A Convenient Synthesis of Highly Substituted 3-*N*,*N*-Dialkylamino-1,2,4-triazoles

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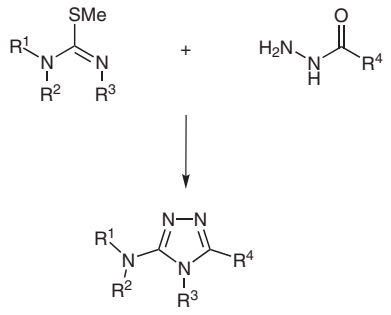
Abstract: The title compounds are prepared from *S*-methylisothioureas and acyl hydrazides in moderate to good yields. The reaction is characterized by relatively mild conditions and very broad functional group tolerance.

Key words: heterocycles, cyclisations, sulfur, medicinal chemistry, drugs

A diverse body of methods is available to the synthetic chemist wishing to prepare 3-*N*,*N*-dialkylamino-1,2,4-triazoles. Apart from specific methods based on dipolar nitrile imines[1] and dichlorodiazabutadienes,[2] a variety of general strategies are available. The first of these, displacement of a halo or thio derivative from an existing triazole ring,[3] often suffers from the need to use multiple equivalents of amine, high temperatures, and prolonged reaction times.[4] The second strategy, cyclisation of an amidrazone,[5] requires the preparation of a Viehe salt, a procedure needing multiple steps and often harsh reagents incompatible with certain functional groups.[6] A third possibility is the condensation of an amino-guanidine with a carboxylic acid[7] (requiring reflux in the neat acid) or corresponding acid chloride.[8] The advantages of using the acid chloride should be qualified by the low yields sometimes experienced with this technique.[9] The synthetic strategy most commonly employed for the preparation of the molecules under discussion was introduced by Maffrand and co-workers[10] and involves the condensation of an *S*-methylisothiourea with an acyl hydrazine (Scheme 1).

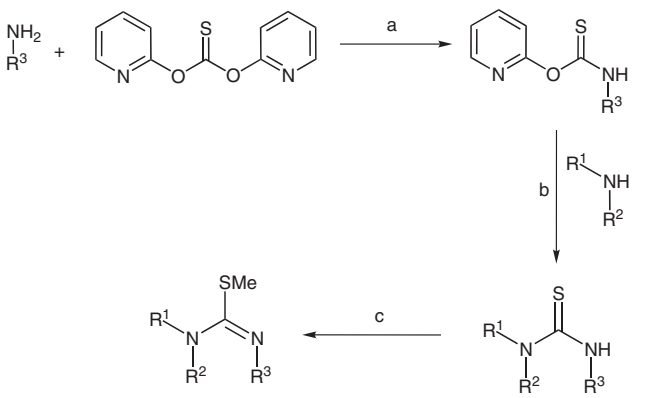


Scheme 1

In the thirty years since this reaction was disclosed its scope has become clearer. The reaction works quickly and well under neutral conditions when R^1–R^3 are small,[11] however, when R^1–R^3 are large, neutral conditions require prolonged reaction times and high temperatures.[12] We therefore postulated that the catalytic PTSA employed by Maffrand must have an important role as he was able to cyclise substrates where R^3 = phenyl.[13] Our experimentation supported this hypothesis: we found that when R^3 = aryl multiple equivalents of acyl hydrazine were often needed along with prolonged heating at reflux in *n*-butanol. We therefore desired to identify conditions for the cyclisation of challenging substrates, which would also be able to tolerate a broad range of functional groups, particularly those amenable to further manipulation. We also wished these conditions to be milder than those used by Maffrand (refluxing pyridine for 40 h).

For the successful realisation of this ambitious synthetic goal, a robust flexible synthesis of the starting *S*-methylisothiourea was required. We have used the method shown in Scheme 2.

