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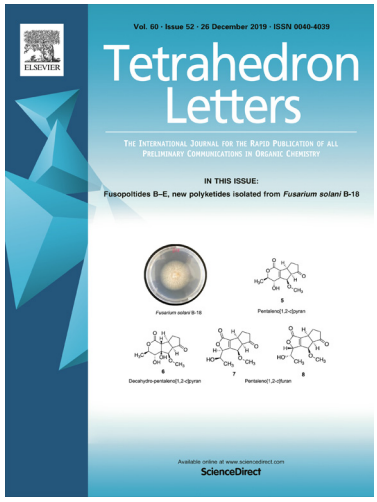

Tandem synthesis of highly functionalized 1,2,3-benzotriazines from isocyanides, aniline and dialkyl azadicarboxylate *via* Cu-catalyzed intramolecular C-H activation reactions

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Tandem synthesis of highly functionalized 1,2,3-benzotriazines from isocyanides, aniline and dialkyl azadicarboxylate *via* Cu-catalyzed intramolecular C-H activation reactions

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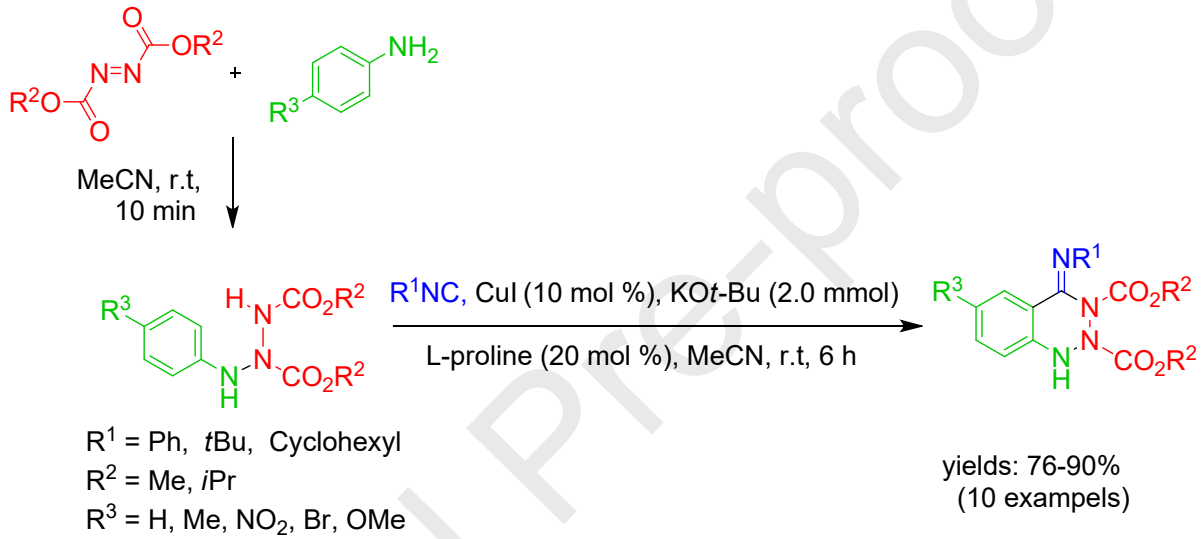

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Tandem synthesis of highly functionalized 1,2,3-benzotriazines from isocyanides, aniline and dialkyl azadicarboxylate *via* Cu-catalyzed intramolecular C-H activation reactions

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ABSTRACT

A class of substituted 1,2,3-benzotriazines are obtained in tandem mode reaction by means of Cu-catalyzed intramolecular C-H activation of aniline, isocyanides and dialkyl azadicarboxylate in acetonitrile at room temperature in good yields. The speed and ease of carrying out this three-component reaction under mild one-pot conditions with available materials, without using column chromatography, make it a method of choice to synthesize substituted 1,2,3-benzotriazines derivatives.

