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Zinc-mediated acylation and sulfonation of pyrrole and its derivatives

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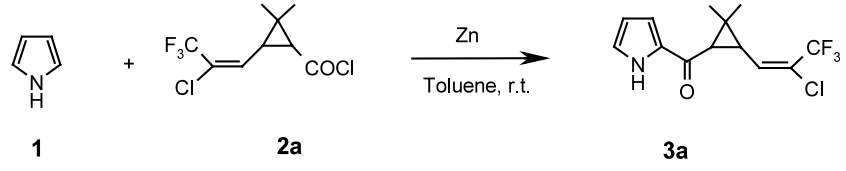
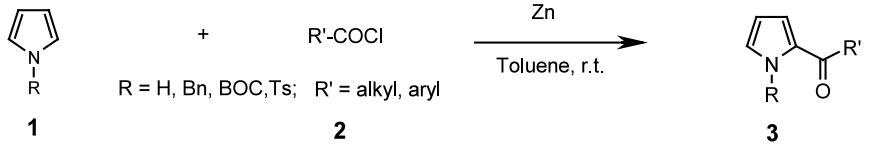
Abstract—Pyrrole and its derivatives react smoothly with acid chlorides and sulfonyl chlorides in the presence of zinc metal in toluene at ambient temperature to afford the corresponding 2-acetyl and 2-sulfonyl pyrrole derivatives in high yields with high regioselectivity.

The 2-ketopyrrole moiety, although rarely reported, is apparently biologically important as evidenced by its presence in naturally occurring molecules such as X-14547A,[1] and A-23187 (calcimycin).[2] Generally, 2-acetyl pyrroles are prepared by the Vilsmeier–Haack method using $POCl_3$ and *N*,*N*-dimethylacetamide.[3] Other methods for the acylation of pyrroles involve the isomerization of *N*-acetyl pyrroles by thermal rearrangement at high temperature, resulting in 2- and 3-acetyl pyrroles.[4] Alternatively, 2- and 3-ketopyrroles are prepared using pyrrolylmagnesium halides and acid chlorides[5] or 2-pyridylthioesters[6] or phenyl selenoesters.[7] These indirect methods are used to obtain 2-ketopyrroles, as they tend to polymerize under most reaction conditions. To date, the direct synthesis of 2-ketopyrroles remains a challenge for synthetic chemists because of their sensitivity to acids and air.[8] 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 acylation of pyrrole with organozinc reagents to give 2-ketopyrrole derivatives.

In continuation of our work on the use of metals such as zinc, indium, and magnesium for various transformations,[9] we herein report a novel and highly efficient method for the preparation of 2-ketopyrroles from pyrrole and acid chlorides using metallic zinc powder as promoter under very mild and neutral conditions. Thus, treatment of pyrrole with the acid chloride derivative of cyhalothrin and zinc metal in toluene resulted in the formation of the corresponding 2-acyl pyrrole in 87% yield (Scheme 1).



Scheme 1.



Scheme 2.

Keywords: organozinc reagents; *C*-acylation; sulfonylation; pyrrole; 2-substituted pyrrole.
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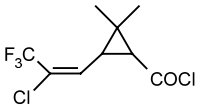
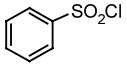
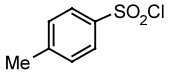
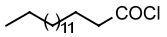
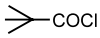
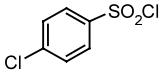
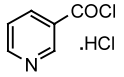
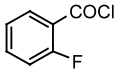
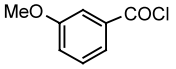
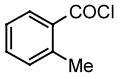
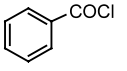
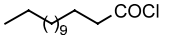
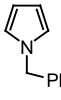
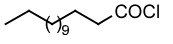
Similarly, pyrrole reacted smoothly with a range of alkyl and aryl substituted acid chlorides to afford the corresponding 2-acyl pyrrole derivatives. The reaction proceeded efficiently at ambient temperature with high regioselectivity. No *N*-acylated products were obtained under these reaction conditions. This method is effective even with the highly hindered pivaloyl chloride (entry f) and nicotinoyl chloride hydrochloride (entry h). Furthermore, *N*-substituted pyrroles also reacted with acid chlorides under the influence of zinc metal giving the corresponding 2-acylated pyrroles in high yields (Scheme 2).

Table 1. Zinc-mediated acylation and sulfonation of pyrrole and its derivatives[a]

Entry	Pyrrole	Acid / sulfonyl chloride	Yield(%)[b]	Time(h)
a			87	1.0
b			85	1.5
c			83	2.0
d			89	2.0
e		CH_3COCl	90	1.5
f			82	2.5
g			85	1.0
h			80	3.0
i			82	1.5
j			87	1.5
k			85	2.0
l			78	2.5
m			75	3.0
n		CH_3COCl	82	2.5
o			80	3.0

a. All products were characterized by ^1H NMR, IR and mass spectroscopy.
b. Isolated and unoptimized yields.

