Bismuth triflate catalyzed conjugate addition of indoles to α,β-enones[☆]

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Dedicated to Prof. Goverdhan Mehta on his 60th birthday

Abstract—Reaction of indoles with electron deficient olefins under the influence of bismuth triflate has been studied at ambient temperature and affords the corresponding 3-alkylated indoles in excellent yields.
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The development of synthetic methods leading to indole derivatives has attracted much attention in organic synthesis because of their biological activities.[1] Various indoles are components of drugs and are commonly found in molecules of pharmaceutical interest in a variety of therapeutic areas. Generally, 3-substituted indoles exhibit numerous biological activities.[2] Since the 3-position in indoles is the preferred site for electrophilic substitution, 3-alkyl or acyl indoles are versatile intermediates for the synthesis of a wide range of indole derivatives. In fact, the 3-substituted ketones are highly interesting building blocks for the synthesis of biologically active compounds as well as natural products.[3]

Over the past few years a variety of methods has been reported for the preparation of 3-substituted indoles.[4,5] Acid catalyzed electrophilic substitution of indoles requires careful control of acidity to prevent side reactions such as dimerisation and polymerization.[6] Other methods for the synthesis of 3-alkylated indoles involve the conjugate addition of indoles to α,β-enones in the presence of protic[4] or Lewis acids.[5] However, several of these procedures suffer from drawbacks, such as the need for strongly acidic conditions, expensive reagents, long reaction times, and low yields of products due to dimerisation of the indoles or polymerization of the vinyl ketones.

Thus, an efficient Lewis acid catalyst is desirable for conjugate addition of indoles to α,β-enones. In this connection we describe the use of bismuth triflate as a Lewis acid catalyst for these reactions. Previously, bismuth triflate has been used as a catalyst for Friedel–Crafts acylations,[7] sulfonylation of arenes,[8] Diels–Alder reactions,[9] aza-Diels–Alder reactions,[10] rearrangements of epoxides,[11] formation of acylals[12] and deprotection of acetals.[13] We have a special interest in bismuth triflate because it is inexpensive[14] and can easily be prepared.[15]
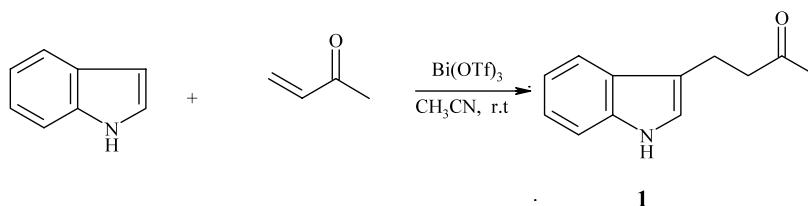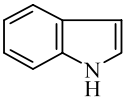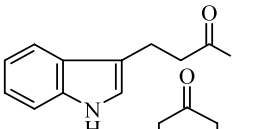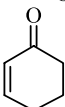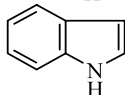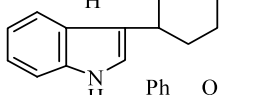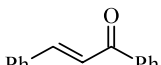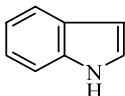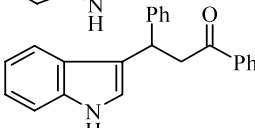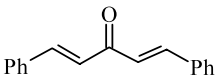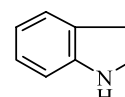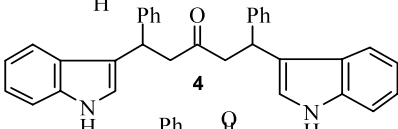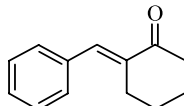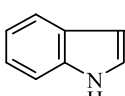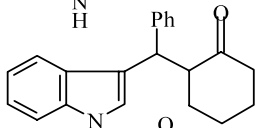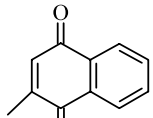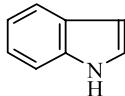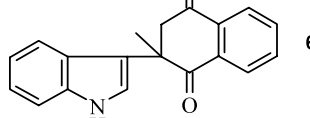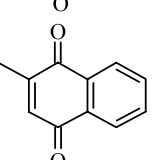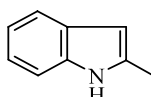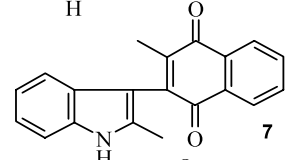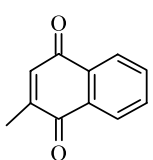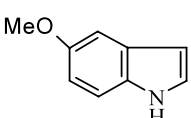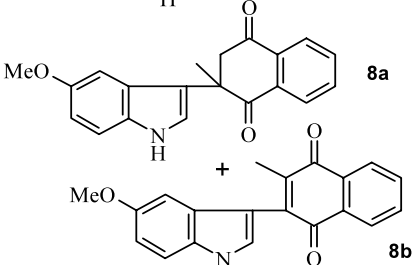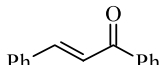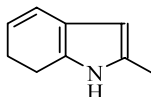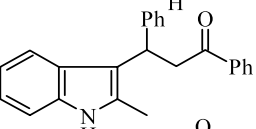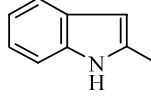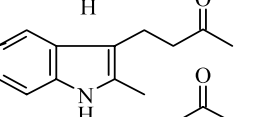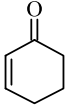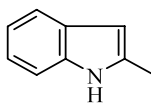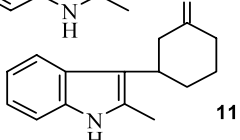

