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$ZrCl_4$-Mediated Regio- and Chemoselective Friedel–Crafts Acylation of Indole

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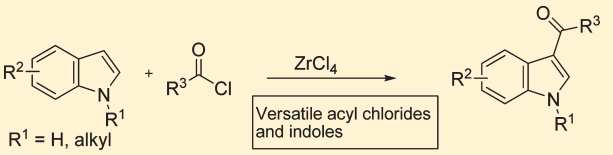
Supporting Information

ABSTRACT: An efficient method for regio- and chemoselective Friedel–Crafts acylation of indole using acyl chlorides in the presence of $ZrCl_4$ has been discovered. It minimizes/eliminates common competing reactions that occur due to high and multiatom-nucleophilic character of indole. In this method, a wide range of aroyl, heteroaroyl alkenoyl, and alkanoyl chlorides undergo smooth acylation with various indoles without NH protection and afford 3-acylindoles in good to high yields.



3-Acylindoles are versatile intermediates in the synthesis of alkaloids, indole derivatives, and several heterocycles.[1] They have been found to exhibit various pharmaceutical activities like anticancer, antidiabetic, inhibitor of HIV-1 integrase, and antinociceptive.[2] Marketed drugs include pravodoline (analgesic) and ramosetron (antiemetic). The synthesis of 3-acylindoles has thus gained considerable attention. The common method for the preparation of 3-acylindoles is Friedel–Crafts reaction.[3−5] The other significant approaches include Vilsmeier–Haack reaction,[6a] indole Grignard reaction,[6b] coupling of 3-indolylzinc chloride with acyl chloride under Pd catalysis,[6c] and the reaction of indole with *N*-(2-haloacyl)pyridinium salt.[6d] As indole is high and multiatom nucleophilic in nature, under Friedel–Crafts acidic conditions it suffers from competing side reactions such as 1-acylation and/or 1,3-diacylation, Mannich-type indole oligomerizations (di-, tri-, and even tetra-), acylation of oligomerized products, and nucleophilic addition of indole to 3-acylindole forming bisindolylalkanol or trisindolylalkane.[3,4] To reduce/eliminate these side reactions, NH-protected or electron-deactivated indoles were used in acylation processes.[5] These methods require additional protection–deprotection steps or limit the structural variation of indole. Aluminum chloride, a Lewis acid (L.A.) traditionally used in Friedel–Crafts reactions, results in oligomerizations of indole because of its strong Lewis acidity.[4a] These challenges have incited the development of alternative promoters/catalysts, for example, alkylaluminium chloride,[4a,b] imidazolium chloroaluminate,[3b] and $SnCl_4$.[4c] However, these Lewis acids suffer from one or more disadvantages such as commercial nonavailability, cost, toxicity, and handling difficulty/hazards, nonfeasibility toward various substituted/functionalized acylating reactants, and the inconvenience of the procedure, especially extraction difficulty of the reaction mixture. In the acylation of indole with acyl chlorides, unavoidable liberation of HCl during the reaction mainly causes the oligomerzations of indole (Scheme 1). The nature of the Lewis acid has been found to be responsible for scavenging HCl or preventing HCl-caused oligomerizations by forming an indole–L.A. complex.[4a−c] In comparison to $AlCl_3$, alkylaluminium chloride (a milder Lewis acid and HCl scavenger) has been found to minimize/eliminate the oligomerizations of indole and other side reactions. To selectively favor the Friedel–Crafts acylation, Lewis acid should also preferably activate the acylating agent to form an acyl cation or a donor–acceptor complex of acylating agent–L.A. Thus, the Lewis acid may play a crucial role for required selectivity in Friedel–Crafts acylation of indole with acyl chlorides. As alternative approach, *N*-acylbenzotriazoles in the presence of $TiCl_4$ that afford 3-acylation of indole without competing reactions[7a] and a nucleophilic catalysis[7b] for acylation of NH-protected indole have been documented. Here, we report $ZrCl_4$-promoted regio- and chemoselective Friedel–Crafts acylation of indole with acyl chlorides. It minimizes/eliminates the common side reactions. A wide range of aroyl, heteroaroyl, alkenoyl, and alkanoyl chlorides undergo smooth acylation with various indoles without NH protection and afford 3-acylindoles in good to high yields (Scheme 2).

