Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3429–3432

A base-catalyzed, direct synthesis of 3,5-disubstituted 1,2,4-triazoles from nitriles and hydrazides

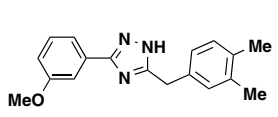
Kap-Sun Yeung,* Michelle E. Farkas, John F. Kadow and Nicholas A. Meanwell

Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, PO Box 5100, Wallingford, CT 06492, USA

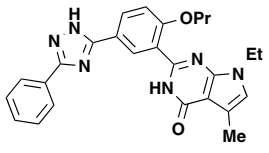
Received 20 January 2005; revised 18 February 2005; accepted 18 February 2005
Available online 2 April 2005

Abstract—A convenient and efficient one step, base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles by the condensation of a nitrile and a hydrazide is presented. A diverse range of functionality and heterocycles are tolerated under the reaction conditions developed, and the reactivity of the nitrile partner is relatively insensitive to electronic effects.

3,5-Disubstituted 1,2,4-triazoles are found in several pharmacologically active compounds. Recent examples include the selective adenosine A_{2A} receptor antagonist **1**[1] and the phosphodiesterase V inhibitor **2**[2] shown in Figure 1. Triazole rings are typically synthesized by a process that represents an overall dehydrative condensation between hydrazides and nitrile derivatives, with the latter usually activated by, for example, conversion to an imidate (**3** in Scheme 1; Pinner reaction) or a thioamide (Pellizzari reaction). These procedures, path b–d, Scheme 1, are usually conducted at elevated temperatures and depend upon a discrete step to derivatize the nitrile and a subsequent step for the formation of the acylamidrazone intermediate **4** prior to cyclization. These conventional procedures not only often involve high reaction temperatures and long reaction times but also result in low yields of product.[3,4]

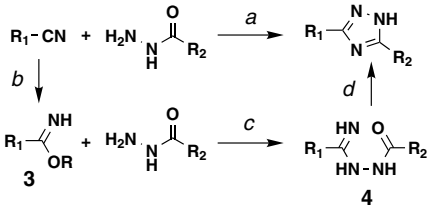


1, A_{2A} receptor antagonist



2, PDE V inhibitor

Figure 1.



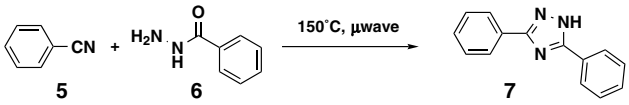
Scheme 1.

Prompted by the need for a more reliable and versatile preparation of 3,5-disubstituted 1,2,4-triazoles in order to rapidly probe structure–activity relationships in one of our drug discovery programs, we investigated different reaction conditions with the view to developing a more convenient, one-step procedure that was amenable to automated solution phase synthesis, analysis, and purification.[5] More specifically, we focused attention on developing reaction conditions that would allow the synthesis of the heterocycle directly from a nitrile and a hydrazide, as depicted in path a, Scheme 1. Although the reaction of a nitrile and a hydrazide has been reported to provide 1,2,4-triazoles, the conditions described are not general, very high temperatures (230 °C) are typically employed, and yields are low.[6] Initially, we were interested in exploring the application of microwave technology to the synthesis of triazoles[5b] as recent examples suggest that microwave irradiation[7] provides advantage with respect to reduced reaction time, and increased product yields when compared to conventional heating.

Keywords: 1,2,4-Triazole; Nitriles; Hydrazide; Microwave; Solution phase synthesis.
* Corresponding author. Tel.: +1 203 677 6897; fax: +1 203 677 7072; e-mail: kapsun.yeung@bms.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.02.167

Table 1. Results of the reaction of benzonitrile with benzoic hydrazide under different conditions



5 6 7

Entry	Solvent	Base (equiv)	Time (h)	Yield (%)
1	—	—	1	No reaction
2	^{n}BuOH	—	3	No reaction
3	EtOH	K_2CO_3 (2)	—	Incompatible
4	DMF	K_2CO_3 (2)	1.25	Little reaction
5	Ethylene glycol	K_2CO_3 (2)	1.25	26
6	^{n}BuOH	K_2CO_3 (2)	2.5	74
7	$BmimPF_6$[a]	K_2CO_3 (2)	1.25	1:1 triazole/oxadiazole
8	^{n}BuOH	Cs_2CO_3 (2)	2.75	30
9	^{n}BuOH	Et_3N (2)	1	No reaction
10	^{n}BuOH	K_2CO_3 (1)	3	72
11	^{n}BuOH	K_2CO_3 (0.5)	3	78 (80, ob)[b]
12	^{n}BuOH	K_2CO_3 (0.1)	7	84 (49, 67[c], ob)

