from chloroxime **23**.

A similar approach based on the use of acetylpyruvate **24** was also described for the synthesis of pyrazol-4-yl glyoxylate **27** from trifluoro-*N*-(4-methoxyphenyl)-acetohydrazonyl bromide **26**. In this case, glyoxylate **27** was formed together with regioisomeric product **28** in a 1:1 ratio in 75% overall yield (Scheme 13).[20]



Scheme 13. Reaction of acetylpyruvate **24** and hydrazonyl bromide **26**.

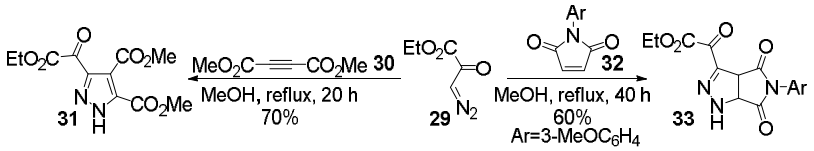
1,3-Dipolar cycloaddition was successfully used for the synthesis of pyrazol-3-yl glyoxylate **31** starting from ethyl 3-diazo-2-oxopropanoate **29** and dimethyl acetylene carboxylate **30**. (3-Methoxyphenyl)maleimide **32** could also be used in the reaction with **29** to obtain the bicyclic pyrazoline **33** (Scheme 14).[21]

Cyclization of (2-(phenyldiazenyl)phenyl)acrylate **34** proceeded in the presence of $[Cp^*RhCl_2]_2$ (Cp^*=pentamethylcyclopentadienyl) and $Cu(OAc)_2$ and gave indazole **35** (Scheme 15).[22] A similar method is based on the intermolecular reaction of azobenzenes **36** and acrylates providing products **37** (Scheme 16).[22]

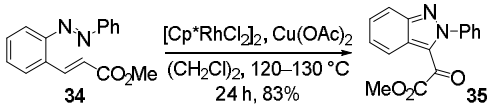
3. Chemical transformations of 1,2-azolyl glyoxylates and their fused analogs

Reductive removal of the carbonyl group in the molecules of 1,2-azolyl glyoxylate **2a** was reported; the reaction was performed by the action of Et_3SiH in TFA to give **38** (Scheme 17).[6] Other examples of the

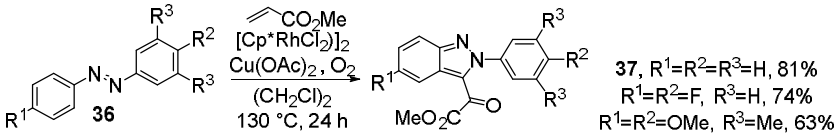
reduction of pyrazolyl glyoxylates to the corresponding pyrazolyl acetates were also described in the literature.[6,17]



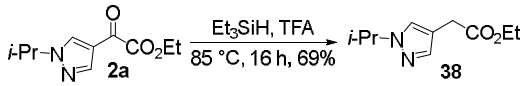
Scheme 14. Synthesis of pyrazole-3-yl glyoxylates **31** and **33** from 3-diazo-2-oxopropanoate **29**.



Scheme 15. Synthesis of indazolyl glyoxylate **35** from (2-(phenyldiazenyl)phenyl)acrylate **34**.

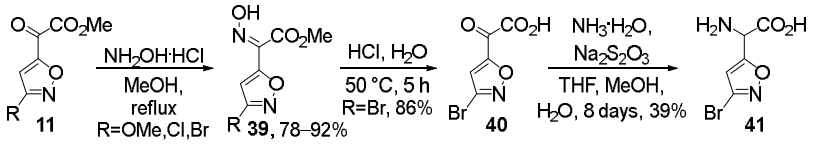


Scheme 16. Synthesis of indazolyl glyoxylates **37** from azobenzenes **36**.



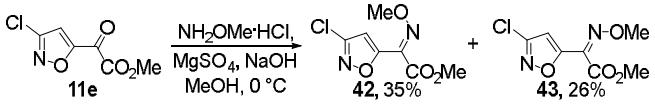
Scheme 17. Synthesis of ethyl 2-(1-isopropyl-1*H*-pyrazol-4-yl)acetate **38**.

Oxime formation is illustrated for isoxazolyl glyoxylates **11** (Scheme 18).[11,14] Hydrolysis of compound **39** (R=Br) resulted in formation of glyoxylic acid **40** that was transformed to amino acid **41** by reductive amination.[14]



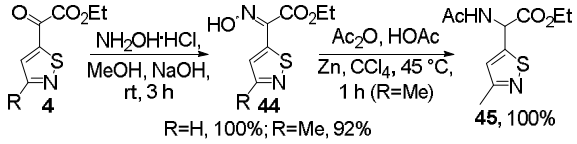
Scheme 18. Synthesis and some chemical transformations of oximes **39**.

Meanwhile, oximation of compound **11e** with *O*-alkylated hydroxylamines, *e.g.* *O*-methylhydroxylamine, led to the formation of *Z*/*E*-isomers **42** and **43** (Scheme 19).[20]



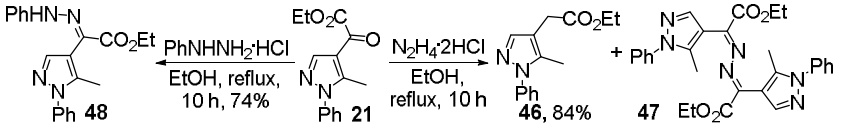
Scheme 19. Oximation of glyoxylate **11e** with *O*-methylhydroxylamine.

The synthetic utility of compounds **4** was shown *via* their transformation into the corresponding oximes **44**, the reduction of one of which was carried out for the synthesis of α-amino ester **45** (Scheme 20).[8]



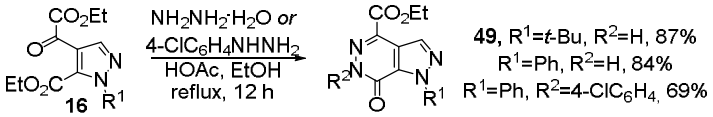
Scheme 20. Synthesis and reactions of 2-(isothiazol-5-yl)-2-oxoacetates **4**.

Interestingly, reaction of glyoxylate **21** with hydrazine dihydrochloride without the addition of alkali resulted in the removal of the ketone group leading to derivative **46**, with the side formation of bis-hydrazone **47** (Scheme 21).[18] Under similar conditions, the reaction with phenylhydrazine led to the formation of standard hydrazone **48**.

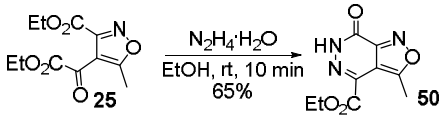


Scheme 21. The reaction of pyrazol-4-ylglyoxylate **21** with hydrazines.

A series of 1*H*-pyrazolo[3,4-*d*]pyridazine-4-carboxylates **49** was synthesized *via* the condensation of pyrazolyl-4-oxoesters **16** with hydrazine and its derivatives (Scheme 22).[15,17] This transformation is also known for **25** for the preparation isoxazoles **50** (Scheme 23).[20] As in the case of the corresponding glyoxylates derived from the five-membered heterocycles with one heteroatom, 1,2-azolyl glyoxylates **16** and **25** served as *CCCC*-bis-electrophiles due to the presence of an additional ester group.



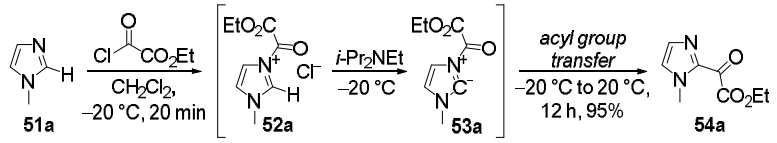
Scheme 22. Synthesis of 1*H*-pyrazolo[3,4-*d*]pyridazine-4-carboxylates **49**.



Scheme 23. Preparation of isoxazolo[3,4-*d*]pyridazine-4-carboxylate **50**.

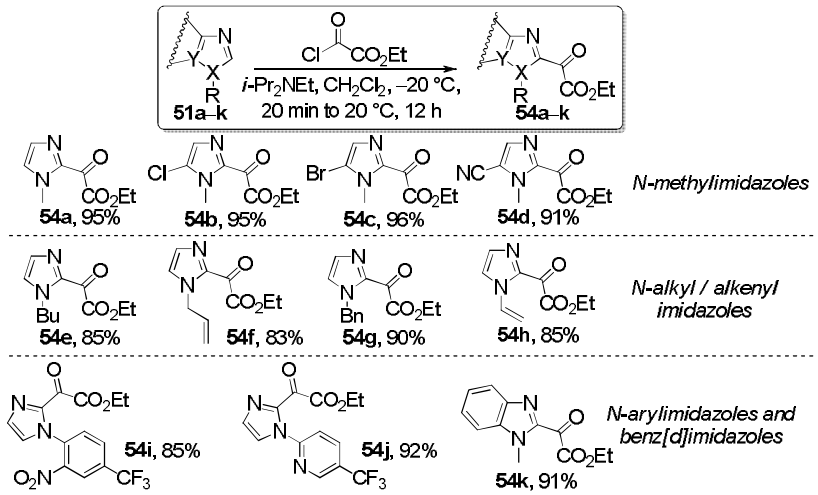
4. Synthesis of 1,3-azolyl glyoxylates and their fused analogs

The direct electrophilic Friedel-Crafts acylation at the C2 position of 1,3-azoles was demonstrated for the first time by the synthesis of 2-(imidazolyl)-2-oxoacetate **54a**, which was obtained from *N*-methylimidazole using triethylamine as a base in average yield of 45%.[23-26] A comprehensive study of these transformations was performed by our group to find that the addition of ethyl oxalyl chloride within 20 min to a solution of imidazole *N*-methylimidazole **51a** in CH_2Cl_2 at 20 °C led to the formation of a precipitate, *i.e.* ionic product **52a**, likely originating from N3-acylation of imidazole (Scheme 24).[27] Further addition of Hünig's base (*i*-Pr_2NEt) to the reaction mixture led to the dissolution of the precipitate and formation of a clear solution presumably containing compound **53a**. After additional stirring of the reaction mixture at rt for 12 h, the target imidazolyl glyoxylate **54a** was obtained in a high yield (95%). It was concluded that the presumable pathway of this reaction is the initial C2-deprotonation of the N3-acylated intermediate **52a** with the formation of the ylide **53a**. Intermediate **53a** then undergoes the acyl group transfer from the nitrogen atom to the C2 position.