Our investigation centered on Lewis acids with suitable hard/soft acidity and charge density of the metal cation. Zr^{4+} has a higher charge-to-size ratio (Z^2/r: 22.22 $e^2\ m^{-10}$) compared to most of the main group elements and lighter and heavier transition metal ions, such as Li^+, Bi^{3+}, In^{3+}, Sc^{3+}, Fe^{3+}, V^{3+}, and Al^{3+} (Z^2/r: 1.35, 8.82, 11.39, 12.33, 13.85, 14.06, 16.98 $e^2\ m^{-10}$, respectively), and is relatively softer hard acid.[8] This inherent chemical feature of $ZrCl_4$ has led it to be a promising catalyst with strong Lewis acid behavior, operational simplicity, and low toxicity (its LD_{50} for oral rat, 1688 $mg \cdot kg^{-1}$, is not considered particularly poisonous).[9] In addition, its relatively high abundance and thus low cost offers attractive use in catalysis.[10,11] $ZrCl_4$ as Lewis acid catalyst in Friedel–Crafts acylation of benzene, toluene, and anthracene is also known.[12] We speculated that $ZrCl_4$ could play a required role and be beneficial in selective acylation of indole. We investigated the

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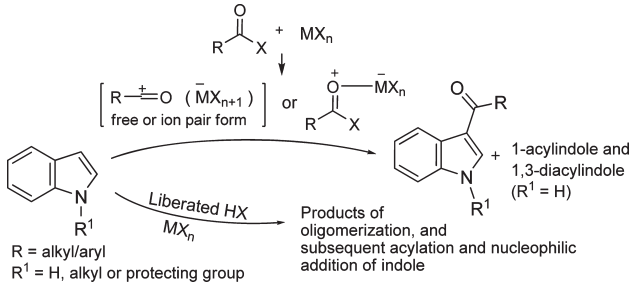
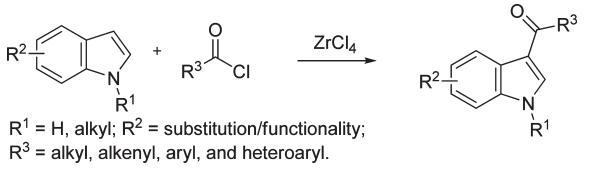
Scheme 1. Friedel−Crafts Acylation of Indoles and Its Common Competitive Side Reactions

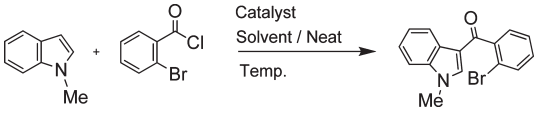


Scheme 2. Our Procedure: $ZrCl_4$-Promoted Regio- And Chemo-Selective Friedel−Crafts Acylation of Indole



efficiency of $ZrCl_4$ and other Lewis acids, additives, solvents, and conditions for the Friedel−Crafts acylation of *N*-methylindole with 2-bromobenzoyl chloride. The results are summarized in Table 1. In most of the Lewis acids, competing side reactions such as oligomerizations (a mixture of dimerization products as major), subsequent acylation, and nucleophilic addition of indole to acylated oligomerized products were found to take place, as revealed by mass and NMR spectroscopic studies, and thus resulted in formation of the desired acylated product in fewer yields. These side reactions were found to be relatively less successful in the presence of $ZrCl_4$. Modification of conditions such as switching the reaction temperature from 30 °C to 0 → 30 °C and neat to solution phase enhanced the desired acylation. Use of $LiClO_4$ as promoter along with catalyst is known to favor Friedel−Crafts acylation. This modification enhanced the yield in the presence of $MoOCl_2$ (Table 1, entry 12) but could not significantly increase the yield in case of $ZrCl_4$ (Table 1, entry 11). In screening of reaction solvents in the presence of $ZrCl_4$, a low dielectric solvent like DCE was found to be best to favor the Friedel−Crafts acylation (Table 1, entries 13−16). IR studies of a mixture of CH_3COCl and $ZrCl_4$ (1:1) in neat, DCE, DCM, DMF, and $MeNO_2$ at 0→30 °C were performed. They showed the bathochromic shift of 182−216 cm^{-1} from 1826 cm^{-1} (for C═O stretching in CH_3COCl) without any peak of hypsochromic shift. It indicates that $ZrCl_4$ formed the donor−acceptor complex (not the acyl cation) with acyl chloride in these solvents. The highest bathochromic shift (216 cm^{-1}) observed in DCE solvent signifies that the maximum activation of acyl chloride in donor−acceptor complex occurred in this solvent. Among the Lewis acids screened, $ZrCl_4$ was found to be best for 3-acylation of indole plausibly due to its suitable combination of higher charge-to-size ratio and relatively softer hard acidity which favored the formation of donor−acceptor complex. The presence of $ZrCl_4$ is needed for acylation, as the reaction did not proceed without it (Table 1, entry 21). Changing the sequential addition of acyl chloride in DCE followed by Lewis acid to indole in DCE resulted in increased side reactions. In our optimized protocol, 1.5 equiv of

