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Conjugate addition of pyrroles to α,β-unsaturated ketones using copper bromide as a catalyst

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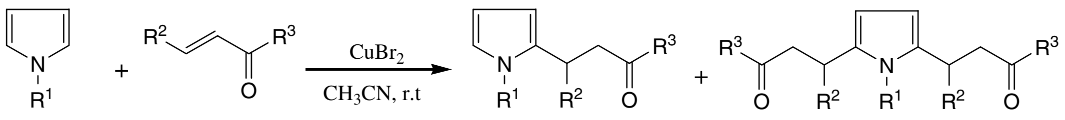
Abstract—Copper bromide was used as a catalyst for the addition of pyrroles to enones. When both the reactants were used in equimolar amounts, mono and dialkylated products were obtained. However, the use of excess enone furnished only dialkylated products. Thus, copper bromide was shown to be an efficient catalyst for the dialkylation of pyrroles.

Pyrrole and alkylated pyrroles are present as important structural components, and can serve as precursors for the synthesis of various biologically active compounds.[1] Amongst the various methods available, a useful procedure for C-alkylating pyrroles involves the Friedel–Crafts type conjugate addition of pyrrole to α,β-unsaturated aldehydes or ketones. Acid-catalyzed reactions of pyrrole are limited and require careful control of the acidity to prevent side reactions such as polymerization. As catalysts, indium chloride,[2] bismuth nitrate[3] and yttrium triflate[4] or metal triflates[5] have all been used for this reaction. An enantioselective conjugate addition of pyrrole using benzyl imidazolidinone salts has also been reported.[6] Recently, a microwave-assisted method was used[7] for the alkylation of pyrroles. There is only one report of the use of copper bromide as a catalyst for Friedel–Crafts type conjugate addition of indoles.[8] All the earlier reports mention the synthesis of mono-alkylated pyrroles except for one where indium chloride was used as a catalyst. We found that the use of an excess of enone gave dialkylated pyrroles in 2–5 h. In the present study, a very efficient method using copper bromide as a catalyst has been developed to achieve the dialkylation of pyrroles within 10 min in good yields.

Initially, pyrrole and chalcone were dissolved in acetonitrile and copper bromide (20 mol %) was added. The reaction mixture instantaneously changed colour from pale yellow to green to brown and TLC indicated the absence of a starting material. After work-up and chromatographic separation, 2-alkyl pyrrole, **10a**, and 2,5-dialkylpyrrole, **10b**, were obtained in a ratio of 1:3 in 85% yield (Scheme 1 and Table 1). Pyrrole alkylation was performed[9] using other α,β-unsaturated ketones, **5**–**8** and all the reactions resulted in mono- and dialkylated pyrroles in 25–85% yields, in various ratios



1-3 **4-8** **10a –20a** **10b –20b**

1. R^1= H, **2** R^1= Me, **3** R^1= COPh, **4** R^2= R^3 = Ph, **5** R^2= Ph, R^3= CH_3, **6** R^2= 4-ClC_6H_4, R^3= 3-$MeOC_6H_4$, **7** R^2= 4-ClC_6H_4, R^3 = Ph, **8** R^2=2-$MeOC_6H_4$, R^3 = Ph.

Scheme 1.

Keywords: Copper bromide; Pyrrole; α,β-Unsaturated ketones; Conjugate addition.

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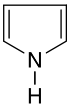
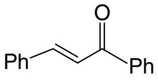
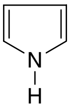
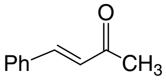
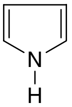
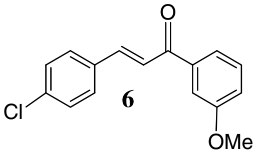
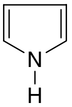
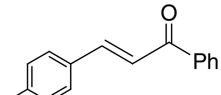
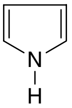
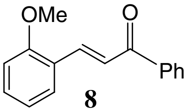
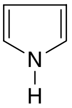
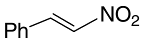
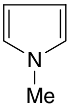
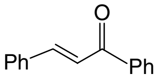
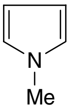
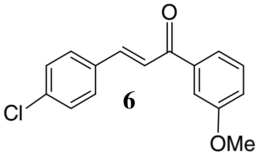
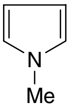
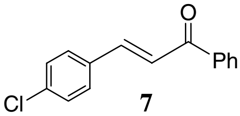
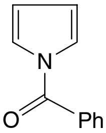
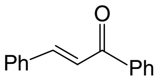
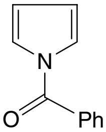
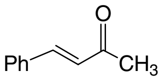
Table 1. $CuBr_2$-Catalyzed alkylation of pyrroles with α,β-unsaturated compounds using an equimolar ratio of reactants

Product	Nucleophile	Electrophile	2-Alkyl pyrrole (**a**) and 2,5-dialkyl pyrrole (**b**) total yield (%)	Ratio **a**:**b**
10		 **4**	85	1:3
11		 **5**	62	1:2
12		 **6**	68	1:1
13		 **7**	73	1:1
14		 **8**	64	1:2
15		 **9**	62	3:1
16		 **4**	69	1:2
17		 **6**	42	1:2
18		 **7**	25	1:2
19		 **4**	49	2:1
20		 **5**	28[a]	—

[a] Only monoalkylated pyrrole was obtained.

Table 2. Effect of solvents on the reaction of pyrrole **1** with enone **4**

Entry	Solvent	Time (s)	Yield (%)
1	Acetonitrile	10	85
2	Chloroform	120	48
3	Ethyl acetate	120	51
4	Dioxane	180	54

(Scheme 1 and Table 1). In accordance with the earlier report,[5] no C-alkylated product was detected in the reaction of pyrrole with cinnamaldehyde and the starting material was recovered. Although similar products were obtained in the reaction of pyrrole with nitrostyrene **9**, interestingly, the ratio of mono- to dialkylated products was reversed to 3:1 (Table 1).

