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Facile synthesis of N-substituted pyrroles via microwave-induced bismuth nitrate-catalyzed reaction

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ABSTRACT

Simple synthesis of N-substituted pyrroles using microwave-induced bismuth nitrate-catalyzed reaction has been accomplished with an excellent yield. A plausible mechanism has been advanced. This reaction also provides a simple method to prepare diverse varieties of N-substituted pyrrole derivatives with less nucleophilic polyaromatic amines.

1. Introduction

Pyrroles are an important class of compounds with different biological activities.[1] Many methods for the synthesis of diversely substituted pyrroles have been developed.[2] Conjugate addition reactions,[3] transition metal-mediated reactions,[4] reductive couplings,[5] aza-Wittig reactions,[6] and other multistep operations[7] have been performed for the synthesis of pyrroles. Despite these huge developments, the Paal-Knorr[8] reaction is considered to be the most attractive method for the synthesis of pyrroles. In this Letter, we describe a simple method for synthesis of N-substituted pyrroles starting from commercially available 2, 5-dimethoxytetrahydrofuran and various (aliphatic, aromatic, heteroaromatic, and polyaromatic) amines by bismuth nitrate-catalyzed reaction in a microwave oven. This reaction is extremely rapid and produces products in excellent yields.

2. Results and discussion

Our research group demonstrated several studies directed toward the synthesis of β-lactams and polycyclic aromatic compounds. We[9] performed a structure–activity relationship study of various polyaromatic compounds toward the development of novel anticancer agents. It was reported that the modification of the terminal heterocyclic ring is crucial in determining the biological activity of these compounds. Because of the biological activities of these derivatives, we became interested in the synthesis of pyrroles bound to the amines of different structures. Since Paal–Knorr method requires a 1,4-dicarbonyl compound and Lewis acids as catalysts, we envision that our work on bismuth nitrate-catalyzed[10] reactions on acetal and glycosylation may prove useful for the facile synthesis of pyrroles under mild conditions if we select 2, 5-dimethoxytetrahydrofuran (**1**) as one of the reactants. Our hypothesis has been tested by reacting different types of amines (**2**) and 2,5-dimethoxytetrahydrofuran in a microwave oven in the presence of bismuth nitrate as a catalyst. It is remarkable to note that the reaction proceeded extremely well in the absence of any solvent.[11] However, solvent can also be used. Reactions performed without solvent (Table 1, entries 1, 4, and 7) are faster and high yielding than those performed in THF and water (Table 1, entries 2, 3, 5, 6, 8, and 9). Most of the reactions are completed within 5–15 min of irradiation at 75 °C and at 300 W power level. The yields of the products are also shown in Table 1. Aliphatic and aromatic amines produce pyrroles in very high yields. Importantly, the reaction with naphthylamine proceeded faster than that with monocyclic aromatic amino compounds (Scheme 1 and Table 1). This method has been applied with other bismuth-based reagents in catalytic proportion (5–10 mol %; bismuth chloride, bismuth subnitrate, bismuth oxide, and bismuth bromide). Stannic chloride, zinc chloride, and boron trifluoride etherate failed to improve the yield of the products. The best results have been observed with bismuth nitrate as the catalyst.

The methoxy groups in **1** can be deprotected under acidic conditions and microwave irradiation. The intermediate can easily

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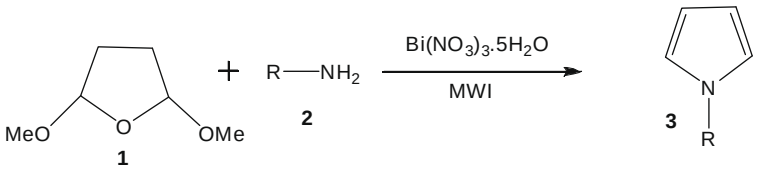
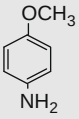
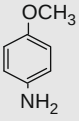
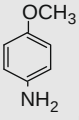
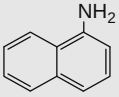
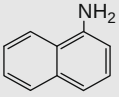
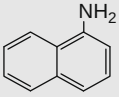
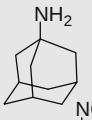
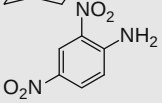


Scheme 1.

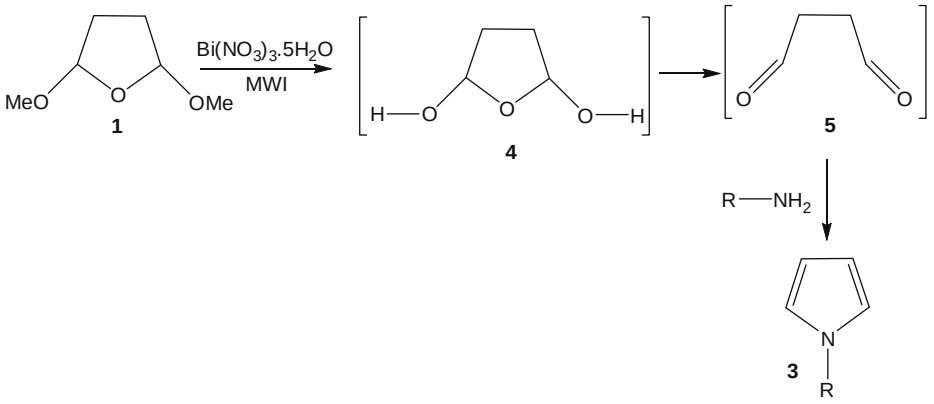
Table 1
Bismuth nitrate pentahydrate-catalyzed microwave-assisted synthesis of pyrroles from the reaction between amine (1 mmol) and 2,5-dimethoxytetrahydrofuran (1 mmol)