Table 1. Screening of Lewis Acids and Conditions for Friedel−Crafts Acylation of Indole[a]



entry	Lewis acid	mol %	neat/solvent	time (h)	yield[b] (%)
		reaction temperature: 30 °C			
1	$ZrCl_4$	50	neat	4	38
2	$MoOCl_2$	50	neat	6.5	26
3	$VOCl_3$	50	neat	6	12
4	$Sc(OTf)_3$	50	neat	5.5	18
5	$FeCl_3$	50	neat	7	15
6	$BiCl_3$	50	neat	6	12
7	$ZnCl_2$	50	neat	6	16
		addition at 0 °C, 0 → 30 °C, then continuation at 30 °C			
8	$ZrCl_4$	50	neat	4	54
9	$MoOCl_2$	50	neat	7	34
10	$VOCl_3$	50	neat	6.5	15
11	$ZrCl_4 + LiClO_4$	50, 100	neat	5	57
12	$MoOCl_2 + LiClO_4$	50, 100	neat	4.5	52
13	$ZrCl_4$	100	DCE	4	60
14	$ZrCl_4$	100	DCM	4	55
15	$ZrCl_4$	100	DMF	4.5	36
16	$ZrCl_4$	100	$MeNO_2$	4.5	48
17	$ZrCl_4$	150	DCE	4	64
18[c]	$ZrCl_4$	150	DCE	4	72
19[d]	$ZrCl_4$	150	DCE	4	68
20[e]	$ZrCl_4$	150	DCE	4	64
21	no Lewis acid		DCE	48	0

[a] Indole/acyl chloride = 1:1. Anhydrous solvent used: 3 mL. [b] Isolated yields. [c] Indole/acyl chloride = 1.3:1. [d] Indole/acyl chloride = 1.5:1. [e] Indole/acyl chloride = 1:1.5.

$ZrCl_4$ was found to be necessary. The variation in equivalence of reactants (Table 1, entries 18−20) revealed that 1.3 equiv of indole and 1 equiv of acyl chloride were optimal. The experimental procedure is simple and straightforward.

With the optimized Friedel−Crafts acylation protocol in hand, we next set out to explore its scope. To our delight, versatile alkanoyl, alkenoyl, aroyl and heteroaroyl chlorides, and indoles including NH-unprotected indole produced diverse 3-acylindoles in good to high yields (Table 2). *N*-Acylation and 1,3-diacylation of indole without NH-blocking are known in the literature. In contrast, negligible *N*-acylated (1−3% yield) and no 1,3-diacylated products were isolated by this method. Pivoloyl chloride, which is known for its susceptibility toward decarbonylative alkylation in the Friedel−Crafts acylation reaction, was found to be a feasible acylating agent in our developed protocol affording 3-pivoloylindole in 75% yield (Table 2, entries 9 and 10). In place of acid chloride, acid anhydride was also found to produce 3-acylindole in similar yields (Table 2, entries 7a and 7b). The electron-rich indole such as 5-methoxyindole, which is known to be more susceptible toward oligomerizations, was found to afford aroylated product in good yield (Table 2, entry 20).