Thus di-2-pyridyl-thiocarbonate[14] was treated sequentially with the primary amine bearing the R^3 residue followed by the secondary amine corresponding to the desired *N*,*N*-dialkylamino side chain. The thioureas accessed in this way could be converted into the *S*-methylisothioureas by treatment with potassium *tert*-butoxide and methyl tosylate.[15] Alternatively, the thioureas could be prepared in one step from an isothiocyanate of the R^3 group where that was commercially available.[16] Either of these meth-



Scheme 2 *Reagents and conditions*: a) CH_2Cl_2, r.t.; b) CH_2Cl_2, r.t.; c) KO*t*-Bu, MeOTs, THF, r.t. All steps typically 90–100%.

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ods required, at the very most, a slight excess of each amine component.

We then identified two sets of conditions capable of producing the desired aminotriazoles. Our preferred conditions involved adding 0.5 equivalents of TFA to the reaction – this promotes the transformation so that it can now be performed in refluxing THF. Less acidic conditions were also identified: an excess of AcOH also allows the reaction to be performed in refluxing THF. A representative range of examples is shown in Table 1.

Table 1 Synthesis of Aminotriazoles

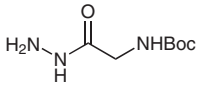
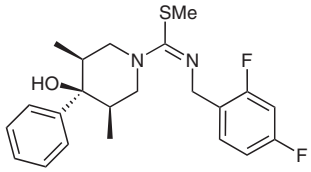
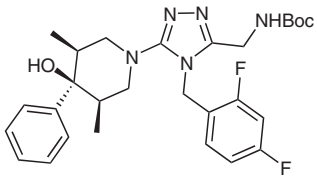
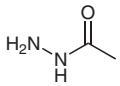
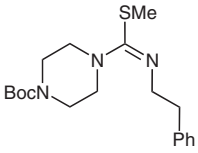
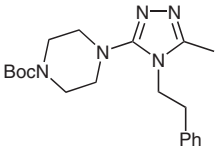
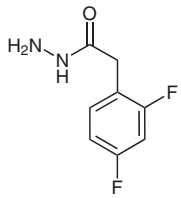
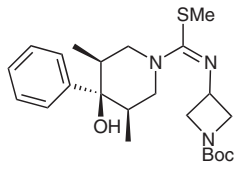
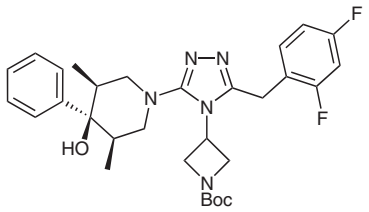
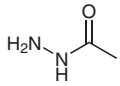
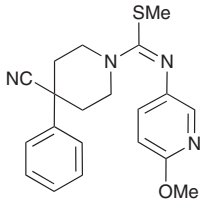
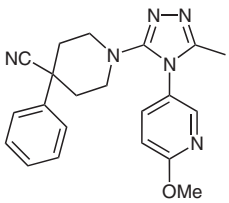
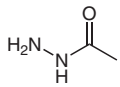
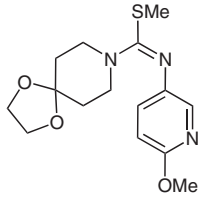
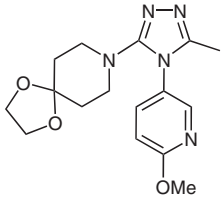
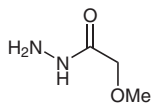
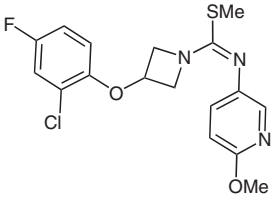
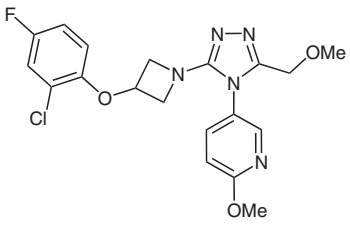
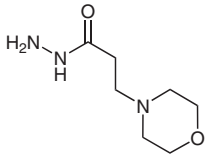
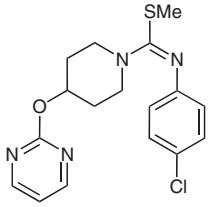
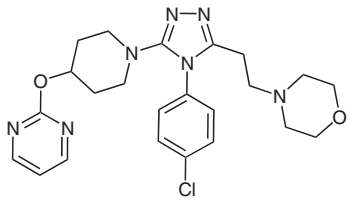
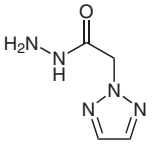
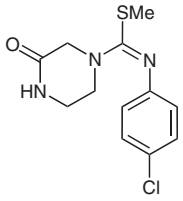
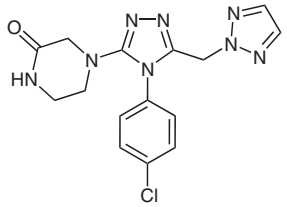
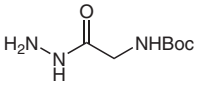
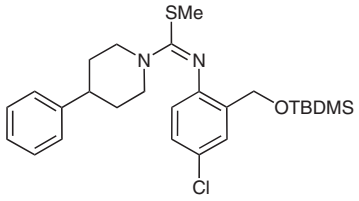
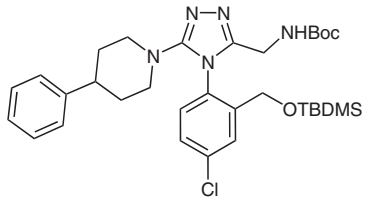
Acyl hydrazide	Isothiourea	Conditions[a]	Reaction time (h)	Yield (%)[b]	Product
 **1a**	 **2a**	A	4	46	 **3a**
 **1b**	 **2b**	B	6	52	 **3b**
 **1c**	 **2c**	A	16	33	 **3c**
 **1b**	 **2d**	B	4	53	 **3d**
 **1b**	 **2e**	B	3	57	 **3e**
 **1d**	 **2f**	B	1.5	67	 **3f**

