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Facile synthesis of 3,5-diaryl-1,2,4-triazoles via copper-catalyzed domino nucleophilic substitution/oxidative cyclization using amidines or imidates as substrates

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ABSTRACT

Two methods for the synthesis of 3,5-diaryl-1,2,4-triazoles, both domino reactions, are reported. The first procedure, the $Cu(OTf)_2$-catalyzed reaction between two amidines using $NaHCO_3$ as a base, 1,10-phenanthroline as an additive and $K_3[Fe(CN)_6]$/atmospheric oxygen as the oxidant, delivers 3,5-diaryl-1,2,4-triazoles with yields up to 68%. The second procedure for the synthesis of 3,5-diaryl-1,2,4-triazoles with yields up to 64% rests on the $Cu(OTf)_2$-catalyzed reaction between two imidates and ammonium carbonate. This method features the formation of three bonds in a single synthetic step.

1. Introduction

Currently, the synthesis of heterocycles is receiving a strong impetus from copper-catalysis.[1,2] The main reasons are that copper-catalyzed cross couplings, such as the arylation between aryl halides and different nucleophiles, can be successfully performed under relatively mild reaction conditions, are highly selective, tolerate a wide range of functional groups and use cheap reagents.[3] Another advantage is that copper-catalyzed cross couplings can be coupled with numerous other transformations to new domino processes. In particular, the combination of copper-catalyzed C-, N-, O- and S-arylations with copper-catalyzed oxidations[4] opens up new prospects for the selective and efficient synthesis of heterocycles in one pot.

1,2,4-Triazoles are important heterocycles since they exhibit a wide range of significant biological activities, including antifungal, antibacterial, anticancer, antimicrobial and anticonvulsant activities.[5,6] More recently, it has been reported that symmetrical triazoles like the trisubstituted compound **A** are effective in inhibiting the replication of the hepatitis C virus (Fig. 1).[7a] Trisubstituted 1*H*-1,2,4-triazoles **B** are compounds with promising antimycobacterial and antimicrobial activities.[7b] 3,5-Disubstituted 1,2,4-triazoles act as A_{2A} receptor antagonists[7c] and 3,5-diaryl-1,2,4-triazoles, such as **C** have been identified as selective inhibitors of 11β-hydroxysteroid dehydrogenases type 1.[7d] Of particular interest are compounds like 3-(2-ethylphenyl)-5-(3-methoxyphenyl)-1*H*-1,2,4-triazole (DL111-IT) (Fig. 1, **D**) that has been identified as a non-hormonal antifertility agent.[8] It was demonstrated that DL111-IT inhibits the synthesis of progesterone by inactivation of 3β-hydroxysteroid dehydrogenase that it induces apoptosis in corpus luteum, and inhibits the growth of embryos. In addition, there are also a number of natural products with a 1,2,4-triazole skeleton. Typical examples include the cytotoxic penipanoid A (Fig. 1, **E**), which has been isolated from the marine sediment derived fungus *Penicillium paneum* SD-44,[9] and 1-(β-D-ribofuranosyl)-1,2,4-triazole from the sea urchin *Glyptocidaris crenularis*.[10] 1,2,4-Triazoles and their derivatives also play an important role as ligands in organometallic compounds, as precursors for *N*-heterocyclic carbenes, as ionic liquids and as corrosion inhibitors.[11] This is why the synthesis of 1,2,4-triazoles is a topic receiving much attention.

Over the years, a number of general synthetic methods have been developed for the preparation of the 1,2,4-triazoles.[12] Many of them are based on the intramolecular condensation of acylamidrazones,[13] which can be obtained from amides or thioamides and

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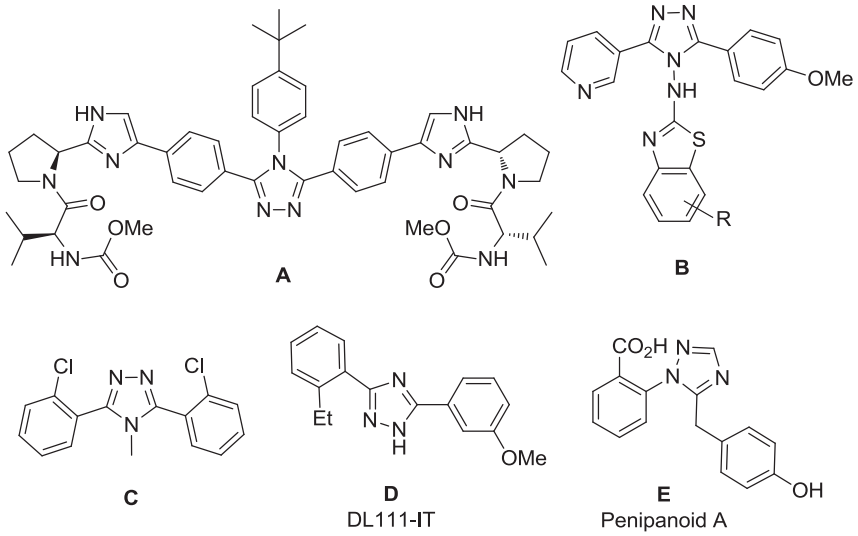


Fig. 1. Selected biologically active compounds with a 1,2,4-triazole core.