Tandem synthesis of highly functionalized 1,2,3-benzotriazines from

Triazines are heterocyclic compounds with three nitrogen atoms that form benzotriazines by bonding to benzene ring [1]. The two possible isomers of benzotriazine (1,2,3-benzotriazines and 1,2,4-benzotriazines) are of great importance in pharmaceutical chemistry and pesticides because of their wide spectrum of action [2]. For example, azinphos-ethyl and azinphos-methyl are commonly used in agriculture as acaricides (see Figure 1) [1]. 1,2,3-Benzotriazine compounds have attracted considerable attention due to potential pharmacological properties, such as diuretic, sedative, anti-arthritis, analgesic, antineoplastic, hypoxia-selective cytotoxicity, fungicide and anti-

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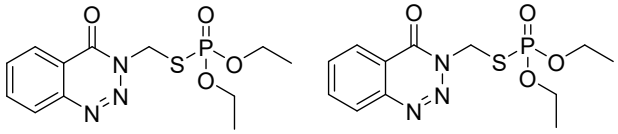
chemistry [3-10]. Some of 1,2,3-benzotriazines are considered as the HBp-3 area (hydrogen bond point area) on well-known GABAA receptor in the benzodiazepine site [11]. Additionally, these compounds exhibit inhibitory activity against the VEGFR-2 kinase and the proliferation of human microvascular endothelial cells (MVECs) [12].

Numbers of method have been reported for the synthesis of these scaffolds that mainly require toxic reagents, costly

catalysts, harsh conditions and difficult multi-step processes [13-17]. Therefore, the further development of novel high performance methods for the synthesis of 1,2,3-benzotriazine is still valuable.



azinphos-ethyl azinphos-methyl

Figure 1. acaricide with benzotriazine structure

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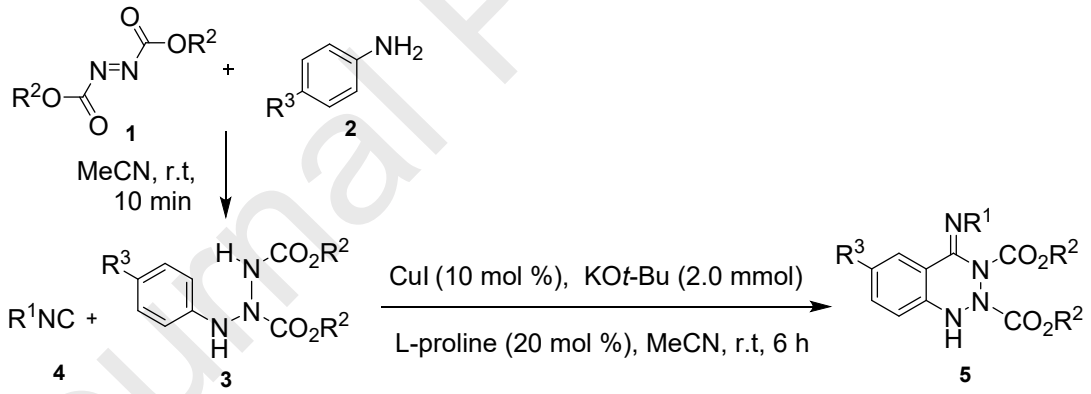
have previously been reported. The intramolecular heterofunctionalization of sp^2 C–H bond in the aromatic ring is perfect strategy achieving complex fused-ring heterocycles, especially for those containing nitrogen with higher atom efficiency, and easy synthetic approach [18-21].

Our research team have been discovered a novel multicomponent reactions (MCRs) to prepare new heterocyclic compounds by Cu(I)-catalyzed C-H activation [22-25]. Continuing our previous work and taking into account the importance of the 1,2,3-benzotriazine scaffold, we developed a three-component, tandem reaction of isocyanides, aniline and dialkyl azadicarboxylate in MeCN at room temperature using the catalyst activation reaction catalyzed by Cu (see Scheme 1). The developed method was run under mild conditions, with simple processing and purification, available low-cost starting reagents and catalysts, and more purified products.