The tolerance of functionalities such as chloro, bromo, nitro, and methoxy in this protocol provides the opportunity for their

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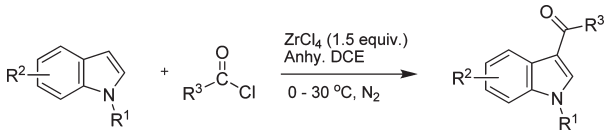
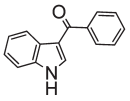
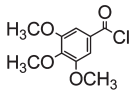
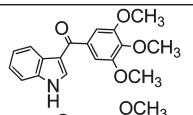
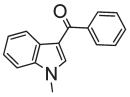
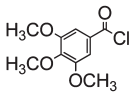
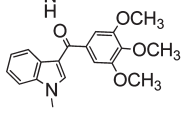
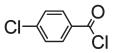
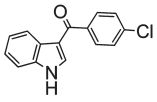
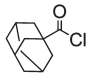
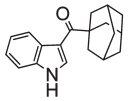
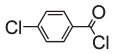
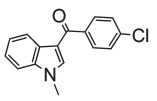
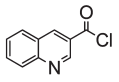
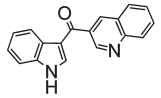
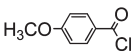
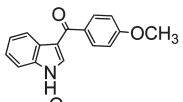
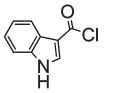
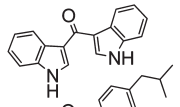
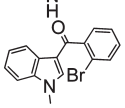
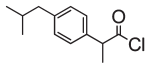
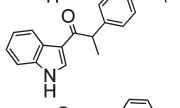
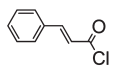
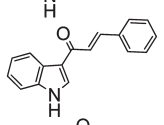
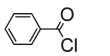
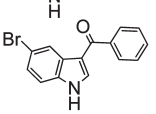
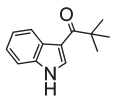
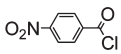
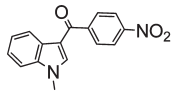
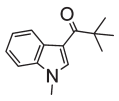
Table 2. Friedel−Crafts 3-Acylation of Various Indoles with Versatile Aroyl, Heteroaroyl, Alkenoyl, And Alkanoyl Chlorides[a]



Entry	Acylating agent	Time (h)	Product	Yield (%)[b]	Entry	Acylating agent	Time (h)	Product	Yield (%)[b]
1		4		71	11		6		51
2		4		78	12		5.5		58
3		4.5		62	13		3.5		82
4		4.5		69	14		6		71
5		4		77	15		6.5		66
6		6		72	16		5.5		54
7 a)		3.5		69	17		4		67
b)		4		67					
8		3.5		71	18		5		63
9		3		75	19		7		64
10		3		77	20		6.5		62

[a] Indole/acyl chloride/$ZrCl_4$ = 1.3: 1: 1.5. [b] Isolated yields.

various further chemical manipulations in 3-acylindole derivatives. Several moieties, which are present in drugs, therapeutic agents, or their precursors, could be incorporated easily by this acylation methodology into 3-acylindole products in good to high yields. These groups are trimethoxyphenyl (anticancer agent), adamantyl (antimalarial agent), isoquinoline (antitubercular agent), 2-(4-isobutylphenyl)propanoyl (ibuprofen, anti-inflammatory drug), and cinnamoyl (anticancer agent). Since the indole scaffold is omnipresent in natural products and bioactive compounds, the method enabling the incorporation of therapeutically important versatile moieties into 3-acylindoles is much more useful in the medicinal chemistry research.

In conclusion, we have developed $ZrCl_4$-mediated regio- and chemoselective Friedel−Crafts 3-acylation of indole with minimization/elimination of competing side reactions which are common in Lewis/Brönsted acid conditions. In this method, a wide range of aroyl, heteroaroyl, alkenoyl, and alkanoyl chlorides undergo smooth acylation with various indoles without NH protection. This protocol offers several advantages including use of economical, low toxic, and easy-handling Lewis acid, a simple procedure, good to high yields of products, generality, and feasibility for incorporation of therapeutically important motifs, which render its potential application.

EXPERIMENTAL SECTION

General considerations: The starting materials and solvents were used as received from commercial suppliers without further purification. The

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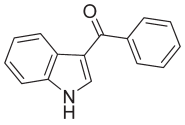
^{1}H and ^{13}C spectra were recorded in $CDCl_3$/DMSO-d_6/CD_3OD solvents on a 400 MHz spectrometer using TMS as internal standard. Melting points determined are uncorrected.