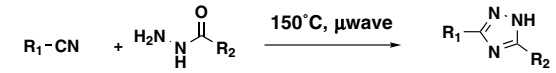
These experiments were carried out using 0.33 mmol of benzoic hydrazide and 1 mmol of benzonitrile: see Ref. 9 for experimental procedure.
[a] $BmimPF_6$ = 1-butyl-3-methylimidazolium hexafluorophosphate.
[b] ob = oil bath heating.
[c] Fresh bottle of K_2CO_3 was used.

The reaction between benzonitrile (**5**) and benzoic hydrazide (**6**) was used as a model system to identify reaction parameters that would provide optimal results. As presented in Table 1, condensation of the two reactants, either neat (entry 1) or as a solution in ^{n}BuOH (entry 2), was ineffective under microwave irradiation at 150 °C. However, in the presence of 2 equiv of K_2CO_3 as base, the use of ^{n}BuOH as a solvent provided 3,5-diphenyl-1,2,4-triazole (**7**) in 74% yield (entry 6), conditions superior to using either DMF (entry 4) or ethylene glycol (entry 5) as the reaction medium, while the lower boiling EtOH was incompatible with the reaction conditions (entry 3). Interestingly, the use of the ionic liquid, 1-butyl-3-methylimidazolium hexafluorophosphate, led to a 1:1 mixture of 1,2,4-triazole and 1,3,4-oxadiazole (entry 7), an outcome not observed when using other solvents. The alternative bases Cs_2CO_3 and Et_3N were also examined but found to be inferior to K_2CO_3 (Table 1, entries 8 and 9). The use of 1 equiv or a sub-stoichiometric amount of K_2CO_3 was found to be sufficient to provide satisfactory results (entries 10 and 11). Most significantly, the use of 0.1 equiv of K_2CO_3 provided the highest yield of product, albeit a longer reaction time was required (entry 12). When conventional oil bath heating was employed to conduct the reaction, lower yields of the product were observed when 0.1 equiv of K_2CO_3 were used but yields were comparable in the presence of 0.5 equiv of K_2CO_3 (compare entries 11 and 12).[8] Based on these results, we chose to use the optimized conditions of entry 11 as a protocol to test the generality of the method and a survey of select examples is compiled in Table 2.[9]

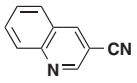
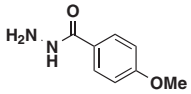
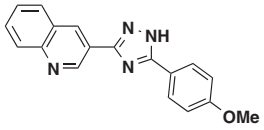
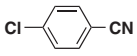
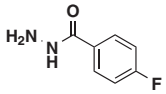
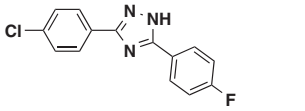
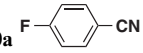
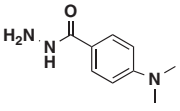
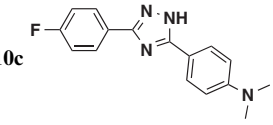
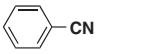
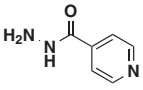
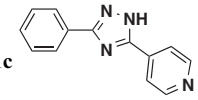
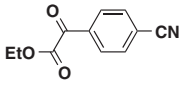
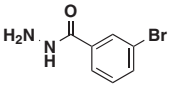
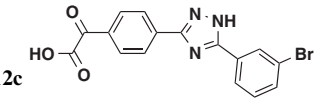
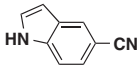
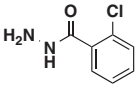
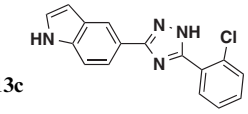
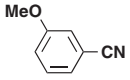
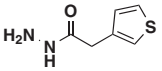
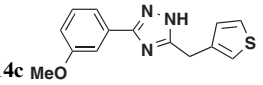
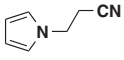
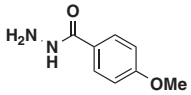
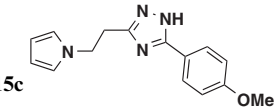
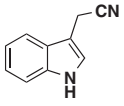
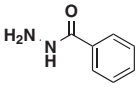
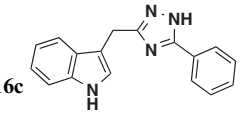
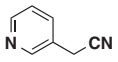
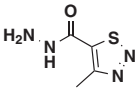
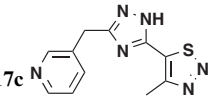
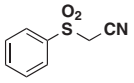
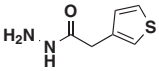
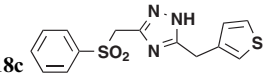
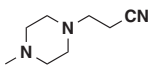
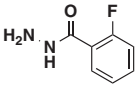
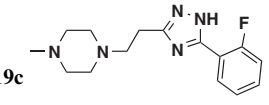
The results presented in Table 2, entries 1–7 demonstrate that, in general, the success of this reaction protocol is not heavily dependent on electronic factors associated with either reaction partner. Both electron-donating and electron-withdrawing substitutions deployed at different positions of the aryl ring of the nitriles and the hydrazides are tolerated, as are 5- and 6-membered heterocycles, with synthetically useful yields obtained.[10] Compound **11c** (entry 4) and its analogs have been evaluated as orally active xanthine oxidase inhibitors that were prepared from an intermediate acylamidrazone, obtained, in turn, via an imidate, in yields of 15–32% by heating at 285 °C.[3c,11] The reaction between nitrile **12a** and hydrazide **12b** was complete in 1 h but gave a mixture of acid **12c**, its ethyl, and *n*-butyl esters in a ratio of 1:2:2 (entry 5). This mixture was not purified but was subjected to saponification with NaOH/MeOH to provide acid **12c** in 82% overall yield over the two steps. It is perhaps somewhat surprising that the condensation between **12a** and **12b** shows excellent chemoselectivity for the cyano group over the activated carbonyl element presented by the α-keto ester moiety since no product arising from this alternative reaction manifold was detected. We attribute the inertness of the α-keto ester moiety to a facile in situ protection by the addition of ^{n}BuOH solvent to afford the hemiketal derivative, a reaction facilitated by the electron withdrawing cyano group.

