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Efficient and Regiospecific One-Pot Synthesis of Substituted 1,2,4-Triazoles

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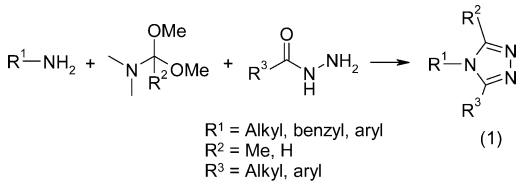
ABSTRACT

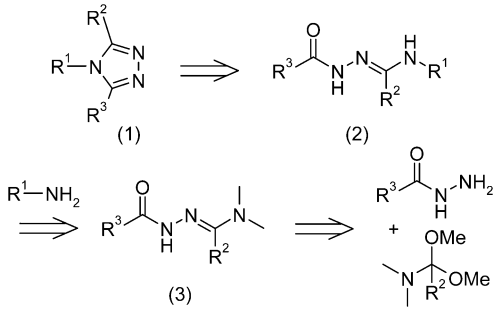


An efficient one-pot, three-component synthesis of substituted 1,2,4-triazoles has been developed, utilizing a wide range of substituted primary amines and acyl hydrazides.

Many 1,2,4-triazoles are of biological interest,[1] and as a consequence, a number of synthetic methods have been developed to construct this ring system.[2] To date, there have been no viable one-pot convergent syntheses reported. We wish to communicate our initial work for an efficient one-pot synthesis of substituted 1,2,4-triazoles **1**, employing readily available starting materials.

We envisaged that substituted 1,2,4-triazoles **1** could be obtained from the reaction of *N*′-acetyl-*N*,*N*-dimethylhydrazonoformamide (**3**, $R^2 = H$, $R^3 = Me$) with a primary amine followed by acid-catalyzed ring closure.[3] The starting *N*′-acetyl-*N*,*N*-dimethylhydrazonoformamide could be generated in situ from the reaction of acetic hydrazide with dimethylformamide dimethyl acetal **DMFDMA** (Scheme 1).

Scheme 1. Proposed Retrosynthetic Pathway



In our initial studies, *N*′-acetyl-*N*,*N*-dimethylhydrazonoformamide[4] **4** was generated by combining acetic hydrazide with DMFDMA in acetonitrile at 50 °C (see Scheme 2); however, upon addition of a primary amine no further reaction occurred, even at elevated temperatures. This is in

(1) For selected recent examples, see: (a) Armour, D. R.; Baxter, A. D.; Bryans, J. S.; Dack, K. N.; Johnson, P. S.; Lewthwaite, R. A.; Newman, J.; Rawson, D. J.; Ryckmans, T. WO2004037809, 2004; *Chem. Abstr.* **2004**, *140*, 370921. (b) Cho, I.; Park, H.-J.; Noh, J.; Ryu, H.; Park, S.; Jung, S.; Lee, S.; Kim, J.; Lim, J.; Lyu, C.; Kim, D.; Kim, Y.; Yeon, K.; Chae, M.; Min, I.; Jin, H.; Kang, K. WO2004014878, 2004; *Chem. Abstr.* **2004**, *140*, 181455. (c) Krueger, M.; Petrov, O.; Thierauch, K.-H.; Siemeister, G. WO2002094814, 2002; *Chem. Abstr.* **2002**, *138*, 4620. (d) Geslin, M.; Gully, D.; Maffrand, J.-P.; Roger, P. WO2001044207, 2001; *Chem. Abstr.* **2001**, *135*, 46184. (e) Pascal, J.-C.; Carniato, D. EP1099695, 2001; *Chem. Abstr.* **2001**, *134*, 353312. (h) Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoregh, I.; Hessellink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112. (f) Armour, D. R.; Price, David A.; Stammen, B. L. C.; Wood, A.; Perros, M.; Edwards, M. P. WO2000039125, 2000; *Chem. Abstr.* **2000**, *133*, 74024.

