1,2,4-Triazole Synthesis via Amidrazones

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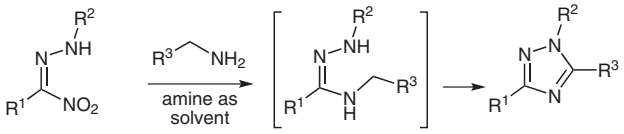
Received 13 April 2010

Abstract: We present a two-step procedure for the synthesis of 1,2,4-triazole derivatives from a primary amide and a hydrazine via an oxidative process.

Key words: triazoles, hydrazone, oxidation

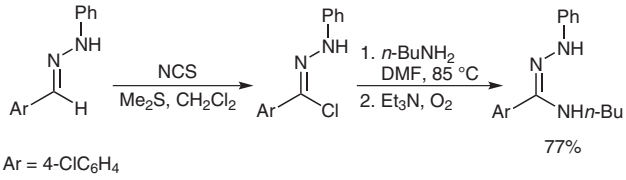
Faced with growing concern about environmental issues, chemists have had to revise many synthetic processes that used one or several equivalents of reagents associated with waste disposal problems. In the case of oxidative processes, this trend has led to shifting from traditional reactions with stoichiometric amounts of metals (chromium, lead, silver) to catalytic transformations using oxygen or peroxides as cooxidants.[1] Thus, recent years have seen a renewed interest in copper- and palladium-catalyzed oxidations.[2] Whenever heterocyclic derivatives are concerned, the formation of aromatic systems is an additional driving force for these reactions and some oxidations may even be observed under air without any metal assistance.[3]



Scheme 1 1,2,4-Triazole access from amidrazones

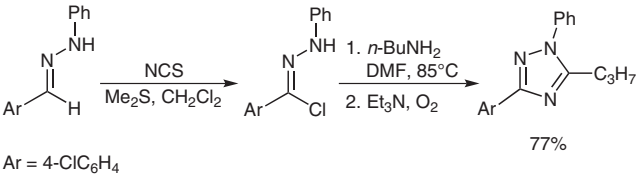
Following our interest in hydrazone chemistry,[4] we reported a few years ago a triazole synthesis based on the coupling of a nitrohydrazone and a primary amine used as solvent (Scheme 1).[5] This process involved multiple oxidation steps from an intermediate amidrazone. Such a transformation had previously been observed on treatment with silver or lead as oxidant,[6] leading us to assume that a key step in the mechanism involved nitrite anion loss. The fact that the yields were raised by the addition of sodium nitrite further endorsed this analysis (Scheme 1).

In order to study this reaction more carefully, we decided to form the intermediate amidrazone using a synthetic path that avoided preparation of the nitrohydrazone[7] and chlorohydrazones were initially investigated.[8] These were generated by the chlorination of the corresponding hydrazones with *N*-chloro succinimide.[6b] The resulting crude chloro hydrazones were then treated with one equivalent of a primary amine in acetonitrile in the presence of two equivalents of triethylamine to form the desired amidrazones (Scheme 2).

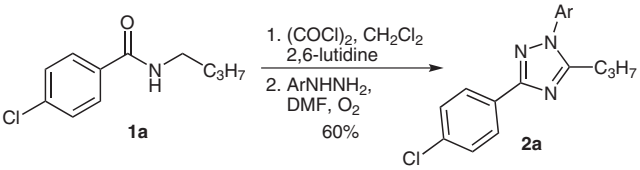


Scheme 2 Amidrazone synthesis from hydrazones

The oxidation process was then evaluated under classical conditions using a base, such as triethylamine and a catalytic amount of $Pd(OAc)_2$ in *N*,*N*-dimethyl formamide (DMF) as solvent at 85 °C. The reaction was performed in an open flask to ensure oxygenation of the reaction mixture. Under these conditions, the corresponding 1,2,4-triazole was isolated in a 96% yield. However, it turned out that the reaction did not require a catalyst as similar results were obtained without adding palladium salts and within the same length of time. The whole sequence was further optimized, leading to a one-pot procedure. For this purpose, after completion of the hydrazone chlorination in dichloromethane, the solvent was removed under reduced pressure. DMF was then added to the crude chlorohydrazone, followed by butylamine and then triethylamine. The resulting mixture was heated for 12 hours to provide the corresponding triazole in 77% yield (Scheme 3). Despite this simple and high-yielding overall procedure, we were not yet fully satisfied, as the reactions were very sensitive to the quality of the amine (distilled or not) and, although

