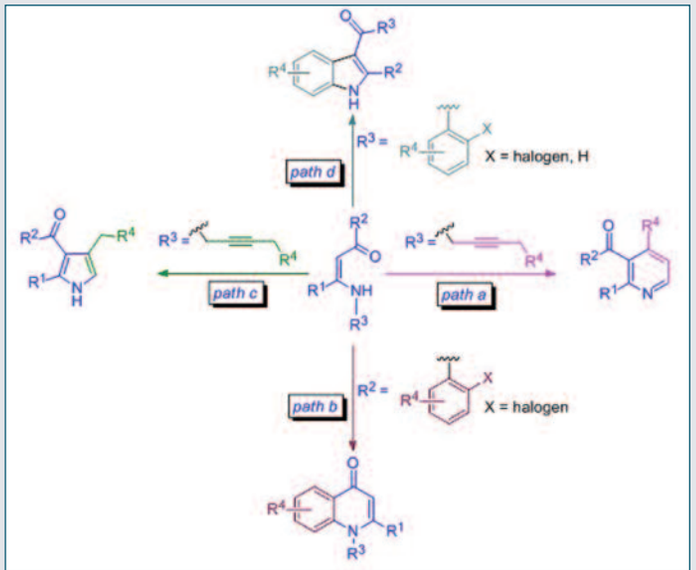

Scheme 1 - β-Enaminones as building blocks for the synthesis of 2,3,5-trisubstituted pyridines (*path a*); 1,2-disubstituted 4-quinolones (*path b*); 2,3,4-trisubstituted pyrroles (*path c*); 2,3-disubstituted indoles (*path d*)

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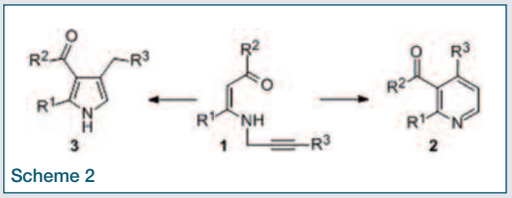
COPPER-CATALYZED SYNTHESIS OF HETEROCYCLE DERIVATIVES: USE OF β-ENAMINONES

The use of β-enaminones in synthesis is a subject of great current interest, mostly because of their electronic properties. An appropriate design of the starting β-enaminone could allow for obtaining several classes of heterocyclic derivatives through base- or transition metal-catalyzed reactions.

The use of β-enaminones in organic synthesis is a subject of great current interest. Indeed, the ambident nucleophilic character of the enamine moiety and the ambident electrophilic character of the enone moiety make them very useful and versatile synthetic intermediates [1]. Many intra- [2] and intermolecular [3] reactions have been performed taking advantage of their electronic properties including transition metal-promoted [4] and -catalyzed [5] processes. In the last few years copper-catalyzed methods have achieved a remarkable place in organic synthesis, mostly because of the economic attractiveness and good functional tolerance of this metal [6].

Particularly, it has been shown that by using appropriate ligands a large number of reactions can be carried out in the presence of catalytic instead of stoichiometric amounts of copper, providing an attractive alternative to palladium-catalyzed reactions and paving the way to its utilization in large scale applications. Therefore, because of our continuing interest in the transition metal-catalyzed construction of heterocyclic rings [7] we became interested in investigating the feasibility of copper-catalyzed cyclizations of β-enaminones. Particularly, we envisaged that an appropriate design of the starting β-enaminone could allow for obtaining several classes of heterocycles as illustrated in Scheme 1.

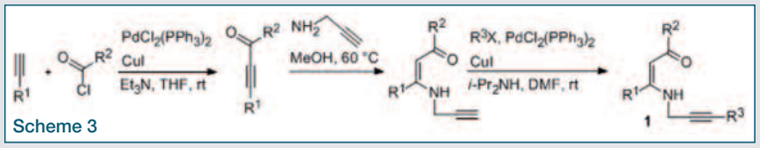


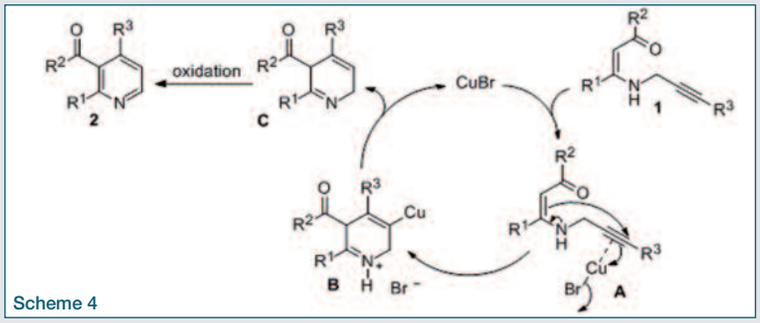
Scheme 2

Path a and c

*N-propargylic β-enaminones **1** as common intermediates for the synthesis of pyridines **2** and polysubstituted pyrroles **3** (Scheme 2)[8]*

