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Synthesis of 3-substituted indole by $AlCl_3$-promoted reaction of β,γ-unsaturated ketone with indole

Adam Shih-Yuan Lee · Yu-Chi Wu · Yu-Ting Chang · Bo-Cheng Wang

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Abstract A one-pot Lewis acid-promoted reaction condition of β,γ-unsaturated ketone with indole was developed for the synthesis of 3-substituted indoles with moderate to good yields. A Lewis acid such as $AlCl_3$ was shown to be a promising promoter for in situ isomerization of β,γ-unsaturated ketone to its corresponding α,β-unsaturated ketone, then undergoing Friedel–Crafts Michael addition reaction with indole to afford 3-substituted indole.

Keywords Friedel–Crafts reaction Michael reaction · 3-Substituted indole · β,γ-Unsaturated ketone · α,β-Unsaturated ketone

Introduction

Indoles are widely distributed in biological systems and well known as biologically active substances [1–3]. The indole nucleus is a privileged structural moiety with a broad spectrum of pharmaceutical and biological activities across the entire chemical industry [4–8]. Synthetic multistep procedures for the synthesis of two carbon–carbon bonds catalyzed by single multiacting Lewis acids are poorly documented [9–14], and several manipulations of functional groups such as protection or activation are required. In the last few years, several Lewis acid-mediated Friedel–Crafts-type additions of electron-rich aromatic compounds such as indoles to enones, in the presence of a catalytic or stoichiometric amount of Lewis acids, have been published [15–17]. 3-Alkylation of indole can be accomplished even with mild electrophiles such as alkenes with electron-withdrawing groups under acidic catalysis. However, since the indole ring is quite reactive against protic and Lewis acids, only procedures which generate electrophilic species under relatively mild conditions are likely to

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produce good yields [18–20]. Friedel–Crafts alkylation of indoles with α,β-unsaturated carbonyl compounds can give rise to the specific formation of a new β-position bond of carbonyl compounds [21–27]. Combination of Friedel–Crafts alkylation of indole with α,β-unsaturated carbonyl compound presents a molecularly economic reaction and is among the most practical and widely used methods for the synthesis of 3-substituted indoles [28, 29]. Our group reported that a Barbier-type reaction of allylic bromide with nitrile could generate β,γ-unsaturated ketone at room temperature [30, 31], and this β,γ-unsaturated ketone was isomerized to α,β-unsaturated ketone under DABCO (1,4-Diazabicyclo-[2.2.2]octane)/*i*PrOH reaction condition [32]. Thus, we expected that the preparation of 3-substituted indole might be achieved by the one-pot isomerization of β,γ-unsaturated ketone to α,β-unsaturated ketone followed by Friedel–Crafts Michael addition reaction with indole (Scheme 1).

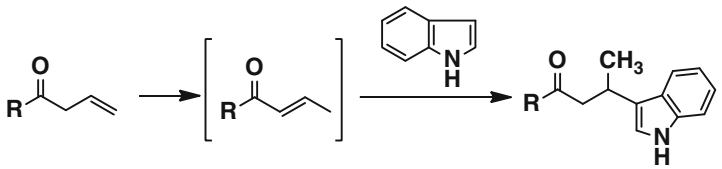
Experimental

General

All reagents (Table 1) were purchased from Aldrich, Merck, and Riedel–deHaen, and all were used directly without further purification. β,γ-Unsaturated ketones (which are shown in Table 1, below) were prepared by the reported method [30]. Methylene chloride was distilled from calcium hydride and recirculated prior to use. Hexane and ethyl acetate were distilled from calcium hydride. The ^{1}H-NMR (proton nuclear magnetic resonance) spectra were recorded at 300 MHz (Bruker-AC300P) with deuteriochloroform ($CDCl_3$, Aldrich, 99.8 atom % D) as the solvent and the internal standard. The ^{13}C-NMR (carbon nuclear magnetic resonance) spectra were recorded at 75.5 MHz (Bruker-AC300P) with $CDCl_3$ as the solvent and the internal standard. MS spectra (MS) were recorded on a Finnigan MAT 95S spectrophotometer. Column chromatography was performed using silica gel (Merck 230–400 mesh) and ethyl acetate/hexane mixture as the eluent.