The example provided by **13c** (entry 6) illustrates that a relatively electron-rich nitrile of the type exemplified by **13a** participates readily in this process to give the desired product under both microwave and oil bath conditions. However, an extended reaction time was required to complete this reaction, presumably a reflection of unfavorable steric interactions in the cyclization step and the electron-rich nature of the nitrile. The aryl-substituted acetonitrile derivatives **15a**–**18a** (entries 8–11) reacted with various hydrazide derivatives to afford products **15c**–**18c** in satisfactory yields. The results presented in entries 8, 9, and 12 are particularly notable because β-elimination of the nitrile starting materials might be anticipated as a potential side reaction. Gratifyingly, nitriles **17a** and **18a** (entries 10 and 11), both of which contain acidic α-methylene protons, reacted smoothly

Table 2. Direct synthesis of a variety of 3,5-disubstituted 1,2,4-triazoles from nitriles and hydrazides



5, 8a-19a **6, 8b-19b** **8c-19c**

Entry	Nitrile	Hydrazide	Time[a] (h)	Product	Yield (%)
1	 **8a**	 **8b**	3.5	 **8c**	83[b]
2	 **9a**	 **9b**	3	 **9c**	61
3	 **10a**	 **10b**	4	 **10c**	50[b]
4	 **5**	 **11b**	3	 **11c**	57[b]
5	 **12a**	 **12b**	1	 **12c**	82[c] two steps
6	 **13a**	 **13b**	14 (20)[d]	 **13c**	41 (77)[d]
7	 **14a**	 **14b**	2.5	 **14c**	50
8	 **15a**	 **8b**	5	 **15c**	74[b]
9	 **16a**	 **6**	4	 **16c**	45
10	 **17a**	 **17b**	2	 **17c**	45[b]
11	 **18a**	 **14b**	1	 **18c**	62
12	 **19a**	 **19b**	7	 **19c**	34[b] (42)[d]

[a] See Ref. 9 for the experimental procedure; the reaction temperature for each individual example was not optimized.
[b] Isolated as TFA salt.
[c] Obtained after hydrolysis, see text.
[d] Oil bath heating and using a fresh bottle of K_2CO_3.

under these conditions. Finally, the aliphatic nitrile **19a** (entry 12) also participated as a substrate, providing triazole **19c**, albeit in modest yield. This appears to be a limitation of this process since the simpler aliphatic derivatives, acetic, and formic hydrazide, reacted with benzonitrile to provided triazole products in yields of only 14% and 12%, respectively. However, the thiophenyl-substituted acetic hydrazide derivative **14b** participated as a reaction partner to provide products **14c** and **18c** in moderate yields (entries 7 and 11).

