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A Facile and Efficient Synthesis of Substituted Pyrroles by Three Component Coupling Reaction of Amines, Aldehydes and Nitroalkanes

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Abstract: A facile and efficient synthesis of highly substituted pyrroles has been achieved by a one-pot three-component coupling reaction of aldehyde, amine and nitroalkane by triethyl orthoformate.

Keywords: Pyrrole, nitroalkane, aldehyde.

Pyrroles are very important heterocyclic compounds. They constitute the core unit of many natural products and serve as building blocks for porphyrin synthesis[1]. Several substituted pyrroles have been shown to posses extensively pharmacological activities[2] and have been used clinically. Although there are quite a number of methods for the synthesis of pyrroles, most of them involve multistep synthetic operations which lower the overall yield[3-5]. Recently, a few one-step procedures have been reported[6-8], but they are not very satisfactory with regard to reaction conditions (such as the use of catalyst and the prolonged reaction time), yield, generality and scope of substitution at the ring. Therefore, it is necessary to develop a simple, efficient and more general method for the synthesis of this useful heterocyclic nucleus.

In the course of our study on the synthesis of pyrroles, we found that the three-component coupling reaction of amines, aldehydes and nitroalkanes gave the corresponding pyrroles in good yield in the presence of triethyl orthoformate(**Scheme 1**).

A mixture of butylamine(**1a**), butylaldehyde(**2b**) and nitroethane (**3a**) in ethanol was allowed to react at 60°C for 5h in the presence of triethyl orthoformate. N-Butyl-2-methyl-4-ethyl-3-propylpyrrole(**4c**) was obtained in 88% yield. On the basis of this result, a wide range of structurally varied α-H aldehydes could couple with a varity of aliphatic and aromatic amines and nitroalkanes to give the corresponding pyrroles, the results are summarized in **Table 1**. Except for acetaldehyde with which the reaction proceeded smoothly at 0°C for 1 h, and then at room temperature for 2 h). From the above results, regard to nitroalkanes for the coupling reaction, the reaction with nitromethane provides fair yield, however, higher homologues like nitropropane underwent smooth reaction, as well as nitroethane. Aliphatic α-H aldehydes have

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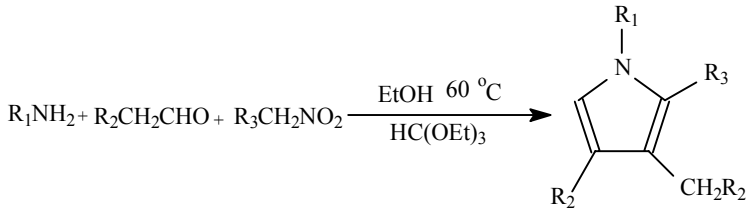
proved to react easily, while aromatic α-H aldehydes produce the corresponding pyrroles in lower yields, for its bulk in the formation α,β-unsaturated imines.

Scheme 1



1 **2** **3** **4**

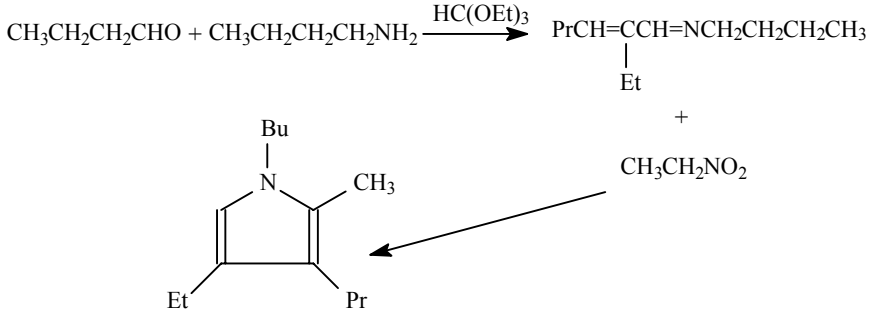
In order to investigate the reaction mechanism, the α,β-unsaturated imine **5** was allowed to react with nitroethane **3a** in ethanol at 60°C for 5h in the presence of triethyl orthoformate, the reaction afforded **4c** in 88% yield. Therefore, α,β-unsaturated imine 5

Table 1 Pyrroles prepared by three component couping reaction *via* **Scheme 1**

Compound	R_1	R_2	R_3	Isolated Yields (%)
4a	*n*-Bu (1a)	H (2a)	Me (3a)	84
4b	CH(Me)Ph (1b)	H (2a)	Me (3a)	80
4c	*n*-Bu (1a)	Et (2b)	Me (3a)	88
4d	CH(Me)Ph (1b)	Et (2b)	Me (3a)	83
4e	*n*-Bu (1a)	i-Pr (2c)	Me (3a)	80
4f	CH(Me)Ph (1b)	i-Pr (2c)	Me (3a)	77
4g	*n*-Bu (1a)	Ph (2d)	Me (3a)	75
4h	CH(Me)Ph (1b)	Ph (2d)	Me (3a)	70
4i	*n*-Bu (1a)	Et (2b)	H (3b)	61
4j	*n*-Bu (1a)	Et (2b)	Et 3c)	72
4k	Bn 1c)	Et (2b)	Me (3a)	86
4l	*t*-Bu (1d)	Et (2b)	Me (3a)	79
4m	CH_2COOEt (1e)	Et (2b)	Me (3a)	84
4n	CH(Me)COOEt (1f)	Et (2b)	Me (3a)	80