N-propargylic β-enaminones **1** were readily prepared through a three-step procedure involving: a) a Sonogashira cross-coupling of terminal alkynes with acyl chlorides [9], b) the conjugate addition of propargylamine with the resultant α,β-enones, 3) another Sonogashira cross-coupling of the propargyl derivative with aryl halides (Scheme 3). *N*-propargylic β-enaminones **1** have always been isolated as *Z* isomers. Subjecting *N*-propargylic β-enaminones **1** to recrystallized CuBr in anhydrous DMSO at 60 °C under neutral conditions led to the selective formation of substituted pyridines **2**. Our preparative results are sum-


Scheme 3


Scheme 4

marized in Tab. 1. By analogy with other Cu-catalyzed cyclizations of acetylenic compounds [12], the proposed mechanism for the formation of the pyridine ring from **1** involves the following basic steps (Scheme 4): a) coordination of the alkyne moiety with copper to give **A**, b) 6-*endo-dig* cyclization of **A** via the intramolecular nucleophilic attack of the carbon α to the carbonyl group to the activated C-C triple bond, c) substitution of the C-H bond for the C-Cu bond of the resultant vinylic-copper intermediate **B** affording **C** with concomitant regeneration of CuBr, d) oxidation of **C** to give the pyridine derivative **2**. The cyclization to pyridines does not occur omitting copper. However, when *N*-propargylic β-enaminones **1** were treated with bases in the absence of copper, formation of free NH pyrroles **3** was observed. The best results were obtained using Cs_2CO_3 in anhydrous DMSO at room temperature (Tab. 2). Most probably [10], this carbocyclization proceeds through: a) a 5-*exo-dig* cyclization involving an intramolecular nucleophilic attack of the C_α terminus of the anion generated *in situ* from **1** on the closer acetylenic carbon [11]; b) a protonation step to afford a five-membered ring methylidene intermediate, c) an isomerization to the pyrrole product **3** (Scheme 5). The different behavior of *N*-propargylic β-enaminones in the presence of copper (under neutral conditions) compared with that in the presence of bases (omitting copper) might be due to the coordination of the C-C triple bond to the transition metal that would decrease its bond order and introduce strain on the transition state leading to the 5-*exo-dig* cyclization product thus favoring the 6-*endo-dig* cyclization (Fig. 1a). Under basic conditions, one of the orbitals of the acetylenic system allows for a nearly planar mode of approach of the nucleophile and the 5-*exo-dig* cyclization can take place (Fig. 1b).

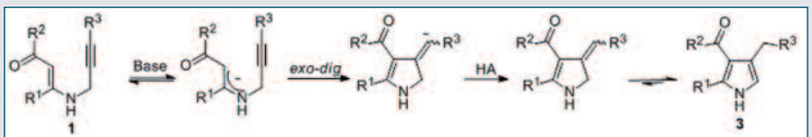
Path b

*Copper-catalyzed cyclization of 1-(2-halophenyl)-3-enaminones **4** to 1,2-disubstituted 4-quinolones **5** (Scheme 6) [13]*

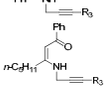
In this study, we investigated the potential of β-enaminones containing a (2-halophenyl) fragment bound to the carbonyl group as building blocks for the assembly of the 4-quinolone skeleton **5** (Scheme 6). 1-(2-Bromophenyl)- and 1-(2-chlorophenyl)-3-enaminones **4** were prepared through a two-step procedure involving a Sonogashira cross-coupling of terminal alkynes with commercially available 2-bromo- and 2-chlorobenzoyl chlorides [9] followed by the conjugate addition of primary amines with the resultant α,β-ynones **6** [5c] (Scheme 7).

The best results were obtained using CuI, *N,N'*-dimethylethylendiamine (DMEDA) and K_2CO_3 in DMSO at 80 °C. Under these conditions, the reaction allowed for the preparation of a wide variety of funtionalized quinolones (Tab. 3).