In summary, an expedient synthesis of 3,5-disubstituted 1,2,4-triazoles that proceeds by the direct reaction of a nitrile and a hydrazide in the presence of catalytic amount of K_2CO_3 in ^{n}BnOH has been developed. The scope of this process has been demonstrated by examining reaction partners that incorporate a range of electron-donating and withdrawing functional groups and heterocycles, all of which are readily tolerated. The reaction of nitriles anticipated to be relatively unreactive also proceeded to provide the desired products. Thus, diverse, small molecule, drug-like structures can be assembled in a solution phase, automated synthesis fashion enabling expeditious SAR studies.

Acknowledgements

We thank Katharine Grant-Young for proof-reading the manuscript.

References and notes

1. Alanine, A.; Anselm, L.; Steward, L.; Thomi, S.; Vifian, W.; Groaning, M. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 817.
2. Dumaître, B.; Dodic, N. *J. Med. Chem.* **1996**, *39*, 1635.
3. For examples: (a) Olesen, P. H.; Sorensen, A. R.; Urso, B.; Kurtzhals, P.; Bowler, A. N.; Ehrbar, U.; Hansen, B. F. *J. Med. Chem.* **2003**, *38*, 3333; (b) Breslin, H. J.; Miskowski, T. A.; Kukla, M. J.; De Winter, H. J.; Somers, M. V. F.; Roevens, P. W. M.; Kavash, R. W. D. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4467; (c) Baldwin, J. J.; Kasinger, P. A.; Novello, F. C.; Spradue, J. M.; Duggen, D. E. *J. Med. Chem.* **1975**, *18*, 895.
4. A high yielding synthesis of 3,5-disubstituted 1,2,4-triazole from the less reactive amidine has been reported, however, it only applied to acetamidine and benzamidine: Francis, J. E.; Gorczyca, L. A.; Mazzenga, G. C.; Meckler, H. *Tetrahedron Lett.* **1987**, *28*, 5133.
5. (a) In our laboratories, Shimadzu analytical LC/MS and preparative HPLC with auto-sampling are used; (b) The automation capacity of a microwave synthesizer that can be coupled to the Shimadzu instruments is also an attractive feature for this purpose.
6. (a) Neat thermal fusion between benzonitrile (**5**) and hydrazides at 230 °C: Weidinger, H.; Kranz, J. DE Patent 1076136, 1958; (b) Reaction between benzonitrile (**5**) and benzoic hydrazide (**6**) in refluxing MeOH provided a mixture of 1,2,4-triazole (26%) and 1,3,4-oxadiazole (20%): Neelima; Bhaduri, A. P. *Indian J. Chem.* **1993**, *22B*, 79.
7. For recent reviews see: (a) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250; (b) Hayes, B. L. *Aldrichim. Acta* **2004**, *37*, 66.
8. (a) The insignificant difference in yield between microwave and oil bath conditions when using 0.5 equiv of K_2CO_3 was presumably because the equilibration of temperature was equally achieved over the 3 h under both conditions, and assuming equal internal pressure. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199; (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225.
9. All reagents were used as received from commercial sources. A representative procedure is as follows: A mixture of nitrile (3 mmol), hydrazide (1 mmol), and K_2CO_3 (0.5 mmol) in ^{n}BuOH (2 mL) in a microwave synthesizer tube was placed under microwave irradiation in an Emrys Optimizer (*Personal Chemistry*) with normal absorption level and the temperature set to 150 °C. Alternatively, the mixture was stirred in a reusable sealed tube at 150 °C in an oil bath. The progress of the reaction was monitored by the disappearance of the hydrazide using LC/MS. After completion, the mixture was evaporated, diluted with MeOH, and then purified by reverse phase preparative HPLC (MeOH/H_2O/0.1% TFA). Due to concern about the stability of the hydrazides over the >1 h time period under the basic reaction conditions, 3 equiv of the nitriles were used in all examples. In general, hydrazides show toxicity (e.g., hepatotoxicity), which is usually because of the formation of reactive radical metabolites in vivo.
10. This protocol was found to be incompatible with the presence of nitroaromatic derivatives in either reaction partner. Complex reaction mixtures containing insignificant amounts of product were obtained when either nitrobenzonitrile or nitrobenzoic hydrazide were used.
11. Duggen, D. E.; Noll, R. M.; Baer, J. E.; Novello, F. C.; Baldwin, J. J. *J. Med. Chem.* **1975**, *18*, 900.