Entry	RNH_2	Solvent	$Bi(NO_3)_3{\cdot}5H_2O$ (mg)	MWI (temp/time/pressure)	Yield[a] (%)
1		Neat	20	300 W 90 °C 5 min	100
2		THF	50	300 W 75 °C 15 min	90
3		H_2O	20	300 W 90 °C 5 min	95
4		Neat	30	300 W 90 °C 10 min	95
5		THF	40	300 W 90 °C 10 min	85
6		H_2O	30	300 W 90 °C 10 min	85
7		Neat	20	300 W 75 °C 5 min	100
8		THF	20	300 W 90 °C 10 min	90
9		H_2O	20	300 W 90 °C 10 min	95
10		Neat	20	300 W 90 °C 10 min	85
11		THF	30	300 W 140 °C 40 min	74
12		Neat	20	300 W 110 °C 40 min	92

[a] NMR indicated the formation of the product without any side reactions. Starting materials were consumed completely.

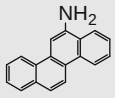
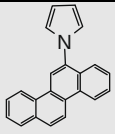
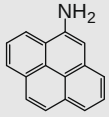
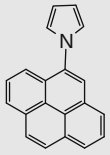
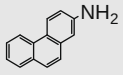
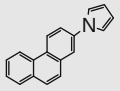
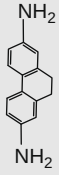
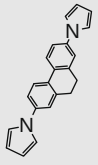
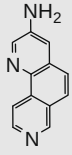
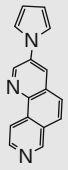
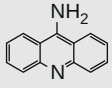
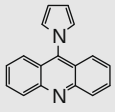
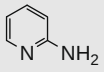
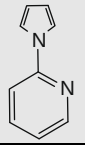
form the reactive dialdehyde **2**. The reactive dialdehyde **2** on reaction with amines can lead to pyrroles **3** following a nucleophilic addition and subsequent dehydration-aromatization route. This reaction suggests the capability of bismuth nitrate to serve as a Lewis activator (Scheme 2).

Proton NMR spectroscopy has been used to strengthen the proposed mechanism as shown in Scheme 2. ^1H NMR has been taken upon irradiation of a $CDCl_3$ solution of **1** for 5 min. A downfield signal due to the –CHO group is observed. The intensity of the –CHO group becomes more predominant in the ^1H NMR when **1** is



Scheme 2. Bismuth nitrate-catalyzed pyrrole synthesis: plausible mechanism of the reaction.

Table 2
Microwave-induced synthesis of pyrroles attached with polyaromatic/heteroaromatic systems

Entry	Anime	Solvent	$Bi(NO_3)_3{\cdot}5H_2O$ (mg)	MWI (power/temp/time)	Product	Yield[a] (%)
1		THF	20	300 W 120 °C 5 min		85
2		THF	20	300 W 110 °C 15 min		82
3		THF	20	300 W 120 °C 5 min		89
4		THF	20	300 W 150 °C 35 min		80
5		THF	20	300 W 150 °C 50 min		77
6		THF	20	300 W 110 °C 30 min		82
7		Neat	20	300 W 90 °C 5 min		95

[a] NMR indicated the formation of the product without any side reactions. Starting materials were consumed completely.

irradiated in $CDCl_3$ in the presence of catalytic amounts of bismuth nitrate. This suggests the formation of **5** in the reaction media in the presence of bismuth nitrate and microwave irradiation.

The reaction between **1** and **2** can give pyrrole (about 60%) in the absence of bismuth nitrate on irradiation of the reaction mixture for a long time. However, in the presence of bismuth nitrate,

in most of the cases, the reaction gives products within 5–15 min (Table 1). The presence of small amounts of bismuth nitrate (~5 mol %) is necessary for the success of the reaction. The reaction fails to produce the product in satisfactory yields at room temperature (without microwave irradiation), the reaction produces the product in a low yield at a high temperature (150 °C, 1 h, without microwave irradiation) along with uncharacterized materials.

As part of our continuous research[9] in the field of polyaromatic anticancer drug development, we have applied our newly developed procedure in the synthesis of polyaromatic and heteroaromatic pyrrole derivatives. It has been found that the method is equally effective with much less nucleophilic amines. However, for polyaromatic amines, THF is the solvent of choice for the preparation of N-substituted pyrroles. Polyaromatic amines are not soluble in water. It has also been found that these types of compounds give poor yields of products in the absence of a solvent. The results are summarized in Table 2.

