

FeCl₃-catalyzed alkylation of indoles with 1,3-dicarbonyl compounds: an expedient synthesis of 3-substituted indoles

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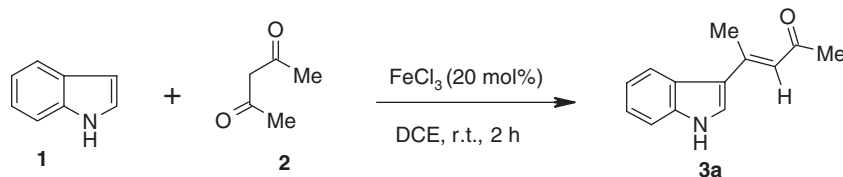
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Abstract—Indoles undergo smooth alkylation at the 3-position with 1,3-dicarbonyl compounds in the presence of 20 mol % of FeCl₃ under mild reaction conditions to produce a wide range of 3-substituted indoles in excellent yields and with high *E*-selectivity. © 2007 Elsevier Ltd. All rights reserved.

The indole nucleus is frequently found in natural products, pharmaceuticals, functional materials, and agrochemicals.¹ Substituted indoles are capable of binding to many receptors with high affinity. Therefore, the synthesis and selective functionalization of indoles have been the focus of active research over the years.^{2–4} 3-Substituted indoles are important building blocks for the synthesis of various biologically active molecules. Consequently, there is a continuing interest in the development of improved methods for the synthesis of 3-substituted indoles.⁵ One such reaction is the transition metal mediated intermolecular C–C bond formation between these heterocycles and other organic substrates.⁶ Typically, organometallic couplings require that one or both entities are prefunctionalized as halides or with another disposable functionality.⁷ Particular focus is devoted to developing new methods to couple indoles and pyrroles with carbonyl compounds directly, without modification of either coupling partner. In this context, the reaction of indoles at C-3 and of pyrroles

at C-2 with the α -carbon of carbonyl compounds has been reported using transition metal-catalysis.⁸ Recently, the reaction of indoles and pyrroles with 1,3-dicarbonyl compounds has also been reported using gold(III) catalysis.⁹ However, this method involves long reaction times, high temperatures, expensive reagents, and low conversions and selectivity, which limit its practical utility in organic synthesis. In recent years, iron(III) chloride has emerged as a powerful Lewis acid catalyst and performs many useful organic transformations under mild reaction conditions.¹⁰ Moreover, iron-salts are inexpensive, easy to handle and are environmentally friendly. There have been no previous reports on the direct coupling of indoles with 1,3-dicarbonyl compounds using FeCl₃ as a catalyst.

In this Letter, we report a direct FeCl₃-catalyzed selective 3-alkenylation of indoles with 1,3-dicarbonyl compounds under mild conditions. We first attempted the coupling of indole (**1**) with acetylacetone (**2**). The


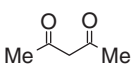
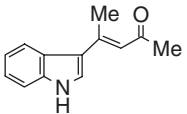
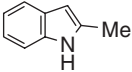
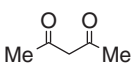
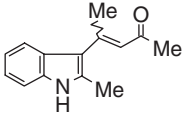
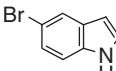
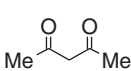
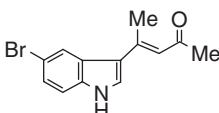
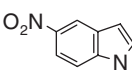
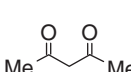
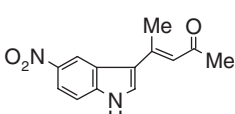
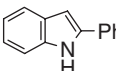
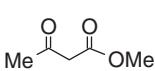
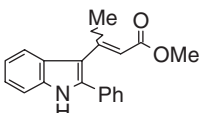
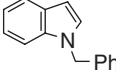
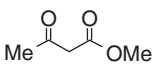
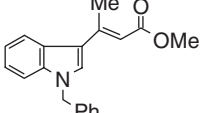


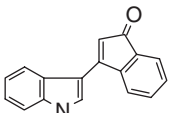
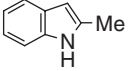

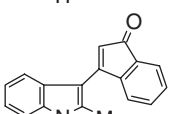

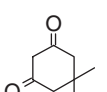
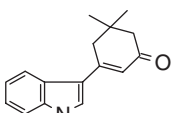
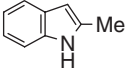
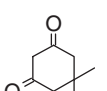
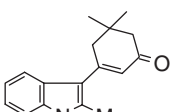
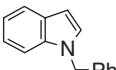
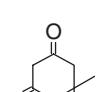
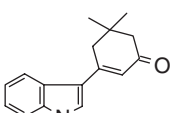
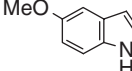

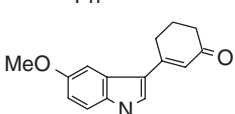


Scheme 1.

Keywords: Indoles; Iron(III) reagents; 1,3-diketones; C-3 alkylation.

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Table 1. FeCl₃-catalyzed alkenylation of indoles with 1,3-dicarbonyl compounds

Entry	Indole	1,3-Dicarbonyl compound	Product ^a	Time (h)	Yield ^b (%)
a				2.0	88
b				2.0	90 ^c
c				2.0	84
d				2.5	85
e				2.5	82 ^c
f				2.0	85
g				5.0	80
h				4.5	83
i				6.0	80
j				5.5	90
k				5.0	91
l				6.0	86

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