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Synthesis of 1,2,4-triazoles employing isocyanides

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ABSTRACT

A conceptually new, two-step synthesis of medicinally important 1,2,4-triazoles from isocyanides and thiosemicarbazones was developed. The method is based on the recently discovered TMSCl-promoted reaction of isocyanides that yields rare N^1,N^3-disubstututed formamidrazones.

1. Introduction

The synthetic utility of isocyanides extends far beyond the preparation of α-acyloxy and α-acylaminocarboxamides via the 'classical' Passerini[1] and Ugi[2] reactions, respectively, as this reagent class continues to prove instrumental in de novo heterocycle construction. The unique reactivity of α-acidic *p*-toluenesulfonylmethylisocyanide (TosMIC) enabled the van Leusen imidazole[3] and oxazole[4] syntheses; numerous cases of successful use of bifunctional reagents[5] and post-condensational modifications[6] in conjunction with the Ugi reaction clearly attest to the power of isocyanide chemistry to reach into new areas of heterocyclic chemical space, aromatic and saturated alike (Scheme 1).

1,2,4-Triazoles constitute an important class of heterocycles and have been reported as key to a number of pharmacologically active compounds: potent 5HT antagonist **1**,[7] arginine vasopressin V_{1A} receptor antagonist **2**,[8] Ras farnesyl transferase inhibitor **3**,[9] δ opioid receptor antagonist **4**,[10] tubulin polymerization inhibitor **5**,[11] high-affinity ligand to the human ghrelin receptor **6**[12] and glycine transporter 1 inhibitor **7**[13] are only a few examples illustrating the privileged character[14] of the 1,2,4-triazole core for the drug design (Fig. 1).

Recently, we described a new reaction of isocyanides with aldehyde thiosemicarbazones **8** that yields rare N^1,N^3-disubstituted formamidrazone hydrochlorides **9**.[15] The reaction is promoted by chlorotrimethylsilane (TMSCl) and is thought to proceed via isocyanide N–H insertion followed by the elimination of isothiocyanic acid (Scheme 2). Given the novelty of this reaction and an intriguing arrangement of potentially reactive electrophilic hydrazone and nucleophilic amidine moieties in **9**, we became interested in identifying the utility of the latter for ring-forming processes.[16] Herein we described the application of isocyanide-derived formamidrazones **9** toward facile preparation of diversely substituted 1,2,4-triazoles.

2. Results and discussion

As we reported earlier,[15] in some cases formamidrazone hydrochlorides **9** precipitate from the reaction mixture and can be conveniently isolated and characterized. Their free-base counterparts **10**, however, exist as a mixture of tautomers (presumably, **10′** and **10″**) that complicate their spectroscopic characterization. In principle, ring tautomer **10‴** could also exist in equilibrium with the open-chain tautomers **10′** and **10″** (although only two major tautomers could be detected by ^{1}H NMR spectroscopy). We reasoned that if this was the case, 2,3-dihydro-1,2,4-triazole **10‴** could be aromatized under appropriate dehydrogenation conditions and thus provide a convenient access to 1,2,4-triazoles **11** (Scheme 3).

A model formamidrazone hydrochloride **9a** (R^1=3-chlorophenyl, R^2=*t*-Bu) that was prepared in high yield (90%) and isolated, in analytically pure form, from the TMSCl-promoted reaction of *t*-BuNC with 3-chlorobenzaldehyde thiosemicarbazone[15] was converted to the free-base formamidrazone (**10a**) and subjected to a number of dehydrogenation conditions. Treatment of **10a** with DDQ[17] in toluene or acetonitrile (at reflux temperatures) as well as with silica gel

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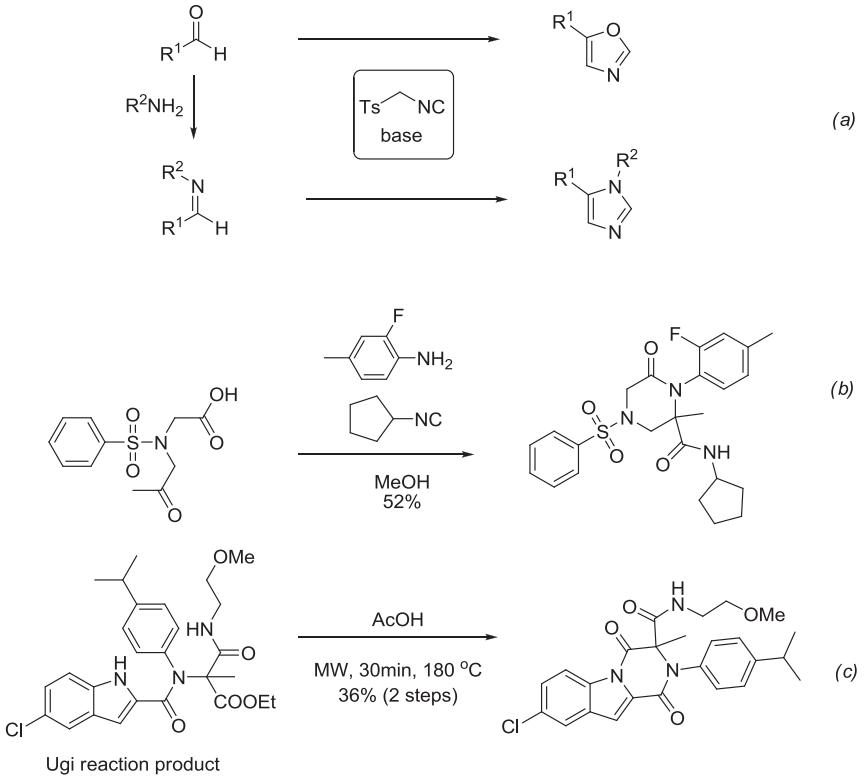

