A Practical Synthesis of Piperidine-/Tropane-Substituted 1,2,4-Triazoles

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This work is dedicated to Prof. Steven V. Ley to thank him for all his contributions to the chemistry community here in Sandwich.

Abstract: A robust synthesis of 1,2,4-triazoles is disclosed with a particular focus on developing methodology capable of delivering gram quantities and minimising hazardous waste.

Key words: heterocycles, triazoles, isostere, tropane, piperidine

Heterocycles are well known as potential isosteres to replace carboxylic acids, esters and amides in the design of orally bioavailable drug candidates.[1] As part of our research it became necessary to design a range of trisubstituted 1,2,4-triazoles wherein the triazole 4-nitrogen is linked to a piperidine or tropane (Figure 1). From a medicinal chemistry perspective this is an attractive motif and a practical synthesis was required. For expedience we were keen that the methodology would enable us to readily vary the alkyl/aryl substituents R and R′.[2] A recent publication has prompted us to disclose our results in this area of heterocycle synthesis.[3]

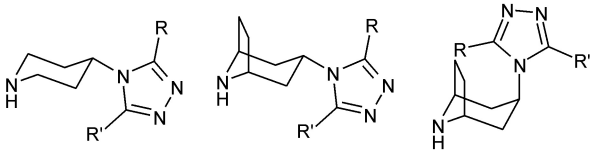
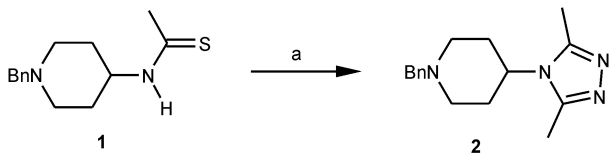


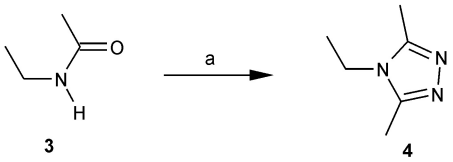
Figure 1 Targets of interest.

Initially attempts to construct the 3,5-dimethyl substituted triazole **2** were made in one step from the corresponding thioamide **1** and acetic hydrazide (Scheme 1). Although precedented in the literature,[4] in our hands we found the reaction to be low yielding and product isolation non-trivial; we suspected the problem to be associated with the quality of the thioamide used in the reaction. Disappointingly, this route presented significant difficulties on scaling due to the use of Lawesson's[5] or Belleau's[6] reagent in formation of the thioamide and disposal of mercuric residues.



Scheme 1 *Conditions*: a. acetic hydrazide, HgO, BuOH, reflux, 20%.

After a review of the literature we were intrigued at the publications that used the iminoyl chloride as a precursor for reaction with an acyl hydrazide and subsequent cyclisation to the 1,2,4-triazole.[7] In particular the work of Atkinson and Polya was of interest with the one-pot preparation of triazole **4** using conditions that appeared simple to perform.[8] We also felt the reported low yield was open to optimization (Scheme 2).



Scheme 2 *Conditions*: a. $POCl_3$, $CHCl_3$, pyridine, r.t. then acetic hydrazide, $CHCl_3$, reflux, 23%.

For our initial attempt we focused on the equatorially substituted tropane **5** and used identical conditions to those described by Atkinson and Polya. We were delighted to find complete consumption of the starting material and formation of a new compound, however, the mass spectrum indicated that we had only formed the intermediate *N*-acyl amidrazone **6**. Various conditions were examined to complete the cyclisation and the optimum conditions were determined to be heating under reflux in toluene with addition of a catalytic quantity (typically 5 mol%) of *p*-toluenesulfonic acid to furnish **7** in a satisfactory yield of 59% (Scheme 3).

It is reasonable to postulate that the low yield reported by Atkinson and Polya is due to incomplete cyclisation of the corresponding intermediate to the 1,2,4-triazole. *N*-Acyl amidrazone **6** is stable to an aqueous work up, and washing out the phosphorous oxychloride residues appeared to make the cyclisation proceed with greater consistency, however, due to the polar nature of the *N*-acyl amidrazone care is needed with the wash if undertaken. From an analysis of the literature it would appear that cyclisation of amidrazones typically requires forcing conditions such as heating in acetic acid at 120 °C[3] or heating in 1,2-dichlorobenzene at 140 °C.[7a] It would also appear that a yield of 59% compares highly favourably with yields cited in the literature which range from 20–70% depending upon substrate.

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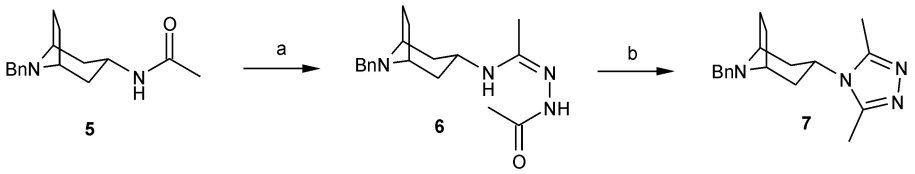


5 6 7

Scheme 3 *Conditions*: a. $POCl_3$, $CHCl_3$, pyridine, r.t. then acetic hydrazide, $CHCl_3$, reflux; b. PhMe, reflux 59%.