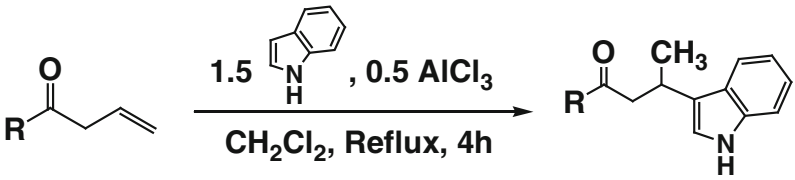
A representative procedure for synthesis of 3-substituted indoles

$AlCl_3$ (0.5 mmol) was added to a reaction mixture of β,γ-unsaturated ketone (1.0 mmol) and indole (1.5 mmol) in CH_2Cl_2 (5 mL) at room temperature and the reaction mixture was refluxed for 4 h. After the reaction was completed (monitored by TLC), the reaction mixture was extracted with ethyl acetate (20 mL × 3). The



Scheme 1 Synthetic scheme of 3-substituted indoles

Table 1 Syntheis of 3-substituted indoles



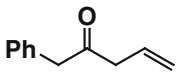
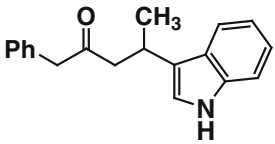
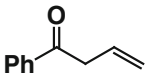
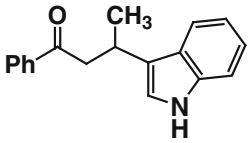
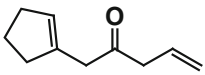
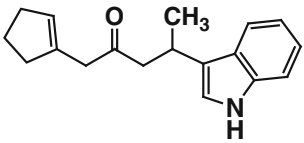
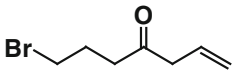
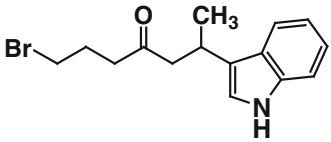
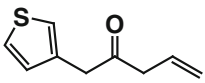
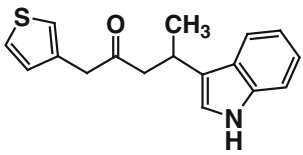
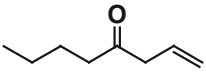
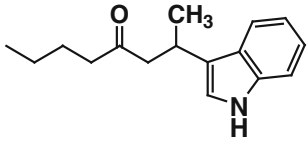
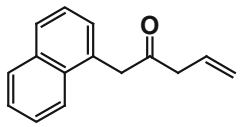
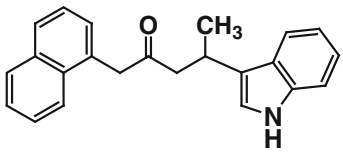
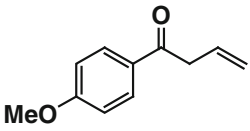
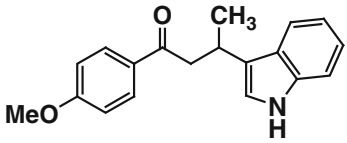
Entry	Substrate	Product	Yield (%)
1			87
2			45
3			57
4			63
5			72
6			68

Table 1 continued

Entry	Substrate	Product	Yield (%)
7			73
8			78

combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, and the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with ethyl acetate/hexane as eluent.