1-(2-Chlorophenyl)-3-enaminones can also be used in this chemistry. Reaction rates are lower, but yields are equally high to excellent, at least with the examples that we have tested (Tab. 4). The process can also be performed in a one-flask fashion, omitting the isolation of enaminone **4** intermediates, proceeding as follows: after the reaction

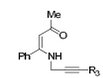
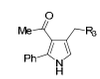
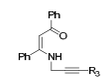
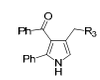
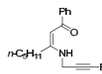
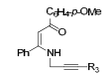
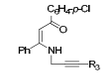
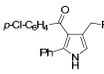

Scheme 5

Tab. 1 - Synthesis of polysubstituted pyridines 3[a]

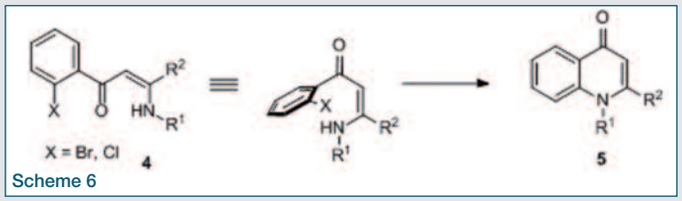
entry	substrate **1** and **4**		product **3**	time (h)	R^3	yield % of **2**[b]	
1		**1a**		0.5	*p*-MeO-C_6H_4-	**2a**	69
2		**1d**		1.5	*m*-Br-C_6H_4-	**2b**	55
3		**1c**		0.5	*p*-MeCO-C_6H_4-	**2c**	60
4		**1p**		2	Ph	**2d**	61
5		**4a**		2	H	**2e**	60
6		**1q**		2.5	*p*-MeCO-C_6H_4-	**2f**	51[c]
7		**1h**		5	*p*-Cl-C_6H_4-	**2g**	66
8		**1k**		5	*p*-Me-C_6H_4-	**2h**	60
9		**1r**		2.5	*m*-EtO_2C-C_6H_4-	**2i**	76
10		**1s**		5.5	*m*-MeO-C_6H_4-	**2j**	54

[a]Unless otherwise stated, reactions were carried out under argon on a 0.2-0.25 mmol scale using 0.4 equiv of recrystallized CuBr in 3 mL of anhydrous DMSO at 60 °C
[b]Yields are given for isolated products - [c]At 80 °C

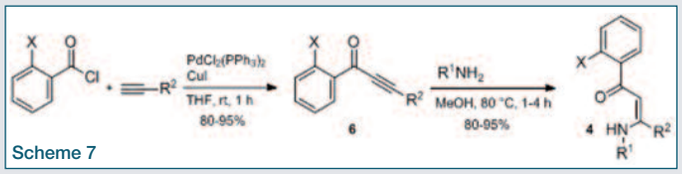
Tab. 2 - Synthesis of free NH polysubstituted pyrroles 3[a]

entry	substrate **1** and **4**		product **2**	time (h)	R^3	yield % of **3**[b]	
1		**1a**		2	*p*-MeO-C_6H_4-	**3a**	75[c]
2		**1b**		0.5	*p*-EtOCO-C_6H_4-	**3b**	65
3		**1c**		1	*p*-MeCO-C_6H_4-	**3c**	69[c]
4		**1d**		1	*m*-Br-C_6H_4-	**3d**	86
5		**4a**		0.5	H	**3e**	69[c,d]
6		**1e**		1	*m*-Me-C_6H_4-	**3f**	59
7		**1f**		0.2	*m*-EtOCO-C_6H_4-	**3g**	81
8		**1g**		0.2	*p*-NO_2-C_6H_4-	**3h**	42
9		**1h**		0.5	*p*-Cl-C_6H_4-	**3i**	69
10		**1i**		0.2	*m*-CF_3-C_6H_4-	**3j**	95
11		**1j**		1	3,5-Me_2-C_6H_4-	**3k**	64
12		**1k**		1	*p*-Me-C_6H_4-	**3l**	60
13		**1l**		0.25	*p*-MeCO-C_6H_4-	**3m**	96
14		**1m**		0.5	*m*-$HOCH_2$-C_6H_4-	**3n**	93
15		**1n**		0.2	3,5-Me_2-C_6H_4-	**3o**	74
16		**1o**		0.2	*m*-F-C_6H_4-	**3p**	75

