ORGANIC LETTERS

2005
Vol. 7, No. 12
2429−2431

Microwave-Assisted Synthesis of *N*,*N*′-Diaryl Cyanoguanidines

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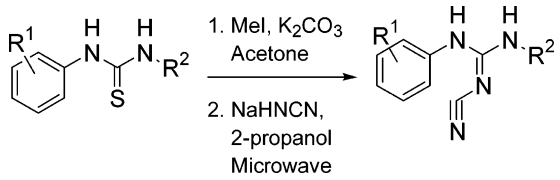
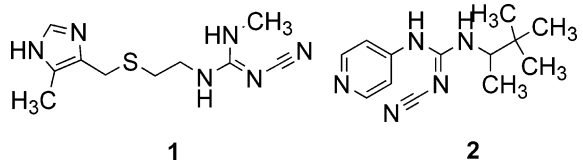
Received April 5, 2005

ABSTRACT



A mild, efficient, and high-yielding method for the synthesis of *N*,*N*′-diaryl cyanoguanidines from their corresponding thioureas under microwave-assisted conditions is described. A series of cyanoguanidines were synthesized containing both electron-donating and electron-withdrawing substituents. The reactions were facilitated by the use of polar solvents along with moderate temperatures.

The cyanoguanidine functionality is commonly referred to as a bioisostere of the urea and thiourea moieties. They share several physicochemical properties such as pK_a. The cyanoguanidine moiety can be found in several biologically active agents such as cimetidine (**1**), a histamine-H_2 antagonist,[1] and pinacidil (**2**), an antihypertensive (Figure 1).[2] Additionally, aryl cyanoguanidines are currently being investigated as potassium channel activators and inhibitors of insulin release.[3] As a result, there is enormous interest in developing novel approaches toward their synthesis. The most widely employed strategy for the synthesis of cyanoguanidines involves the treatment of diphenyl *N*-cyanocarbonimidate with an alkyl or arylamine, followed by conversion of the corresponding *N*-cyano-alkyl or *N*-cyano-aryl isourea with a basic amine, generally, in a sealed flask at high temperatures (Scheme 1). While other methods are known in the literature[4] such as those that take advantage of carbodiimide or *S*-alkylisothiouronium salts as intermediates, they often require harsh conditions and long reaction times and suffer from poor yields. Furthermore, there is a paucity of effective methods for the synthesis of *N*,*N*-diaryl cyanoguanidines. In our attempt to synthesize this type of compounds, most published methodologies were unsuccessful, even in cases where the amines were activated using trimethylaluminum.[5]



1 **2**

Figure 1. Cimetidine (**1**) and pinacidil (**2**).

(1) Roberts, S. M.; Price, B. J. *Medicinal Chemistry, The Role of Organic Chemistry in Drug Research*; Academic Press: New York, 1985; p 93.

(2) McBurney, A.; Farrow, P. R.; Ward, J. W. *J. Pharm. Sci.* **1987**, *12*, 940.

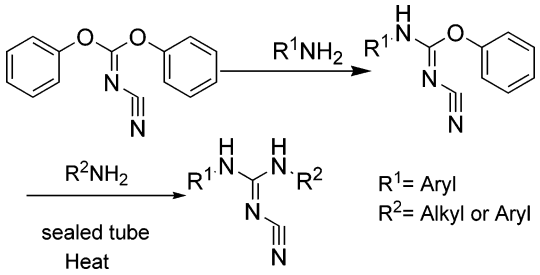
(3) Tagmose, T. M.; Schou, S. C.; Mogensen, J. P.; Nielsen, F. E.; Arkhammar, P. O. G.; Wahl, P.; Hansen, B. S.; Worsaae, A.; Boonen, H. C. M.; Antoine, M. H. *J. Med. Chem.* **2004**, *47*, 3202.

(4) (a) Iwanowicz, E. J.; Watterson, S. H.; Liu, C.; Gu, H. H.; Mitt, T.; Leftheris, K.; Barrish, J. C.; Fleener, C. A.; Rouleau, K.; Sherbina, N. Z.; Hollenbaugh, D. L. *Bioorg. Med. Chem. Lett.* **2002**, *20*, 2931. (b) Yoshiizumi, K.; Ikeda, S.; Goto, K.; Morita, T.; Nishimura, N.; Sukamoto, T.; Yoshino, K. *Chem. Pharm. Bull. (Tokyo)* **1996**, *44*, 2042. (c) Atwal, S. K.; Ahmed, S. D.; O'Reilly, B. C. *Tetrahedron Lett.* **1989**, *30*, 7313.