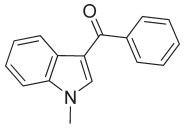
Representative Experimental Procedure for the Synthesis of 3-Benzoylindole (Table 2, Entry 1). To a solution of indole (153 mg, 1.3 mmol) in anhyd DCE (1.5 mL) taken in a round-bottom flask at 0 °C under nitrogen was added benzoyl chloride (140 mg, 1 mmol) in anhyd DCE (1.5 mL) by a syring under nitrogen. Zirconium tetrachloride (349.5 mg, 1.5 mmol) was added under a flow of nitrogen. The reaction temperature was then gradually increased to 30 °C, and the reaction was continued at 30 °C. After completion of the reaction as indicated by TLC (4 h), the resultant mixture was quenched with water (5 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layer was washed with water (10 mL), dried with anhyd Na_2SO_4, and concentrated under vacuum. The column chromatographic purification of crude mass on silica gel eluting with EtOAc−petroleum ether provided 3-benzoylindole (157 mg, 71% yield).

All acylation reactions (Table 2) were carried out following this representative procedure.

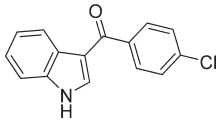
1*H*-Indol-3-yl-phenylmethanone (Table 2, entry 1):[4b,13a]. white solid; mp 243−245 °C; yield 71% ; IR (KBr) ν_{max} 3144, 2935, 1598 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.26 (d, J = 7.2 Hz, 1H), 7.93 (s, 1H), 7.79 (d, J = 7.4 Hz, 2H), 7.60 (d, J = 6.8 Hz, 1H), 7.55 (t, J = 7.6 Hz, 3H), 7.29−7.24 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 190.5, 140.9, 137.1, 136.3, 131.5, 128.9, 128.8, 126.6, 123.6, 122.4, 121.9, 115.4, 112.7; MS (APCI) m/z 222 (MH$^+$).



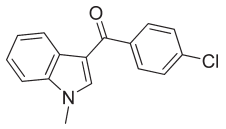
1-Methyl-1*H*-indol-3-yl-phenylmethanone (Table 2, entry 2):[7b]. white solid; mp 116−118 °C; IR (KBr) ν_{max} 3150, 2926, 1596 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43−8.41 (m, 1H), 7.77 (d, J = 7.1 Hz, 2H), 7.52−7.48 (m, 1H), 7.45−7.41 (m, 3H), 7.32−7.29 (m, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 190.8, 140.9, 138.0, 137.5, 131.1, 128.6, 128.3, 127.0, 123.7, 122.7, 122.6, 115.4, 109.7, 33.5; MS (APCI) m/z 236 (MH$^+$).



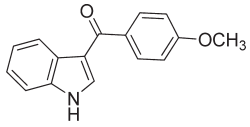
4-Chlorophenyl(1*H*-indol-3-yl)methanone (Table 2, entry 3):[4b]. yellowish white solid; mp 241−242 °C; IR (KBr) ν_{max} 3297, 3006, 1737, 1591 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.24 (d, J = 7.2 Hz, 1H), 7.96 (s, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 7.2 Hz, 1H), 7.33−7.23 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 189.2, 139.5, 137.1, 136.5, 136.3, 130.7, 128.9, 126.5, 123.7, 122.5, 121.8, 115.2, 112.7; MS (APCI) m/z 256 (MH$^+$).



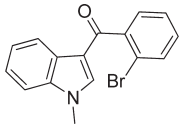
4-Chlorophenyl(1-methyl-1*H*-indol-3-yl)methanone (Table 2, entry 4): off-white solid; mp 144−145 °C; IR (KBr) ν_{max} 3367, 2946, 1699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39−8.36 (m, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 7.43 (d, J = 8.4 Hz, 2H), 7.35−7.32 (m, 3H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.4, 139.1, 137.7, 137.5, 137.2, 130.0, 128.5, 127.0, 123.8, 122.8, 122.6, 115.3, 109.7, 33.6; HRMS (ESI) calcd for $C_{16}H_{13}ClNO$ [M + H]$^+$ 270.0686, found m/z 270.0685, calcd for $C_{16}H_{12}ClNNaO$ [M + Na]$^+$ 292.0505, found m/z 292.0508.



