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Efficient Methodology for the Synthesis of 3-Amino-1,2,4-triazoles

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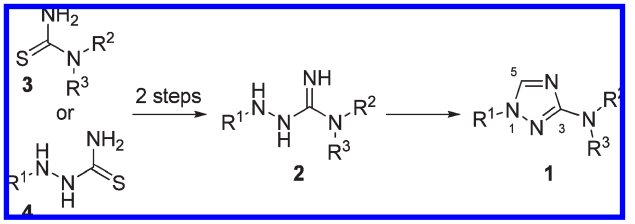
Received August 6, 2009



A general and efficient method for the preparation of 3-amino-1,2,4-triazoles has been developed. The desired 3-amino-1,2,4-triazoles (**1**) were prepared in good overall yield via two convergent routes. The key intermediate within both routes is substituted hydrazinecarboximidamide derivative **2**.

Triazole heterocycles occupy a central position in modern heterocyclic chemistry, principally because this heterocyclic ring is an important recognition element in biologically active molecules. Consequently new and efficient methods for the preparation of this important heterocyclic ring system are of contemporary interest. 3-Amino-1,2,4-triazole and its derivatives have also been the subject of numerous studies because of the many reported applications in the fields of medicinal and agrochemistry. For example, 3-aminotriazole derivatives are inhibitors of catalase[1] and histidine[2] biosynthesis. Sufotidine bismuth citrate, a complex with an aminotriazole motif that is a histamine H2-receptor antagonist, is used in the treatment of duodenal and gastric ulceration and other conditions where histamine is a known mediator.[3] 3-Aminotriazoles have also been found effective for the treatment of chronic bronchial asthma,[4] used as herbicides,[5] and patented as neuropeptide Y receptor ligands.[6] Aminotriazoles have also been described as potent CRF1 receptor antagonists,[7] as well as inhibitors of methionine aminopeptidase-2.[8]

Numerous methods have been developed for the synthesis of 1,5-disubstituted 3-amino-1,2,4-triazoles.[9] However, few of these describe direct synthesis of the triazole lacking substitution at the 5-position. Methods do exist to synthesize 5-amino-substituted analogues which are then diazotized to remove the amino group, but this is laborious as it requires an additional step for every analogue synthesized.[10] Additionally, other published routes to 5-unsubstituted triazoles suffer some disadvantages including the following: (1) not atom economical,[11] (2) low yielding[11a,12] and (3) limited scope with regards to substitution of the 3-amino group[13] or in the N-1 position[14] (the substituent in this position was added in an additional step). In some cases, chemistry is limited to symmetric bisaryl substitution patterns, which may not find general use.[15] In other approaches, there are only a few examples given. Hence, the breadth and applicability of these methods to synthesize a variety of substituted (alkyl, aryl, primary or secondary alkyl or aryl amine) 3-amino-1,2,4-triazoles is lacking.[11]

As part of our medicinal chemistry research program, we required a robust facile synthesis of 3-aminotriazole derivatives (devoid of C-5 substitution) **1** wherein we could vary the R^1, R^2, and R^3 groups. Herein we report a convergent and convenient method for the preparation of these derivatives.

We envisioned that 3-aminotriazole **1** could be obtained by cyclization of hydrazinecarboximidamide derivative **2** with a formic acid equivalent (Scheme 1). This precursor could be prepared by two different methods. One route begins with thiourea **3** and the other with hydrazinecarbothioamide **4** wherein the $R^1/R^2/R^3$ groups are introduced

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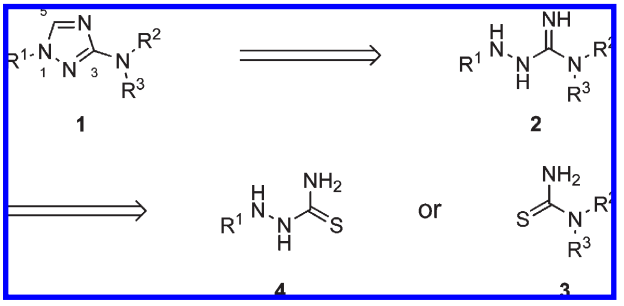
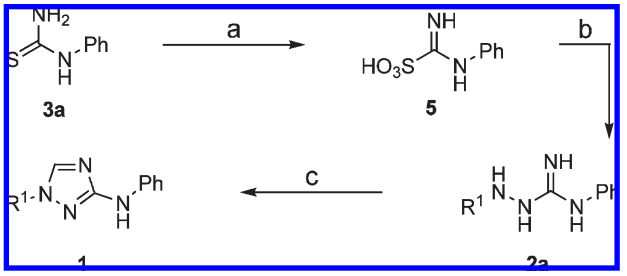
DOI: 10.1021/jo9016502 Published on Web 09/04/2009

SCHEME 1. Retrosynthesis



SCHEME 2. Synthesis of 3-Amino-1,2,4-triazole from 3a



Reagents and conditions: (a) $Na_2MoO_4 \cdot 2H_2O$ (0.05 equiv), 30% H_2O_2 (5 equiv), NaCl (0.4 equiv), H_2O, 0 °C to rt; (b) R^1NHNH_2 (1 equiv), without or with triethylamine (2.2 equiv), CH_3CN, rt or 80 °C, 1.5 h; (c) $HC(OMe)_3$, 140 °C, overnight.