Scheme 1.

Table 1. Conjugate addition of indoles to α,β-enones

Entry	Electrophile	Nucleophile	Product [a]	Time (h)	Yield (%)[b]
1			**1**	1	95[4e]
2			**2**	2	85[4c]
3			**3**	1	90[4c]
4			**4**	2	80[4f] (1:1)
5			**5**	2	85[16] (7:3)
6			**6**	2	86[16]
7			**7**	2	92[16]
8			**8a** + **8b**	2	90[16] (1:1)
9			**9**	2	94[4f]
10			**10**	1	95[4e]
11			**11**	1	95[4f]

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

The reaction of indole with methyl vinyl ketone in the presence of a catalytic amount of bismuth triflate in acetonitrile gave 1-(3′-indolyl)butan-3-one, **1** in 95% yield (Scheme 1).[16] Similarly, various α,β-unsaturated ketones such as cyclic enones, acyclic enones such as chalcones and naphthoquinone were reacted with indole, 2-methylindole and 5-methoxyindole to give the corresponding Michael adducts in excellent yields. In all cases the reactions proceeded smoothly at ambient temperature with high selectivity (Table 1).

The products were characterized by ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. In the case of entries 4 and 5, the reaction of indole with 1,5-diphenyl-1,4-pentadien-3-one and 2-benzylidenecyclohexanone gave 1:1 and 7:3 diastereomeric mixtures of the products **4** and **5**, respectively. Interestingly, when indole reacts with 2-methyl-1,4-naphthoquinone, it attacks at the more hindered position and gave exclusively **6** (entry 6). The product **6** was characterized by the presence of methylene signals at δ 3.30 (1H, d, $J=16$ Hz) and 3.64 (1H, d, $J=16$ Hz) and a tertiary methyl at δ 1.79 (s, 3H) in its ^{1}H NMR spectrum. However, in the case of 2-methylindole attack at the less hindered position was observed to give product **7**, which was characterized by the presence of two vinylic methyls at δ 2.08 (3H, s) and δ 2.14 (3H, s) in its ^{1}H NMR spectrum. Under similar conditions, 5-methoxyindole adds to the 2- and 3-positions of 2-methyl-1,4-naphthoquinone to give **8a** and **8b** in a 1:1 ratio. The reaction is highly efficient and 3 mol% of bismuth triflate was sufficient to catalyze the reaction which proceeded smoothly at ambient temperature with high yields.

In summary, we have demonstrated that bismuth triflate is a catalyst for alkylation of indoles.