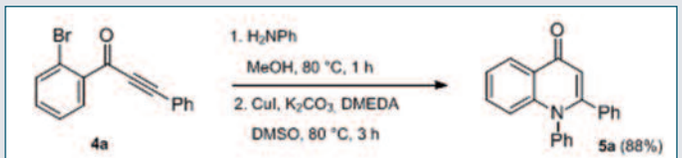
[a]Unless otherwise stated, reactions were carried out under argon on a 0.2 mmol scale using 2 equiv of Cs_2CO_3 in 3 mL of anhydrous DMSO at room temperature
[b]Yields are given for isolated products - [c]Carried out on a 0.3 mmol scale using the same amount of solvent - [d]At 60 °C



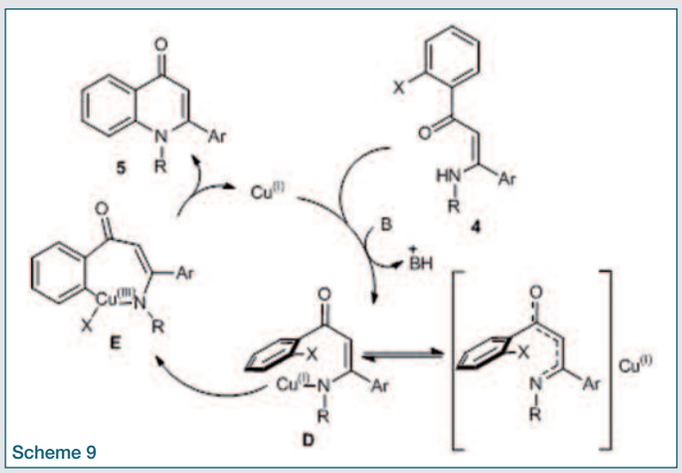
Scheme 6



Scheme 7



Scheme 8



Scheme 9

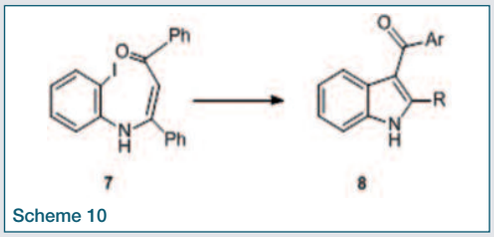
of primary amines with α,β-ynones is completed, the volatile materials are evaporated and DMSO, CuI, DMEDA, and K_2CO_3 are added to the crude mixture. An example of a quinolone derivative prepared according to this protocol is shown in Scheme 8. A likely mechanism for this quinolone ring formation (Scheme 9), which is based on previous observations on related Cu-catalyzed heterocyclizations involving $C_{aromatic}$-X bonds [14], begins with the initial coordination of nitrogen with copper to give the complex **D** that undergoes an oxidative addition of the C-X bond to copper to afford the Cu(III) intermediate **E**. Subsequent reductive elimination releases the product with simultaneous regeneration of the Cu(I) species.

Path d

*Copper-catalyzed cyclization of N-(2-Iodoaryl)enaminones **7** to 3-aroylindoles **8** (Scheme 10) [15]*

3-Acylindoles are useful intermediates for the preparation of pyrido carbazole alkaloids [16] and important therapeutic agents [17].

For example, A-85783 is a potent and selective antagonist of PAF [14e] and pravadoline is a non-acidic analogue of non steroidal anti-inflammatory drugs (NAIDs) [14a]. Although many methods are known for their preparation, most of them are based on the acylation



Scheme 10

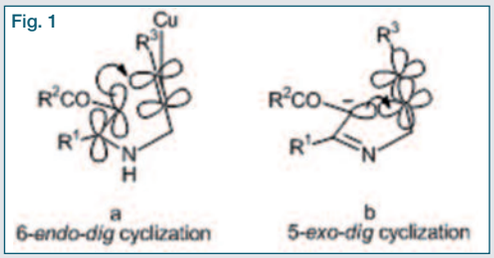


Fig. 1

Tab. 3 - Synthesis of 1,2-disubstituted 4-quinolones 5 from 1-(2-bromophenyl)-3-enaminones[a]

