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A straightforward highly efficient Paal–Knorr synthesis of pyrroles

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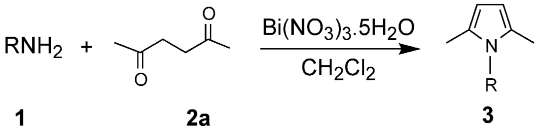
Abstract—A straightforward simple synthesis of substituted pyrroles using bismuth nitrate-catalyzed modified Paal–Knorr method has been accomplished with an excellent yield. This method produces pyrroles with multicyclic aromatic amines.

From the extensive work on the synthesis of pyrroles, the Paal–Knorr method has received increasing attention from synthetic perspectives.[1] These techniques clearly extend the scope of this objective, but success with less nucleophilic aromatic amines has not been reported. Moreover, microwave irradiation or considerable amounts of acids are always necessary in the Paal–Knorr reaction.[2–4] Therefore, mild reaction conditions that can overcome the shortcomings of the previous methods are necessary. In this letter, we describe a straightforward synthesis of substituted pyrroles by bismuth nitrate-catalyzed modified Paal–Knorr reactions.

In our earlier paper, we[5] performed a structure–activity relationship study of various polyaromatic compounds prepared from their corresponding amines toward the development of novel anticancer agents. Based on the promising biological activity of these compounds, we became interested in the synthesis of pyrroles bound to the polyaromatic amines. It was realized that our own work on bismuth nitrate-catalyzed[6] organic transformations could be very fruitful for the facile synthesis of pyrroles under very mild conditions.

In our procedure, the starting materials (amines and ketones) are mixed with bismuth nitrate (5 mol %) in the presence of dichloromethane and the solution is kept at room temperature for the specified time. Several amines **1** were used for this study. The other starting material was 2,5-diketone **2** (Scheme 1). The less basic aromatic amines needed longer reaction time for the generation of the products although the yields are comparable to the more basic amino compounds. If one of the reactants is a liquid, the reaction can proceed without solvent. If the reaction mixture is very thick slurry, a small amount of solvent (1 g of the substrate/1 mL solvent) is necessary for better yield of the product.



Scheme 1.

This method of pyrrole formation proceeds exceedingly well with multicyclic aromatic amines (Table 1, entries 3–7) without the need for strong Lewis acids or other strong acids. In addition, all of the reactions were successful at room temperature. In contrast, previously even with simple aniline derivatives, high temperature and/or microwave irradiation were required.

To improve the scope of this bismuth nitrate-catalyzed method of pyrrole formation, substituted diketones **2b** and **2c** were used. Under identical conditions, a clean formation of pyrrole **3k** was observed with **2b** and 1,2,5-trisubstituted pyrroles were accessible. However, the yield of the product **3l** was low when **2c** was used as the ketone component (Scheme 2).

Keywords: Pyrroles; Bismuth nitrate; Paal–Knorr reaction.

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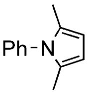
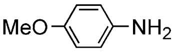
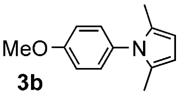
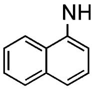
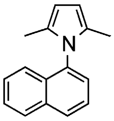
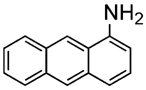
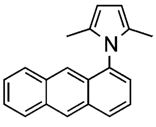
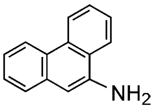
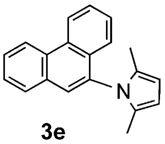
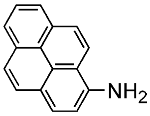
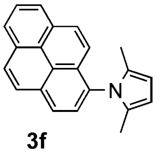
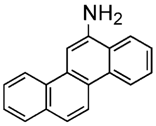
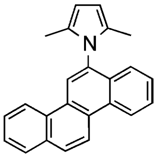
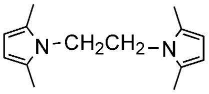
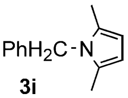
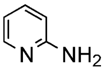
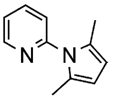
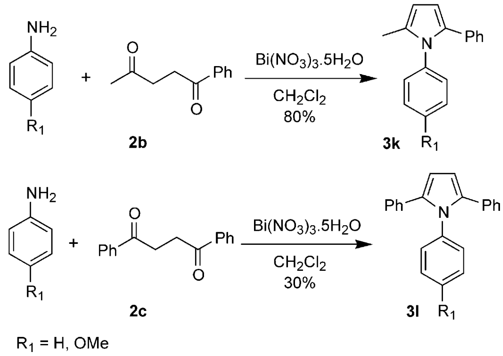
Table 1. Bismuth nitrate-catalyzed synthesis of pyrrole **3**

Entry	Amine	Product	Time (h)	Yield (%)
1	Ph·NH_2	 **3a**	10	96
2		 **3b**	15	81
3		 **3c**	11	83
4		 **3d**	19	98
5		 **3e**	18	94
6		 **3f**	20	88
7		 **3g**	22	85
8	$NH_2(CH_2)_2NH_2$	 **3h**	10	85
9	$PhCH_2NH_2$	 **3i**	10	95
10		 **3j**	25	70



Scheme 2.

