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$InBr_3/Cu(OTf)_2$-catalyzed *C*-alkylation of pyrroles and indoles with α-diazocarbonyl compounds

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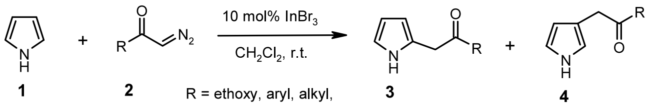
Abstract—Pyrroles and indoles react smoothly with α-diazocarbonyl compounds in the presence of 10 mol% of $InBr_3$ under mild conditions to afford the corresponding 2- and 3-alkyl pyrrole and 3-alkyl indole derivatives, respectively, in good yields with high selectivity.

α-Diazocarbonyl compounds are extremely versatile in organic synthesis especially in the total synthesis of complex natural products.[1] The ready availability, relative stability and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical, acid, base and transition metal catalysis conditions make them useful intermediates in organic synthesis.[2] α-Diazoketones undergo a variety of transformations such as cyclopropanation, aziridine formation, ylide formation, C–H, X–H insertion reactions and cyclization reactions.[3] Carbene-insertion reactions are of great interest as these methods allow new carbon–carbon and carbon–hetero atom bond formation under mild conditions. Typically, transition metal catalysts, mostly rhodium and copper salts, are employed to promote the carbene-insertion reactions.[4] However, there are no examples on the alkylation of indoles with α-diazocarbonyl compounds. Recently, indium halides have emerged as mild and water-tolerant Lewis acids imparting high regio-, stereo- and chemoselectivity in various organic transformations.[5] Compared to conventional Lewis acids, indium tribromide has advantages of low catalyst loading, moisture stability and catalyst recycling. Recently, indium tribromide has been found to be a more efficient catalyst over conventional Lewis acids in promoting various transformations including glycosidation, thioacetalization, cyanation of ketones and conjugate addition reactions.[6,7]

In this paper, we wish to report a simple and straightforward method for the alkylation of pyrroles and indoles with α-diazocarbonyl compounds using indium tribromide as the catalyst. Accordingly, treatment of pyrrole with ethyl diazoacetate in the presence of 10 mol% of $InBr_3$ afforded *C*-alkylated pyrroles as a mixture of ethyl 2-(2-pyrrolyl)acetate **3** and ethyl 2-(3-pyrrolyl)acetate **4** in 60 and 25% yields, respectively (Scheme 1).

In a similar manner, pyrrole reacted smoothly with α-diazoketones to produce the corresponding 2- and 3-substituted pyrroles in fairly good yields (Table 1). Pyrrole also underwent alkylation with the α-diazoketone derived from cyhalothric acid (entry b). Both aryl and alkyl substituted diazoketones worked well under the reaction conditions and the results are presented in Table 1. In all cases, the reactions proceeded efficiently at room temperature with high selectivity. No *N*-alkylation of pyrrole was observed under these reaction conditions. The reaction probably proceeds through the formation of the cyclopropyl adduct from the diazocarbonyl compound and pyrrole. Then, the cyclopropyl adduct can undergo either C-2 or C-3 cleavage through activation of the carbonyl group by indium(III) resulting in the formation of the 2- and 3-substituted pyrroles (Scheme 2).



Scheme 1.

Keywords: indium compounds; diazo compounds; *C*-alkylation; heteroaromatics.