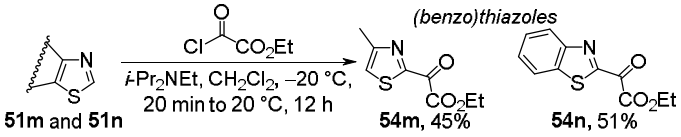
Scheme 24. Acylation of *N*-methylimidazole **51a** with ethyl oxalyl chloride.

The method worked well for a series of substituted imidazoles and their benzo analogs **51** to give the corresponding imidazol-2-ylglyoxylates **54** in 83-96% yield (Scheme 25).



Scheme 25. Acylation of *N*-substituted imidazoles **51** with ethyl oxalyl chloride.

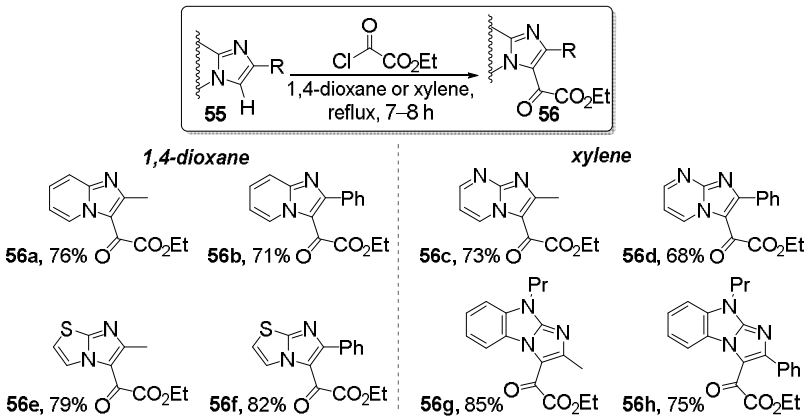
The acylation of 4-methylthiazole **51m** and benzo[*d*]thiazole **51n** proceeded with the predominant formation of target products **54m** and **54n** with moderate yields of 45% and 51%, together with some side products.[27] These results indicate that the activity of the carbonyl group in azolyl glyoxylates **54** and steric effects have a significant influence on the overall yield of products and the possibility of side processes. In particular, the carbonyl group of thiazole derivatives **54m** and **54n** (and corresponding intermediates **53m** and **53n**) is more reactive towards nucleophiles as compared to that of imidazolyl counterparts **54a-k** (**53a-k**) (Scheme 26). In turn, increased activity led to the considerable contribution of the side processes with the participation of either primarily formed zwitterionic intermediates of type **53** or target compounds **54**.[27]



Scheme 26. Acylation of (benzo)thiazol-2-ylglyoxylates **54m** and **54n**.

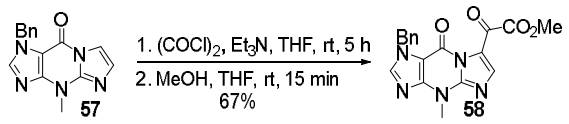
Our group also described the synthesis of fused imidazolyl glyoxylates **56**, which relied on the acylation of imidazo[1,2]heterocycles **55a-h** with varied electronic properties (Scheme 27).[28] Thus, acylation with ethyl oxalyl chloride was carried out by refluxing in 1,4-dioxane in the case of imidazo[1,2-*a*]pyridines **55a** and **55b**, as well as imidazo[2,1-*b*][1,3]thiazoles **55e** and **55f**. At the same time, the acylation of imidazo[1,2-*a*]pyrimidines **55c** and **55d** required prolonged refluxing of the starting compounds in xylene. The conversion of imidazo[1,2-*a*]benzimidazoles **55g** and **55h** in 1,4-dioxane was successful for the synthesis

of glyoxylates **56g** and **56h** with average yields of 40-50%, amd better results (75-85% yield) were also achieved by carrying out the reaction in refluxing xylene. Thus, the following order of substrate reactivity was observed in the acylation reaction of compounds **55**: imidazo[2,1-*b*]thiazoles > imidazo[1,2-*a*]benzimidazoles > imidazo[1,2-*a*]pyridines > imidazo[1,2-*a*]pyrimidines. The reactivity of heterocycles with a phenyl electron-withdrawing substituent was comparable to or lower than that of methylated analogs.



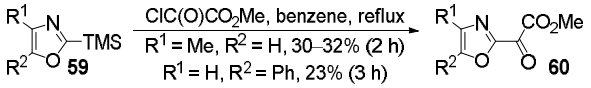
Scheme 27. Acylation of fused imidazo[1,2]heterocycles **55a-h**.

In a similar manner, the reaction of 1*H*-imidazo[1,2-*a*]purin-9-one **57** with oxalyl chloride in the presence of triethylamine followed by methanolysis leads to the formation of glyoxylate **58** in 67% yield (Scheme 28).[29]



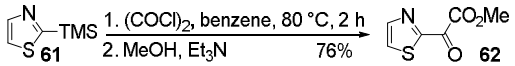
Scheme 28. Synthesis of imidazo[1,2-*a*]purinyl glyoxylate **58**.

Other electrophilic reactions included the *ipso*-substitution of silyl groups, which, however, proceeded with low yields in the case of 4- or 5-substituted 2-(trimethylsilyl)oxazoles **59** to give **60** (Scheme 29).[30,31]



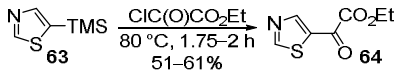
Scheme 29. *ipso*-Electrophilic substitution for the synthesis of oxazol-2-ylglyoxylates **60**.

A similar transformation was disclosed for C2-trimethylsilyl-substituted thiazole **61**; product **62** was formed in higher yield (76%) as compared to oxazoles (Scheme 30).[32-34]



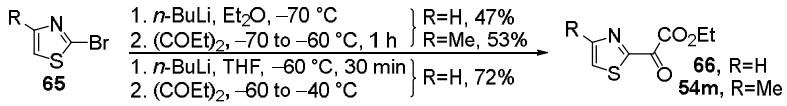
Scheme 30. Preparation of methyl 2-(thiazol-2-yl)-2-oxoacetate **62**.

At the same time, the synthesis of 1,3-thiazol-5-yl glyoxylate **64** also relied on the *ipso*-electrophilic substitution of 5-(trimethylsilyl)thiazole **63** providing product **64** in 51-61% yield (Scheme 31).[35,36]



Scheme 31. Synthesis of ethyl-2-oxo-2-(thiazol-5-yl)acetate **64**.

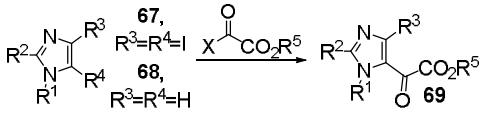
An alternative approach towards 1,3-azolyl glyoxylates is the metalation followed by a reaction with dialkyl oxalates. The method was used for the parent and methylated 2-bromothiazoles **65** for the preparation of **54m** and **66** (Scheme 32).[37] Higher yields of **66** were achieved by using THF instead of Et_2O.



Scheme 32. Metallation-acylation to obtain (thiazol-2-yl)oxoacetates **54m** and **66**.