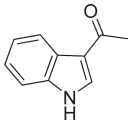
1*H*-Indol-3-yl(4-methoxyphenyl)methanone (Table 2, entry 5):[4b]. light yellow solid; mp 88−89 °C; IR (KBr) ν_{max} 3442, 2934, 1624 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (d, J = 7.0 Hz, 1H), 7.94 (s, 1H), 7.80 (d, J = 7.8 Hz, 2H), 7.52 (d, J = 7.1 Hz, 1H), 7.23−7.21 (m, 2H), 7.05 (d, J = 7.8 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 188.8, 161.6, 136.5, 134.8, 132.8, 130.5, 126.3, 122.9, 121.6, 121.4, 115.0, 113.6, 112.1, 55.3; MS (APCI) m/z 252 (MH$^+$).



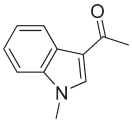
2-Bromophenyl(1-methyl-1*H*-indol-3-yl)methanone (Table 2, entry 6): white solid; mp 150−152 °C; IR (KBr) ν_{max} 3352, 2970, 1738, 1606 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38−8.36 (m, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.44−7.31 (m, 7H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.3, 142.3, 138.8, 137.8, 133.2, 130.4, 128.6, 127.0, 126.4, 123.8, 123.0, 122.7, 119.5, 116.1, 109.8, 33.6; HRMS (ESI) calcd for $C_{16}H_{12}BrNNaO$ [M + Na]$^+$ 336.0000, found m/z 335.9999.



1-(1*H*-Indol-3-yl)ethanone (Table 2, entries 7a and 7b):[13a]. white solid; mp 189−190 °C; IR (KBr) ν_{max} 3155, 2920, 1612 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ = 8.22 (d, J = 7.2 Hz, 1H), 8.13 (s, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.23−7.20 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ = 196.8, 138.4, 135.6, 126.7, 124.3, 123.2, 122.8, 118.4, 112.9, 27.2; MS (APCI) m/z 160 (MH$^+$).



1-(1-Methyl-1*H*-indol-3-yl)ethanone (Table 2, entry 8):[13b]. white solid; mp 106−107 °C; IR (KBr) ν_{max} 3468, 3106, 1642, 1529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.37−8.32 (m, 1H), 7.62 (s, 1H), 7.30−7.28 (m, 3H), 3.76 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 192.9, 137.4, 135.8, 126.2, 123.2, 122.5, 122.4, 116.8, 109.6, 33.5, 27.5; MS (APCI) m/z 174 (MH$^+$).



1-(1*H*-Indol-3-yl)-2,2-dimethylpropan-1-one (Table 2, entry 9):[4b]. white solid; mp 160−162 °C; IR (KBr) ν_{max} 3275, 2969, 1609, 1260 cm^{-1}; ^{1}H NMR (400 MHz,CD_3OD) δ = 8.32 (d, J = 7.5 Hz, 1H), 8.20 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.22−7.15 (m, 2H), 1.41 (s, 9H);

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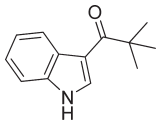
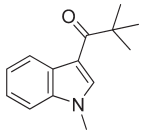
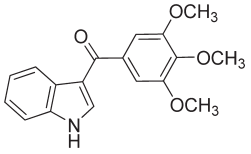
^{13}C NMR (100 MHz, CD_3OD) δ = 205, 137.4, 133.6, 128.7, 124.0, 123.5, 123.0, 114.4, 112.5, 45.0, 29.4; MS (APCI) m/z 202 (MH^+).



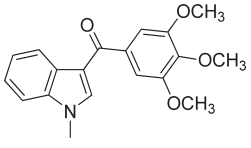
2,2-Dimethyl-1-(1-methyl-1*H*-indol-3-yl)propan-1-one (Table 2, entry 10):[13c]**.** white solid; mp 139−140 °C; IR (KBr) ν_{max} 3680, 2967, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.52−8.50 (m, 1H), 7.78 (s, 1H), 7.30−7.28 (m, 3H), 3.82 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.0, 136.4, 134.3, 128.2, 123.4, 123.2, 122.4, 112.7, 109.2, 44.0, 33.5, 28.9; MS (APCI) m/z 216 (MH^+).