Scheme 1. Isocyanides in heterocycle synthesis: (a) van Leusen azole syntheses; examples of (b) a bifunctional ketocarboxylic acid use in the Ugi reaction and (c) a post-Ugi modification leading to a novel heterocyclic framework.

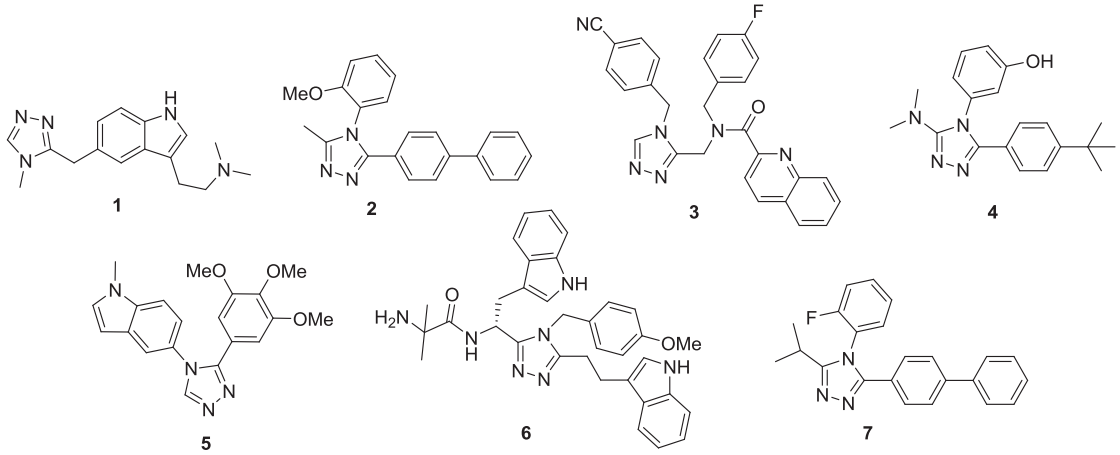

Fig. 1. Examples of pharmacologically active 1,2,4-triazoles.

supported $KMnO_4$[18] (acetonitrile, rt) gave a complex mixture of unidentified products. However, a promising result was obtained upon treatment of **10a** with 10% Pd on activated charcoal (toluene, 110 °C).[19] Under these conditions, **10a** underwent a steady (albeit somewhat slow) conversion to a more polar product that was isolated chromatographically in 72% yield and its identity as the desired 1,2,4-triazole **11a** was established by ^1H and ^{13}C NMR spectroscopy, LCMS, and high-resolution mass-spectrometry. In contrast, under the same reaction conditions, hydrochloride **9a** remained unchanged upon extended heating (7 days). This observation appears to be consistent with the formamidrazone hydrochloride being 'locked' as open-chain tautomer **10′** (as was earlier established by X-ray crystallography),[15] which renders it unavailable for the formation of the postulated ring tautomer **10‴** and subsequent dehydrogenation.

The newly established synthetic approach was applied to a diverse range of free-base formamidrazones **10b**–**z** that were also prepared via the TMSCl-promoted reaction of thiosemicarbazones **8** with aliphatic isocyanides, followed by basic work-up of the reaction mixture. In principle, the crude formamidrazones could be used in the dehydrogenative cyclization step directly (Scheme 4). However, better yields and easier purification of the target 1,2,4-triazoles were obtained from formamidrazones that were briefly fractionated by silica gel chromatography to achieve at least 80% purity (as judged by LC MS analysis). The isolated yields of the 1,2,4-triazoles **11b**–**z** from thiosemicarbazones **8**, were fair to excellent (Table 1).[20] Notably, when we repeated the synthesis of **11a** without the isolation of **9a** and proceeded with the basic work-up of the reaction mixture and fractionation of the free-base product, the yield of **11a** was even slightly higher (76%) than that obtained via isolation of the formamidrazone hydrochloride by filtration (possibly due to a partial solubility of **9a** in acetonitrile).