4-(1H-indol-3-yl)-1-phenylpentan-2-one (Table 1, Entry 1)

^{1}H-NMR: δ 1.33 (3H, H_5, d, J = 6.0 Hz), 2.67 (1H, H_3, dd, J = 16.5, 7.5 Hz), 2.93 (1H, H_3, dd, J = 15.0, 6.0 Hz), 3.59 (2H, H_1, s), 3.65 (1H, H_4, m), 6.89 (1H, d, J = 2.3 Hz), 7.08–7.36 (8H, m), 7.57 (1H, d, J = 6.0 Hz), 7.94 (1H, br). ^{13}C-NMR: δ 21.3, 27.3, 49.9, 50.9, 111.5, 119.4, 119.5, 120.4, 121.2, 122.3, 126.5, 127.1, 128.9, 129.7, 134.3, 136.7, 208.1. HRMS: m/z 277.1477 (calcd. for $C_{19}H_{19}NO$, 277.1467).

3-(1H-indol-3-yl)-1-phenylbutan-1-one (Table 1, Entry 2)

^{1}H-NMR: δ 1.45 (3H, H_4, d, J = 6.8 Hz), 3.20 (1H, H_2, dd, J = 16.3 Hz, 8.8), 3.45 (1H, H_2, dd, J = 16.3, 4.8 Hz), 3.84 (1H, H_3, m), 7.02 (1H, d, J = 2.2 Hz), 7.12–7.22 (2H, m), 7.34 (1H, d, J = 7.8 Hz), 7.41 (2H, t, J = 5.7 Hz), 7.52 (1H, t, J = 5.9 Hz), 7.67 (1H, d, J = 7.7 Hz), 7.94 (2H, d, J = 7.4 Hz), 7.97 (1H, br). ^{13}C-NMR: δ 21.2, 27.4, 46.7, 111.5, 119.5, 120.4, 121.8, 122.3, 126.6, 128.3, 128.8, 133.1, 136.8, 137.6, 200.0.

1-(cyclopent-1-en-1-yl)-4-(1H-indol-3-yl)pentan-2-one (Table 1, Entry 3)

^{1}H-NMR: δ 1.37 (3H, H_5, d, J = 6.9 Hz), 1.77-1.87 (2H, m), 2.15-2.31 (4H, m), 2.66 (1H, H_3, dd, J = 16.2, 8.2 Hz), 2.93 (1H, H_3, dd, J = 16.2, 5.7 Hz), 3.11 (2H, H_1, s), 3.64 (1H, H_4, m), 5.44 (1H, t, J = 1.9 Hz), 6.96 (1H, d, J = 2.2 Hz), 7.08–7.21 (2H, m), 7.34 (1H, d, J = 8.1 Hz), 7.62 (1H, d, J = 7.8 Hz), 7.93 (1H, br). ^{13}C-NMR: δ 21.3, 23.7, 27.2, 32.8, 35.4, 46.4, 49.9, 111.4, 119.4, 120.4, 121.4,

122.2, 126.5, 128.9, 136.8, 137.3, 208.6. HRMS: m/z 267.1633 (calcd. for $C_{18}H_{21}NO$, 267.1623).

1-bromo-6-(1H-indol-3-yl)heptan-4-one (Table 1, Entry 4)

^{1}H-NMR: δ 1.38 (3H, H_7, d, $J = 6.9$ Hz), 2.00-2.09 (2H, H_2, m), 2.49 (2H, H_3, t, $J = 7.2$ Hz), 2.66 (1H, H_5, dd, $J = 15.7$, 7.9 Hz), 2.89 (1H, H_5, dd, $J = 15.7$, 6.2 Hz), 3.31–3.37 (2H, H_1, m), 3.65 (1H, H_6, m), 6.98 (1H, d, $J = 2.1$ Hz), 7.09–7.21 (2H, m), 7.34 (1H, d, $J = 8.2$), 7.62 (1H, d, $J = 8.0$ Hz), 7.94 (1H, br). ^{13}C-NMR: δ 21.5, 26.5, 27.4, 30.6, 33.5, 41.4, 51.0, 111.5, 119.4, 120.4, 121.2, 122.3, 127.4, 136.8, 209.4.