(5) Atwal, S. K.; Ferrara, F. N.; Ahmed, S. Z. *Tetrahedron Lett.* **1994**, *35*, 8085.

10.1021/ol050728q CCC: $30.25
Published on Web 05/17/2005

Scheme 1. General Synthesis of Cyanoguanidines[a]



[a] When R^2 is an alkyl group, a sealed tube is not necessary.

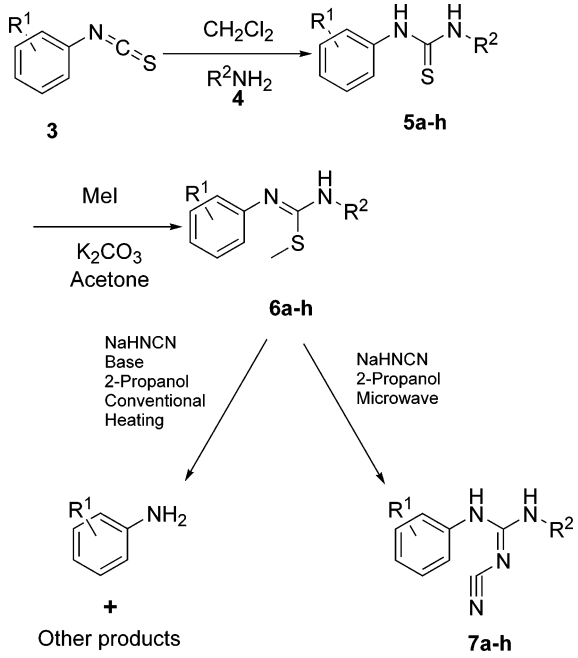
Recently, Novak et al.[6] reported the synthesis of *N*,*N*′-diphenyl cyanoguanidine in moderate yield. This method required conversion of *N*,*N*′-diphenyl thiourea to *N*,*N*′-diphenyl cyanoguanidine via the thioether under extensive heating in the presence of a strong base as a catalyst. However, there are two major limitations to this approach. First, it precluded the use of compounds with base-sensitive moieties. Second, we found that this method was incapable of synthesizing *N*,*N*′-diaryl cyanoguanidines bearing electron-withdrawing groups. Conventional heating of the reaction for an extended period of time caused decomposition of the thioether to the aniline before it reacted with the nucleophile.

Microwave synthesis has received a great deal of attention in recent years. Several publications[7] have shown that microwave irradiation can circumvent the need for prolonged heating and generally accelerate the rate of chemical reactions, often with increased yields. This increase in reaction rate is due in large part to the vast amount of microwave energy being absorbed by the system as compared with the required energy necessary to attain the requisite activation energy.[8]

Herein, we wish to report a clean, mild, efficient, and high-yielding procedure under microwave conditions for the synthesis of *N*,*N*′-diaryl cyanoguanidines, including those bearing strong electron-withdrawing substituents, which, to the best of our knowledge, are not known in the literature.

The synthesis of the cyanoguanidines is outlined in Scheme 2. Phenyl isothiocyanate **3** was treated with several aromatic amines **4** in methylene chloride to provide thioureas **5**. Upon treatment with methyl iodide and potassium carbonate in acetone, **5** was smoothly converted to thioethers **6** in >95% yield. Heating of compounds **6** in 2-propanol with sodium hydrogen cyanamide in the presence of a catalytic amount of the strong base 1,4-diazabicyclo[2.2.2]octane in many cases produced no product or poor yields of **7** were obtained. Further analysis of the reaction mixtures revealed decomposition of **6** to substituted anilines and other unidentified products. However, when the reaction mixtures were

Scheme 2. Synthesis of *N*,*N*′-Diaryl Cyanoguanidines



subjected to microwave heating (typically <20 min), efficient conversion of thioethers **6** to cyanoguanidines **7** were observed without any decomposed products.

