

A convenient new synthesis of fused 1,2,4-triazoles: the oxidation of heterocyclic hydrazones using copper dichloride

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Received 13 October 2004; revised 26 January 2005; accepted 27 January 2005

Available online 10 May 2005

Abstract—A series of 1,2,4-triazoles have been prepared by oxidative intramolecular cyclization of heterocyclic hydrazones with copper dichloride. General applicability of this simple transformation was confirmed by the synthesis of moderate to high yields of 1,2,4-triazolo[4,3-*a*]pyridines, 1,2,4-triazolo[4,3-*a*]pyrimidines, 1,2,4-triazolo[4,3-*b*]pyridazines, 1,2,4-triazolo[4,3-*a*]phthalazines, and 1,2,4-triazolo[4,3-*a*]quinoxalines. A 1,2,4-triazolo[4,3-*e*]purine-6,8(7*H*)-dione was obtained in a lower yield.

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1. Introduction

Triazoles are an important class of heterocyclic compounds. In particular, fused 1,2,4-triazoles **1–5** (Fig. 1) express antifungal,¹ bactericidal,^{1,2} anxiolytic,^{3,4} anticonvulsant⁵ or herbicidal⁶ activities or can act as antidepressants.⁷ Therefore, versatile and widely applicable methods for the synthesis of **1–5** are of considerable interest. Most methods for the preparation of **1–5** are based on heterocyclic hydrazones or hydrazides as precursors. However, these methods have some restrictions as regards their applicability and the use of toxic reagents like lead tetraacetate,^{8,9} bromine^{9,10} or phosphorus oxychloride.⁸ In order to overcome these limitations, the oxidant chloramine T¹¹ and (diacetoxy)iodobenzene^{12,13} as well as an electrochemical method¹⁴ have been introduced.

Recently, we have shown that heterocyclic substituted imines undergo copper-catalyzed oxidation, thus forming imidazo[1,5-*a*]pyridines, imidazo[1,5-*a*]imidazoles, and imidazo[1,5-*a*]isochinolines using the nonhazardous, less toxic, and inexpensive reagent copper dichloride.^{15,16}

As part of our ongoing studies dealing with copper(II) in synthesis, we now describe a novel copper-mediated oxidative heterocyclization of hydrazones yielding the corresponding 1,2,4-triazoles (Scheme 1).

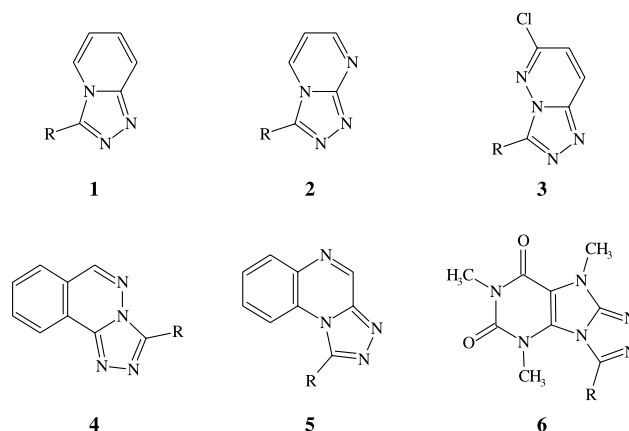
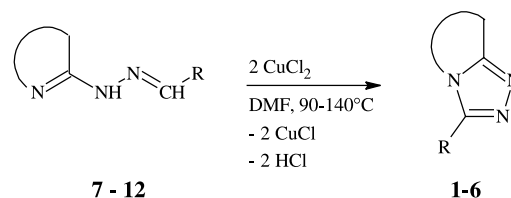


Figure 1.



Scheme 1.

2. Results and discussion

The synthesis of 1,2,4-triazolo derivatives from hydrazones has a remarkably wide scope of application. Hydrazones of aromatic and aliphatic aldehydes **7–11** (Fig. 2) with both electron-withdrawing and electron-donating substituents

Keywords: Oxidation; Copper; Hydrazones; 1,2,4-Triazoles.

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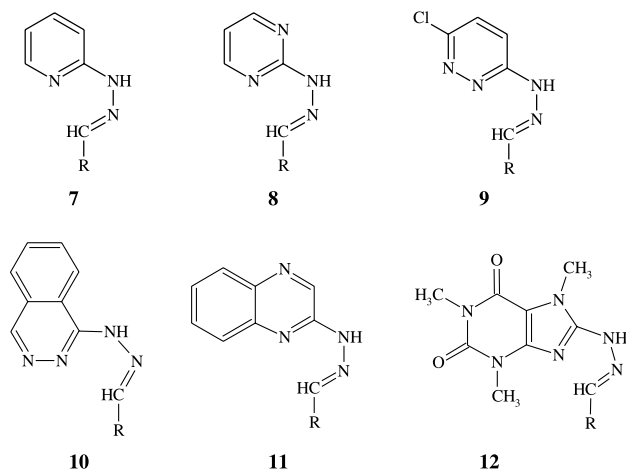


Figure 2.

were oxidized to give the corresponding 1,2,4-triazolo[4,3-*a*]pyridines **1**, 1,2,4-triazolo[4,3-*a*]pyrimidines **2**, 1,2,4-triazolo[4,3-*b*]pyridazines **3**, 1,2,4-triazolo[4,3-*a*]phthalazines **4**, and 1,2,4-triazolo[4,3-*a*]quinoxalines **5** in high yields (Table 1). Heterocyclization of **12a** was achieved in the same way, but the yield of the 1,2,4-triazolo[4,3-*e*]purine-6,8(7*H*)-dione **6a** was rather poor.

