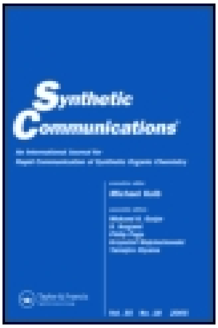

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A Facile Synthesis of N-Substituted Pyrroles

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A FACILE SYNTHESIS OF *N*-SUBSTITUTED PYRROLES

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Abstract: Phosphorous pentoxide is the catalyst of choice for the facile conversion of primary amines, aromatic amines, sulfonamides and primary amides into the corresponding *N*-substituted pyrroles from 2,5-dimethoxytetrahydrofuran.

A variety of methods exists for the preparation of *N*-substituted pyrroles[1]. One of the most commonly used methods is condensation of primary amines[2,3], aromatic amines[4], sulfonamides[5] and primary amides[6] (**1**) with 2,5-dimethoxytetrahydrofuran (**2**) to give the corresponding pyrroles **3**. Usually, this reaction is accomplished by using acetic acid as both the catalyst and the solvent. The employment of other acids has hardly been reported for this purpose[7].

Studying this procedure, we treated phenylalanine methyl ester **1** (R = $CH(PhCH_2)COOCH_3$) with **2** in refluxing acetic acid and obtained the corresponding pyrrole **3** (R = $CH(PhCH_2)COOCH_3$) in only 14% yield. This low yield is apparently due to the lability of the pyrrole moiety under these acidic reaction conditions. Buffering the reaction medium by addition of sodium acetate to acetic acid (ratio 1 : 1) gave **3** (R = $CH(PhCH_2)COOCH_3$) in a better yield (80%); however, this procedure required laborious purification.

Here we report a simple, efficient and more general method for the synthesis of *N*-substituted pyrroles **3**.

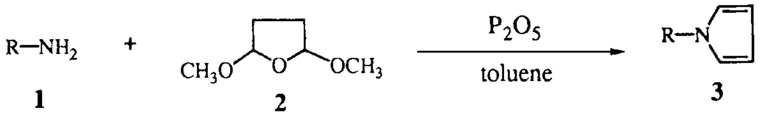
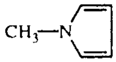
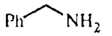
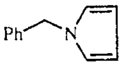
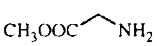
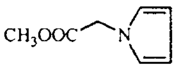
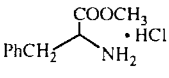
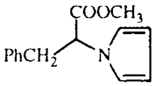


Table 1 Conversion of primary amines into *N*-alkyl pyrroles

entry	primary amines	*N*-alkyl pyrroles	conditions	yield (%)	ref.
1	CH_3NH_2 •HCl		A, 20 min	46 *	2b
2			A, 10 min	96	2a
3			A, 10 min	91	2c
4			A, 20 min	62	3b

* The yield was determined by GC.

It is well-known that phosphorous pentoxide reacts with alcohols to give the corresponding phosphoric acid esters[8]. Based upon this property and its low acidity, we anticipated that phosphorous pentoxide, under suitable conditions, should be a superior condensating reagent for the condensation of **1** and **2**.

The results exceeded our expectation. Phosphorous pentoxide is convenient to use and the required reaction time was short (10-45 min). Progress of the reaction can be monitored by following the color of the reaction mixture; it changes from yellow to brawn to black upon completion. Primary amines (Table 1) and sulfonamides (Table 3) require shorter reaction times (10-20 min) than aromatic amines (Table 2) and amides (Table 4); for these last two classes of compounds we observed that yields improved when the reaction mixture is kept first at 60 °C (30 min) and then at 110 °C (15 min). Remarkably, when the hydrochloride of methyl glycinate (Table 1, entry 3) was used, the yield dropped from 91% to 30%. From this we concluded that the yields of entries 1 and 4 are amenable to improvement if the free amine is used instead of the hydrochloride salts.

This procedure works also for the conversion of aroyl amides (entries 12 and 13) and stearamide (entry 11) into acylpyrroles. However, with these acylamides the formation of acylpyrroles is accompanied by the formation of the corresponding nitriles as minor components. Acetamide yielded even exclusively acetonitrile (entry 10).

Table 2 Conversion of aromatic amines into *N*-aryl pyrroles

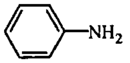
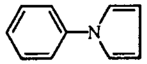
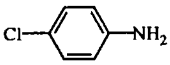
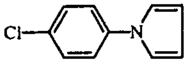
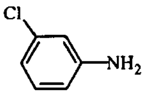
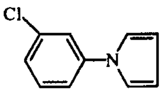
entry	aromatic amines	*N*-aryl pyrroles	conditions	yield (%)	ref.
5			**B**	87	4
6			**B**	79	4
7			**B**	89	4