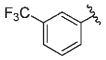
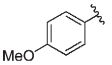
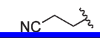
just prior to cyclization. This convergent synthesis facilitates the study of structure−activity relationships for **1** depending on the starting material **3** or **4**. To illustrate the potential of this approach, we decided to optimize the chemistry using commercially available derivatives: 1-phenylthiourea **3a** (R^2 = Ph and R^3 = H) and 1-phenyl-3-thiosemicarbazide **4a** (R^1 = Ph).

Thiourea **3a** was converted to the known sulfonic acid **5** following the reported literature procedure (Scheme 2).[16] Oxidation of thiourea **3a** with hydrogen peroxide in the presence of sodium molybdate dehydrate gave **5** in excellent yield.[17] The reaction of **5** with a variety of commercially available aryl- or alkyl-hydrazines afforded intermediates **2a** which when treated with trimethyl orthoformate provided the desired 3-aminotriazoles **1**.

Our initial reaction of **5** with phenylhydrazine at room temperature (without base) showed good conversion to the expected compound **2a** (R^1 = Ph). Because of the aqueous solubility of this intermediate the crude reaction mixture was simply concentrated in vacuo, and taken to the next step. Heating of this intermediate in trimethyl orthoformate at 140 °C for 14 h produced the 3-aminotriazole **1a** in 66% isolated yield (Table 1, entry 1).

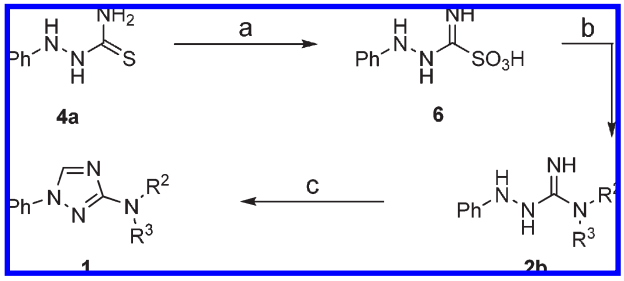
The same procedure was then applied to the other hydrazines in Table 1. In the cases where R^1 is a substituted phenyl ring (Table 1, entries 2 and 3), the 3-aminotriazoles were obtained with moderate yields. When the reaction was performed with 2-hydrazinopyridine (Table 1, entry 4), the conversion of the first step was very slow at room

TABLE 1. Preparation of 1 from 5

Entry	R^1	Temp.[a]	Products	Yield (%)[b]
1		rt	**1a**	66[c]
2		rt	**1b**	42[c]
3		rt	**1c**	39[c], 43[d]
4		80°C	**1d**	48[c]
5		80°C	**1e**	n.r.[c], 65[d]
6		80°C	**1f**	6[c], 41[d]
7		rt	**1g**	52[c]
8		rt	**1h**	54[c]

[a]Reaction condition of the first step. [b]Isolated yield over two steps. [c]Without additive. [d]With 2.2 equiv of triethylamine.

SCHEME 3. Synthesis of 3-Amino-1,2,4-triazole from 4a



Reagents and conditions: (a) $Na_2MoO_4 \cdot 2H_2O$ (0.05 equiv), 30% H_2O_2 (5 equiv), NaCl (0.4 equiv), H_2O, 0 °C to rt; (b) R^2R^3NH (1 equiv), pyridine (2.2 equiv), CH_3CN, 120 °C, 30 min; (c) $HC(OMe)_3$, 140 °C, overnight.

temperature, but proceeded more efficiently at 80 °C. With *tert*-butylhydrazine hydrochloride (Table 1, entry 5), the first step did not occurr even at 80 °C and starting material was recovered. However, the reaction did progress smoothly in the presence of an external base. Of the different bases tried (pyridine, 1,4,6-collidine, diisopropylethylamine, cesium carbonate, sodium hydroxide, triethylamine, and DBU) triethylamine proved to give the highest overall yields for the two steps. Base was required in all reactions starting with hydrazine hydrochloride salts (Table 1, entries 3, 5, and 6). Other (free base) aliphatic hydrazines (Table 1, entries 7 and 8) reacted smoothly at room temperature without additive to give the desired product in good yield. Although the yields are modest in some cases, the two-step one-pot method provided rapid access to the desired compounds not readily available via other synthetic methods.