4-(1H-indol-3-yl)-1-(thiophen-3-yl)pentan-2-one (Table 1, Entry 5)

^{1}H-NMR: δ 1.35 (3H, H_5, d, $J = 6.9$ Hz), 2.68 (1H, H_3, dd, $J = 15.9$, 8.1 Hz), 2.93 (1H, H_3, dd, $J = 16.0$, 6.0 Hz), 3.62 (2H, H_1, s), 3.58 (1H, H_4, m), 6.85 (1H, t, $J = 4.1$ Hz), 6.91 (1H, $J = 2.3$ Hz), 6.97 (1H, d, $J = 0.8$ Hz), 7.08–7.26 (3H, m), 7.33 (1H, d, $J = 7.8$ Hz), 7.58 (1H, d, $J = 7.8$ Hz), 7.94 (1H, br). ^{13}C-NMR: δ 21.3, 27.3, 45.1, 49.8, 111.5, 119.4, 119.5, 120.4, 121.2, 122.3, 123.1, 126.0, 126.4, 128.8, 134.0, 136.7, 207.6. HRMS: m/z 283.1044 (calcd. for $C_{17}H_{17}NOS$, 283.1031).

2-(1H-indol-3-yl)octan-4-one (Table 1, Entry 6)

^{1}H-NMR: δ 0.82 (3H, H_1, t, $J = 7.2$ Hz), 1.20-1.28 (2H, H_2, m), 1.36 (3H, H_8, d, $J = 6.9$ Hz), 1.45 (2H, H_3, m), 2.31 (2H, H_4, t, $J = 7.4$ Hz), 2.63 (1H, H_6, dd, $J = 15.9$, 8.4 Hz), 2.87 (1H, H_6, dd, $J = 15.9$, 5.7 Hz), 3.62 (1H, H_7, m), 6.97 (1H, d, $J = 2.3$ Hz), 6.97 (1H, d, $J = 2.3$ Hz), 7.11–7.21 (2H, m), 7.34 (1H, d, $J = 7.8$ HZ), 7.63 (1H, d, $J = 7.5$ Hz), 7.94 (1H, br). ^{13}C-NMR: δ 14.0, 21.4, 22.5, 26.0, 27.2, 43.3, 50.8, 111.4, 119.4, 119.5, 120.3, 121.5, 122.3, 126.5, 136.8, 211.1.

4-(1H-indol-3-yl)-1-(naphthalen-1-yl)pentan-2-one (Table 1, Entry 7)

^{1}H-NMR: δ 1.30 (3H, H_5, d, $J = 6.8$ Hz), 2.65 (1H, H_3, dd, $J = 16.0$, 7.9 Hz), 2.93 (1H, H_3, dd, $J = 16.0$, 6.4 Hz), 4.02 (2H, H_1, s), 6.84 (1H, d, $J = 2.2$ Hz), 7.07–7.25 (4H, m), 7.32–7.52 (6H, m), 7.68–7.84 (3H, m), 7.85 (1H, br). ^{13}C-NMR: δ 21.4, 27.4, 49.2, 49.4, 111.4, 119.4, 119.5, 120.5, 121.1, 122.3, 124.1, 125.7, 126.0, 126.4, 126.6, 128.2, 128.5, 128.9, 131.1, 132.5, 134.1, 136.7, 208.5. HRMS: m/z 327.1638 (calcd. for $C_{23}H_{21}NO$, 327.1623).

3-(1H-indol-3-yl)-1-(4-methoxyphenyl)butan-1-one (Table 1, Entry 8)

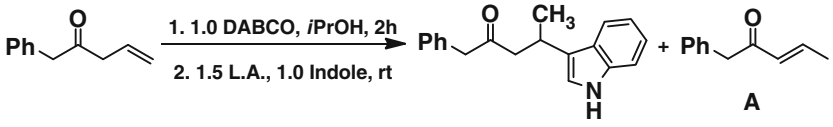
^{1}H-NMR: δ 1.43 (3H, H_4, d, $J = 6.7$ Hz), 3.14 (1H, H_2, dd, $J = 16.1$, 8.9 Hz), 3.38 (1H, H_2, dd, $J = 15.9$, 4.8 Hz), 3.80 (1H, H_3, m), 3.83 (3H, s), 6.89 (2H, d, $J = 6.8$ Hz), 7.02 (1H, d, $J = 2.3$ Hz), 7.09-7.21 (2H, m), 7.35 (1H, J = 7.1 Hz), 7.67 (1H, d, $J = 8.0$ Hz), 7.92 (2H, d, J = 6.8 Hz), 7.95 (1H, br). ^{13}C-NMR: δ 21.2,