Entry	Enaminone **4** (X = Br) R^1	R^2		Time (h)	Yield (%)[b] of **5**
1		Ph	**4a**	2.5	**5a** 93
2		3-CF_3-C_6H_4	**4b**	1.5	**5b** 92
3		4-MeO-C_6H_4	**4c**	2	**5c** 89
4		4-MeCO-C_6H_4	**4d**	1.5	**5d** 87
5	Ph		**4e**	2	**5e** 92
6		4-CN-C_6H_4	**4f**	25	**5f** 82
7		2,4-F_2-C_6H_3	**4g**	1.5	**5g** 72
8		3,4,5-$(MeO)_3$-C_6H_2	**4h**	2	**5h** 81
9		4-Cl-C_6H_4	**4i**	2	**5i** 91
10		*n*-Bu	**4j**	1	**5j** 86[c]
11		$PhCH_2$	**4k**	1	**5k** 55[c]
12		Cy	**4l**	2	**5l** 36[c]
13		*t*-Bu	**4m**	5	**5m** -[c,d]
14		3-MeO-C_6H_4	**4n**	2.5	**5n** 87
15	4-Cl-C_6H_4	4-Me-C_6H_4	**4o**	1.5	**5o** 85
16		4-F-C_6H_4	**4p**	2	**5p** 87
17		4-MeO_2C-C_6H_4	**4q**	2.5	**5q** 75
18	3-MeO-C_6H_4	3-CF_3-C_6H_4	**4r**	2.5	**5r** 72
19		4-F-C_6H_4	**4s**	4	**5s** 83
20	4-MeCO-C_6H_4	4-Cl-C_6H_4	**4t**	2	**5t** 81
21		4-MeO-C_6H_4	**4u**	2.5	**5u** 70
22	*n*-C_5H_{11}	Ph	**4v**		**5v** -[c,e]
23		4-MeO-C_6H_4	**4w**		**5w** -[c,f]

[a]Unless otherwise stated, reactions were carried out on a 0.25 mmol scale using 0.05 equiv of CuI, 0.05 equiv of DMEDA, 2 equiv of K_2CO_3 in 2.5 mL of DMSO at 80 °C
[b]Yields are given for isolated products - [c]NaO-t-Bu (2 equiv) was used instead of K_2CO_3
[d]4m was recovered in 90% yield - [e]1v was recovered in 92% yield - [f]4w was recovered in 91% yield

Tab. 4 - Synthesis of 1,2-disubstituted 4-quinolones from 1-(2-chlorophenyl)-3-enaminones[a]

Entry	Enaminone **4** (X = Br) R^1	R^2		Time (h)	Yield (%)[b] of **5**
1		Ph	**4x**	6	**5a** 95
2		4-MeO-C_6H_4	**4y**	7	**5c** 83
3	Ph	4-MeCO-C_6H_4	**4z**	3	**5d** 83
4		4-Cl-C_6H_4	**4za**	3	**5i** 92
5		*n*-Bu	**4zb**	4	**5j** 89

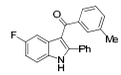
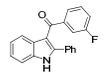
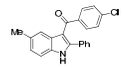
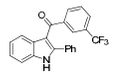
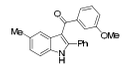
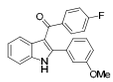
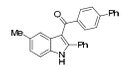
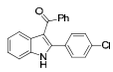
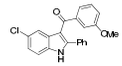
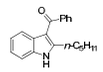
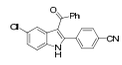
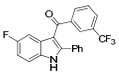
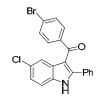
[a]Unless otherwise stated, reactions were carried out on a 0.25 mmol scale using 0.05 equiv of CuI, 0.05 equiv of DMEDA, 2 equiv of K_2CO_3 in 2.5 mL of DMSO at 80 °C
[b]Yields are given for isolated products - [c]NaO-t-Bu (2 equiv) was used instead of K_2CO_3

of preformed indole derivatives [18]. The direct construction of the 3-acylindole skeleton from acyclic precursors has received less attention. We showed that treatment of *N*-(2-haloaryl)enaminones **7**, prepared as outlined in Scheme 11, with CuI and 1,10-phenanthroline as ligand at 100 °C in DMF provides a convenient entry into this class of compounds. A variety of 3-acylindoles can be prepared in high to excellent yields. Several useful functionalities are tolerated, including ether, keto, cyano, bromo, and chloro substituents (Tab. 5). This indole synthesis can also be carried out through a process that omits the isolation of the enaminone intermediates. Excellent results can be obtained by adding CuI, 1,10-phenanthroline, K_2CO_3, and DMF to the crude mixture derived from the reaction of 2-iodoanilines with α,β-ynones after evaporation of the volatile materials (Scheme 12).