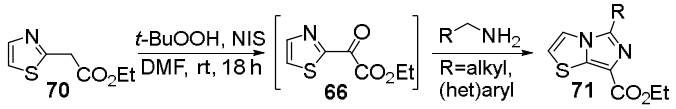
The synthesis of imidazol-5-yl glyoxylates **69** was based on the reactions of iodoimidazoles **67a,b** with organocuprates (Table 1, Entries 1 and 2) or metalation of **68a,b** with LDA or *n*-BuLi (Entries 3 and 4) followed by acylation with oxalic acid derivatives. In addition to that, examples of carbonylation reactions of halogenated 1,3-azoles in the presence of $PdCl_2(PPh_3)_2$ have been mentioned in the literature.[38]

Table 1. Synthesis of (1*H*-imidazol-5-yl)-2-oxoacetates **69**.



n.	Starting material	R^1	R^2	R^3	R^4	R^5	X	Conditions	Yield %	Ref
1	**67a**	CH_2OEt	H	I	I	Et	Cl	1. $(NPhyl)_2CuLi$(1.2 equiv.), THF-Et_2O-NMP (8:2:1, v/v/v), –78 °C, 0.5-1 h 2. $ClC(O)CO_2Et$, rt, 30 min	74	39
2	**67b**	Ts							76	
3	**68a**	Me	SPh	H	H	Me	OMe	1. LDA, DME-Et_2O, hexane, –78 to 0 °C, 1.25 h; 2. $(CO_2Me)_2$, rt, 3 h	41	40
4	**68b**	CH_2OMe	SPh	H	H	Me	OMe	1. *n*-BuLi, THF, hexane, –78 °C, 1 h 2. $(CO_2Me)_2$, THF, –78 °C, 1.25 h	66	41

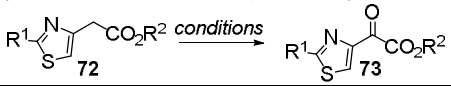
Aside from methods based on the direct introduction of glyoxylate moiety into the heterocyclic scaffold, other known approaches to 1,3-azolyl glyoxylates include oxidation of the methylene group of the corresponding hetaryl acetates. For example, reaction of ethyl 2-(thiazol-2-yl)acetate **70** with *t*-butyl hydroperoxide in the presence of *N*-iodosuccinimide (NIS) led to the *in situ* formation of the corresponding glyoxylate **66**. The latter product was introduced into the cyclization reaction with primary amines for the synthesis of imidazo[5,1-*b*]thiazole-7-carboxylates **71** (Scheme 33).[42]



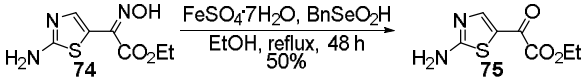
Scheme 33. Synthesis of imidazo[5,1-*b*]thiazoles **71** *via* the *in situ* generations of glyoxylates **66**.

The synthesis of regioisomeric 1,3-azol-3-yl glyoxylates also involved the oxidation of thiazol-4-yl acetates **72** to the corresponding glyoxylates **73** (Table 2). Oxidative cleavage of oxime **74** was reported to give glyoxylate **75** (Scheme 34).[43]

Table 2. Synthesis of 2-substituted (thiazol-5-yl)-2-oxoacetates **73**.

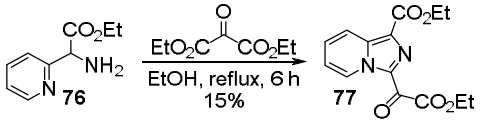


n.	R^1	R^2	Conditions	Yield %	Ref.
1	NHC(O)H	Et	*N*-hydroxyphtalimide, O_2, $Co(OAc)_2$, HOAc, 40 °C, 16 h	21	44
2			$Mn(OAc)_2$, $KMnO_4$, HOAc	N.A.	45
3	$NHC(O)CH_2Cl$	Et	1,4-dioxane, HOAc, 110-115 °C, 4 h	63	46
4	$4\text{-}ClC_6H_4$	Me	SeO_2, xylene, reflux, 8 h	53	47



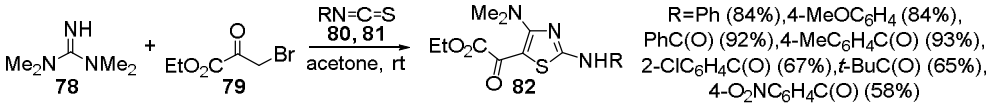
Scheme 34. Synthesis of ethyl 2-(2-aminothiazol-5-yl)-2-oxoacetate **75**.

Construction of the heterocyclic ring with simultaneous incorporation of the glyoxylate group is also possible for the 1,3-diazole series. In particular, condensation of pyrid-2-yl-substituted aminoester **76** with diethyl-2-oxomalonate resulted in the of 2-(imidazo[1,5-*a*]pyridine-3-yl) glyoxylate **77**, albeit in low yield of 15% (Scheme 35).[48]

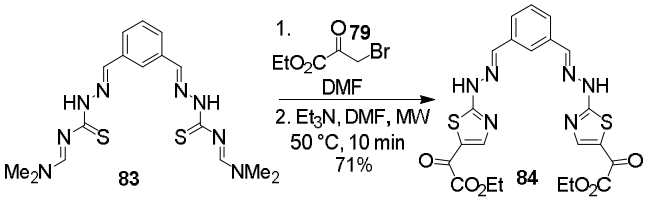


Scheme 35. Synthesis of imidazo[1,5-*a*]pyridine-derived glyoxylate **77**.

The synthesis of 1,3-azolyl-5-glyoxylates **82** was also achieved by the condensation of 1,1,3,3-tetramethylguanidine **78**, bromopyruvate **79**, and aryl- or acyl isothiocyanates **80** and **81**, respectively (Scheme 36).[49,50] A related example included formation of bis(thiazol-5-yl)glyoxylate **84** in the condensation of compound **83** and bromopyruvate **79** (Scheme 37).[51]

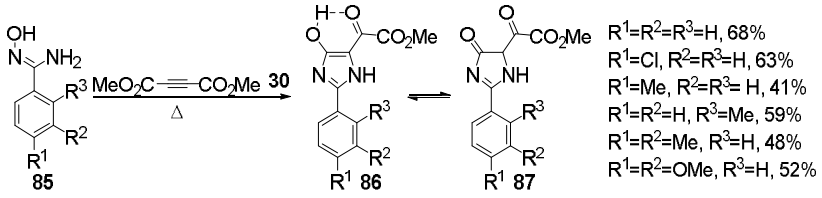


Scheme 36. Synthesis of 2-(2-amino-4-(dimethylamino)thiazol-5-yl)-2-oxoacetates.

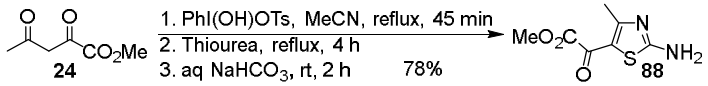


Scheme 37. Synthesis of bis(thiazol-5-yl)glyoxylate **84**.

Condensation of aryl amidoximes **85** with dimethyl acetylene dicarboxylate **30** proceeded through a Claisen-type rearrangement step, followed by pyrolytic decarboxylation (Scheme 38).[52] It is worth noting that imidazolinone glyoxylates **87** (existing in equilibria with tautomers **86**) were evaluated as central nervous system depressants. A similar method for the assembly of thiazoles **88** included condensation of acetylpuruvate **24** with PhI(OH)OTs and then thiourea (Scheme 39).[51]

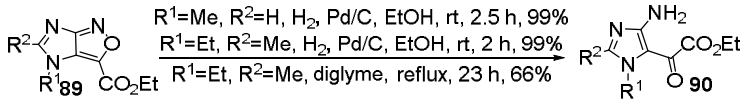


Scheme 38. Synthesis of imidazole-5-ylglyoxylates **86**.



Scheme 39. Synthesis of methyl 2-(2-amino-4-methylthiazol-5-yl)-2-oxoacetate **88**.

Reductive ring opening of fused isoxazole-5-carboxylates **89** for the synthesis of 4-aminoimidazoles **90** with the glyoxylate fragment at the C5-position was also described in the literature (Scheme 40).[53]

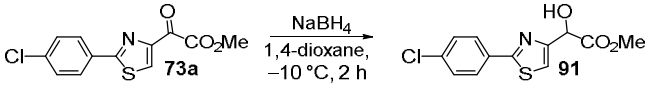


Scheme 40. Reductive ring opening of imidazo[4,5-*c*]isoxazole-3-carboxylates **90**.

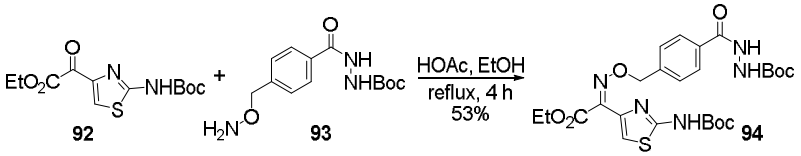
5. Chemical transformations of 1,3-azolyl glyoxylates and their fused analogs

5.1. Functional group interconversions

As compared to pyrroles, furanes, and thiophenes, the scope of chemical transformations of 1,3-diazolyl glyoxylates was studied to a lesser extent. The reported chemical transformations include the reduction of **73a** (*i.e.* for the synthesis of **91**, Scheme 41),[47] as well as oxime formation from **92** with *O*-substituted hydroxyamine **93** carried out in the presence of HOAc in refluxing EtOH providing derivative **94** (Scheme 42).[54]

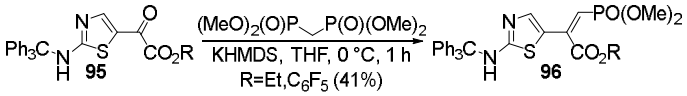


Scheme 41. Synthesis of 2-(2-(4-chlorophenyl)thiazol-4-yl)-2-hydroxyacetate **91**.



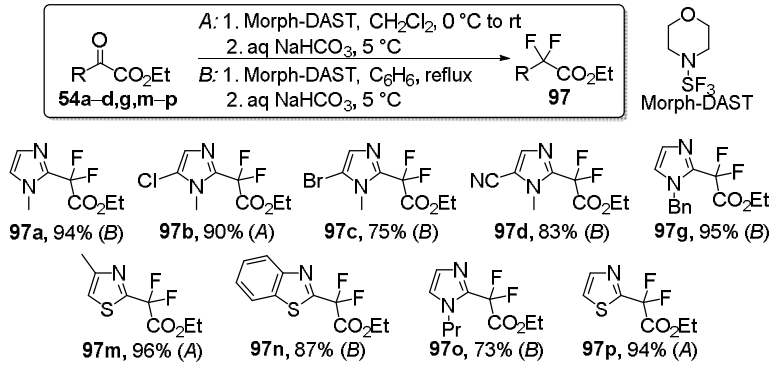
Scheme 42. Oximation of thiazol-4-ylglyoxylate **92** with hydroxylamine **93**.