To investigate substitution of the 3-position of triazole **1**, we envisioned an alternative route featuring 1-phenyl-3-semithiocarbazide **4a** as the starting material in place of 1-phenylthiourea **3a** (Scheme 3). The synthesis of sulfonic acid derivative **6** had not been reported in the literature, but was readily prepared in 93% yield from **4a** following the same procedure described to synthesize **5**.[17] The reaction of **6** with a variety of commercially available aryl- or alkylamines led to intermediates **2b** which when treated with trimethyl

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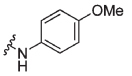
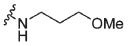
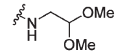
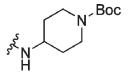
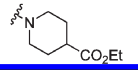
(17) While crude **5** or **6** could be used directly, better yields were obtained if **5** or **6** were purified on silica gel.

TABLE 2. Preparation of 1 from 6

Entry	R^2, R^3	Products	Yield (%)[a]
1		**1a**	43
2		**1i**	44
3		**1j**	56
4		**1k**	58
5		**1l**	56
6		**1m**	58
7		**1n**	49
8		**1o**	71
9		**1p**	52
10		**1q**	52

[a]Isolated yield over two steps.

orthoformate afforded the desired 3-aminotriazoles **1**. A study was carried out to optimize the reaction conditions.

Treatment of **6** with aniline at 120 °C for 30 min (without base) gave a very low conversion to intermediate **2b**. The reaction was then tried in the presence of different bases. When the reaction was performed with DBU, triethylamine, sodium hydroxide, or cesium carbonate, we noted that the formation of byproducts was considerably increased in relation to the conversion to **2b**. However, we found that conversion to **2b** was dramatically improved in the presence of pyridine. We also tried the reactions in different solvents (DMF, EtOH, CH_3CN) with the cleanest conversions occurring in acetonitrile. The cyclization of intermediates **2b** was performed as before at 140 °C for 14 h to afford the desired products **1** in good yields for the two steps.

As reported in Table 2, the 3-aminotriazoles **1** were obtained in all cases in good yields. In examples where the reaction was performed with aniline derivatives (Table 2, entries 1 and 2), the yields are slightly lower perhaps reflecting the reduced reactivity of these nucleophiles toward intermediate **6**. It is noteworthy that the reactions are compatible with primary and secondary amines as well as anilines. Moreover, the reactions are compatible with several functional groups such as olefins, acetals, carbamates, and esters.

In conclusion, we have developed an efficient and convergent method to synthesize differently substituted 3-amino-1,2,4-triazoles **1** from readily available starting materials. To vary the substitution at the N-1 position, the synthesis of aniline derived sulfonic acid intermediate **5** is followed by addition of hydrazine and then cyclization. To vary the 3-amino substitutents, the synthesis of sulfonic acid **6** is followed by amine addition and then cyclization. The yields are good for the two-step, one-pot protocol and mild enough to accommodate a range of functional groups. Our ongoing efforts toward the synthesis of biologically active compounds containing the 3-aminotriazole motif using this methodology will be reported elsewhere.

Experimental Section

Representative Experimental Procedure for the Preparation of Compound 1: General Procedure A. A mixture of **5** (240 mg, 1.2 mmol) and phenylhydrazine (108 mg, 1.0 mmol) in anhydrous acetonitrile (1 mL) was stirred at room temperature for 1.5 h. The reaction mixture was then concentrated to a solid, which was added with trimethyl orthoformate (1 mL) and heated overnight at 140 °C in a sealed tube. The resulting mixture was cooled to room temperature, filtered through a short pad of silica gel, and flushed with 20% MeOH in CH_2Cl_2. The filtrate was concentrated and purified by preparative HPLC to provide the desired product **1a** (156 mg, 66%) as a solid.

General Procedure B. A mixture of **6** (100 mg, 0.465 mmol), aniline (37 μL, 0.406 mmol), and pyridine (72 μL, 0.890 mmol) in anhydrous acetonitrile (470 μL) was stirred at 120 °C for 30 min in a sealed tube. The reaction mixture was then concentrated. The residue was diluted with methyl orthoformate (1.2 mL) and heated overnight at 140 °C in a sealed tube. The resulting mixture was partitioned between a saturated solution of $NaHCO_3$ (5 mL) and EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to provide the desired product **1a** (41 mg, 43%) as a solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.83−6.87 (m, 1H), 7.26−7.30 (m, 2H), 7.33−7.37 (m, 1H), 7.52−7.56 (m, 2H), 7.64−7.66 (m, 2H), 7.84−7.87 (m, 2H), 9.07 (s, 1H), 9.44 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 116.0, 118.1, 119.5, 126.6, 128.7, 129.7, 136.9, 140.8, 141.5, 160.8; MS (ESI) $[M + H]^+$ 237.19

Acknowledgment. Professor William R. Roush (The Scripps Research Institute, Scripps Florida) is gratefully acknowledged for proofreading the manuscript. The efforts of P.R.G. and M.J.C. were supported by the National Institutes of Health (NIH) Molecular Library Screening Center Network (MLSCN) grant U54MH074404 (Hugh Rosen, Principal Investigator).

Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.