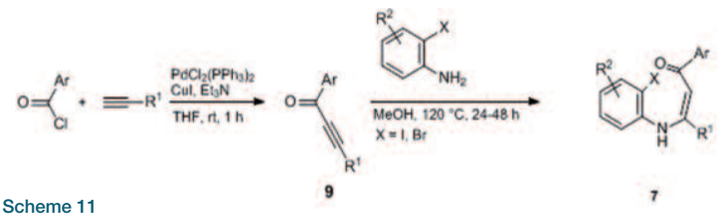
A reasonable mechanism for this indole ring formation (Scheme 13) begins with the initial coordination of carbon with copper. The resulting complex **F** undergoes an oxidative addition of the C-X bond to copper to afford the Cu(III) intermediate **G**. Subsequent reductive elimination releases the product with concomitant regeneration of the Cu(I) species.

Another possible mechanism involves the formation of **G** via oxidative addition of the C-I bond to CuI to produce a Cu(III) intermediate followed by nucleophilic displacement of iodide by the anionic fragment.

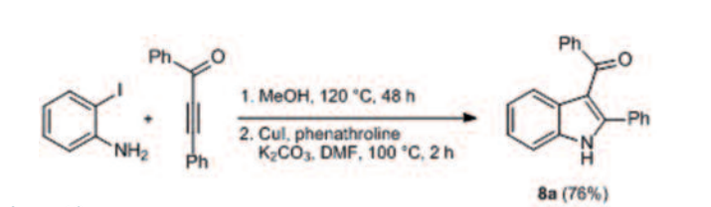
Tab. 5 - Synthesis of 3-acylindoles 8 via copper-catalyzed cyclization of N-(2-Iodoaryl)enaminones 7[a]

Entry	Product		Time (h)	Yield[b] %	Entry	Product		Time (h)	Yield[b] %
1		**2a**	2.5	92	8		**2h**	13	86
2		**2b**	5	95	9		**2i**	8	88
3		**2c**	3.5	93	10		**2j**	4	96
4		**2d**	10	96	11		**2k**	8	88
5		**2e**	10	91	12		**2l**	3	91
6		**2f**	3	87	13		**2m**	2	93
7		**2g**	4	89	14		**2n**	6	92

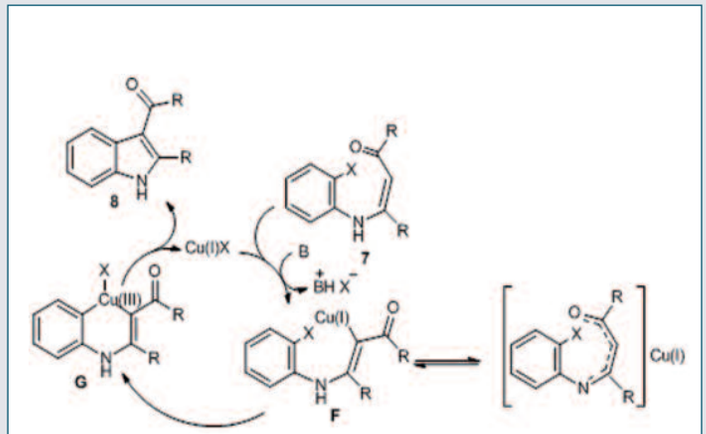
[a]Reaction were carried out at 100 °C on a 0.25 mmol scale using 0.05 equiv. of CuI, 0.05 equiv. of 1,10-phenantroline, 2 equiv. of K_2CO_3 in 2.5 mL of DMF
[b]Yield are given for isolated products



Scheme 11



Scheme 12



Scheme 13

References

[1] For recent reviews, see: a) , A.-Z.A.Elassar, A.A. El-Khair, *Tetrahedron*, 2003, **59**, 8463; b) B. Stanovnik, J. Svete, *Chem. Rev.*, 2004, **104**, 2433.

[2] For some recent references, see: a) C. Tietcheu *et al.*, *J. Heterocyclic Chem.*, 2002, **39**, 965; b) J.D. White, D.C. Ihle, *Org. Lett.*, 2006, **8**, 1081; c) E. Bellur, P. Langer, *Tetrahedron Lett.*, 2006, **47**, 2151; d) M.C. Cruz *et al., Synlett*, 2006, 749; e) U. Ursic *et al., Synthesis*, 2006, 2376; f) F.A. Davis *et al., J. Org. Chem*,. 2007, **72**, 2046; g) S. Yan *et al., Synlett*, 2007, 2699.