Another example is the olefination of glyoxylate **96** with methylene diphosphonate in the presence of KHMDS. It was established that a higher *E/Z* selectivity is observed for pentafluorophenyl ester **95** as compared to ethyl ester to give product **96** in 41% yield (Scheme 43).[55]



Scheme 43. Olefination of glyoxylate **95**.

Deoxofluorination of 1,3-azolyl glyoxylates **54** has been studied thoroughly by our group. Mild reaction conditions, which includes the use of a 2.5-fold excess of morpholinosulfur trifluoride (morph-DAST) in CH_2Cl_2 at rt (Scheme 44, Method *A*),[56] were suitable only for about a third part of the studied glyoxylates to give the corresponding difluoroacetates **97b**, **97m**, and **97p** in 90-96% yields. In all other cases, the conversion of the starting glyoxylates **54** was incomplete (up to 55% of starting material remained intact). The deoxofluorination reaction in refluxing benzene (Scheme 44, Method *B*) was effective, and resulted in the formation of the target difluoroacetates **97** in good to high yield (75-96%). It was established that using the corresponding *t*-butylglyoxylates was unfruitful for the formation of deoxofluorinated products using any of the above methods; decomposition of the starting materials was observed instead. A possibility of synthetic modifications of difluoroacetates of the general formula **97** was demonstrated by mild alkaline hydrolysis with NaOH in H_2O-MeOH with subsequent treatment with HCl (to obtain carboxylic acids), reaction with NH_3 in H_2O-MeOH (to give amides) followed by treatment with $POCl_3$ in pyridine (for the synthesis of nitriles), as well as reduction with $NaBH_4$ in THF-methanol (4:1 v/v) (to synthesize *gem*-difluorinated alcohols).



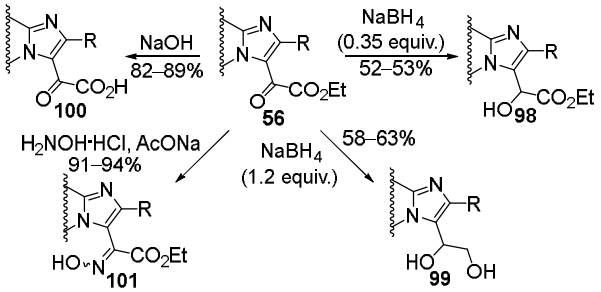
Scheme 44. Synthesis of 1,3-diazolyl difluoroacetates **97**.

Known synthetic transformations of imidazo[1,2]hetaryl glyoxylates **56** also include reactions with $NaBH_4$, NaOH, and NH_2OH (Scheme 45).[28] Depending on the amount of the reducing agent, reduction of glyoxylates with $NaBH_4$ led to the formation of α-hydroxyesters **98** (0.35 equiv. of $NaBH_4$) or 1,2-diols **99** (1.2 equiv. of $NaBH_4$). Alkaline hydrolysis of glyoxylates **56** in the presence of NaOH was used for the synthesis of glyoxylic acids **100**, while the reaction with hydroxylamine hydrochloride in the presence of a base resulted in the formation of the corresponding oximes **101**.

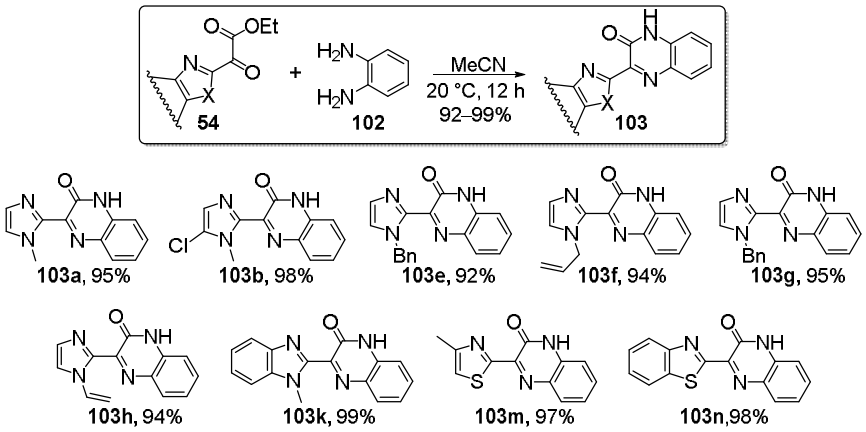
5.2. Heterocyclizations

The use of azol-2-yl-glyoxylates in condensation reactions with ethylene diamines and 1,2-diaminobenzenes (*o*-phenylenediamines) is a powerful tool for the synthesis of corresponding 5,6-dihydropyrazin-2-ones and quinoxalin-2-ones *via* the *NCCN+CC* cyclization.[57] In particular, ethylazol-2-yl-glyoxylates **54** reacted in MeCN at rt with unsubstituted *o*-phenylenediamine **102** for the synthesis of 3-azolyl-1*H*-quinoxalin-2-ones **103** in high yields (92-98%, Scheme 46). The method also worked

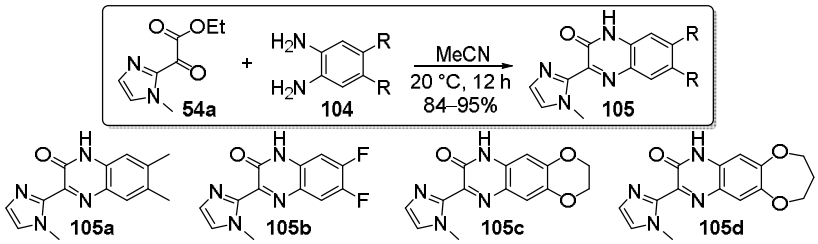
well for symmetrically substituted *o*-phenylenediamines **104a-d** as the nucleophilic components to give **105** (Scheme 47),[57] as well as imidazo[1,2]hetaryl glyoxylates **56** as bis-elecrophiles in reactions with **102** (for the preparation of **106**, Scheme 48) and ethylenediamine **107** for the synthesis of **108** (Scheme 49).[28]



Scheme 45. Reactions of imidazo[1,2]hetaryl glyoxylates **56** with $NaBH_4$, NaOH, and NH_2OH (for the structures of compounds **56**, see Scheme 27).



Scheme 46. Synthesis of 3-azolyl-1*H*-quinoxalin-2-ones of general formula **103**.

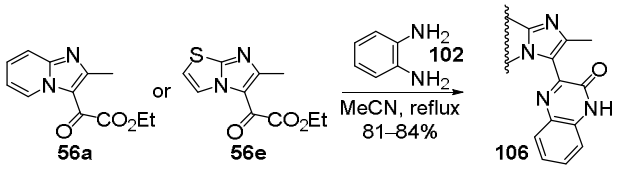


Scheme 47. Condensation of glyoxylate **54a** with 4,5-disubstituted *o*-phenylenediamines **104a-d**.

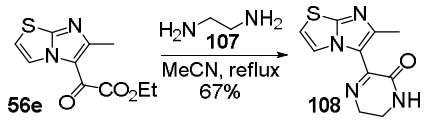
Furthermore, azol-2-yl-glyoxylates **54a**, **54f**, **54g**, and **54k** reacted with 1,2-diaminocyclohexane (**109**, as a ca. 1:1 mixture of *cis*- and *trans*-diastereomers) to give the corresponding hexahydroquinazolin-2-one **110**, which was precipitated from the reaction mixture exclusively as *trans*-diastereomers due to the plausible epimerization during the formation of Schiff base intermediates (Scheme 50).[57]

A method for the synthesis of pyridazinones relied on the condensation of ethyl3-hydrazinyl-3-oxopropanoate with hetaryl glyoxylate **64** to give intermediate **111** that was transformed

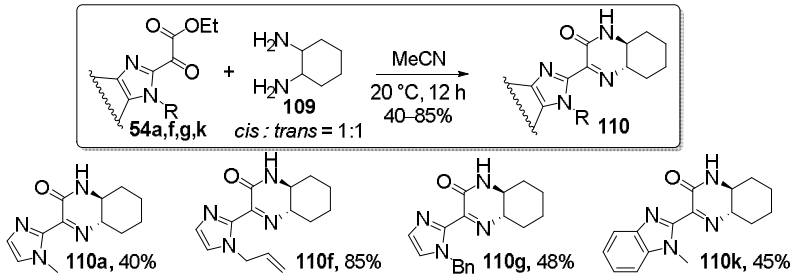
into the corresponding 6-azolyl pyridazin-3-one **112** in 82% yield upon treatment with NaOAc in DMF (Scheme 51).[36]



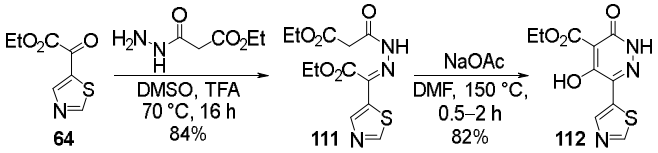
Scheme 48. Condensation of glyoxylates **56a** and **56e** with *o*-phenylenediamine **102**.



Scheme 49. Condensation of glyoxylate **56e** with ethylenediamine **107**.



Scheme 50. Reaction of azol-2-yl-glyoxylates **54** with 1,2-diaminocyclohexane **110** (relative configurations are shown).