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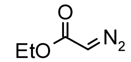
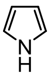
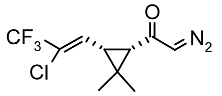
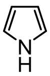
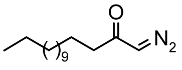
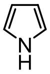
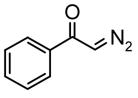
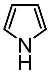
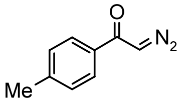
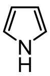
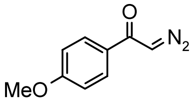
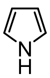
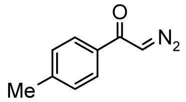
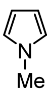
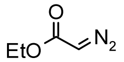
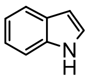
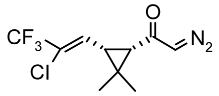
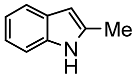
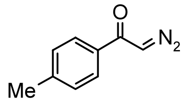
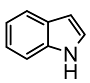
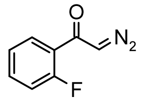
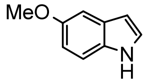
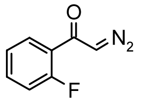
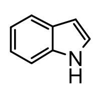
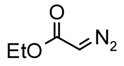
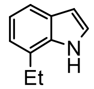
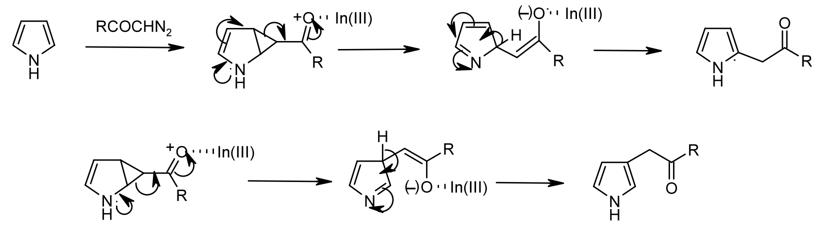
Table 1. $InBr_3$-catalyzed alkylation of pyrrole and indoles with α-diazocarbonyl compounds

Entry	Diazo compound	Pyrrole/Indole	Product[a]	10% $InBr_3$		5% $Cu(OTf)_2$	
				Time(h)	Yield(%)[b]	Time(h)	Yield(%)[b]
a			**3a** **4a**	3.5	60 25	3.0	65 15
b			**3b** **4b**	5.0	58 20	3.5	60 10
c			**3c** **4c**	5.5	65 10	4.5	60 12
d			**3d** **4d**	5.0	60 12	4.0	55 15
e			**3e** **4e**	5.5	63 15	3.5	60 10
f			**3f** **4f**	6.0	70 10	4.5	65 12
g			**3g** **4g**	7.5	50 15	6.0	40 20
h			**5h**	5.0	88	3.0	85
i			**5i**	5.5	82	4.5	75
j			**5j**	6.5	85	4.0	80
k			**5k**	5.0	87	4.5	82
l			**5l**	4.5	84	3.0	79
m			**5m**	5.5	90	4.0	85

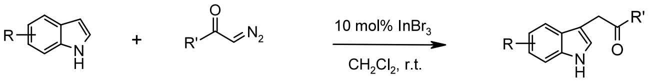
[a] All products were identified by ^1H NMR, IR and mass spectroscopy.
[b] Yield refers to pure products after column chromatography.

N-Methyl pyrrole also reacted smoothly with *p*-tolyl diazoketone to produce a *C*-alkylated product (entry g). These results encouraged us to study further the decomposition of various α-diazocarbonyl compounds with indoles. Interestingly, alkyl and aryl substituted diazo compounds underwent reaction with indoles in the presence of 10 mol% of $InBr_3$ to give 3-alkylated products in high yields (Scheme 3).

Similarly, various α-diazocarbonyl compounds reacted readily with indoles to furnish 3-alkyl indoles, with only 3-alkylated products being obtained. No side products



Scheme 2.



Scheme 3.

arising either from Wolff rearrangement or carbene dimerization was observed under these conditions. As a solvent, dichloromethane appeared to give the best results. All products were characterized by ^{1}H NMR, IR and mass spectroscopy. To compare the efficiency of this procedure, we performed the reactions with various indium salts such as indium tribromide, indium trichloride and indium triflate. Among these catalysts, indium tribromide was found be the most effective and gave the best results. Copper triflate (5 mol%) was also equally effective for this conversion and the results are presented in Table 1. The scope and generality of the method is illustrated with respect to various diazocarbonyl compounds, pyrroles and indoles and the results are summarized in Table 1.[8]

In summary, this paper describes a novel method for the alkylation of indoles and pyrrole with α-diazocarbonyl compounds using indium tribromide as catalyst. This method provides a new route to indoles and pyrroles functionalize at the 3- and 2-positions respectively.