[3] For some recent references, see: a) R.K Vohra *et al., Adv. Synth. Catal*., 2006, **348**, 2571; b) H.-Y. Hu *et al., Synlett*, 2006, 1913; c) N. Nishiwaki *et al., Synlett*, 2006, 1437; d) M. Pešková *et al., Organometallics*, 2006, **25**, 2025; e) S. Tu *et al., Org. Biomol. Chem*., 2006, **4**, 3664;

f) J. Huang *et al., Org. Lett*., 2007, **9**, 5345; g) S. Tu *et al., J. Comb. Chem*., 2007, **9**, 1144; h) X.-M. Cheng, X.-M. Liu, *J. Comb. Chem*., 2007, **9**, 906; i) S. Cunha *et al., Tetrahedron Lett*., 2007, **48**, 5795; j) D. Xiang *et al., J. Org. Chem*., 2007, **72**, 8593.

[4] a) A. Osuka *et al., Chem. Lett.*, 1982, 2031; b) S.C. Yang *et al., Heterocycles*, 1991, **32**, 2399; c) D. Gravestock, M.C. Dovey, *Synthesis*, 2003, 523; d) D. Gravestock, M.C. Dovey, *Synthesis,* 2003, 1470.

[5] For some selected Pd-catalyzed reactions, see: a) H. Iida *et al., J. Org. Chem*., 1980, **45**, 2938; b) A. Kasahara *et al., Bull. Chem. Soc. Jpn*., 1986, **59**, 927; c) T. Sakamoto *et al., Synthesis*, 1990, 215; d) J.P. Michael *et al., Tetrahedron Lett*., 1993, **34**, 8365; e) K. Koerber-Plé, G. Massiot, *Synlett*, 1994, 759; f) L.-C. Chen *et al., Synthesis*, 1995, 385; g) E.J. Latham, S.P. Stanfoth, *Chem. Commun*., 1996, 2253; h) E.J. Latham, S.P. Stanfoth, *J. Chem. Soc., Perkin Trans*. 1 1997, 2059; i) Y. Blache *et al., J. Org. Chem.*, 1997, **62**, 8553; j) S.D.Edmonson *et al., Org. Lett*., 2000, **2**, 1109; k) K. Yamazaki, Y. Kondo, *J. Comb. Chem*. 2002, **4**, 191; l) K. Yamazaki *et al., J. Org. Chem*., 2003, **68**, 6011; m) U.S. Sorensen, E. Pombo-Villar, *Helv. Chim. Acta*, 2004, **87**, 82; n) B. Dajka-Halász *et al., Tetrahedron*, 2004, **60**, 2283. For Cu-catalyzed reactions, see: o) S. Yan *et al., Synlett*, 2007, 2699. For Au-catalyzed reactions, see: p) A. Arcadi *et al., Tetrahedron: Asymmetry*, 2001, **12**, 2715. For Ag-catalyzed reactions, see: q) R.S. Robinson *et al., Tetrahedron Lett*., 2004, **45**, 6787.

[6] For recent reviews, see: a) S.V. Ley, A.W. Thomas, *Angew. Chem*., 2003, **115**, 5558; b) G. Evano *et al., Chem. Rev*., 2008, **108**, 3054; c) C. Deutsch *et al., Chem. Rev.*, 2008, **108**, 2916; d) S. Reymond, J. Cossy, *Chem. Rev*., 2008, **108**, 5359; e) A. Alexakis *et al., Chem. Rev.*, 2008, **108**, 2796; f) K.I. Yamada, K. Tomioka, *Chem. Rev*., 2008, **108**, 2874; g) L.M. Stanley, M.P. Sibi, *Chem. Rev*., 2008, **108**, 2887; h) M. Shibasaki, M. Kanai, *Chem. Rev*., 2008, **108**, 2853; i) M. Carril *et al., Chem. Soc. Rev*., 2008, **37**, 639.

[7] a) S. Cacchi, G. Fabrizi, *Chem. Rev.*, 2005, **105**, 2873; b) S. Cacchi, G. Fabrizi, *Chem. Rev.*, 2011, **111**, 215; c) S. Cacchi *et al., Org. Lett.*, 2003, **5**, 3843.

[8] S. Cacchi *et al., Org.Lett.*, 2008, **10**, 2629.