(2) For selected methods of synthesis, see: (a) Garratt, P. J. In *Comprehensive Heterocyclic Chemistry II*; Storr, R. C., Ed.; Elsevier: Oxford, 1996; Vol. 4, pp 127−163, 905−1006. (b) Turnbull, K. In *Progress in Heterocyclic Chemistry*; Elsevier: Oxford, 1998; Vol. 10, p 153. (c) Balasubramanian, M.; Keay, J. G.; Scriven, E. F. V.; Shobana, N. *Heterocycles* **1994**, *37* (3), 1951. (d) Vanek, T. Velkova, V.; Gut, T. *Collect. Czech. Chem. Commun.* **1984**, *249*, 2492. (e) Dunstan, A. R.; Weber, H.-P.; Rihs, G.; Widner, H.; Dziadulewicz, E. K. *Tetrahedron Lett.* **1998**, *39*, 7983. (f) Vanden Eynde, J. J.; Estievenart, L.; Haverbeke, Y. V. *Heterocycl. Commun.* **2000**, *6*, 412. (g) Lee, C. H.; Lee, K.-J. *J. Heterocycl. Chem.* **2002**, *39*, 845.

(3) Bartsch, H.; Erker, T. *J. Heterocycl. Chem.* **1990**, *27*, 991.

(4) Isolated as a crystalline solid; see the Supporting Information.

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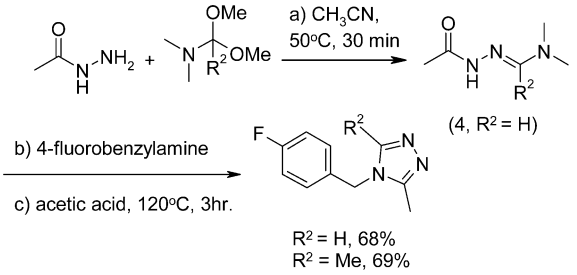
Scheme 2. Initial Results Employing 4-Fluorobenzylamine



agreement with Maquestiau,[5] who suggested that the proposed aminolysis would be disfavored by the presence of a strong electron-donating group (NMe_2) on the imino bond.

We decided to investigate this reaction further and subjected the reaction to acidic catalysis as we envisaged that protonation of the *N*′-acetyl-*N*,*N*-dimethylhydrazonoformamide **3** would enhance the subsequent transamination process. Interestingly, no reaction was observed with either 4 molar equiv of anhydrous hydrogen chloride or trifluoroacetic acid. However, gratifying evidence by LCMS of conversion to *N*′-acetyl-*N*-(4-fluorobenzyl)hydrazonoformamide (**2**, R^1 = 4-fluorobenzyl, R^2 = H, R^3 = Me) was observed by the addition of either 4 molar equiv of acetic or formic acid.

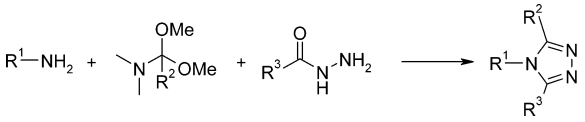
It has previously been reported that 1,2,4-triazoles can be synthesized by cyclizing substituted (ethylamino)methylenehydrazides **2** in acetic acid at elevated temperatures.[3] With this knowledge, addition of acetic acid to the reaction mixture containing the primary amine and **3**, followed by increasing the reaction temperature to 120 °C, afforded the desired 1,2,4-triazoles[6] (Scheme 2).

Further examination of the scope of the reaction revealed that substituted anilines, benzylamines, and alkylamines can also participate in the reaction. The role of the acyl group in the hydrazide was also examined. The results are summarized in Table 1.

Mechanistically, a second possible reaction pathway could be envisaged (Scheme 3). In this process, **5** (R^2 = Me) could cyclize under acidic conditions to generate 2,5-dimethyl-1,3,4-oxadiazole[7] **6,** which could then further react with a primary amine to generate the substituted 1,2,4-triazole[8] **7**.