was proved to be the key intermediate of pyrrole, and a plausible reaction path for the presence coupling reaction is shown in **Scheme 2**. It is also shown that the α-H aldehyde with amine can condense smoothly to α,β-unsaturated imine in the presence of triethyl orthoformate.

Scheme 2



In conclusion, we have developed a new protocol for the synthesis of substituted pyrroles by three-component coupling reaction of amines, aldehydes and nitroalkanes, using triethyl orthoformate as catalyst. This protocol provided a cheap, easily- available and efficient catalysis for the synthesis of pyrrole by one-pot-three-component coupling reaction in comparison with the existing methods.

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9. Typical experimental procedure for the synthsis pyrrole **4a-4b**. The mixture was amine **1** (10.0 mmol) and nitroethane **3a** (20.0 mmol) in ethanol (30 mL) cooled with an ice-water bath. Acetaldehyde **2a** (20.0 mmol) was added by dropwise. The mixture was stirred at 0°C for 1 h, and then raise to room temperature for 2 h. After the solvent was removed under reduced pressure, the products were purified by silica gel column [silica gel H 60], eluting with hexane. The first fraction was collected and the solvent was evaporated.
Typical experimental procedure for the synthsis pyrrole **4c-4o** To a solution of amines **1** (10.0 mmol), nitroalkanes **3** (20 mmol) in ethanol (30 mL) were added aldehydes **2** (20.0 mmol) dropwise, and then triethyl orthoformate (10 mmol) was introduced. The mixture was stirred at 60°C for 5 h. After the solvent was removed under reduced pressure, the products were purified by silica gel column [silica gel H 60], eluting with hexane. The first fraction was collected and the solvent evaporated. The know compounds (**4c,4i-4l**) have been identified by comparison of the spectral data with reported. The spectra of all new compounds are presented below in order of their entries.
The structure of pyrroles. **4a** ^{1}H NMR($CDCl_3$, δ ppm): 6.49 (s, 1H), 5.91(s, 1H), 3.74 (t, 2H, *J* = 7.4 Hz.), 2.11 (s, 3H), 2.02 (s, 3H), 1.67-1.64 (m, 2H), 1.36-1.31 (m, 2H), 0.93 (t, 3H, *J* = 7.3 Hz.); ^{13}C NMR($CDCl_3$, δ ppm) : 124.6, 118.6, 114.7, 108.1, 46.8, 33.8, 20.3 , 14.0, 11.6, 9.7; **MS** (70 eV): *m/z* 151(M^+, 100%), 136(12%), 122(9%), 109(66). IR (neat): 2958, 2929, 2864, 1491, 1460, 1333, 1199, 700, 638 cm^{-1},
4h ^{1}H NMR($CDCl_3$, δ ppm) : 7.37-7.10(m, 13H), 7.03(d, 2H *J* = 7.5 Hz), 6.97 (s, 1H), 5.32(q, 1H, *J* = 7.0 Hz), 3.94 (s, 2H), 1.96 (s, 3H), 1.85 (d, 3H, *J* = 7.1 Hz.); ^{13}C NMR($CDCl_3$, δ ppm): 144.1, 142.7, 137.0, 129.0, 128.8, 128.6128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.4, 126.3, 126.0, 125.9, 125.6, 125.5, 124.4, 116.2, 114.9, 55.5, 30.7, 22.7, 10.5; MS (70 eV): *m/z* 351(M^+, 19%), 275(20), 247(18%), 105(100), 77(33). IR (neat): 3059, 3030, 2972, 2918, 2860, 1598, 1527, 1490, 1453, 1374, 1232, 1190, 1074, 1028, 741, 703cm^{-1}, **4m** ^{1}H NMR($CDCl_3$, δ ppm) : 6.67 (s, 1H), 2.59 (q, 2H, *J* =7.6 Hz), 2.48(t, 2H, *J* = 7.9 Hz), 2.47 (s, 3H), 1.72(s, 3H), 1.63-1.59 (m, 2H), 1.35 (t, 3H, *J* = 7.6 Hz), 0.89 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR($CDCl_3$, δ ppm): 124.8, 121.6, 120.9. 113.2, 55.3, 30.8, 27.0, 24.5, 18.6, 14.4, 14.3, 13.4; MS (70 eV): *m/z* 207(M^+, 26%), 178(100%), 136(19%). IR (neat): 2961, 2930, 2870, 1526, 1463, 1367, 1216, 912 cm^{-1},

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