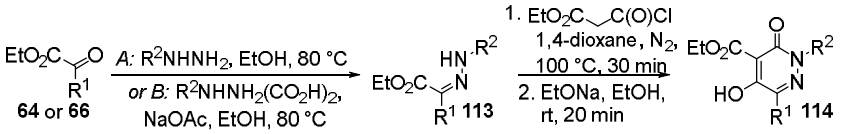


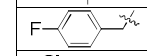
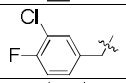
Scheme 51. Synthesis of 6-azolylpyridazin-3-ones **112**.

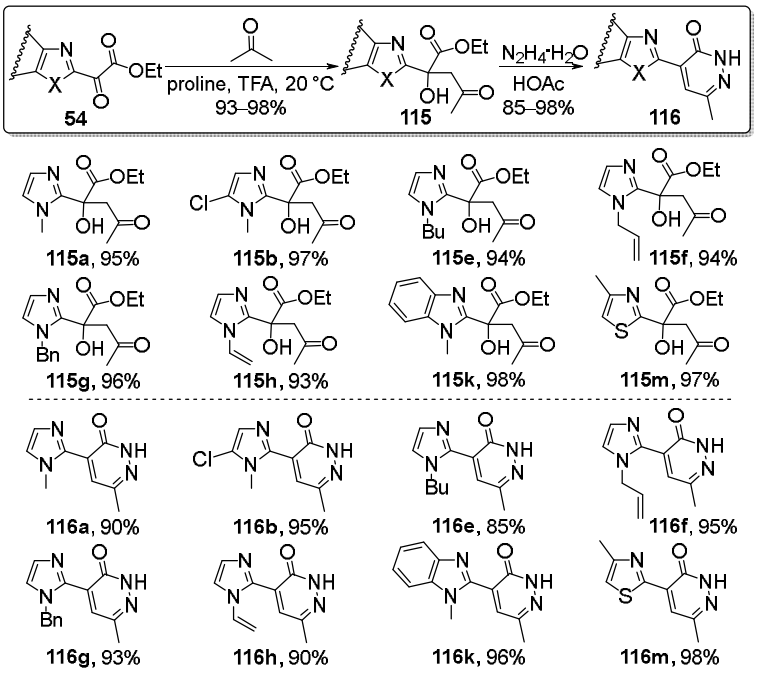
A similar approach includes the formation of hydrazones **113** from 1,3-azolyl glyoxylates **64** or **66**, which was used for the synthesis of the corresponding 6-(1,3-azolyl)-pyridazin-3-ones **114** (Table 3)[35,36,58] The heterocylization step involved the use of ethyl 3-chloro-3-oxopropanoate in 1,4-dioxane and then sodium ethylate.

A two-step organocatalytic approach to the preparation of 4-azolyl-(2*H*)-pyridazin-3-ones **116** from ethyl-azol-2-yl glyoxylates **54** was described by our group. For this purpose, condensation of glyoxylates **54** with acetone in the presence of catalytic amounts of proline and TFA led to the formation of the corresponding 1,3-azolyl aldols **115** in high yields of 93-98% (Scheme 52).[59] The second step in the proposed scheme was the cyclization of aldols **115** by heating in acetic acid in the presence of a three-fold excess of hydrazine hydrate to form the target pyridazinones **116** in 85-98% yield.

Table 3. Synthesis of 6-azolylpyridazin-3-ones **114**.

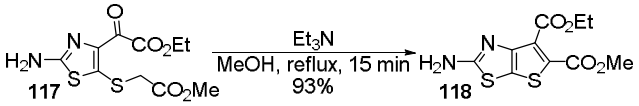


n.	R^1	R^2	Method	Yield % of **113**	Yield % of **114**
1	 **64**		*B*	71	81
2			*B*	70	54
3			*B*	57	42
4			*B*	75	63
5			*B*	91	70
6			*A*	35	75
7			*A*	47	75
8	 **66**		*A*	38	36
9			*B*	75	74
10			*B*	75	79

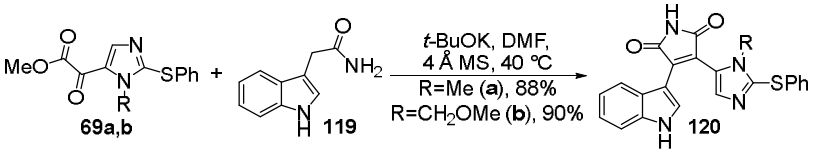


Scheme 52. Synthesis of 4-azolyl-(2*H*)-pyridazin-3-ones **116** from glyoxylates **54**.

Other examples of heterocyclizations with 1,3-azolyl glyoxylates include intramolecular cyclization of derivative **117** that was used to synthesize 2-aminothieno[3,2-*d*]thiazole-5,6-dicarboxylate **118** in 93% yield (Scheme 53),[60] as well as a reaction of glyoxylate **69** with 2-(1*H*-indol-3-yl)acetamide **119** for the synthesis of diarylmaleimides **120** (Scheme 54).[40]

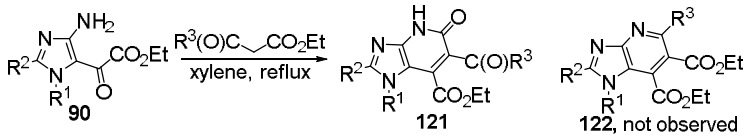


Scheme 53. Synthesis of 6-ethyl-5-methyl-2-aminothieno[3,2-*d*]thiazole-5,6-dicarboxylate **118**.



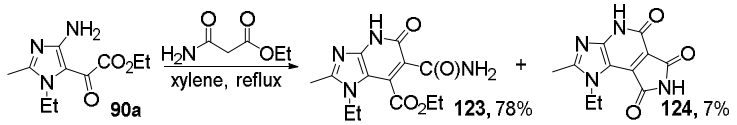
Scheme 54. Synthesis of diarylmaleimides **120**.

Condensations of 1,3-azolyl glyoxylates bearing an amino group at the adjacent position with active methylene compounds was used for the synthesis of various 5*H*-imidazo[4,5-*b*]pyridine-5-ones.[61] In details, ethyl 2-(4-amino-1*H*-imidazol-5-yl)-2-oxoacetates **90** reacted with β-ketoesters to form imidazo[4,5-*b*]pyridine-5-ones **121** (Scheme 55). Notably, the formation of an alternative regioisomer, *e.g.* fused pyridinedicarboxylate **122**, was not observed.

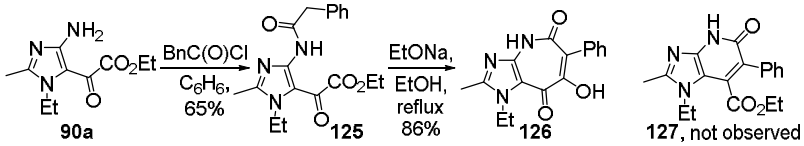


Scheme 55. Reaction of imidazolyl glyoxylates **90** with β-ketoesters.

Similarly, reaction of glyoxylate **90a** with ethyl 3-amino-3-oxopropanoate resulted in the formation of compounds **123** and **124** (Scheme 56), while the reaction with phenacetyl chloride proceeded as *N*-acylation, and after treatment with EtONa, exclusive formation of the seven-membered derivative **126** (instead of the six-membered regioisomer **127**) was observed via the formation of **125** (Scheme 57).



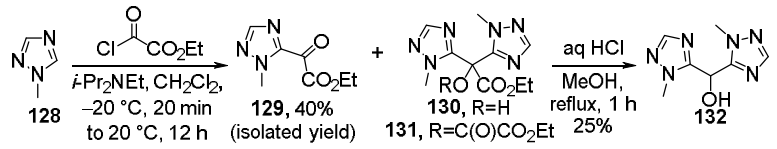
Scheme 56. Reaction of glyoxylate **90a** with ethyl 3-amino-3-oxopropanoate.



Scheme 57. The reaction of glyoxylate **90a** with phenacetylacetyl chloride.

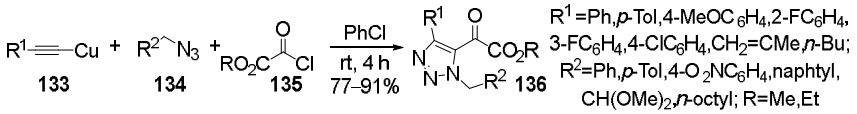
6. Synthesis and chemical transformations of triazolyl glyoxylates

In contrast to the direct electrophilic acylation of imidazoles, the analogous reaction of 1-methyl-1*H*-1,2,4-triazole **128** with ethyl oxalyl chloride led to the formation of a complex mixture of products containing mainly compounds **129**, **130**, and **131** (Scheme 58).[27] A mixture of compounds **130** and **131** was transformed into alcohol **132** upon acidic hydrolysis. The formation of by-products observed with thiazoles may be related to the high activity of the carbonyl group in product **129** or the corresponding intermediate.[27]



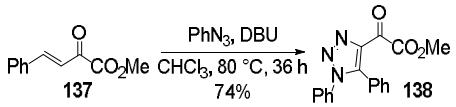
Scheme 58. Acylation of triazole **128** and synthesis of bistriazolylmethanol **132**.

The synthesis of 2-oxo-2-(1*H*-1,2,3-triazol-5-yl)acetates **136** was based on the azide-alkyne click reaction of copper acetylides **133** with azides **134** and alkyl oxalyl chlorides **135**. This transformation was described for the case of arylacetylenes and benzyl azides as the substrates and led to 1,2,3-triazol-5-yl glyoxylates **136** in high yields (77-91%, Scheme 59).[62,63]



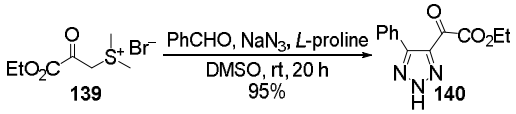
Scheme 59. Synthesis of 1,2,3-triazol-5-ylglyoxylates **136**.