The reaction between **1** and **2** does not proceed without bismuth nitrate.[7] The presence of small amounts of bismuth nitrate (1–0.05 mmol) is essential for the success of the reaction. To confirm the role of bismuth nitrate, a few other salts were investigated. Ferric nitrate, sodium nitrate, zinc nitrate, copper nitrate, copper sulfate and zinc sulfate proved to be ineffective. Bismuth chloride produced low yield of the products with more nucleophilic amines (Table 1, aniline and *p*-anisidine, entries 1 and 2). However, with polyaromatic amines (Table 1, 6-aminochrysene, entry 7), the reaction failed to produce pyrrole. The failure of these salts to promote a Paal–Knorr reaction indicates the importance of bismuth nitrate in this reaction. The present bismuth nitrate-catalyzed reaction is much superior over the Lewis acid-mediated synthesis of pyrroles in terms of yield of the products. The reaction proceeds in the presence of small amount of nitric acid, although the isolated yields of the products are not comparable with those of bismuth nitrate-catalyzed process. Therefore, the use of commercially available nontoxic bismuth nitrate as the catalyst seems to be very convenient for Paal–Knorr reaction. Notably, this method has been proved to be highly effective for the synthesis of pyrroles with several less nucleophilic polyaromatic aromatic amines.[8] In addition, unlike many other procedures, no extra energy source, like microwave irradiation or ultrasound is needed for the success of the reaction. This method has great potential for future application.

Acknowledgements

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References and notes

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6. We have devised several bismuth nitrate-induced methods. For example, see: (a) Samajdar, S.; Becker, F. F.; Banik, B. K. *Tetrahedron Lett.* **2000**, *41*, 8017; (b) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (c) Banik, B. K.; Samajdar, S.; Banik, I.; Ng, S.; Hann, J. *Heterocycles* **2003**, *61*, 97; (d) Banik, B. K.; Adler, D.; Nguyen, P.; Srivastava, N. *Heterocycles* **2003**, *61*, 101; (e) Srivastava, N.; Dasgupta, S. K.; Banik, B. K. *Tetrahedron Lett.* **2003**, *44*, 1191.
7. The application of bismuth salts-mediated reaction is gaining attention in synthetic chemistry. For some examples, see: (a) Carrigan, M. D.; Sarapa, D.; Smith, R. C.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2002**, *67*, 1027; (b) Eash, K. J.; Paulia, M. S.; Wieland, L. C.; Mohan, R. S. *J. Org. Chem.* **2000**, *65*, 8399.
8. General procedure for the synthesis of pyrroles (**3**): To a solution of the amine **1** (1 mmol) and hexane-2,4-dione **2** (1.1 mmol) in dichloromethane (2 mL) at room temperature, bismuth nitrate pentahydrate (1–0.5 mmol) was added. The mixture was allowed to stir at this temperature for a period specified in Table 1. This resulting mixture was washed successively with saturated $NaHCO_3$ solution (2 mL) and brine (2 mL). The organic layer was dried with sodium sulfate and concentrated. The residue was purified by filtration through a short column of florisil using ethyl acetate–hexanes (30:70) as the solvent system to afford the pyrroles (70–98% yield).
1-(1-Naphthalenyl)-2,5-dimethylpyrrole: mp 118 °C; IR (CH_2Cl_2) 3062, 1595, 1578, 1522, 1506, 1468 cm^{-1}; ^1H NMR (300 MHz) δ 1.89 (6H, s), 6.00 (2H, s), 7.13 (1H, d, $J = 8.34$ Hz), 7.39–7.57 (4H, m), 7.91 (2H, d, $J = 8.25$ Hz)
1-(6-Chrysenyl)-2,5-dimethylpyrrole: mp 225 °C; ^1H NMR (300 MHz) δ 1.97 (6H, s), 5.99 (2H, s), 7.25 (1H, m), 7.58–7.74 (4H, m), 8.03 (1H, m), 8.08 (1H, d, $J = 9.09$ Hz), 8.69 (2H, m), 8.76 (1H, d, $J = 9.10$ Hz), 8.84 (1H, d, $J = 8.20$ Hz).