27.6, 46.3, 55.7, 111.4, 113.9, 119.5, 120.3, 122.0, 122.2, 126.6, 130.6, 130.7, 136.8, 163.6, 198.5.

Results and discussion

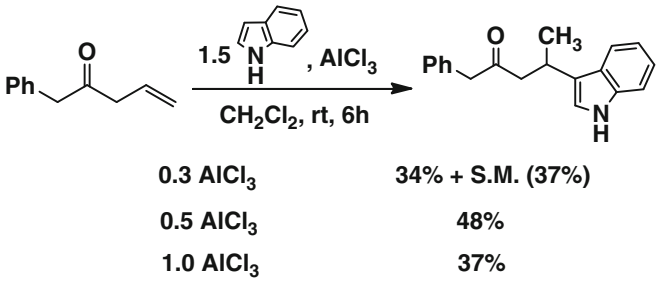
The first feasibility of our approach was to investigate the isomerization of 1-phenyl-pent-3-en-one by the reported reaction condition (DABCO/*i*PrOH) [21–27] followed by treatment of Lewis acids and indole at room temperature to generate Friedel–Crafts Michael reaction product 3-substituted indole (Scheme 2).

A reaction mixture of of 1-phenyl-pent-3-en-one (1.0 eq.) and DABCO (2.0 eq.) in *i*PrOH was stirred at room temperature for 2 h and then $AlCl_3$ (1.5 eq.) and indole (1.0 eq.) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 7 h and the expected 3-substituted indole was produced with 79 % yield. Lewis acids such as $TiCl_4$ can also behave as the promoters for this one-pot reaction to generate 3-substituted indole. Other Lewis acids such as $SnCl_4$, BBr_3, $FeCl_3$, $ZnCl_2$, BF_3OEt_2 and Me_3SiOTf were investigated and isomerized compound A was obtained as the major product with minor product 3-substituted indole. The experimental results showed that $AlCl_3$ is the best choice of promoter for the one-pot isomerization and Friedel–Crafts Michael reaction for synthesis of 3-substituted indoles. The introduction of $AlCl_3$ may promote the isomerization reaction and Friedel–Crafts Michael reaction in one-pot reaction condition. Thus, we investigated the existence of $AlCl_3$ as isomerizing and Friedel–Crafts alkylating agent without using DABCO/*i*PrOH for the isomerization step and the results showed that 3-substituted indole could also be produced under the reaction condition. The introduced amount of $AlCl_3$ was investigated and the results are shown in Scheme 3.

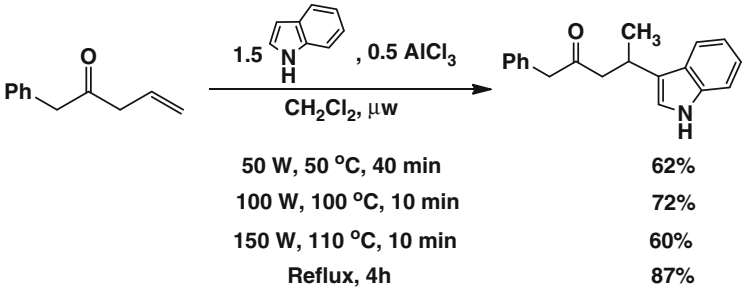


$AlCl_3$, 7h	79%
$TiCl_4$, 7h	76%
$SnCl_4$, 69h	26% + A (37%)
BBr_3, 71h	20% + A (52%)
$InCl_3$, 72h	7%
$FeCl_3$, 18h	15% + A (36%)
$ZnCl_2$, 73h	1% + A (67%)
$BF_3 \cdot OEt_2$, 71h	7% + A (55%)
Me_3SiOTf, 71h	9% + A (44%)