Also, methyl cinnamate **137** reacted with PhN_3 in the presence of DBU to form the diphenyl derivative **138** in 74% yield (Scheme 60).[64]



Scheme 60. Synthesis of 2-(1,5-diphenyl-1*H*-1,2,3-triazol-4-yl)-2-oxoacetate **138**.

Finally, reaction of (3-ethoxy-2,3-dioxopropyl)dimethylsulfonium bromide **139** with sodium azide and benzaldehyde in DMSO served as a method for the synthesis of triazolyl glyoxylate **140** in 95% yield (Scheme 61).[65]



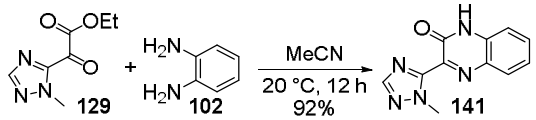
Scheme 61. Synthesis of ethyl 2-oxo-2-(5-phenyl-2*H*-1,2,3-triazol-4-yl)acetate **140**.

Azol-2-yl-glyoxylate **129** was condensated with 1,2-diaminobenzene **102** for the synthesis of the corresponding 3-azolyl-1*H*-quinoxalin-2-one **141** in high yield (Scheme 62).[57]

7. Synthesis of azine-derived glyoxylates

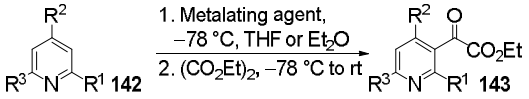
As might be expected, electrophilic acylation has not used for the synthesis of electron-poor azine-derived glyoxylates. Instead, metalation followed by acylation has been typically involved. A

representative example includes the synthesis of 2-oxo-2-(pyridine-3-yl)acetates **143** *via* metalation of **142** upon action of *n*-BuLi or LDA (Table 4).



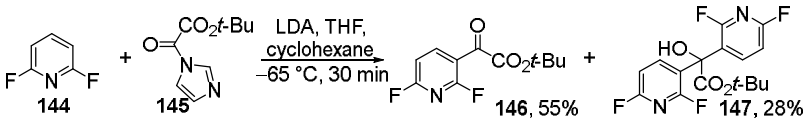
Scheme 62. Synthesis of 3-(1-methyl-1*H*-1,2,4-triazol-5-yl)quinoxalin-2(1*H*)-one **141**.

Table 4. Synthesis of pyrid-3-yl glyoxylates **143**.



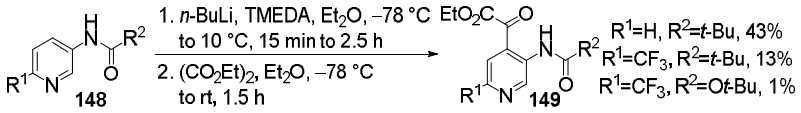
n.	R^1	R^2	R^3	Metalating agent	Solvent	Yield %	Ref.
1	H	$NHCO_2t$-Bu	H	*n*-BuLi/TMEDA	Et_2O	51	61,66,67
2	$NHCO_2t$-Bu	H	H	*n*-BuLi/TMEDA	Et_2O	50	68,69
3	F	H	F	LDA	THF	58	70
4	OMe	H	β-naphtyl	*t*-BuLi or LDA	THF	N.A.	71

Directed *ortho*-metalation was one of the most promising methods for the introduction of glyoxylate moiety into the pyridine core. Thus, when *t*-butyl-2-(1*H*-imidazol-1-yl) glyoxylate was used as an acylating agent **145** for lithiated 2,6-difluoropyridine **144** for the preparation of **146**, the reaction was accompanied by the formation of the side product **147** of nucleophilic addition to the carbonyl group of pyridyl glyoxylate (Scheme 63).[72]



Scheme 63. Synthesis of 3-(difluoropyridyl)glyoxylate **146**.

3-Acylaminopyridine **148** was selectively metalated at the γ-position with *n*-BuLi in the presence of TMEDA. Further reaction with ethyl oxalate resulted in the selective formation of pyridyl-4-glyoxylate **149** (Scheme 64).[68] Meanwhile, the synthesis of 2-oxo-2-(pyridine-2-yl)acetates **151** typically relied on the metal-halogen exchange of **150** followed by the interaction of the organometallic species thus formed with ethyl oxalate (Table 5).

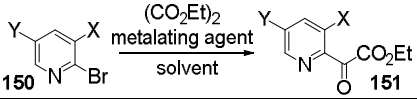


Scheme 64. Synthesis of 2-oxo-2-(pyridine-4-yl)acetates **149**.

This approach was extended to other isomeric glyoxylates, which was demonstrated by the synthesis of 2-oxo-2-(pyridine-3-yl)acetates **153** from **152** (Table 6).

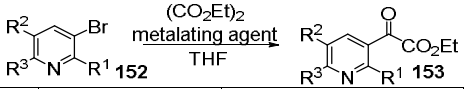
The metalation-acylation of 3-bromo-4,6-dichloro-2,5-dimethylpyridine **154** was performed for the preparation of derivative **155** using the "turbo-Grignard" reagent (*i*PrMgCl·LiCl) in THF at –20 °C (Scheme 65).[78] Another example of regioselective glyoxylate formation is the reaction of 3-bromo-2-methoxypyridine **156** with Mg in THF and then with di-*t*-butyl oxalate (35% yield of product **157**) (Scheme 66).[79]

Table 5. Synthesis of 2-oxo-2-(2-pyridyl)acetates **151**.

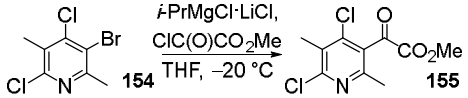


Substituent	Metalating agent	Solvent	Temperature, °C	Product	Yield %	Ref.
X=H, Y=H	*i*-PrMgCl	THF	34 °C	**151a**	65	73
X=H, Y=F	*i*-PrMgCl·LiCl	THF	1. 0-20 °C; 2. –78 °C to rt	**151b**	47	74
X=(CH_2=CMe_2), Y=H	*n*-BuLi	THF, hexane	–78 °C	**151c**	63	75

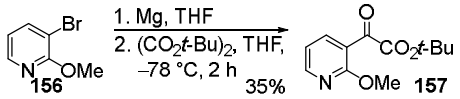
Table 6. Synthesis of 2-oxo-2-(3-pyridyl)acetates **153**.



n.	R^1	R^2	R^3	Metalating agent	Temperature, °C	Yield %	Ref.
1	H	H	H	*n*-BuLi	1. –78 °C; 2. 0 °C to rt	15	76
2	H	F	H	*i*-PrMgCl·LiCl	1. 0 °C to rt; 2) –78 °C	47	74
3	H	H	Cl	*n*-BuLi	1. –78 °C; 2. –78 °C	N.A.	71
4	Cl	H	OMe	*i*-PrMgCl	1. 0 °C to rt; 2. –5 °C	77	77

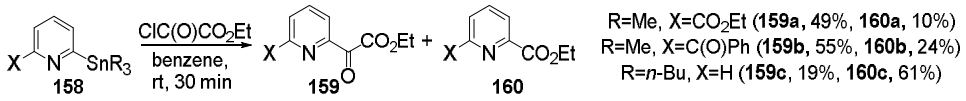


Scheme 65. Synthesis of methyl 2-(4,6-dichloro-2,5-dimethylpyridine-3-yl)-2-oxoacetate **155**.

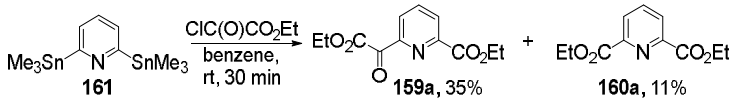


Scheme 66. Synthesis of *t*-butyl 2-(2-methoxypyridine-3-yl)-2-oxoacetate **157**.

An alternative approach to the regioselective synthesis of pyridine-α-oxoesters **159** was based on the reaction of pyridine trialkylstannanes **158** with an acylating agent in benzene (Scheme 67).[80] The formation of corresponding decarbonylated esters **160** was also observed. Furthermore, the reaction of 2,6-bis(trimethylstannyl)pyridine **161** proceeded with the formation of the corresponding glyoxylate **159a** bearing ester group (35% yield) and pyridine-2,6-dicarboxylate **160a** in 11% yield (Scheme 68).

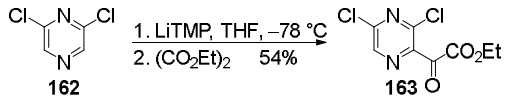


Scheme 67. Synthesis of 2-oxo-2-(pyridine-2-yl)acetates **159** from trialkylstannates **158**.

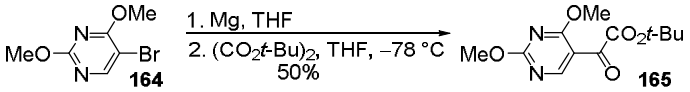


Scheme 68. Synthesis of 2-oxo-2-(pyridine-2-yl)acetate **159a** from bis-trialkylstannate **161**.

