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Zinc-mediated Barbier reactions of pyrrole and indoles: a new method for the alkylation of pyrrole and indoles

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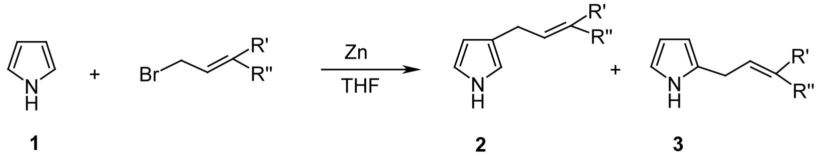
Abstract—Pyrrole and indoles react smoothly with alkyl halides such as allyl bromide, prenyl bromide, crotyl bromide and propargyl bromide in the presence of zinc metal in THF to afford the corresponding 3- and 2-alkyl pyrrole and 3-alkyl indole derivatives in good yields with high regioselectivity. © 2002 Elsevier Science Ltd. All rights reserved.

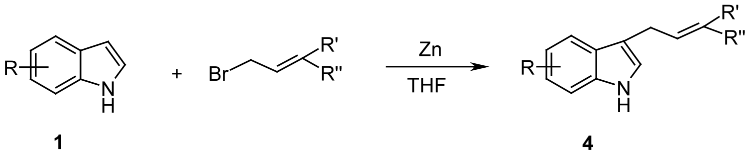
Organometallic reactions have found wide applications in organic synthesis.[1] In particular, organozinc reagents[2] have attracted much attention due to their compatibility with many organic functional groups (eg. R-OH, CO_2R), stability, reactivity and to their selectivity. Furthermore, zinc-mediated reactions exhibit a low nucleophilicity thus permitting chemoselective transformations of groups of similar reactivity. Allylzinc reagents, generated in situ from allyl halides and zinc metal, react with various electrophiles[3–5] such as carbonyl compounds, C=N unsaturated systems, C–C multiple bonds, sulfonyl halides and epoxides to generate homoallyl products. To date, the reactions of pyrrole remain a challenge for the synthetic chemists because of its sensitivity to acids and air.[6] The acid catalyzed reactions of pyrrole are limited and require the careful control of acidity to prevent side reactions. As such, there are no reports on the regioselective alkylation of pyrrole and indoles with organometallic reagents.

In continuation of our work on the applications of metals such as zinc, indium, and magnesium for various transformations,[7] we herein report a novel and efficient method for the preparation of 3- and 2-alkyl pyrrole as well as 3-alkyl indoles through the zinc-mediated Barbier reaction of pyrrole and indole. Thus treatment of pyrrole with zinc metal and allyl bromide in THF resulted in the formation of 3- and 2-allyl pyrrole derivatives in good yields (Scheme 1).

Similarly, pyrrole reacted smoothly with crotyl, prenyl and propargyl bromides to afford the corresponding 3- and 2-alkyl pyrrole derivatives in good yields. Furthermore, the reactions of indoles with allylzinc bromide in



Scheme 1.



Scheme 2.

Keywords: organozinc reagents; Barbier reaction; *C*-alkylation of heterocycles.

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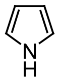
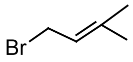
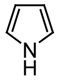
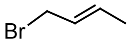
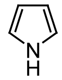
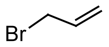
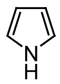
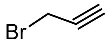
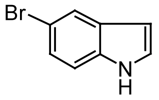
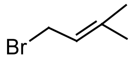
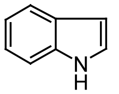
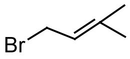
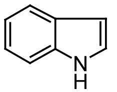
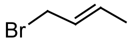
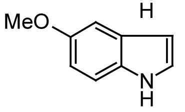
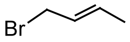
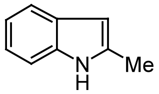
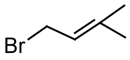
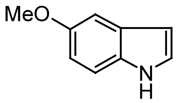
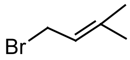
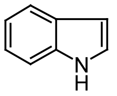
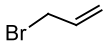
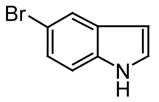
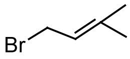
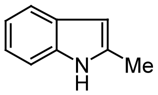
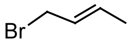
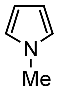
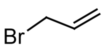
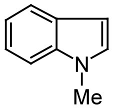
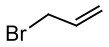
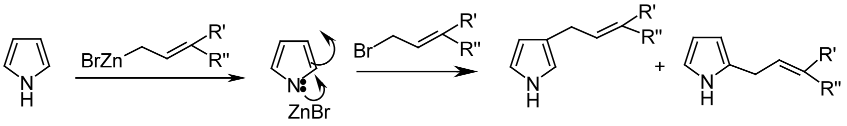
Table 1. Zinc-mediated alkylation of pyrrole and indoles with allylic bromides

Entry	Substrate	Nucleophile	Product[a]	Yield(%)[b]	Time(h)
a.			2a 3a	70 10	4.5
b.			2b 3b	68 15	4.0
c.			2c 3c	65 12	5.5
d.			2d 3d	60 10	6.0
e.			4e	85	4.5
f.			4f	90	4.0
g.			4g	87	5.0
h.			4h 5h	15 75	6.5
i.			4i	89	5.0
j.			4j	87	5.5
k.			2k	85	4.5
l.			4l	80	6.0
m.			4m 5m	10 75	3.5
n.			-	-	6.5
o.			-	-	8.0

a. All the products were characterized by ^{1}H NMR, IR and mass spectra.
b. Isolated and unoptimized yields.