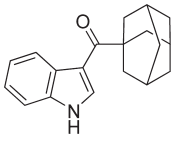
1*H*-Indol-3-yl(3,4,5-trimethoxyphenyl)methanone (Table 2, entry 11):[13d]**.** white solid; mp 132−134 °C; IR (KBr) ν_{max} 3193, 2938, 1575 cm^{-1}; ^{1}H NMR (400 MHz DMSO-d_6) δ = 8.27−8.25 (m, 1H), 8.1 (d, J = 2.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.29−7.23 (m, 2H), 7.11 (d, J = 2.5 Hz, 2H), 3.86 (s, 6H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 189.4, 153.0, 140.4, 137.1, 136.2, 136.1, 126.8, 123.5, 122.3, 121.8, 115.2, 112.6, 106.4, 60.5, 56.3; MS (APCI) m/z 312 (MH^+).



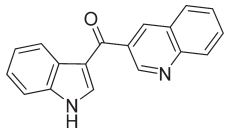
1-Methyl-1*H*-indol-3-yl(3,4,5-trimethoxyphenyl)methanone (Table 2, entry 12):[13e]**.** white solid; mp 167−170 °C; IR (KBr) ν_{max} 3338, 2937, 1618, 1580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36−8.34 (m, 1H), 7.56 (s, 1H), 7.32−7.29 (m, 3H), 7.06 (s, 2H), 3.91 (s, 3H), 3.86 (s, 6H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 189.8, 152.9, 140.7, 137.5, 137.4, 136.2, 127.2, 123.6, 122.6, 122.5, 115.3, 109.7, 106.3, 60.9, 56.3, 33.5; MS (APCI) m/z 326 (MH^+).



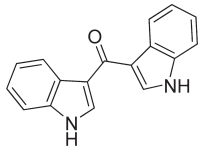
1*H*-Indol-3-yl(tricyclo[3.3.1.13,7]dec-1-yl)methanone (Table 2, entry 13): off-white solid; mp 192−196 °C; IR (KBr) ν_{max} 3218, 2923, 1622, 1605 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.45 (s,1H), 8.26 (d, J = 7.4 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.18−7.10 (m, 2H), 2.03 (s, 9H), 1.81−1.71 (m, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 200.9, 135.4, 132.1, 127.2, 122.4, 122.1, 121.4, 112.2, 111.6, 45.9, 36.2, 27.9; HRMS (ESI) calcd for $C_{19}H_{21}NNaO$ $[M + Na]^+$, 302.1521, found m/z 302.1515.



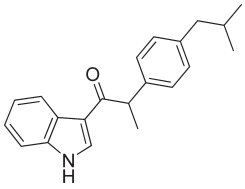
1*H*-Indol-3-yl(quinolin-3-yl)methanone (Table 2, entry 14): yellowish brown solid; mp 235−239 °C; IR (KBr) ν_{max} 2925, 1606 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.2 (s, 1H), 9.24 (s, 1H), 8.84 (s, 1H), 8.33 (d, J = 5.9 Hz, 1H), 8.19 (s, 2H), 8.14 (d, J = 8.3 Hz, 1H), 7.90 (t, J = 7.0, 1H), 7.73 (t, J = 7.1 Hz, 1H), 7.58 (d, J = 6.0 Hz, 1H), 7.30 (d, J = 3.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 188.0, 149.5, 148.3, 136.7 (2CH), 136.5, 132.8, 131.1, 129.4, 128.6, 127.2, 126.6, 126.0, 123.4, 122.2, 121.4, 115.2, 112.3; HRMS (ESI) calcd for $C_{18}H_{12}N_2NaO$ $[M + Na]^+$ 295.0847, found m/z 295.0850.



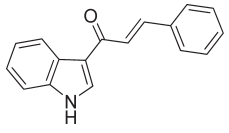
Bis(1*H*-indol-3-yl)methanone (Table 2, entry 15):[13f]**.** reddish brown solid; mp 287−289 °C; IR (KBr) ν_{max} 3180, 2920, 1736, 1584 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.28 (d, J = 7.1 Hz, 2H), 8.17 (s, 2H), 7.51 (d, J = 7.3 Hz, 2H), 7.21 (t, J = 7.7, 4H), ^{13}C NMR (100 MHz, DMSO-d_6) δ = 184.6, 136.4, 131.9, 126.5, 122.5, 121.4, 121.0, 116.8, 111.9; MS (APCI) m/z 261 (MH^+).