Alkylation was also carried out with *N*-methyl and *N*-benzoyl pyrroles. *N*-Methyl pyrrole afforded monoalkylated compounds as the minor products and dialkylated pyrroles as the major products, while the reactions with *N*-benzoyl pyrrole showed a reverse ratio of the products (Table 1). The reaction of *N*-benzoyl pyrrole with enone **5** resulted in only monoalkylated product in 28% yield. This can be attributed to the reduced electron density on the ring carbon due to the electron-withdrawing benzoyl group on the ring nitrogen. *N*-Benzoyl pyrrole failed to give any reaction with enone **7**. *N*-Methyl and *N*-benzoyl pyrroles gave no reaction with nitrostyrene **9** under similar reaction conditions.

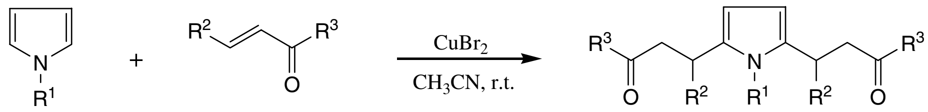
All the dialkylated pyrroles obtained were mixtures of two diastereomers. Typically, the two diastereomers of products **16–18** were successfully separated and characterized[10] using ^{1}H NMR and ^{13}C NMR.

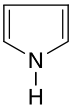
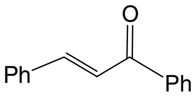
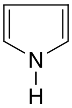
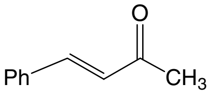
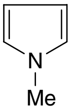
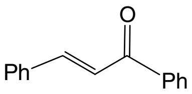
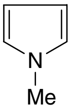
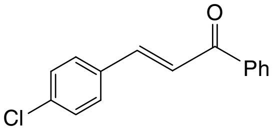
The reaction of pyrrole **1** with chalcone was performed using four different solvents and acetonitrile was found to be the best, giving an 85% yield of the products in 10 s (Table 2). The reaction was attempted at low temperature to try to achieve only monoalkylation, but it was very slow and nonselective. Thus, the reaction of equimolar amounts of pyrrole and enones gave mono- and dialkylated products.

Dialkylation was achieved selectively when the reaction was carried out in excess amount of enone. Thus the reaction of pyrrole **1** and chalcone (1:3 ratio) in the presence of copper bromide (20 mol %) in acetonitrile showed colour changes from pale yellow to green to brown as in the earlier case and furnished only dialkylated product after work-up and chromatographic separation, in 78% yield. The same reaction when carried out using other pyrroles and chalcones resulted in dialkylated products, as expected, in 8–12 min (Table 3). The dialkylated pyrroles could serve as important intermediates for the synthesis of biologically active compounds by constructing rings on both sides to develop tricyclic systems. Further work in this direction is in progress.

In conclusion, an efficient method has been developed using copper bromide as a catalyst for the dialkylation of pyrroles. However, the use of equimolar amounts of pyrrole and enones resulted in fast reactions with less selectivity, furnishing both mono- and dialkylated products.

Table 3.



Entry	Nucleophile	Electrophile	2,5-Dialkylated pyrrole	
			Yield (%)	Time (min)
1			78	10
2			82	12
3			72	8
4			76	12

Acknowledgements

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8. Nayak, S. K. *Synth. Commun.* **2006**, *36*, 1–9.
9. *General experimental procedure*: *Alkylation of pyrrole*: A solution of pyrrole (1 mmol), α,β-unsaturated carbonyl compound (1 or 3 mmol) and $CuBr_2$ (20 mol %) in dry acetonitrile (10 ml) was stirred at room temperature for the appropriate time. The mixture was concentrated, diluted with water and ethyl acetate and filtered through Celite. It was then extracted with ethyl acetate and dried (Na_2SO_4). Removal of the solvent followed by silica gel chromatography (hexane/ethyl acetate, 85:15) afforded pure product/s.
10. ^{1}H NMR of the major diastereomer of **16b** (300 MHz, $CDCl_3$): δ 3.01 (s, 3H), 3.46 (dd, 2H, $J = 16.77, 7.42$ Hz), 3.69 (dd, 2H, $J = 16.7, 6.60$ Hz), 4.67 (t, 2H, $J = 6.87$ Hz), 6.00 (s, 2H), 7.1–7.52 (m, 16H), 7.86 (d, 4H, $J = 7.42$ Hz). ^{13}C NMR of the major diastereomer of **16b** (75 MHz, $CDCl_3$): 30.65, 38.68, 45.46, 104.20, 126.30, 127.78, 127.90, 128.40, 128.45, 132.84, 134.26, 137.00, 143.20, and 197.75. $M^+ = 497$.

   ^{1}H NMR of the minor diastereomer **16b** (300 MHz, $CDCl_3$): δ 2.98 (s, 3H), 3.43 (dd, 2H, $J = 16.50$, 6.87 Hz), 3.72 (dd, 2H, $J = 16.77$, 6.82 Hz), 4.73 (t, 2H, $J = 6.87$), 5.98 (s, 2H), 7.07 (m, 16H), 7.88 (d, 4H, $J = 7.15$ Hz). ^{13}C NMR of the minor diastereomer **16b** (75 MHz, $CDCl_3$): 29.08, 37.88, 45.16, 104.58, 126.27, 127.64, 127.94, 128.30, 128.43, 128.51, 129.00, 132.10, 133.07, 134.21, 136.76, 141.78, and 197.27. $M^+ = 497$.