Toluene appears to be the best choice of solvents. This reaction proceeded smoothly in commercial toluene (containing 0.1% water) but the attempted 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 known 2-acyl substituted pyrrole derivatives.[8] The reactions were clean and complete within 1–3 h. Among the various metals such as zinc, indium, samarium, and yttrium studied for this transformation, zinc was found to be more effective in terms of selectivity and conversion.[10] This method is equally effective for the sulfonation of pyrrole with sulfonyl chlorides to afford the corresponding 2-sulfonyl pyrroles (entries b, c, g, Table 1). The scope and generality of this process is illustrated with respect to various acid chlorides, sulfonyl chlorides and *N*-substituted pyrrole derivatives and the results are summarized in the Table 1.

In summary, we have demonstrated a novel and highly efficient method for the acylation and sulfonation of pyrrole and its derivatives using zinc metal under mild and neutral reaction conditions. The method offers several advantages including high yields of products, cleaner reaction profiles, greater regioselectivity, and simple experimental/product isolation procedures, which make it a useful and attractive strategy for the acylation and sulfonation of pyrrole and its derivatives of synthetic importance.

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10. ***General procedure***: A mixture of pyrrole (5 mmol), acid chloride (7.5 mmol), zinc powder (10 mmol) in toluene (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 quenched with saturated sodium bicarbonate solution (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 the pure 2-acyl pyrrole derivative.
Spectroscopic data for selected products: **3a**: Solid, mp 118°C, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 1.42 (s, 3H), 2.32 (dd, 1H, $J=8.1$, 8.5 Hz), 2.78 (d, 1H, $J=8.1$ Hz), 6.29 (dd, 1H, $J=2.5$, 3.7 Hz), 6.90 (dd, 1H, $J=2.9$, 3.7 Hz), 7.0 (d, 1H, $J=2.9$ Hz), 7.20 (d, 1H, $J=8.5$ Hz), 10.40 (brs, NH, 1H).
^{13}C NMR ($CDCl_3$, proton decoupled, 50 MHz) δ: 14.7, 28.6, 30.9, 33.1, 37.0, 110.7, 116.5, 123.2, 124.9, 130.7, 130.8, 133.4, 186.5. IR (KBr) ν: 3285, 3089, 1622, 1416, 1295, 1108, 963, 777 cm^{-1}. EI MS: m/z: 291 M^+, 258, 200, 179, 95, 66, 39.
3c: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 6.18 (dd, 1H, $J=2.5$, 3.7 Hz), 6.75 (dd, 1H, $J=2.9$, 3.7 Hz), 6.90 (d, 1H, $J=2.9$ Hz), 7.20 (d, 2H, $J=8.0$ Hz), 7.80 (d, 2H, $J=8.0$ Hz), 11.80 (brs, NH, 1H).
IR (KBr) ν: 3324, 1578, 1445, 1380, 1296, 1226, 1141, 1090, 752 cm^{-1}. EI MS: m/z: 221 M^+, 156, 138, 113, 91, 81, 39.
3d: Solid, mp 70°C, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.90 (t, 3H, $J=6.8$ Hz), 1.20–1.40 (m, 24H), 1.70–1.80 (m, 2H), 2.80 (t, 2H, $J=6.7$ Hz), 6.20 (dd, 1H, $J=2.7$, 3.7 Hz), 6.80 (dd, 1H, $J=2.7$, 3.5 Hz), 7.0 (d, 1H, $J=2.7$ Hz), 9.40 (brs, NH, 1H). ^{13}C NMR ($CDCl_3$, proton decoupled, 50 MHz) δ: 14.0, 22.6, 25.3, 29.4, 29.6, 31.9, 38.0, 110.4, 115.8, 124.2, 132.1, 191.1. IR (KBr) ν: 3287, 2917, 1641, 1406, 1297, 1113, 920, 771 cm^{-1}. EI MS: m/z: 305 M^+, 122, 109, 94, 43, 36.
3j: Liquid, ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 6.24 (dd, 1H, $J=2.7$, 3.7 Hz), 6.80 (dd, 1H, $J=2.7$, 3.5 Hz), 7.10 (dd, 1H, $J=8.0$, 2.1 Hz), 7.15 (d, 1H, $J=2.7$ Hz), 7.30 (d, 1H $J=8.0$ Hz), 7.40 (d, 1H, $J=2.1$ Hz), 7.50 (dd, 1H, $J=8.0$, 2.1 Hz), 10.6 (brs, NH, 1H). ^{13}C NMR ($CDCl_3$, proton decoupled, 50 MHz) δ: 55.3, 110.9, 113.6, 118.0, 119.7, 121.5, 125.6, 129.2, 131.0, 139.6, 159.4, 184.6. IR (KBr) ν: 3276, 1604, 1577, 1420, 1395, 1252, 1041, 913, 771 cm^{-1}. EI MS: m/z: 201 M^+, 186, 170, 158, 135, 130, 107, 94, 66, 39.