We discount this alternative reaction pathway for the following reasons: (1) the oxadiazole **6** was not detected in the reaction mixture; (2) reaction of an authentic sample of the oxadiazole under the reaction conditions gave only a trace amount of the desired compound **7**; and the proposed intermediary *N*′-acetyl-*N*,*N*-dimethylhydrazonoformamide **2** could be observed in the reaction mixture by LCMS, and although isolation was difficult, a sample was obtained to confirm the structure (**2**, R^1 = 4-fluorobenzyl, R^2 = H).

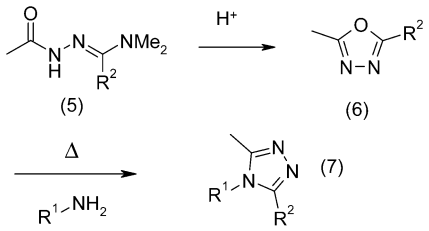
Table 1. Results of Substituted 1,2,4-Triazole Synthesis



entry	R^1-NH_2	R^2	R^3	yield[a] (%)
1	4-fluorobenzylamine	Me	Me	69
2	4-fluorobenzylamine	H	Me	68
3	benzylamine	H	Me	39
4	4-methoxybenzylamine	H	Me	22
5	4-nitrobenzylamine	H	Me	48
6	aniline	H	Me	64
7	aniline	Me	Me	55
8	4-methoxyaniline	H	Me	87
9	4-methoxyaniline	Me	Me	60
10	ethyl 4-aminobenzoate	H	Me	43
11	4-fluorobenzylamine	H	4-methylphenyl	65
12	4-fluorobenzylamine	H	4-methoxyphenyl	33
13	4-fluorobenzylamine	H	4-nitrophenyl	51
14	4-pyridylmethylamine	H	Me	42
15	allylamine	H	Me	56
16	propargylamine	H	Me	13
17	cyclohexylamine	H	Me	9
18	cyclohexylamine	H	4-methylphenyl	13

[a] Yields refer to fully characterized and purified products.

Scheme 3. Alternative Reaction Pathway



As can be seen from Table 1, the reaction is applicable to a wide range of substituted primary amines, benzylamines, and anilines; however, reaction with simple alkylamines affords a low yield of product, and indeed in the case of cyclohexylamine (entry 17), the major products detected were the amidines **8** and **9** when DMFDMA was used (Scheme 4).

To investigate this reaction further, a series of dialkylformamide dimethyl acetals were prepared,[9] and these were subjected to the standard reactions conditions (see Table 2).

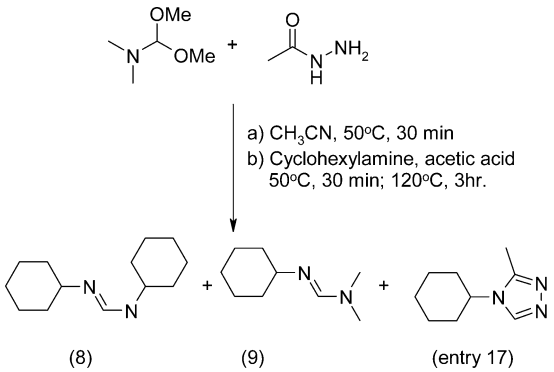
(5) Maquestiau, A.; Vanden Eynde, J.-J. *Tetrahedron* **1987**, *43*, 4195.

(6) **General Procedure.** In an open vessel, acetic hydrazide (407 mg, 5.5 mmol) was dissolved in acetonitrile (2 mL) and dimethylacetamide dimethyl acetal (732 mg, 5.5 mmol) was added. The reaction mixture was warmed to 50 °C for 30 min, and then 4-fluorobenzylamine (625 mg, 5 mmol) in acetonitrile (1 mL) was added followed by acetic acid (3 mL). The reaction temperature was raised to 120 °C for 3 h, and then the mixture was cooled and concentrated and the residue purified by chromatography on silica gel eluting initially with ethyl acetate followed by 5% 0.7 N ammonia in methanol in ethyl acetate to afford 4-(4-fluorobenzyl)-3,5-dimethyl-4*H*-1,2,4-triazole (702 mg, 69%) as a white solid after trituration with diethyl ether.