Table 1. Effects of Solvent and Temperature on the Yield of **7a**

T °C	2-propanol	CH_3CN	CH_2Cl_2
23	77	60	5
40	90	67	7
80	95	78	
100	90	80	

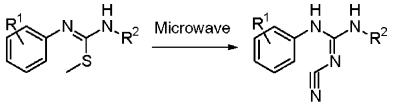
To explore the full scope and versatility of this method, various conditions were investigated, including solvent and temperature variations, and different substituents on the phenyl rings. Highlighted in Table 1 for compound **7a**, for example, is the influence of solvent and temperature on the reaction yield. It was found that 2-propanol provided the best yield at 80 °C, although other polar solvents such as acetonitrile gave moderate yields. Negligible product formation was observed in methylene chloride and other nonpolar solvents.

These results are consistent with what is known in the literature reports, namely, that solvent polarity plays a pivotal role in nucleophilic reactions. In addition, polar solvents tend to couple with microwave energy efficiently, thus resulting in a rapid rise in temperature of the reaction mixture and accelerated reaction rates.

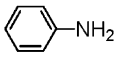
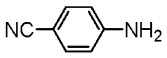
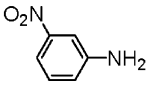
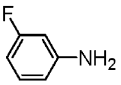
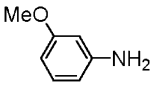
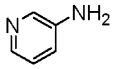
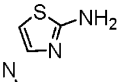
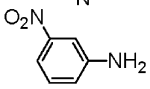
It is noteworthy that when microwave conditions were utilized, a cleaner reaction accompanied with higher yields was observed in the absence of base catalyst.

(6) Novak, L.; Hanania, M.; Kovacs, P.; Kovacs, C. E.; Kolonits, P.; Szantay, C. *Synth. Commun.* **1999**, *29*, 1757.
(7) Xu, G.; Wang, Y. G. *Org. Lett.* **2004**, *6*, 985.
(8) Hayes, B. L. *Microwave Synthesis, Chemistry at the Speed of Light*; CEM Publishing: Matthews, North Carolina, 2002; Chapter 1, p 16.

Table 2. Microwave Synthesis of Cyanoguanidines[a,9]



6a-h 7a-h

entry	6	R^1	R^2	compound 7 (yield%)[b]
1	6a	H		7a (95)
2	6b	H		7b (90)
3	6c	H		7c (86)
4	6d	H		7d (95)
5	6e	H		7e (99)
6	6f	H		7f (92)
7	6g	H		7g (88)
8	6h	NO_2		7h (90)

[a] Reactions were irradiated for 20 min in 2-propanol at 80 °C with CEM Discovery. [b] Isolated yields.

As shown in Table 2, a study of the electronic effect with various substituents on the phenyl rings was conducted. Under our reaction conditions, electron-donating substituents readily provided cyanoguanidines in high yields (Table 2, entry 5). Surprisingly, electron-withdrawing-substituted cyanoguanidines were obtained in high yields as well, as highlighted by nitro-containing **7c** and **7h**, which were obtained in 86 and 90% yield, respectively. It is worth noting that Atwal et al.[5] had reported 0% yield in their efforts to synthesize a similar compound. This result is significant since there is no literature precedent for the synthesis of *N*,*N*′-diaryl cyanoguanidines bearing electron-withdrawing groups. Furthermore, the reaction is not limited to arylamines but can be used with heterocyclic amines such as pyridine (Table 2, entry 6) and thiozole (Table 2, entry 7) as well.

In conclusion, we have described a straightforward and high-yielding method for the synthesis of *N*,*N*′-diaryl cyanoguanidines from their corresponding thioethers under mild conditions using microwave irradiation. This method is independent of electronic factors and compatible with a variety of substituent groups.

Supporting Information Available: Experimental procedures and spectral data for compounds **7a**−**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050728Q

(9) **Typical Procedure for the Preparation of Cyanoguanidine.** (**7a** as an example) Thioether **6a** (0.5 g, 2 mmol) was dissolved in 2-propanol (5 mL), treated with NaHNCN (0.16 g, 2.5 mmol), and heated in a microwave (20 min, powermax, 80 °C). The solvent was evaporated, and the residue was partitioned between EtOAc and H_2O. The organic layer was dried with $MgSO_4$ and filtered, and the solvent was evaporated. Column chromatography of the residue provided **7a** in 95% yield. ^{1}H NMR (300 MHz, DMSO) δ: 7.01−7.04 (m, 2H); 7.21 (bs, 8H); 9.37 (s, 2H), mp = 198−200 °C. MS (ESI): 235.1 (MH^-). Analytical data are in agreement with literature values.