Table 1 Synthesis of Aminotriazoles (continued)

Acyl hydrazide	Isothiourea	Conditions[a]	Reaction time (h)	Yield (%)[b]	Product
 **1e**	 **2g**	B	4	68	 **3g**
 **1f**	 **2h**	A	16	72	 **3h**
 **1a**	 **2i**	B	22	61[c]	 **3i**

[a] Conditions A: hydrazide (2.1 equiv), THF–AcOH (10:1), reflux. Conditions B: hydrazide (1–2 equiv), TFA (0.5 equiv), reflux.
[b] Yields refer to isolated pure material.
[c] Yield could be improved to 89% overall (34% product and 55% of the desilyated product) by using 1 equiv of TFA.

As will be readily seen from Table 1, this reaction is tolerant of a broad range of functional groups including nitriles (compound **3d**) and amides (compound **3h**). Tertiary alcohols (compounds **3a** and **3c**) also survive the reaction unscathed although primary alcohols cause the yields to reduce significantly (examples not shown). Sensitive alkoxy-substituted heterocycles are also immune to the reaction conditions (compounds **3d**–**g**). Perhaps more significantly, various protecting groups can also be carried in this reaction, including Boc (compounds **3a**–**c**,**i**), ketal (compound **3e**), and TBDMS (compound **3i**). We were unable to prepare any of compound **3i** under neutral conditions even with prolonged heating, demonstrating that the acid-mediated conditions reported herein cope remarkably well with severe steric encumbrance. This is also shown in the fact that a variety of R^3 substituents could be tolerated (*n*-alkyl in compounds **3a**,**b**; cycloalkyl in compound **3c** and aryl in compounds **3d**–**i**) in contrast to the neutral conditions.[12] It is possible to reduce the amount of acid used in the reaction (e.g., to add only 0.25 equiv of TFA) but not without significantly extending the reaction time. The reaction has been performed on scales up to 4 g, for the preparation of compound **3e** amongst others, indicating its suitability for larger-scale synthesis.