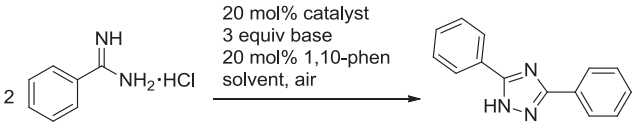
hydrazides (Pellizzari reaction),[14] from diacylamines and hydrazines (Einhorn–Brunner reaction),[15] from 1,2-diacylhydrazines and ammonia,[12e] or the acylation of amidrazones.[16] Recently, 1,2,4-triazoles have been obtained by in situ generation of primary acylamidines and their reaction with hydrazines.[17] More specific, the synthesis of 3,5-diaryl-1,2,4-triazoles can be achieved by Pellizzari reaction,[12–14,18] the reaction between a hydrazide and a nitrile,[19a,b] an imidate,[19c] or an amidine.[19d] Other methods for the synthesis of 3,5-diaryl-1,2,4-triazoles include the reaction between 3,6-diaryl-1,2,4,5-tetrazines with acetonitrile derivatives under basic conditions,[20] the 1,3-dipolar cycloaddition between azodicarboxylates and münchnones, which is accompanied by elimination of carbon dioxide,[21] and the photolysis of 1,3,4-oxadiazoles in alcohols.[22]

In an early study T. Kauffmann et al. reported that 3,5-diphenyl-1,2,4-triazole can be prepared by dimerization of sodium benzamidine with equimolar amounts of CuCl or $CuCl_2$ in 1,2-dimethoxyethane in the presence of oxygen.[23a] However, so far only a few methods are known, which allow for the copper-catalyzed synthesis of 3,5-diaryl-1,2,4-triazoles. Among them is the CuBr-catalyzed one pot reaction between 1.5 equiv of an amidine and 1 equiv of a nitrile using 3 equiv Cs_2CO_3 as the base and aerial oxygen as the oxidant.[23b] Recently, Fu et al. reported on the intramolecular oxidative cyclization of 2,4-diaryl-1,3,5-triazapenta-1,3-dienes to the corresponding 3,5-diaryl-1,2,4-triazoles using elemental copper as the catalyst and oxygen as the oxidant for 48 h at 120 °C.[23c] The 2,4-diaryl-1,3,5-triazapenta-1,3-dienes, which were not isolated were obtained by the copper-catalyzed reaction of two amidines using Cs_2CO_3 as the base under an atmosphere of nitrogen for 24 h at 120 °C. Here, we report a) that both the intermolecular nucleophilic substitution and the copper-catalyzed intramolecular oxidative ring closure to the 3,5-diaryl-1,2,4-triazoles can be performed as a domino reaction under identical reaction conditions and b) that 3,5-diaryl-1,2,4-triazoles can be obtained by a copper-catalyzed domino reaction between two imidates and an ammonium source in a single synthetic operation.

2. Results and discussion

For the transformation between two amidines, the reaction of two molecules benzamidine hydrochloride (**1a**) was chosen as a model. When 1 mmol **1a** was reacted in the presence of 20 mol % CuBr as the catalyst and 3 equiv K_2CO_3 in DMF at 110 °C for 20 h in a sealed vial the required 3,5-diphenyl-1,2,4-triazole (**2a**) was isolated with 17% yield (Table 1, entry 1). The yield of **2a** could be improved slightly to 24% and 27%, respectively, when the model reaction was performed in the presence of 20 mol % 1,10-phenanthroline (1,10-phen) as an additive at 130 °C for 24 h in DMF and *o*-dichlorobenzene, respectively (Table 1, entries 2 and 3). Interestingly, the yield of **2a** could be almost doubled to 53% when CuBr was replaced with $Cu(OTf)_2$ (Table 1, entry 4). A similar yield was observed with $NaHCO_3$ as the base (Table 1, entry 5).

Table 1
Initial experiments for the copper-catalyzed synthesis of 3,5-diphenyl-1,2,4-triazole (**2a**) from benzamidine hydrochloride (**1a**)[a]



Entry	Catalyst	Base	Solvent	*T* (°C)	Time (h)	Yield (%)
1[b]	CuBr	K_2CO_3	DMF	110	20	17
2	CuBr	K_2CO_3	DMF	130	24	24
3	CuBr	K_2CO_3	*o*-Dichlorobenzene	130	24	27
4	$Cu(OTf)_2$	K_2CO_3	*o*-Dichlorobenzene	130	24	53
5	$Cu(OTf)_2$	$NaHCO_3$	*o*-Dichlorobenzene	130	24	50

[a] All reactions were performed using 1 mmol of **1a** in 3 mL solvent in a sealed vial. The temperatures given refer to oil bath temperatures.
[b] The reaction was performed in the absence of 1,10-phenanthroline.

We assumed that the yield of the intramolecular oxidative coupling could be improved by running the reaction with a more suitable oxidant. J. D. Bower and G. R. Ramage have reported that the oxidative ring closure of 2-(2-aminoethyl)pyridine to 1,7a-diazaindene via intramolecular oxidative *N*,*N*-coupling can be achieved by using an aqueous alkaline solution of $K_3[Fe(CN)_6]$ as the oxidant.[24] When benzamidine hydrochloride (**1a**) was reacted with 20 mol % $Cu(OTf)_2$ as the catalyst, 3 equiv $NaHCO_3$ as a base, 20 mol % 1,10-phenanthroline as an additive and 20 mol % $K_3[Fe(CN)_6]$ as the oxidant in *o*-dichlorobenzene at 130 °C for 44 h under air the desired 3,5-diphenyl-1,2,4-triazole (**2a**) was obtained in 59% (Table 2, entry 1). The yield of **2a** was further increased to 63% by shortening the reaction time to 24 h (Table 2, entry 2). The yield failed to improve with K_2CO_3 as the base (Table 2, entry 3). It