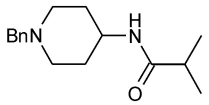
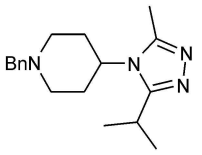
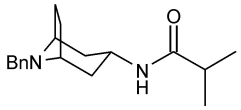
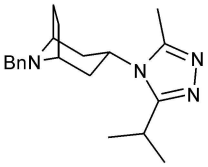
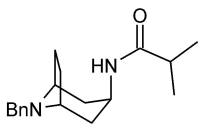
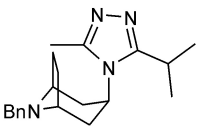
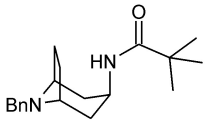
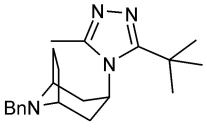
Further examination of the chlorination conditions were conducted and phosphorous pentachloride gave the most reproducible high yields using dichloromethane as solvent. With the iminoyl chloride formation and cyclisation conditions optimised we were now in a position to prepare the required range of substituted piperidines and tropanes (Table 1).

We were pleased to find that these conditions worked across a range of piperidine and tropane substitution patterns. Comparing entries 2 and 3 there is essentially no change in yield regardless of whether the amide is an axial or equatorial disposition in the tropane structure. Also in entry 4 with both the tropane bridge and the *t*-butyl group hindering the reaction the yield remained consistent with the other less sterically demanding analogues. Entry 3 has also been prepared in similar yield in the 'reversed fashion' using the tropane acetamide and isobutyric acid hydrazide. All these examples were debenzylated in high yield using transfer hydrogenation conditions.[9]

The main limitation in this methodology is ensuring the amide substituents are compatible with the use of phosphorous pentachloride for iminoyl chloride formation.

In conclusion we have demonstrated an efficient methodology for the multigram preparation of 1,2,4-triazoles and their linkage to synthetically/medicinally useful piperidines and tropanes. After debenzylation these can be further modified to give biologically active molecules for potential drug development. The reaction conditions are milder than those previously reported in the literature and do not require special handling techniques or disposal of hazardous mercuric residues. The range of substitutions is limited by their compatibility with the use of the chlorination conditions rather than any steric considerations.

Table 1 Triazoles prepared.

Entry	Amide precursor	Product	Yield (%)
1[10]			50
2			65
3			61
4			60

References

(1) (a) Wermuth, C. G. In *The Practice of Medicinal Chemistry*; Wermuth, C. G., Ed.; Academic Press: San Diego, **2001**. (b) Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.

(2) Wadsworth, H. J.; Jenkins, S. M.; Orlek, B. S.; Cassidy, F.; Clark, M. S. G.; Brown, F.; Riley, G. J.; Graves, D.; Hawkins, J.; Naylor, C. B. *J. Med. Chem.* **1992**, *35*, 1280.

(3) Stocks, M. J.; Cheshire, D. R.; Reynolds, R. *Org. Lett.* **2004**, *6*, 2969.

(4) (a) Boeglin, D.; Cantel, S.; Heitz, A.; Martinez, J.; Fehrentz, J. A. *Org. Lett.* **2003**, *5*, 4465. (b) Jagodzinski, T. S. *Chem. Rev.* **2003**, *103*, 197.

(5) (a) Clausen, K.; Thorsen, M.; Lawesson, S. O. *Tetrahedron* **1981**, *37*, 3635. (b) Voss, J. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 1; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, **1995**.

(6) Barrett, A. G. M.; Lee, A. C. *J. Org. Chem.* **1992**, *57*, 2818.

(7) (a) Klingsberg, E. *J. Am. Chem. Soc.* **1958**, *80*, 5786. (b) See examples contained within patent GB670,480. (c) Garrat, P. J. In *Comprehensive Heterocyclic Chemistry II*, Vol. 4; Storr, R. C., Ed.; Elsevier: Oxford, **1996**.

(8) Atkinson, M. R.; Polya, J. B. *J. Chem. Soc.* **1954**, 141.

(9) (a) *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W.; Wuts, P. G. M., Eds.; John Wiley and Sons: Chichester, **1999**. (b) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515.

(10) **Preparation of Entry 1.**
PCl_5 (20.5 g, 98 mmol) was added portionwise to a stirred CH_2Cl_2 (200 mL) solution of the amide (19.7 g, 76 mmol) at 0 °C. After 2 h stirring at 0 °C acetic hydrazide (16.8 g, 227 mmol) and *t*-amylalcohol (195 mL) were added and the reaction was stirred for 12 h and then allowed to warm to r.t. The solvent was removed in vacuo and toluene (200 mL) and *p*-TsOH (474 mg, 2.5 mmol) were added and the reaction was heated under reflux for 6 h. The reaction was cooled to r.t., the solvent was decanted, and CH_2Cl_2 (200 mL) and H_2O (200 mL) were added with stirring; 1 N aq NaOH was slowly added to take the pH to >9. The organic layer was separated and the aqueous was washed with CH_2Cl_2 (2 × 100 mL), the organics were combined and washed with H_2O (2 × 200 mL), brine (200 mL) and dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel eluting with 10% MeOH in EtOAc to give the product of entry 1 (11.0 g, 50%) as a white solid. ^1H NMR (400 MHz, CD_3OD): δ = 7.30 (5 H, m), 4.13 (1 H, m), 3.58 (2 H, s), 3.23 (1 H, sept, *J* = 7.0 Hz), 3.08 (2 H, m), 2.54 (3 H, s), 2.23 (4 H, m), 1.84 (2 H, m), 1.38 (6 H, d, *J* = 7.0 Hz). LRMS: *m/z* = 299 [MH^+].