Metalation of 2,6-dichloropyrazine **162** occurred at the C3-position upon the action of 2,2,6,6-tetramethylpiperidinyllithium in THF at –78 °C; after reaction with diethyl oxalate, product **163** was obtained in 54% yield (Scheme 69).[81] 5-Bromo-2,4-dimethoxypyrimidine **164** was glyoxylated at the C5 position through the intermediate formation of Grignard reagent in 50% yield of product **165** (Scheme 70).[79]

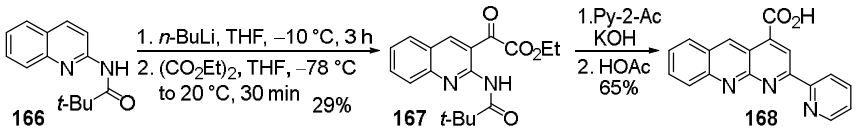


Scheme 69. Synthesis of ethyl 2-(3,5-dichloropyrazin-2-yl)-2-oxoacetate **163**.



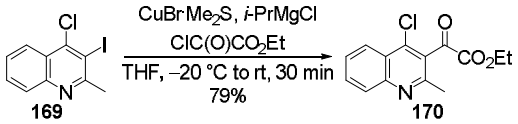
Scheme 70. Synthesis of *t*-butyl-2-(2,4-dimethoxypyrimidin-5-yl)-2-oxoacetate **165**.

(Quinolin-2-yl)-*t*-butylcarboxamide **166** was selectively lithiated at the C3-position, and further reaction of the ensuing organolithium derivative with ethyl oxalate led to the formation of quinoline-3-yl glyoxylate **167** in 29% yield, which was used for the preparation of fused derivative **168** (Scheme 71).[70]



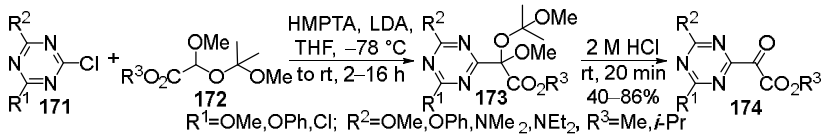
Scheme 71. Preparation of quinoline-3-yloxalate **167** by directed *ortho*-metalation of **166**.

4-Chloro-3-iodo-2-methylquinoline **169** was transformed into β-glyoxylate **170** upon treatment with CuBr·SMe$_2$ and *i*-PrMgCl (Scheme 72).[82]

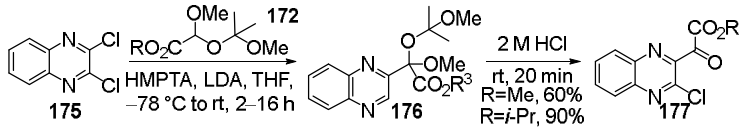


Scheme 72. Synthesis of ethyl 2-(4-chloro-2-methylquinolin-3-yl)-2-oxoacetate **170**.

A similar transformation was described for the 3-bromoquinoline derivative, which was transformed into glyoxylate in 47% yield.[83] Another way to introduce the glyoxylate moiety into azine heterocyclic core have been disclosed for the case of triazines and quinoxalines. In particular, the synthesis of 1,3,5-triazine derivatives **174** (Scheme 73)[84] and 2-(3-chloroquinoxalin-2-yl)-2-oxoacetates **177** (Scheme 74) was achieved by using *C*-deprotonated acetal **172** as the nucleophile that was arylated with **171** and **175** and then subjected to the deprotection step of derivatives **173** and **176** thus formed.

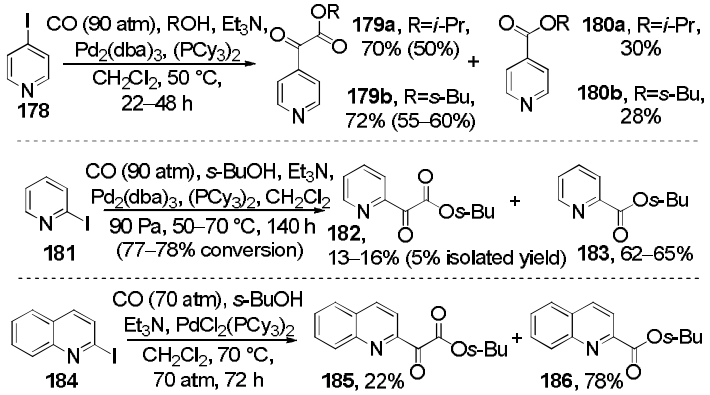


Scheme 73. Synthesis of 1,3,5-triazine glyoxylates **174**.



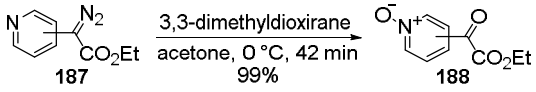
Scheme 74. Synthesis of 2-(3-chloroquinoxalin-2-yl)-2-oxoacetates **177**.

Several examples of palladium-catalyzed double carbonylations providing α-/γ-pyridyl[85,86] and α-quinolyl[87] glyoxylates **180**, **182**, and **185**, respectively, have also been reported in the literature (Scheme 75). In the case of 2-iodopyridine **181** and 2-iodoquinoline **184**, the glyoxylates were obtained as minor products with the corresponding esters **183** and **186** as major ones. At the same time, pyridyl-4-glyoxylates **179a,b** were major products in the case of the double carbonylation of **178**.



Scheme 75. Palladium-catalyzed double carbonylations of iodides **178**, **181**, and **184**.

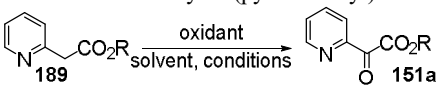
Ethyl 2-diazo-2-(pyridyl)acetates **187** can be transformed into the corresponding glyoxylates **188** with *N*-oxide moiety upon action of dimethyldioxirane (Scheme 76).[88]



Scheme 76. Reaction of ethyl 2-diazo-2-(pyridinyl)acetates with dimethyldioxirane **187**.

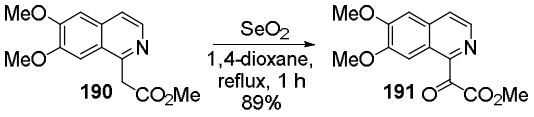
The straightforward oxidation of the methylene group of pyridinyl-2-acetates **189** (Table 7)[89] and isoquinoline-1-acetate **190** (Scheme 77) could be applied for the synthesis of glyoxylates **151a** and **191** without reaction at the azine nitrogen atom.[90] For this purpose, mild oxidants were applied, *e.g.* CuI-O_2, SeO_2.

Table 7. Oxidation of alkyl-2-(pyridine-2-yl)acetates **189**.



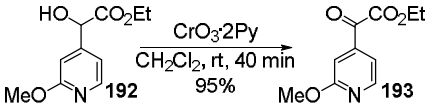
R	Reagents	Solvent	Conditions	Yield %	Ref.
Me	CuI, O_2	*t*-BuOAc	100 °C, 24 h	83	91
Et	TEMPO, di-*t*-butyl peroxide, I_2 (cat.)	1,2-$Cl_2C_6H_4$	120 °C, 24 h	20[a]	92
	SeO_2	1,4-dioxane	100 °C, 12 h	73	93
t-Bu	CuI, trimethylacetic acid, O_2	DMSO	65 °C	89	94

[a] Ethyl-2-(pyridine-2-yl)-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)acetate (25%) was formed.

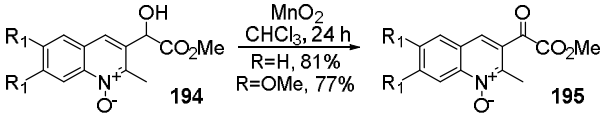


Scheme 77. Synthesis of methyl-2-(isoquinolin-1-yl)-2-oxoacetate **191**.

Other examples of the synthesis of oxoesters **193** and **195** consist in the oxidation reaction of hydroxy esters of pyridine **192** (Scheme 78)[95] and quinoline-*N*-oxide **194** (Scheme 79).[96]

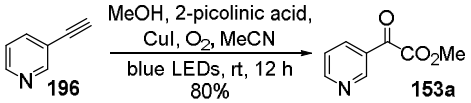


Scheme 78. Synthesis of ethyl 2-(2-methoxypyridine-4-yl)-2-oxoacetate **193**.



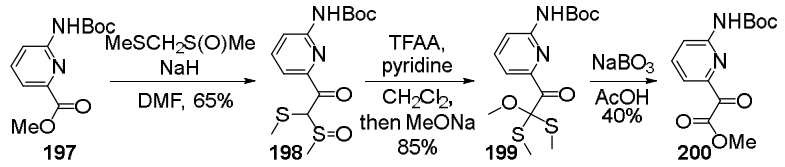
Scheme 79. Synthesis of 3-(2-methoxy-2-oxoacetyl)-2-methylquinoline-1-oxide **195**.

Another method is the oxidative conversion of 3-ethynylpyridine **196** into glyoxylate **153a**, which proceeded in the presence of 2-picolinic acid and oxygen at rt upon blue-LED irradiation (Scheme 80).[97]



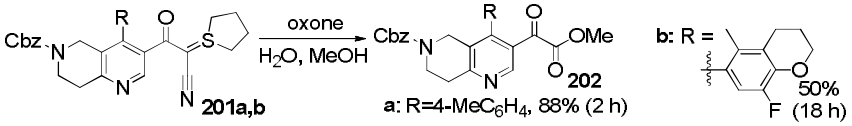
Scheme 80. Synthesis of glyoxylate **153a** from 3-ethynylpyridine **196**.