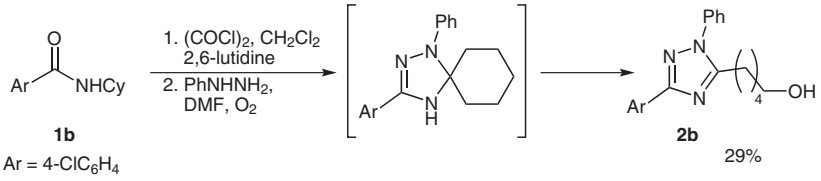


Scheme 3 1,2,4-Triazole synthesis from hydrazones



Scheme 4 1,2,4-Triazole synthesis from primary amides

SYNLETT 2010, No. 12, pp 1771–1774
Advanced online publication: 30.06.2010
DOI: 10.1055/s-0030-1258117; Art ID: D09510ST



Scheme 5 Reactions with α-branched amides

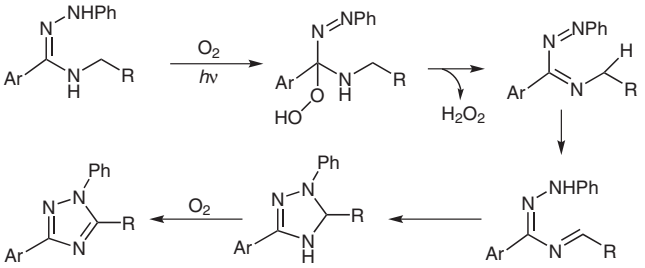
only formed as intermediates, chlorohydrazones are highly allergenic derivatives. As these issues could discourage chemists from using this process, we decided to evaluate alternative strategies.

Amidrazones may also be formed on treatment of imidoyl chlorides with hydrazine derivatives.[9] For this purpose, different sets of conditions – base, solvent, temperature – were tested. The best results were obtained by treating the amide **1a** with 1.3 equivalents of oxalyl chloride and 3 equivalents of 2,6-lutidine in dichloromethane over using 4 Å molecular sieves at 0 °C under argon. After the complete conversion of the starting material, the reaction mixture was diluted with DMF, and one equivalent of the arylhydrazine – pre-dried over potassium carbonate – was added. The resulting solution was stirred at 80 °C under air with protection from moisture for 12 hours. Under these conditions, the resulting 1,2,4-triazole **2a** was isolated in a 60% yield (Scheme 4).

Using this optimized one-pot two-step procedure, various 1,2,4-triazoles were synthesized from the corresponding secondary amides in modest to good yields (Table 1). This reaction gives good results with aromatic amides and tolerates both electron-withdrawing (Table 1, entries 1–8) and electron-donating groups (Table 1, entry 9) on the aromatic core. However, no triazole could be isolated from aliphatic amides (Table 1, entry 10). Tertiary amides do not react either under these conditions.

When the α-branched amide **1b** was involved, we isolated the 1,2,4-triazole **2b** with the aliphatic ring having been opened (Scheme 5). The formation of this product may be explained by the oxidative cleavage of a spiro triazoline intermediate.

Considering the transformation of the amino residue, one might be surprised that an oxidation under such mild conditions could occur. Indeed, α-amino CH_2 groups usually need to be further activated by a aryl group or another electron-donating atom in order to be easily oxidized. The reaction is most probably controlled by the hydrazone moiety. These groups are rather sensitive to oxygen under UV irradiation, yielding hydroperoxides in a radical chain reaction. In the case of amidrazones, the elimination of H_2O_2 forms an azoimine. Further prototropy, cyclization and oxidation finally afford the triazole (Scheme 6).



Scheme 6 Proposed mechanistic pathway

In conclusion, we have described herein a new 1,2,4-triazole synthesis from amidrazones. Based on an open-flask, air-tolerant procedure, the reaction probably starts with a radical oxidative process of the hydrazone moiety.[10] Most interestingly, this reaction implies a formal C–H activation of the amine residue. We are currently exploring the extension of this reaction to a more general C–H activation strategy via the conversion of primary amines to bulky amidrazones reluctant to cyclization.