This study included the synthesis of substituted 1,2,3-benzotriazine derivatives using a copper-catalyzed C-H activation reactions. The reaction conditions were optimized based on a preliminary experiment in which structurally diverse aniline **2a** (1.0 mmol), dialkyl azadicarboxylate **1a** (1.0 mmol) and isocyanides **4a** (1.5 mmol) were reacted in the presence of a copper catalyst. The optimization results are presented in Table 1. Various catalysts, bases and solvents were used to maximize yield. A relatively good yield was obtained from different tested catalysts, bases and solvents when the reaction was carried out in acetonitrile (MeCN), at room temperature and in the presence of $Cu^{(I)}$ iodide (10 mol%) as a catalyst, L-proline (20 mol%) as a ligand and KO*t*-Bu (2.0 mmol) as the base.



Scheme 1. Synthesis of various 1,2,3-benzotriazine derivatives

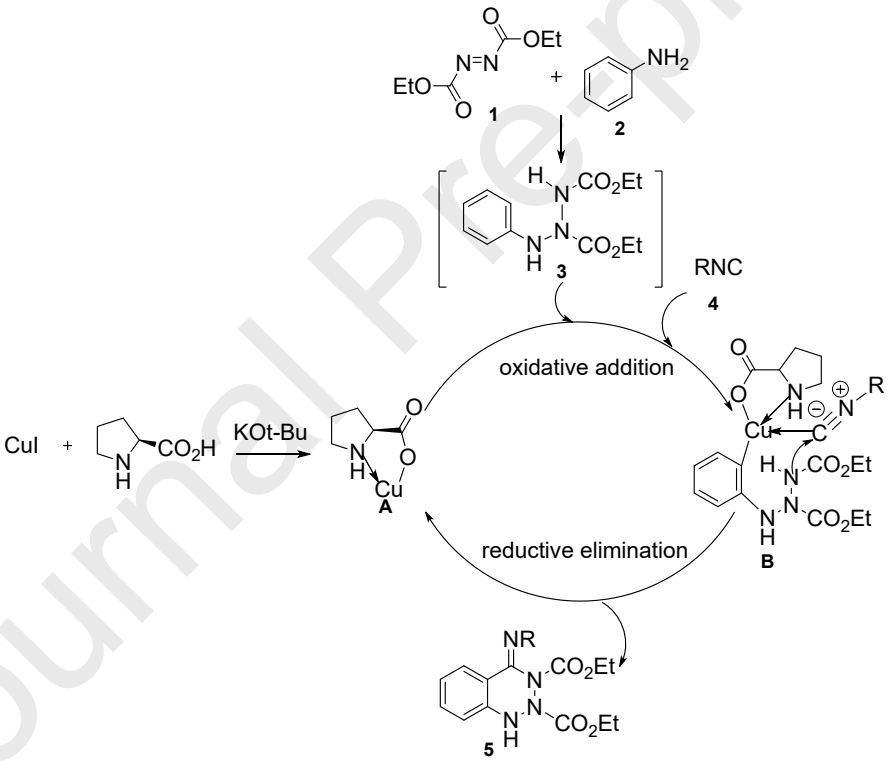
Table 1 Optimization of reaction conditions for the formation of product 5a from 1.5 mmol of isocyanides, 1.0 mmol of diethyl azadicarboxylate, 1.0 mmol of aniline, 10 mol % of copper salt as the catalyst and 2.0 mmol of the base, 20 mol % of L-proline at room temperature

Entry	Catalyst	Solvent	Base	Yield (%)[a]
1[b]	CuI	MeCN	KO*t*-Bu	83
2	CuI	MeCN	NaOH	62
3	CuI	DMF	Cs_2CO_3	69
4	CuI	DMF	KO*t*-Bu	72
5	CuI	THF	KO*t*-Bu	78
6	CuCl	THF	K_2CO_3	41
7	CuCl	THF	KOH	34