Oxidative cleavage of dithioorthoester **199** with sodium perborate in HOAc was used for the preparation of pyrid-2-yl glyoxylate **200**. The synthesis of **199** included Claisen-type reaction of picolinate **197** with 2-methoxy-2,2-bis(methylthio)ethenone and subsequent Pummerer rearrangement of **198** (Scheme 81).[98]

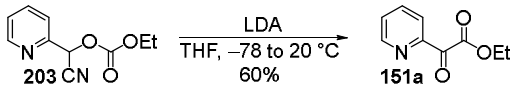


Scheme 81. Synthesis of methyl 2-(6-(*N*-Boc-amino)pyridine-2-yl)-2-oxoacetate **200**.

The reaction of tetrahydrothiophenylidene derivatives **201a,b** with oxone was used for the preparation of fused pyrid-3-yl glyoxylates **202a,b** (Scheme 82).[99] It was also possible to synthesize 2-pyridyl glyoxylate **151a** from *O*-protected cyanohydrin **203** *via* LDA-promoted rearrangement (Scheme 83).[100]

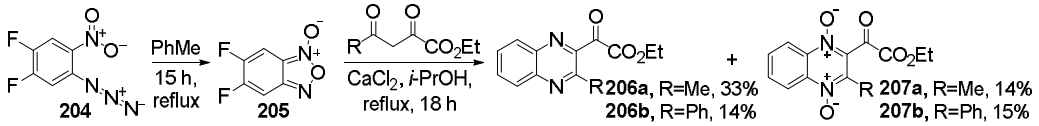


Scheme 82. Synthesis of fused pyrid-3-yl glyoxylates **202**.



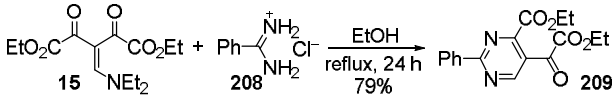
Scheme 83. Synthesis of pyrid-2-yl glyoxylate **151a**.

Other methods for the synthesis of azinyl glyoxylates are based on the construction of the heterocyclic ring. Thus, the synthesis of ethyl 2-oxo-2-(quinoxalin-2-yl)acetates **206a,b** and **207a,b** from 3,5-difluoro-2-nitrophenylazide **204** *via* the formation of benzo[*c*][1,2,5]oxadiazole 1-oxide **205** was described. The latter derivative was involved in the reaction with acetyl and benzoylpyruvates to give quinoxaline glyoxylates (Scheme 84).[101]



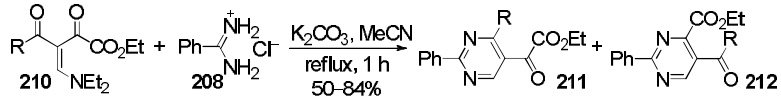
Scheme 84. Synthesis of ethyl-2-oxo-2-(quinoxalin-2-yl)acetates **205a,b** and **207a,b**.

Another approach included the condensation of benzamidine **208** with *CCC* bis-electrophiles, *e.g.* diethyl 3-((diethylamino)methylene)-2,4-dioxopentanedioate **15**, for the preparation of derivative **209** (Scheme 85).[102,103]



Scheme 85. Synthesis of 5-(2-ethoxy-2-oxoacetyl)-2-phenylpyrimidine-4-carboxylate **209**.

The scope of the method was extended to a number of other α-acyl-β-aminovinylglyoxylates **210**, which led to the formation of pyrimidine glyoxylates **211** along with isomeric 4-acylpyrimidine-5-carboxylates **212** via the condensation with **208** (Scheme 86).[104]



211 as the only product: R=CF_3 (50%);
212 as the only product: R=4-MeC_6H_4 (86%),4-$MeOC_6H_4$ (78%),4-FC_6H_4 (82%),thien-2-yl (70%);
212 as the major product: R=Ph (84%, **211**:**212**=1:10),4-BrC_6H_4 (81%, **211**:**212**=1:5),
4-ClC_6H_4 (72%, **211**:**212**=1:10), 4-$O_2NC_6H_4$ (78%, **211**:**212**=1:2), benzofuran-2-yl (81%, **211**:**212**=1:3)

Scheme 86. Reaction of α-acyl-β-aminovinyl glyoxylates **210** with benzamidine **208**.

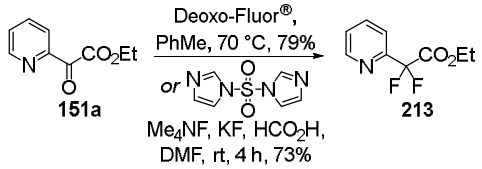
10. Chemical transformations of azine-derived glyoxylates

Deoxofluorination reaction is applicable for the six-membered heterocyclic glyoxylates. The reported examples included reaction of parent pyridyl-2-glyoxylate **151a** with Deoxo-Fluor® or Me_4NF-KF-1,1'-sulfonylbis(1*H*-imidazole) for the synthesis of α,α-difluoroacetate **213** (Scheme 87).[73,105]

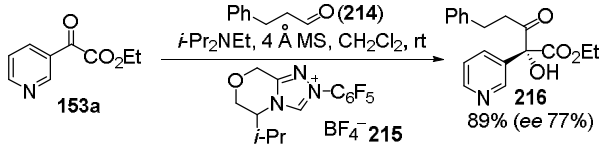
Other interesting synthetic transformations of azinyl glyoxylates include the organocatalytic cross-benzoin condensation of glyoxylate **153a** and 3-phenylpropanal **214** in the presence of organocatalyst **215** for the preparation of derivative **216** (Scheme 88).[76]

Intriguing results were obtained in the photochemical reaction of pyrid-2-yl glyoxylate **151a** with tetramethylethylene **217** (Scheme 89).[106] Normally, a product of the classical Paternò-Büchi reaction (oxetane

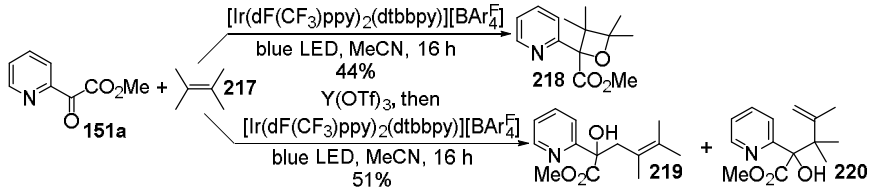
218) was obtained. In the presence of a Lewis acid, however, the Prins-type reaction was observed to give derivatives **219** and **220**.



Scheme 87. Synthetic approaches to hetaryldifluoroacetate **151a** from the corresponding glyoxylate **213**.

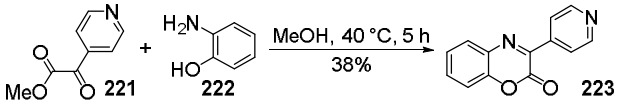


Scheme 88. An example of cross-benzoin condensation at the carbonyl group.



Scheme 89. Reaction of methyl-2-oxo-2-(pyridine-2-yl)acetate **151a** with tetramethylethylene **217**.

Finally, condensation of methyl pyridine-4-yl glyoxylate **221** (as a 1,2-*CC*-bis-electrophile) with 2-aminophenol **222** (as an *NCCO*-binucleophile) providing benzo[*b*][1,4]oxazine derivative **223** was described in the literature (Scheme 90).[107]



Scheme 90. Synthesis of 3-(pyrid-4-yl)-2*H*-benzo[*b*][1,4]oxazin-2-one **223**.

9. Conclusions

Heterocyclic α-oxoesters (also known as heterocyclic α-ketoesters, hetaryl-2-oxoacetates, or hetaryl glyoxylates) are interesting polyfunctional substrates due to the presence of activated ketone and ester moieties, which could be selectively transformed to other functional groups. It is not surprising therefore that heterocyclic glyoxylates have become very important derivatives in common and modern synthetic and medicinal chemistry.[108]

While the simplest mono-heteroatom five-membered hetaryl glyoxylates (that has been well-documented in the literature and surveyed in Part I of this review[109]), 1,2- and 1,3-azolyl glyoxylates represent a slightly less studied type of heterocycles. The known methods for their synthesis were mainly based on the metalation-glyoxylation sequence or the construction of the heterocyclic fragment (*via* 1,3-dipolar cycloadditions, click reactions, condensations *etc.*). In the case of 1,3-azolyl glyoxylates (*i.e.* imidazoles, thiazoles, and their fused analogs), the direct electrophilic acylation with alkyl oxalyl chlorides developed by our group can be a method of choice for the preparation of C2-isomeric compounds.

Only a few examples of triazolyl glyoxylates have been known at the moment; their synthesis usually relied on heterocyclization reactions.

Azinyl glyoxylates have been also reported relatively scarcely in the literature. The most common synthetic approach to their preparation included C–H or C–Hal metalation, followed by treatment with dialkyl oxalates.

Typically, the chemical behavior of hetaryl glyoxylates corresponds to their electronic properties of highly electrophilic ketones; this type of reactivity is prevalent, *e.g.* reduction, formation of oximes, imines, and hydrazones, organometallic reagent addition, condensation, olefination, or deoxofluorination. Selective reactions at the ester group are less common being limited by hydrolysis and amide formation. Many reactions occur at both functional groups; some transformations involve atoms of the heterocyclic ring or side chains of the parent glyoxylate. In this view, heterocyclizations with ketoesters acting as 1,2-*CC*-bis-electrophiles are especially interesting for the preparation of pyrazines, quinoxalines, benzo[*b*][1,4]oxazines, and other heterocycles.

Acknowledgements

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