[9] A.S. Karpov, T.J. Muller, *Org. Lett.*, 2003, **5**, 3451.

[10] For some selected references, see: a) K. Shin, K. Ogasawara, *Synlett*, 1996, 922; b) Y. Kondo *et al., J. Org. Chem.*, 1997, **62***,* 6507; c) A. Arcadi *et al., Synlett*, 1998, 446; d) A.L. Rodriguez *et al., Angew. Chem. Int. Ed.*, 2000, 39*,* 2488; e) W.-M. Dai *et al., Tetrahedron Lett.*, 2002, **42**, 7699; f) C. Koradin *et al., Tetrahedron*, 2003, **59**, 1571; g) N. Suzuki *et al., Chem. Pharm. Bull.*, 2003, **51**, 1170; h) S.H. Wattreson *et al., Bioorg. Med. Chem. Lett.*, 2003. **13**, 1273; i) L.-P. Sun *et al., Tetrahedron*, 2004, **60**, 10983.

[11] a) J.E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 738; b) J.E. Baldwin *et al., J. Org. Chem.*, 1977, **42**, 3846.

[12] a) F. Messina *et al., Tetrahedron: Asymmetry*, 2000, **11**, 1681; b) C. Ma *et al., J. Org. Chem.*, 2001, **66**, 4525; c) K. Hiroya *et al., Tetrahedron Letters*, 2002, **43**, 1277; d) S. Cacchi *et al., Org. Lett.*, 2003, **5**, 3843; e) K. Hiroya *et al., Tetrahedron*, 2005, **61**, 10958. See also: f) D.W. Macomber, M.D. Rausch, *J. Am. Chem. Soc.*, 1983, **105**, 5325.

[13] R. Bernini, *et al., Synlett*, 2009, 1209.

[14] L.-J. Huang *et al., Bioorg. Med. Chem.*, 1998, **6**, 1657.

[15] R. Bernini *et al., Synlett,* 2009, 1480.

[16] W.F.A., Wijsmuller *et al., Heterocycles*, 1986, **24**, 1795.

[17] a) M.R. Bell *et al., J. Med. Chem.*, 1991, **34**, 1099; b) T.E. D'Ambra *et al., J. Med. Chem.*, 1992, **35**, 124; c) G.S. Sheppard *et al., J. Med. Chem.*, 1994, **37**, 2011; d) M. Lehr, *J. Med. Chem.*, 1997, **40**, 2694; e) M.L. Curtin *et al., J. Med. Chem.*, 1998, **41**, 74.

[18] For the acylation of N-protected indoles, see: a) D.M. Ketcha, G.W. Gribble, *J. Org. Chem*., 1985, **50**, 5451. For the acylation of NH free indoles, see: b) O. Otton *et al., Org. Lett.*, 2001, **7**, 1005. For the preparation of 3-acylindoles via the Vilsmeier-Haack reaction, see: c) R.J. Sundberg, The Chemistry of Indoles, Academic Press: New York, 1970. For the acylation of indole Grignard reagents, see: d) R.A. Heacock, S. Kasparek, *Adv. Heterocycl. Chem.*, 1969, **10**, 61. Ref. 3c. For the acylation of 3-indolylzinc chlorides, see: e) J. Bergman, L. Venemalm, *Tetrahedron*, 1990, **46**, 6061; f) M.M. Faul, L.L. Winneroski, *Tetrahedron Lett.*, 1997, **38**, 4749. For other procedures, see: g) J. Bergman *et al., Tetrahedron*, 1973, **29**, 971; h) S.C. Eyley *et al., Tetrahedron Lett*., 1985, **26**, 4649; i) U. Pindur, *et al., Liebigs Ann. Chem.*, 1986, **9**, 1621; j) L. Pfeuffer *et al., Chem. Zeitung*, 1987, **111**, 84.

RIASSUNTO

Uso di β-enamminoni nella sintesi rame-catalizzata di composti eterociclici

I β-enamminoni, argomento di ricerca di continuo interesse, sono intermedi sintetici versatili in quanto dotati sia di carattere bidentato di tipo elettrofilo (nella porzione enonica), che nucleofilo (nella porzione enamminica). Queste proprietà elettroniche ne permettono l'uso in molte reazioni intra- e intermolecolari. L'accurata progettazione della loro struttura può consentire di ottenere diverse classi di composti eterocicli attraverso la catalisi dei metalli di transizione.