Acknowledgements

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8. **General procedure**: A mixture of the pyrrole or indole (2 mmol), the α-diazocarbonyl compound (2.5 mmol), InBr$_3$ (10 mol%) or Cu(OTf)$_2$ (5 mol%) in dichloromethane (10 mL) was stirred at room temperature for the appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (2×15 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate:hexane, 1.5:8.5) afforded the pure alkyl pyrrole or indole derivative. Spectroscopic data for selected products: **3a**: IR (KBr) *ν*: 3364, 2924, 1745, 1679, 1462, 1280, 772 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.25 (t, 3H, *J*=6.9 Hz), 3.60 (s, 2H), 4.20 (q, 2H, *J*=6.9 Hz), 5.95 (d, 1H, *J*=2.5 Hz), 6.08 (dd, 1H, *J*=2.5, 2.9 Hz), 6.67 (dd, 1H, *J*=2.9, 3.7 Hz), 8.80 (brs, NH, 1H). EIMS: *m*/*z*: 153, M$^+$, 151, 139, 79, 56, 42. HRMS calcd for C$_8$H$_{11}$NO$_2$: 153.0789. Found: 153.0735. **4a**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.27 (t, 3H, *J*=6.8 Hz), 3.45 (s, 2H), 4.18 (q, 2H, *J*=6.8 Hz), 6.15 (dd, 1H, *J*=2.5, 2.9 Hz), 6.65–6.70 (m, 2H), 8.20 (brs, NH, 1H). **3b**: IR (KBr) *ν*: 3370, 2931, 1721, 1695, 1454, 1379, 1271, 1138, 1091, 770 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.20 (s, 3H), 1.30 (s, 3H), 2.20 (dd, 1H, *J*=8.1, 8.5 Hz), 2.30 (d, 1H, *J*=8.1 Hz), 3.80 (Abq, 2H, *J*=13.5 Hz), 5.95 (d, 1H, *J*=2.5 Hz), 6.10 (dd, 1H, *J*=2.5, 2.9 Hz), 6.65 (dd, 1H, *J*=2.9, 3.7 Hz), 6.95 (d, 1H, *J*=8.5 Hz), 8.45 (brs, NH, 1H). EIMS: *m*/*z*: 306 M$^+$, 305, 225, 141, 122, 80, 53. HRMS calcd for C$_{14}$H$_{15}$NOF$_3$Cl: 305.0794. Found: 305.0856. **4b**: ^{1}H NMR (200 MHz, CDCl$_3$): δ 1.18 (s, 3H), 1.25 (s, 3H), 2.18 (dd, 1H, *J*=8.1, 8.5 Hz), 2.38 (d, 1H, *J*=8.1 Hz), 3.60 (Abq, 2H, *J*=13.5 Hz), 6.05 (dd, 1H, *J*=2.5, 2.9 Hz), 6.60 (d, 1H, *J*=2.5 Hz), 6.78 (dd, 1H, *J*=2.9, 3.7 Hz), 7.05 (d, 1H, *J*=8.5 Hz), 8.25 (brs, NH, 1H). **3d**: IR (KBr) *ν*: 3418, 2923, 1745, 1685, 1450, 1267, 1026, 762 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): δ 4.20 (s, 2H), 5.90 (d, 1H, *J*=2.5 Hz), 5.98 (dd, 1H, *J*=2.5, 2.9 Hz), 6.60 (dd, 1H, *J*=2.9, 3.7 Hz), 7.40–7.60 (m, 3H), 8.0

(d, 2H, $J=8.0$ Hz), 10.20 (brs, NH, 1H). EIMS: *m*/*z*: 185 M$^+$, 146, 105, 90, 80, 77, 53. HRMS calcd for $C_{12}H_{11}NO$: 185.0840. Found: 185.0879. **4d**: IR (KBr) *v*: 3364, 2924, 1743, 1679, 1462, 1247, 1071, 772 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.20 (s, 2H), 6.15 (dd, 1H, $J=2.5$, 2.9 Hz), 6.65–6.70 (m, 2H), 7.40–7.60 (m, 3H), 8.10 (d, 2H, $J=8.0$ Hz), 8.20 (brs, NH, 1H). **5h**: IR (KBr) *v*: 3409, 3056, 2981, 1728, 1459, 1247, 1161, 1028, 932, 744 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, $J=6.9$ Hz), 3.69 (s, 2H), 4.20 (q, 2H, $J=6.9$ Hz), 6.95 (d, 1H, $J=1.5$ Hz), 7.05–7.22 (m, 3H), 7.60 (d, 1H, $J=8.1$ Hz), 8.10 (brs, NH, 1H). EIMS: *m*/*z*: 203 M$^+$, 130, 77. HRMS calcd for $C_{12}H_{13}NO_2$: 203.0946. Found: 203.0969.