In conclusion, we have demonstrated refined conditions for the synthesis of 3-*N*,*N*-dialkylamino-1,2,4-triazoles which are tolerant of a wide range of functional and protecting groups, and which allow the rapid assembly of molecular complexity from simple starting materials. These conditions give reasonable yields and are scalable to gram quantities. We expect these improved conditions will further popularise the use of this aminotriazole motif in drug discovery.

Representative Experimental Procedures

Method A

To a stirred solution of *S*-methylisothiourea **2a** (1 g, 2.5 mmol) in THF–AcOH (10:1, 11 mL) was added acyl hydrazine **1a** (1 g, 5.2 mmol) and the whole was heated at 60 °C until TLC showed all starting material had been consumed (4 h). The reaction was then cooled and solvent was removed in vacuo. The residue was purified by column chromatography on SiO_2 eluting with 0–5% MeOH in CH_2Cl_2. Appropriate fractions were combined and evaporated to give triazole **3a** as a foam (606 mg, 1.15 mmol, 46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.52 (6 H, d, *J* = 7 Hz), 1.39 (9 H, s), 2.28 (2 H, m), 3.00 (2 H, dd, *J* = 12, 4 Hz), 3.19 (2 H, t, *J* = 12 Hz), 4.39 (2 H, d, *J* = 6 Hz), 5.19 (2 H, s), 5.33 (1 H, br s), 6.84–6.93 (4 H, m), ca. 7.24 (1 H, m, obscured by $CHCl_3$ signal), 7.32–7.37 (3 H, m).

ESI-MS: *m/z* = 528 $[M + 1]^+$.

Method B

To a stirred solution of *S*-methylisothiourea **2i** (300 mg, 0.6 mmol, 1 equiv) in THF (5 mL) was added acyl hydrazine **1a** (140 mg, 0.74 mmol, 1.5 equiv). Then, TFA was added (15 μL, 0.4 mmol, 0.4 equiv) and the whole was heated at reflux for 22 h. The mixture was

cooled, diluted with EtOAc, washed with dil. NH_3 (aq) then with brine, dried over $MgSO_4$, and evaporated to a yellow oil. This was purified by column chromatography on SiO_2 eluting with EtOAc then with 5% MeOH–CH_2Cl_2. Appropriate fractions were combined, evaporated, dissolved in Et_2O, and evaporated again to yield triazole **3i** as a white foam (229 mg, 0.37 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (3 H, s), 0.08 (3 H, s), 0.88 (9 H, s), 1.36 (9 H, s), 1.53–1.68 (2 H, m), 1.71 (1 H, br d, *J* = 13 Hz), 1.88 (1 H, br d, *J* = 13 Hz), 2.60 (1 H, tt, *J* = 12, 3 Hz), 2.84 (1 H, td, *J* = 12, 3 Hz), 3.08 (1 H, td, *J* = 12, 3 Hz), 3.34 (1 H, br d, *J* = 13 Hz), 3.57 (1 H, br d, *J* = 13 Hz), 4.12 (2 H, d, *J* = 5 Hz), 4.37 (1 H, d, *J* = 14 Hz), 4.62 (1 H, d, *J* = 14 Hz), 5.15 (1 H, br s), 7.13–7.19 (4 H, m), 7.21 (1 H, d, *J* = 7 Hz), 7.29 (1 H, d, *J* = 8 Hz), 7.40 (1 H, dd, *J* = 8, 2 Hz), 7.67 (1 H, d, *J* = 2 Hz).

ESI-MS: *m/z* = 634 $[M + 23]^+$.

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