Scheme 2 Optimization of introducing Lewis acid



Scheme 3 Optimization of introducing amount of $AlCl_3$



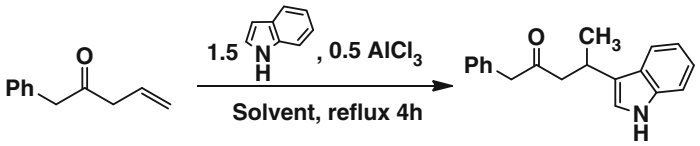
Scheme 4 Optimization of energy source

Introducing 0.5 equivalent of $AlCl_3$ to 1-phenyl-pent-3-en-one in CH_2Cl_2 afforded 48 % yield of 3-substituted indole. Introducing 0.3 or 1.0 equivalent of $AlCl_3$ to the substrate did not increase the formation yield of 3-substituted indole. Therefore, the amount of 0.5 equivalent $AlCl_3$ was determined and tested by different energy sources for this reaction condition. The reaction mixture of $AlCl_3$, 1-phenyl-pent-3-en-one, and indole in CH_2Cl_2 was irradiated by microwave at 50–110 °C and improved the formation yield to 72 % (Scheme 4). It is worth noting that a traditional energy source (refluxing CH_2Cl_2, b.p. = 39 °C) dramatically improved the yield from 48 % (room temperature) to 87 %.

Other solvents of higher refluxing temperature were investigated for this reaction condition (Scheme 5). It is interesting to note that the investigated higher refluxing temperature solvents such as $CHCl_3$ (b.p. = 61 °C), CH_3CN (b.p. = 81 °C), and *i*PrOH (b.p. = 82 °C) afforded lower formation yields of 3-substituted indoles.

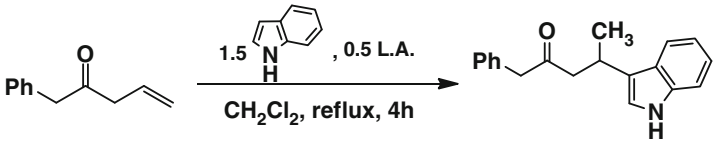
Different Lewis acids were investigated for the optimization of this β-substitution of β,γ-unsaturated ketone with indole reaction (Scheme 6). The experimental results showed that $AlCl_3$ is the best choice of promoter for the production of 3-substituted indole by the reaction of β,γ-unsaturated ketone with indole.

To understand the scope of this one-pot $AlCl_3$ promoted isomerization of β,γ-unsaturated ketone and then the Michael addition reaction of indole, a series of β,γ-unsaturated ketones were investigated under the reaction condition and the results are shown in Table 1. As shown, all β,γ-unsaturated ketones were transformed to their corresponding 3-substituted indoles with moderate to high yields. Both alkyl-



CH_2Cl_2	87%
$CHCl_3$	63%
CH_3CN	83%
*i*PrOH	49%

Scheme 5 Optimization of solvent



$AlCl_3$	87%
$InCl_3$	23% + S.M. (52%)
$FeCl_3$	17% + S.M. (24%)
$FeBr_3$	16%
$FeF_3{\cdot}3H_2O$, 1 day	0% + S.M. (86%)
$Yb(OTf)_3$	11% + S.M. (81%)
$TiCl_4$	45% + S.M. (32%)
$ZrCl_4$	47%
$SnCl_4$	12% + S.M. (87%)

Scheme 6 Optimization of Lewis acid promoters

and aryl-β,γ-unsaturated ketones can undergo this Friedel–Crafts Michael reaction and give the desired products.

In conclusion, this one-pot Lewis acid promoted in situ isomerization of β,γ-unsaturated ketone to their corresponding α,β-unsaturated ketone, then undergoing Michael addition reaction with indole to afford 3-substituted indole which provides a selective C–C bond formation at β-position of ketone and 3-position of indole.

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