Table 3 Conversion of sulfonamides into *N*-sulfonyl pyrroles

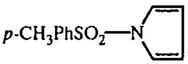
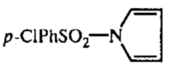
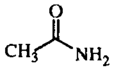
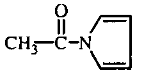
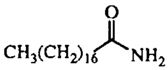
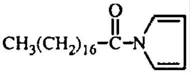
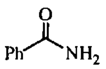
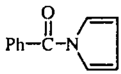
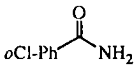
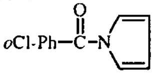
entry	sulfonamides[11]	*N*-sulfonyl pyrroles	conditions	yield (%)	ref.
8	*p*-CH_3PhSO_2—NH_2		A, 20 min	quant.	5
9	*p*-$ClPhSO_2$—NH_2		A, 20 min	85	5

Table 4 Conversion of primary amides into *N*-acyl pyrroles

entry	primary amines	*N*-acyl pyrroles	conditions	yield (%)	ref.
10			A, 20 min. or **B**	0	6a
11			**B**	75*	6b
12			**B**	85**	6b
13			**B**	88***	5

* Ca. 25% of stearonitrile was present in the reaction mixture according to the ^1H NMR spectrum.

** Ca. 15% of benzonitrile was present in the reaction mixture according to the ^1H NMR spectrum.

*** *O*-chlorobenzonitrile was obtained in 3% yield after chromatographic purification.

This is a new and efficient procedure which gives products[10] that can be isolated easily by column chromatography. The yields reported below are, except when indicated, of isolated compounds.

Experimental

Procedure A: The condensation was carried out on a 10 mmol scale in a 50 mL round-bottom flask which was dried in the oven at 125 ℃ overnight and cooled under nitrogen atmosphere. Dry toluene was obtained by storage over 3 Å mol sieves for 24 h at rt. To a stirred suspension of 1.42 g (10 mmol) of phosphorous pentoxide and 10 mmol of RNH_2 (**1**) in 40 mL of dry toluene, kept at rt under nitrogen, was added 1.8 g (15 mmol) of 2,5-dimethoxytetrahydrofuran (**2**). The reaction mixture was subsequently stirred at 110 ℃ for the time indicated in the tables (10-20 min) and was then quenched with 10 mL of 2 N aqueous KOH solution. The solvents were evaporated under reduced pressure and the residue was subjected to column chromatography using a short silica column (7 cm) and a 1/4 mixture of ethyl acetate and hexane as eluent to give the desired, pure product[10].

Procedure B: The reaction mixture, consisting of 1.42 g (10 mmol) of phosphorous pentoxide, 10 mmol of RNH_2 (**1**) and 1.43 g (11 mmol) of 2,5-dimethoxytetrahydrofuran (**2**), was kept at 60 ℃ for 30 min and then at 110 ℃ for another 15 min. The reaction mixture was then worked up as described for procedure A.

References:

1. Bird, C.W. and Cheeseman, G.W.H., "Comprehensive Heterocyclic Chemistry," Katritzky, A.R.F. Ed.; Pergamon Press Ltd. Oxford, 1984; pp. 89.
2. (a) Clauson-Kaas, N. and Tyle, Z., Acta. Chem. Scand., 1952, 6, 667. (b) Clauson-Kaas, N. and Tyle, Z., Acta. Chem. Scand., 1952, 6, 867. (c) Nudelman, A. and Patchornik, A., Chem. Abstr., 1979, 91, 74634k. (d) Box, S.J. and Corbett, D.F., Tetrahedron Lett., 1981, 3293.
3. (a) Ong-Lee, A.; Sylvester, L. and Wasley, J.W.F., J. Heterocyclic Chem., 1983, 20, 1565. (b) Kashima, C.; Maruyama, T.; Harada, K.; Hibi, S. and Omote, Y., J. Chem. Res. (s), 1988, 62.
4. (a) Josey, A.D. and Jenner, E.L., J. Org. Chem., 1962, 27, 2466. (b) Garcia, E.E., Org. Prep. Proced. Int., 1974, 6, 11. (c) Chakrabarti, J.K. and Tupper, D.E., J. Heterocyclic Chem., 1974, 11, 417. (d) Svetlik, J., Heterocycles, 1984, 22, 2513.

5. Wasley, J.W.F. and Chan, K., Synth. Commun., 1973, 3, 303.
6. (a) Rainey, J.L. and Adkins, H., J. Am. Chem. Soc., 1939, 61, 1104. (b) Lee, S.D.; Brook, M.A. and Chan, T.H., Tetrahedron Lett., 1983, 24, 1569.
7. For the condensation of amines with 2,5-dimethoxytetrahydrofuran mediated by HCl, see: Stefancich, G.; Artico, M.; Corelli, F. and Massa, S., Synthesis, 1983, 757.
8. Fieser, L.F. and Fieser, M., "Reagents for Organic Synthesis," John Wiley & Sons, New York, 1967; pp. 892.
9. McElvain, S.M. and Clarke, R.L., J. Am. Chem. Soc., 1947, 69, 2657.
10. Of all compounds isolated, the ^1H NMR, ^{13}C NMR spectra and melting points were compared with literature data.
11. The sulfonamides were prepared from the corresponding sulfonyl chlorides according to: Furniss, B.S., "Textbook of Practical Organic Chemistry," 4th Ed.; Longman Inc., New York, 1986; pp. 650.

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