(7) (a) Tandon, V. K, and Chhor, R. B. *Synth. Commun.* **2001**, *31*, 1727. (b) Ainsworth, C.; Hackler, R. E. *J. Org. Chem.* **1966**, *31*, 3442. (c) Boyd, G. V.; Dando, S. R. *J. Chem. Soc. C* **1970**, 1397.

(8) (a) Reitz, D. B.; Finkes, M. J. *J. Heterocycl. Chem.* **1989**, *26*, 225. (b) Carlsen, P. H. J.; Jorgensen, K. B. *J. Heterocycl. Chem.* **1994**, *31*, 805. (c) Behringer, H.; Ramert, R. *Justus Liebigs Ann. Chem.* **1975**, *7*−*8*, 1264. (d) Whittaker, M.; Davidson, A. H.; Spavold, Z. M.; Bowles, S. A. WO9117157, 1991; *Chem. Abstr.* **1991**, *117*, 26321.

Scheme 4. Reaction of Cyclohexylamine with Acetic Hydrazide and DMFDMA



There was no increase in yield observed when either 1-(dimethoxymethyl)pyrrolidine or 1-(dimethoxymethyl)-piperidine was employed; however, a dramatic increase in yield was observed when *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine was used and probably results from facile intramolecular protonation of the *N*,*N*,*N*′-trimethylethane-1,2-diamine in the transamination process.[10]

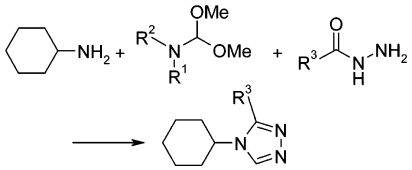
Improvements in the yield of two of the low-yielding compounds noted in Table 1 were gained by using *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine. The 4- to 5-fold increase in yield (entry 16 increased from 13 to 55% and entry 18 from 13 to 41%) enforces the successful replacement using *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine instead of DMFDMA in these low-yielding cases.[11]

(9) (a) Kump, W.; Traxler, P.; Scartazzini, R. EP49683, 1982; *Chem. Abstr.* **1982**, *97*, 72194. (b) Ott, P.; Hansen, H.-J. *Helv. Chim. Acta* **2001**, *84*, 2670.

(10) A similar example of this effect observed employing *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine as a leaving group under acidic catalysis was observed in the comparison of the acidic hydrolysis of substituted benzamides; see: Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1983**, *24*, 5465.

(11) In the case of entry 2, a comparable yield of product was obtained when either DMFDMA or *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine was used.

Table 2. Variation in Dialkylformamide Dimethyl Acetals: Reaction with Cyclohexylamine



R^1	R^2	R^3	yield[a] (%)
	$-(CH_2)_4-$	Me	8
	$-(CH_2)_5-$	Me	11
Me	Me	Me	9
Me	$-(CH_2)_2NMe_2$	Me	52

[a] Yields refer to fully characterized and purified products.

An efficient one-pot, three-component synthesis of substituted 1,2,4-triazoles is reported. The reaction has scope for parallel synthesis employing commercial or readily available compounds. So far, the reaction is applicable to a wide range of substituted primary amines, benzylamines, and anilines; however, reaction with simple alkylamines, such as cyclohexylamine, initially resulted in poor yields. This has been overcome by using *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine instead of DMFDMA. We have concentrated on the use of DMFDMA in the reaction sequence due to its commercial availability. However, the use of *N*-(dimethoxymethyl)-*N*,*N*′,*N*′-trimethylethane-1,2-diamine appears to have a wider potential, and work is underway in our laboratory to further explore the scope of this reaction.

Acknowledgment. We are grateful to Dr. Tony Ingall for helpful discussions.

Supporting Information Available: ^1H and ^{13}C NMR, microanalysis, and MS data for the products illustrated in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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