9	CuBr	MeCN	KO*t*-Bu	69
10	CuBr	DMF	KOH	38
11	CuBr	DMF	NaOH	35
12	CuBr	THF	KO*t*-Bu	60
13	$Cu(OAc)_2$	MeCN	KO*t*-Bu	37
14	$Cu(OAc)_2$	DMF	Cs_2CO_3	21
15	$Cu(OAc)_2$	THF	KO*t*-Bu	30
16	$CuSO_4$	THF	K_2CO_3	22
17	$CuSO_4$	MeCN	Cs_2CO_3	20
18	$CuSO_4$	THF	KO*t*-Bu	12

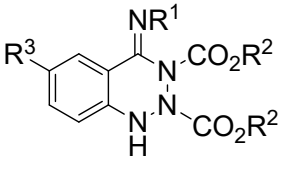
[a] Reaction time 6 h

[b] 5 mol% catalyst, reaction time was 11 h



Scheme 2 Possible formation mechanism of compounds **5**

Table 2 Synthesis of various 1,2,3-benzotriazine derivatives



Compound	R^1	R^2	R^3	Yield of 5 (%)

5a				
5b	*t*-Bu	Et	Br	85
5c	Ph	Et	Me	79
5d	*t*-Bu	Et	NO_2	90
5e	*t*-Bu	Et	H	81
5f	Cy	*i*-Pr	H	80
5g	Cy	*i*-Pr	Me	78
5h	Ph	*i*-Pr	H	82
5i	*t*-Bu	*i*-Pr	OMe	76
5j	*t*-Bu	*i*-Pr	Me	77

Finally, ten analogs of 1,2,3-benzotriazine derivatives were synthesized according to the synthetic route shown in Table 1, from CuI as the catalyst, KO*t*-Bu as the base, L-proline as the ligand, isocyanides (aliphatic and aromatic), dialkyl azadicarboxylate, and anilines with a various of substituents (electron-withdrawing or electron-donating) on the aromatic rings (see Table 2).

As shown in scheme 2, it appears that the reaction of CuI with L-proline gives a five-membered chelate A. Oxidative addition of the chelated Cu (I) with the NH moiety of nucleophilic adduct 3 (generated from dialkyl azadicarboxylate 1 and aniline 2) affords the isocyanide stabilized intermediate B that may coordinate to Cu. Reductive elimination of B allowed to obtain product 5, leaving chelate A and the catalyst.

All structures were verified using Infrared, ^{1}H-NMR, ^{13}C-NMR, and Mass spectroscopy methods. For example, the ^{1}H-NMR spectrum of compound **5a** exhibited one singlet for NH group (δ = 6.00 ppm) together with a cluster of characteristic signals in the aromatic zone for the aromatic C-H bonds. The ^{13}C NMR spectrum of compound **5a** showed 17 signals in accordance with the proposed structure. The NMR spectra of other analogues were similar to spectra **5a**. The signal of molecular ion 5a was shown at m/z = 368 and the fragmentation pattern corresponded to the favored structure.

Conclusion

In summary, this article presented a simple, effective synthesis method in which a new, one-pot, three-component protocol via intramolecular C-H activation reaction of isocyanides, aniline and dialkyl azadicarboxylate, catalyzed by copper(I) iodide in MeCN at room temperature with good yields to synthesize 1,2,3-benzotriazine derivatives is described . The most important points of our proposed method were mild conditions, high yields, low temperature, ease of purification and finally time and cost effective procedure