Table 1 One-Pot Two-Step Triazole Synthesis

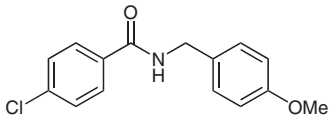
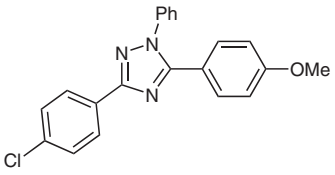
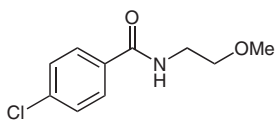
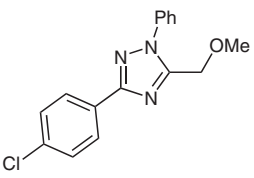
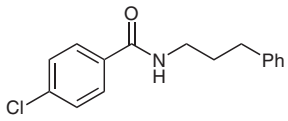
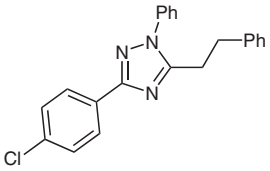
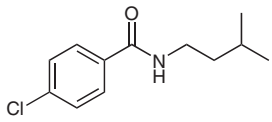
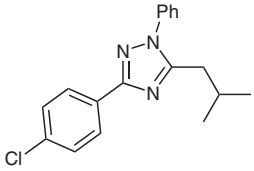
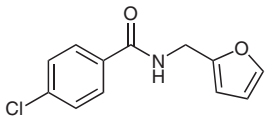
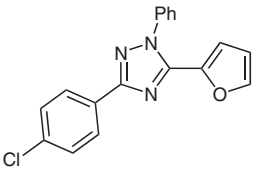
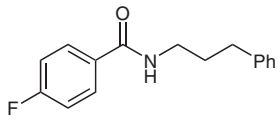
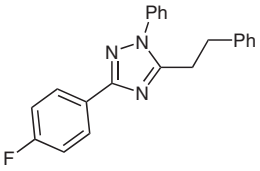
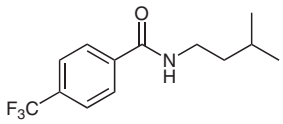
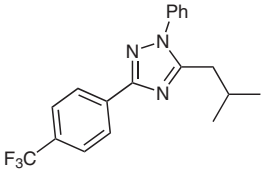
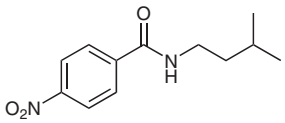
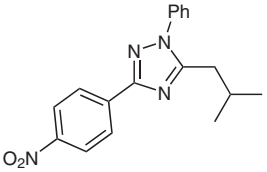
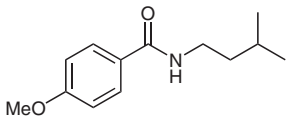
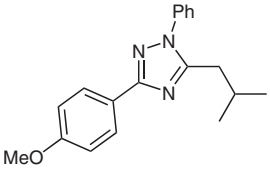
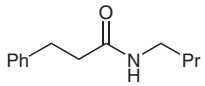
Entry	Starting amide	Product	Yield (%)
1			41
2			38

Table 1 One-Pot Two-Step Triazole Synthesis (continued)

Entry	Starting amide	Product	Yield (%)
3			66
4			64
5			34
6			50
7			55
8			30
9			54
10		–	–

Typical Procedure for 2a

A solution of amide (1 mmol) in CH_2Cl_2 (1.5 mL) over activated 4 Å MS and under an argon atmosphere was cooled to 0 °C. Then, 2,6-lutidine (350 μL, 3.0 equiv) and oxalyl chloride (114 μL, 1.3 equiv) were successively added dropwise. After stirring for 1 h at r.t., DMF (2 mL) and phenylhydrazine (predried over KOH, 130 μL, 1.3 equiv) were added. The flask was equipped with a drying tube filled with KOH, and the reaction mixture was stirred for an additionnal 12 h at 80 °C. The mixture was then extracted with Et_2O (20 mL). The combined organic phases were washed with H_2O (10 × 1 mL), and dried over anhyd $MgSO_4$. The solvent was removed under reduced pressure to afford 5-alkyl-3aryl-1-phenyl-1*H*-1,2,4-triazole **2a** (180 mg, 60% yield) after purification by flash column chromatography (Et_2O–PE = 20:80) on silica gel; mp 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, 2 H, *J* = 8.7 Hz), 7.58–7.48 (m, 5 H), 7.43 (d, 2 H, *J* = 8.7 Hz), 2.82 (t, 2 H, *J* = 7.7 Hz), 1.88–1.79 (m, 2 H), 0.99 (t, 3 H, *J* = 7.3 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 160.9, 157.5, 137.9, 135.4, 130.0, 129.9, 129.5, 129.2, 128.2, 125.7, 28.9, 21.9, 14.2. HRMS: *m/z* calcd for $C_{33}H_{36}N_4O_2$: 520.2838; found: 520.2839.

Acknowledgment

Financial support was provided by ENSTA. M.G. thanks the Délégation Générale de l'Armement for a fellowship.

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