The required hydrazones **7–12** were obtained by treating the corresponding hydrazino heterocycles with aldehydes.

Heterocyclization was carried out in absolute DMF under argon. After the hydrazone had been dissolved, a solution of two equivalents of copper dichloride was added and then, the mixture was heated. The reaction had been completed when its initially brown color turned to yellow due to reduction of the copper(II) ions to copper(I). Isolation of the 1,2,4-triazolo compounds **1–5** was easily carried out. The solvent was distilled off in vacuum, and the residue was treated with an aqueous solution of ammonia in order to remove the copper ions as a water-soluble complex. Then, the precipitated crude products were filtered off and pure 1,2,4-triazolo compounds **1–5** were obtained by recrystallization. Only 1,2,4-triazolo[4,3-*e*]purine-6,8(7*H*)-dione **6a** had to be separated from impurities by column chromatography.

Triazoles **1a**,¹⁷ **1b**,¹⁷ **1d**,¹⁴ **2a**,^{18,19} **3a**,²⁰ and **5b**,²¹ have already been described. Their melting points agree with

those reported in the literature except for **1d** and **2a**. Nevertheless, spectroscopic data of these compounds confirm the structure proposed and are listed in the experimental section. The conditions applied for the synthesis of each compound are listed in Table 1.

Comparison of the reactivities of the tested hydrazones indicates that the cyclization is not strongly affected by the substituent R. The reactivity to copper dichloride remains unchanged when the phenyl group in the hydrazones is replaced by an *n*-alkyl residue. In addition, hydrazones of donor-substituted benzaldehydes (R = 2,3-dimethoxy-phenyl and 4-hydroxy-phenyl) and those bearing an acceptor substituent (R = 2-chloro-phenyl and 4-nitro-phenyl) yielded triazoles under similar conditions. Functionalities of the substrate are maintained, even when substituents susceptible to oxidation, e.g. a hydroxy group, are considered. On the other hand, the influence of the nature of the heterocyclic moiety is more significant. If the –NH–N=CH group is attached to a six-membered nitrogen-containing ring, the triazoles are obtained in a smooth reaction. The lower selectivity in the oxidation of **12** indicates that a five-membered ring is less favorable. However, the difficulties of the heterocyclization of **12** could also be caused by the sterically demanding effect of the methyl group at position 5 or by a stabilized intermediate of the radical-based reaction. Investigations concerning mechanistical studies are still in progress.

Unlike heterocyclic aldimines,¹⁵ the hydrazones **7–12** could not be oxidized by atmospheric oxygen in the presence of catalytic amounts of copper(II)chloride. Copper(I)complexes of substituted hydrazones are not able to coordinate oxygen in order to form copper(II)species and are likely to decompose. Thus, reactive intermediates for a copper-catalyzed oxidative cyclization are not generated.

3. Conclusion

In conclusion, we have developed a convenient and simple method for the preparation of a wide variety of 1,2,4-triazolo compounds by oxidation of heterocyclic substituted hydrazones using copper dichloride as oxidation agent. Besides, the presence of several functionalities in the substrate is tolerated and does not influence the yield of the resulting 1,2,4-triazole. Our current studies are directed to

Table 1. Triazolo (**1–6**) compounds from the reaction of heterocyclic hydrazones (**7–12**) with copper dichloride

Hydrazone	R	Time (h)	Temp. (°C)	Triazole	Yield (%)	mp (°C)
7a	4-Chloro-phenyl	1.0	90	1a	60	198–199
7b	2-Chloro-phenyl	1.0	90	1b	57	130–132
7c	4-Hydroxy-phenyl	1.0	90	1c	71	249–250
7d	4-Nitro-phenyl	1.0	100	1d	59	312–314
8a	4-Chloro-phenyl	1.0	110	2a	63	244–245
8b	3,4-Dimethoxy-phenyl	1.0	110	2b	43	207–209
9a	4-Chloro-phenyl	1.0	130	3a	72	197–198
9b	3,4-Dimethoxy-phenyl	1.5	120	3b	62	235–237
10a	2-Chloro-phenyl	0.5	140	4a	74	214–216
11a	4-Chloro-phenyl	1.0	100	5a	72	192–194
11b	<i>n</i> -Propyl	0.75	100	5b	61	149–153
11c	3,4-Dimethoxy-phenyl	0.5	90	5c	84	262–263
12a	<i>n</i> -Propyl	0.75	100	6a	15	205–208 (dec.)

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