1-*1H*-Indol-3-yl-2-(4-isobutylphenyl)propan-1-one (Table 2, entry 16): white solid; mp 157−160 °C; IR (KBr) ν_{max} 3261, 2955, 1620, 1436 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.42 (s, 1H), 8.20 (d, J = 7.2 Hz, 1H), 7.44 (d, J = 7.2 Hz, 1H), 7.32 (d, J = 7.3 Hz, 2H), 7.21−7.14 (m, 2H), 7.05 (d, J = 7.3 Hz, 2H), 4.68−4.67 (m, 1H), 2.35 (d, J = 6.7 Hz, 2H), 1.78−1.72 (m, 1H), 1.42 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.2 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 195.7, 140.0, 139.1, 136.6, 134.0, 128.9, 127.2, 125.7, 122.8, 121.7, 121.3, 115.4, 112.0, 46.7, 44.1, 29.5, 22.1, 18.8; HRMS (ESI) calcd for $C_{21}H_{23}NNaO$ $[M + Na]^+$, 328.1677, found m/z 328.1674.



1-(1*H*-Indol-3-yl)-3-phenylprop-2-en-1-one (Table 2, entry 17):[13g]**.** yellowish white solid; mp 225−230 °C; IR (KBr) ν_{max} 2924, 1640, 1559 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.75 (s, 1H), 8.35 (d, J = 7.1 Hz, 1H), 7.87−7.83 (m, 3H), 7.65 (d, J = 15.5 Hz, 1H), 7.52−7.44 (m, 4H), 7.28−7.21 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 183.5, 139.5, 136.8, 135.1, 134.7, 129.7, 128.8, 128.3, 125.8, 124.5, 123.1, 121.8, 121.7, 117.6, 112.1; MS (APCI) m/z 248 (MH^+).



5-Bromo-1*H*-indol-3-ylphenylmethanone (Table 2, entry 18):[13a]**.** off-white solid; mp 265−267 °C; IR (KBr) ν_{max} 3155, 2936, 1589 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.41 (d, J = 2 Hz, 1H), 8.03 (s, 1H), 7.81−7.79 (m, 2H), 7.63−7.61 (m, 1H), 7.57−7.50 (m, 3H), 7.41 (dd, J = 8.6, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6)

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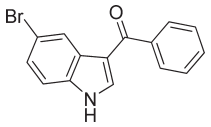
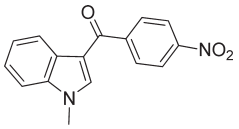
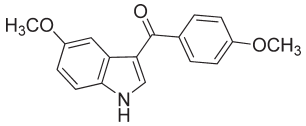
δ = 189.8, 139.9, 136.8, 135.4, 131.3, 128.4, 128.3, 128.0, 125.7, 123.5, 114.7, 114.4, 114.3; MS (APCI) m/z 300 (MH^+).



1-Methyl-1*H*-indol-3-yl(4-nitrophenyl)methanone (Table 2, entry 19):[7a]. yellowish white solid; mp 183−184 °C; IR (KBr) ν_{max} 3430, 2972, 1637 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 8.41−8.39 (m, 1H), 8.33 (d, J = 8.7 Hz, 2H), 7.93 (d, J = 8.7 Hz, 2H) 7.49 (s, 1H), 7.41−7.36 (m, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 188.4, 149.1, 146.3, 138.1, 137.0, 129.3, 126.8, 124.2, 123.6, 123.3, 122.6, 115.2, 109.8, 33.7; MS (APCI) m/z 281(MH^+).



5-Methoxy-1*H*-indol-3-yl(4-methoxyphenyl)methanone (Table 2, entry 20):[13f]. off white solid; 161−164 °C; IR (KBr) ν_{max} 3133, 2926, 1603 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ = 7.89 (s, 1H), 7.78 (t, J=7.6 Hz, 3H), 7.41 (d, J = 8.7 Hz, 1H), 7.08 (d, J=7.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 188.7, 161.6, 155.3, 135.0, 132.9, 131.5, 130.4, 127.1, 114.7, 113.6, 112.8, 103, 55.3, 55.2 MS (APCI) m/z 282 (MH^+).



■ ASSOCIATED CONTENT

Supporting Information. General experimental procedure; ^1H, ^{13}C, IR, and MS for known compounds; ^1H, ^{13}C, HRMS, IR, and melting points for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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