Acknowledgments

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References and notes

[1] Ziarani, G. M.; Mostofi, M.; Lashgari, N. *Curr. Org. Chem.* **2018**, *22*, 2717.
[2]. Fadda, A. A.; Abdel-Latif, E.; Fekri, A.; Mostafa, A. R. *J. Heterocycl. Chem.* **2019**, *56,* 804.
[3] Migawa, M.; Townsend. L. *J. Org. Chem*. **2001**, *66*, 1672.
[4] Migawa, M.; Drach, J.; Townsend. L. *J. Med. Chem.* **2005**, *48*, 3840.
[5] Kelly, J.; Wilson, D.; Styles, V.; Soroko, H.; Hunt, J.; Briggs, E.; Clarke, E.; Whittingham. W. *Bioorg.Med. Chem. Lett*. **2007**, *17*, 5222.
[6] Gadekar, S. M.; Frederick. J. L. *J. Org. Chem*. **1962**, *27*, 1383.
[7] Gadekar, S. M. Ross. E. *J. Org. Chem*. **1961**, *26*, 613.
[8] Kumar, K. S.; Sandra, R. S.; Rambabu, D.; Krishna, G. R.; Reddy, C. M.; Misra, P.; Pal. M. *Bioorg.Med. Chem. Lett*. **2012**, *22*, 1146.
[9] Caliendo, G.; Fiorino, F.; Grieco, P.; Perissutti, E.; Santagada, V.; Meli, R.; Raso, G. M.; Zanesco, A.; Nucci. G. D. *Eur. J. Med. Chem.* **1999**, *34*, 1043.
[10] Xia, Q.; Zhang, L.; Zhang, J.; Sheng, R.; Yang, B.; He, Q.; Hye. Y. Z. *Eur. J. Med. Chem.* **2011**, *46*, 919.
[11] Guerrini, G.; Ciciani, G.; Bruni, F.; Selleri, S.; Melani, F.; Daniele, S.; Martini, C.; Costanzo. A. *Bioorg.Med. Chem. Lett*. **2011**, *19*, 3074.
[12] Zhao, X. W.; Liu, D.; Luan, S. L.; Hu, G. D.; Lv, J. L.; Jing, Y. K.; Zhao. L. X. Bioorg. Med. Chem. **2013**, *21,* 7807.
[13] Colomer, J. P.; Moyano. E. L. *Tetrahedron Lett*. **2011**, *52*, 1561.
[14] Clark, A. S.; Deans, B.; Stevens, M. F. G.; Tisdale, M. J.; Wheelhouse, R. T.; Denny, B. J.; Hartley. J. A. *J. Med. Chem*. **1995**, *38*, 1493.
[15] Fang, Z. J.; Zheng, S. C.; Guo, Z.; Guo, J. Y.; Tan, B.; Liu. X. Y. *Angew. Chem. Int. Ed*. **2015**, *54*, 9528.
[16] Barker, A. J.; Paterson, T. M.; Smalley, R. K.; Suschitzky. H. *J. Chem. Soc. Perkin. Trans 1*. **1979**, 2203.
[17] Yan, Y. Z.; Niu, B.; Xu, K.; Yu, J. H.; Zhi, H. H.; Liu. Y. Q. *Adv. Synth. Catal.* **2016**, *358*, 212.
[18] Godula, K.; Sames. D. *Science* **2006**, *312*, 67.
[19] Alberico, D.; Scott, M. E.; Lautens. M. *Chem. Rev*. **2007**, *107*, 174.
[20] Kakiuchi, F.; Chatani. N. *Adv. Synth. Catal*. **2003**, *345*, 1077.
[21] Ritleng, V.; Sirlin, C.; Pfeffer. M. *Chem. Rev*. **2002**, *102*, 1731.
[22] Nematpour, M.; Rezaee, E.; Tabatabai, S. A.; Jahani. M. *Synlett* **2017**, *12*, 1441.
[23] Nematpour, M.; Rezaee, E.; Jahani, M.; Tabatabai. S. A. *Tetrahydron Lett.* **2018**, *59*, 2054.
[24] Nematpour, M.; Rezaee, E.; Jahani, M.; Tabatabai. S. A. *J. Iran. Chem. Soc.* **2019**, *16*, 603.
[25] Nematpour, M.; Rezaee, E.; Jahani, M; Tabatabai, S. A. *Ultrason. Sonochem*. **2019**, 50, 1.

Supplementary Material

Supplementary data to this article can be found online at