Scheme 3.

THF afforded exclusively 3-allyl indole in good yields (Scheme 2).

Likewise, several substituted indoles reacted well with various alkyl halides such as crotyl, prenyl and propargyl bromides to furnish the respective 3-alkyl indole derivatives in high yields. In all cases, the reactions proceeded smoothly at ambient temperature to give the products in good yields with high regioselectivity. THF appears to be the best choice of solvents. Albeit, this reaction proceeded smoothly in commercial THF (containing 0.2% water) the reaction in water alone was not successful. All products were characterized by ^{1}H NMR, IR and mass spectroscopic data and also by comparison with alkyl substituted of pyrrole and indole derivatives.[8] The results as summarized in Table 1 clearly reveal the scope and generality of the reaction with respect to various alkyl bromides, pyrrole and indoles. The reactions were clean, high yielding and completed within 3.5–6.0 h. Among various metals such as indium, samarium, yttrium and bismuth studied for this transformation, zinc was found to be effective in terms of selectivity and conversion.[9] However, the reactions of *N*-methyl pyrrole, *N*-benzyl pyrrole, *N*-BOC protected pyrrole and *N*-methyl indole with allylic bromides did not yield any product under the reaction conditions. It indicates that the method is only suitable for the allylation of *N*-unprotected pyrrole and indoles. The reaction may proceed through the formation of pyrrolyl or indolyl zinc bromide that in turn reacts with allyl bromide to afford the alkylated products (Scheme 3).

In summary, we have described a novel and convenient method for the alkylation of pyrrole and indoles through the zinc-mediated Barbier reaction. The method offers several advantages including high yields of products, cleaner reaction profiles, greater selectivity, simple experimental/product isolation procedures, which makes it a useful and attractive strategy for the alkylation of pyrrole and indoles.

Acknowledgements

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9. **General procedure**: A mixture of pyrrole or indoles (5 mmol), allyl or prenyl or crotyl bromide (10 mmol), zinc powder (10 mmol) in THF (10 mL) was stirred at room temperature for an appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was quenched with saturated ammonium chloride (15 mL) and extracted with ethyl acetate (2×15 mL). Evaporation of the solvent followed by purification on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 0.5–9.5) afforded pure alkyl pyrrole or indole derivative.
Spectroscopic data for selected products: Compound **2c**: ^{1}H NMR (CDCl$_3$) δ: 3.20 (dd, 2H, $J=1.7$, 10.3 Hz), 4.98–5.15 (m, 2H), 5.90–6.0 (m, 1H), 6.03 (d, 1H, $J=2.7$ Hz), 6.48 (m, 1H), 6.60 (dd, 1H, $J=2.7$, 5.6 Hz), 8.05 (brs, NH). Compound **3c**: ^{1}H NMR (CDCl$_3$) δ: 3.35 (dd, 2H, $J=1.7$, 10.3 Hz), 5.0–5.19 (m, 2H), 5.85 (m, 1H), 5.90–6.0 (m, 1H), 6.03 (dd, 1H, $J=2.7$, 5.6 Hz), 6.60 (d, 1H, $J=2.7$ Hz), 8.05 (brs, NH). Compound **4f**: ^{1}H NMR (CDCl$_3$) δ: 1.78 (s, 6H), 3.40 (dd, 2H, $J=1.7$, 10.3 Hz), 5.40 (m, 1H), 6.85 (d, 1H, $J=1.8$ Hz), 7.0–7.18 (m, 2H), 7.25 (d, 1H, $J=8.0$ Hz), 7.58 (d, 1H, $J=8.0$ Hz), 7.80 (brs, NH). EIMS: *m*/*z*: 185 M$^+$, 172, 131, 118, 78, 39. IR (KBr) ν: 3415, 2923, 1456, 1338, 1218, 1093, 742 cm^{-1}. Compound **4g**: ^{1}H NMR (CDCl$_3$) δ: 1.75 (d, 3H, $J=6.5$ Hz), 3.45 (dd, 2H, $J=1.7$, 10.3 Hz), 5.55–5.65 (m, 2H), 6.93 (d, 1H, $J=1.8$ Hz), 7.05–7.18 (m, 2H), 7.28 (d, 1H, $J=8.0$ Hz), 7.58 (d, 1H, $J=8.0$ Hz), 7.80 (brs, NH). EIMS: *m*/*z*: 171 M$^+$, 158, 131, 118, 78, 39. IR (KBr) ν: 3415, 2921, 1454, 1340, 1225, 1090, 966, 741 cm^{-1}.