In conclusion, the present bismuth nitrate-catalyzed microwave-induced method is superior to the other Lewis acid-mediated syntheses of N-substituted pyrroles in terms of yield of the products (more than 85–100% yields) and time of the reaction. The described synthetic protocol allows for the preparation of a variety of pyrroles without the use of expensive or sensitive reagents. Based on the simplicity of the procedure, products can be isolated very easily. The method as reported herein may find applications in other areas of research.

3. Experimental

General procedure for the synthesis of pyrroles (**3**): Amine **1** (1.0 mmol), 2,5-dimethoxytetrahydrofuran (1.2 mmol), and bismuth nitrate pentahydrate (10–30 mg) were irradiated in a CEM automated microwave oven as specified in Table 1. Ether (10 mL) was added to the reaction mixture and it was then filtered. Pure product was isolated from the reaction mixture after evaporation of ether.

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References and notes

1. For some biologically active pyrroles. see: (a) Lainton, J. A. H.; Hoffman, J. W.; Martin, B. R.; Compton, D. R. *Tetrahedron Lett.* **1995**, *36*, 1401; (b) De Leon, C. Y.; Ganem, B. *Tetrahedron* **1997**, *53*, 7731.
2. Gilchrist, T. L. *J. Chem. Soc., Perkin Trans 1* **1998**, 615.
3. Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283.
4. Iwasawa, N.; Maeyama, K.; Saitou, M. *J. Am. Chem. Soc.* **1997**, *119*, 1486.
5. Furstner, A.; Weintritt, H.; Hupperts, A. *J. Org. Chem.* **1995**, *60*, 6637.
6. Katritzky, A.; Jiang, J.; Steel, P. J. *J. Org. Chem.* **1994**, *59*, 4551.
7. (a) Hantzsch, A. *Chem. Ber.* **1890**, *23*, 1474; (b) Broadbent, H. S.; Burnharm, W. S.; Olsen, R. K.; Sheely, R. M. *J. Heterocycl. Chem.* **1968**, *5*, 757; (c) Bayer, H. O.; Gotthardt, H.; Huisgen, R. *Chem. Ber.* **1970**, *103*, 2356; (d) Huisgen, R.; Gotthardt, H.; Bayer, H. O.; Schaefter, F. C. *Chem. Ber.* **1970**, *103*, 2611; (e) Cooney, J. V.; McEwen, W. E. *J. Org. Chem.* **1981**, *46*, 2570; (f) Berree, F.; Marchand, E.; Morel, G. *Tetrahedron Lett.* **1992**, *33*, 6155; (g) Arcadi, A.; Rossi, E. *Tetrahedron* **1998**, *54*, 15253; (h) Periasamy, M.; Srinivas, G.; Bharati, P. *J. Org. Chem.* **1999**, *64*, 4204.
8. Ruault, P.; Pilard, J.-F.; Touaux, B.; Boullet, F. T.; Hamelin, J. *Synlett* **1994**, 935.
9. (a) Becker, F. F.; Banik, B. K. *Polycyclic. Bioorg. Med. Chem. Lett.* **1998**, *8*, 2877; (b) Becker, F. F.; Mukhopadhyay, C.; Hackfeld, L.; Banik, I.; Banik, B. K. *Bioorg. Med. Chem.* **2000**, *8*, 2693; (c) Banik, B. K.; Becker, F. F. *Bioorg. Med. Chem.* **2001**, *9*, 5936; (d) Banik, B. K.; Becker, F. F. *Curr. Med. Chem.* **2001**, *8*, 1513; (e) Banik, I.; Becker, F. F.; Banik, B. K. *J. Med. Chem.* **2003**, *46*, 12.
10. (a) Samajdar, S.; Basu, M. K.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2001**, *42*, 4425; (b) Basu, M. K.; Samajdar, S.; Becker, F. F.; Banik, B. K. *Synlett* **2002**, 319; (c) Banik, B. K.; Adler, D.; Nguyen, P.; Srivastava, N. *Heterocycles* **2003**, *61*, 101.
11. For some ecologically friendly reactions from our group, see: (a) Banik, B. K.; Suhendra, M.; Banik, I.; Becker, F. F. *Synth. Commun.* **2000**, *30*, 3745; (b) Banik, B. K.; Banik, I.; Hackfeld, L.; Becker, F. F. *Heterocycles* **2001**, *56*, 467; (c) Banik, B. K.; Hackfeld, L.; Becker, F. F. *Synth. Commun.* **2001**, *31*, 129; (d) Samajdar, S.; Becker, F. F.; Banik, B. K. *Synth. Commun.* **2001**, *31*, 2691; (e) Mukhopadhyay, C.; Becker, F. F.; Banik, B. K. *Synth. Commun.* **2001**, *31*, 2399; (f) Dasgupta, S. K.; Banik, B. K. *Tetrahedron Lett.* **2002**, *43*, 9445; (g) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (h) Banik, B. K.; Garcia, I.; Morales, F. R. *Heterocycles* **2007**, *71*, 919.