Acknowledgements

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16. **Typical experimental procedure**: To a solution of indole (5 mmol), and the vinyl ketone (5 mmol) in CH_3CN (10 ml) was added bismuth triflate (3 mol%) and the mixture was stirred for the appropriate time (see Table 1). After completion of the reaction, as indicated by TLC, the catalyst was filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography to afford the pure product.
5: Solid, m.p. 154–155°C; IR (KBr) v_{max} (cm^{-1}): 2937, 1703, 1453, 1231 and 751; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.26 (1H, m), 1.68 (2H, m), 1.88 (2H, m), 2.26 (1H, m), 2.30 (2H, m), 3.72, (1H, m), 4.60 (1H, d, $J=7.8$ Hz), 7.02 (2H, t, $J=7.2$ Hz), 7.13 (2H, t, $J=7.2$ Hz), 7.20 (2H, d, $J=7.8$ Hz), 7.26 (1H, d, $J=7.8$ Hz), 7.32 (2H, d, $J=8.0$ Hz), 7.72 (1H, d, $J=7.8$ Hz) and 7.80 (1H, bs); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 12.60, 24.15, 29.27, 33.61, 41.99, 42.28, 53.96, 110.55, 113.30, 118.79, 119.03, 120.87, 125.90, 127.49, 128.31, 131.72, 135.22, 143.16 and 212.96. EIMS m/z (%): 303 (M$^+$, 8), 221 (100), 205 (12), 178 (14), 155 (8), 141 (16), 119 (12), 91 (25) and 43 (75). Anal. calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62; O, 5.27. Found: C, 83.32; H, 6.66; N, 4.66; O, 5.36.

6: Solid, m.p.163–164°C; IR (KBr) v_{max} (cm^{-1}): 3375, 2929, 1629 and 1594; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.79 (3H, s), 3.30 (1H, d, $J=16.3$ Hz), 3.64 (1H, d, $J=16.3$ Hz), 7.06 (1H, d, $J=2.6$ Hz), 7.12 (2H, t, $J=6.0$ Hz), 7.24 (1H, dd, $J=7.6, 1.2$ Hz), 7.58 (2H, t, $J=7.0$ Hz), 7.70 (1H, dd, $J=7.6, 1.2$ Hz), 7.92 (1H, dd, $J=7.8, 2.2$ Hz) and 7.98 (1H, dd, $J=7.8, 2.2$ Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.62, 49.30, 50.84, 111.30, 117.51, 119.90, 120.44, 121.36, 122.32, 125.35, 125.70, 127.72, 133.51, 134.23, 134.32, 134.44, 136.60, 196.60 and 198.42; EIMS m/z (%): 289 (M$^+$, 98), 274 (100), 246 (50), 218 (10), 141 (16), 115 (12), 104 (12) and 76 (12). Anal. calcd for C$_{19}$H$_{15}$NO$_2$: C, 78.87; H, 5.23; N, 4.84; O, 11.06. Found: C, 79.15; H, 4.74; N, 4.87; O, 11.24.

7: Solid, m.p. 115–117°C; IR (KBr) v_{max} (cm^{-1}): 3393, 1654, 1457 and 1287; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.08 (3H, s), 2.14 (3H, s), 7.14 (4H, m), 7.70 (1H, dd, $J=2.1, 8.2$ Hz), 7.73 (1H, dd, $J=2.1, 8.2$ Hz), 8.14 (1H, dd, $J=2.0, 7.8$ Hz) and 8.18 (1H, dd, $J=2.0, 7.8$ Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 12.98, 15.18, 106.24, 110.80, 118.92, 120.00 121.37, 126.17, 126.66, 127.84, 132.34, 132.46, 133.44, 134.95, 135.46. 140.99, 145.58, 184.14 and 185.78; EIMS m/z (%): 301 (M$^+$, 100), 300 (20), 286 (80), 284 (18), 168 (10), 141 (14), 141(16), 130 (4), 104 (4), 83 (25) and 76 (12). Anal. calcd for C$_{20}$H$_{15}$NO$_2$: C, 79.72; H, 5.02; N, 4.65; O, 10.62. Found: C, 78.31; H, 4.62; N, 4.56, O, 10.51.

8a: Solid, m.p. 137–139°C; IR (KBr) v_{max} (cm^{-1}): 3366, 2929, 1697, 1512 and 1288; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 1.72 (3H, s), 3.40 (1H, d, $J=16.0$ Hz), 3.60 (1H, d, $J=16.0$ Hz), 3.82 (3H, s), 6.67 (1H, d, $J=2.0$ Hz), 7.10 (3H, m), 7.60 (2H, t, $J=7.2$ Hz), 7.90 (1H, dd, $J=2.0, 7.8$ Hz), 7.96 (1H, dd, $J=2.0, 7.8$ Hz) and 9.8 (1H, brs, NH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 24.02, 49.30, 51.04, 56.20, 102.20, 111.40, 117.62, 118.40, 122.00, 126.40, 127.21, 128.46, 129.24, 132.04, 133.12, 154.04, 196.52 and 198.20; EIMS m/z (%): 319 (M$^+$, 100), 304 (80), 276 (46), 174 (8), 102 (10) and 76 (12). Anal. calcd for C$_{20}$H$_{17}$NO$_3$: C, 75.22; H, 5.37; N, 4.39; O,15.03. Found: C, 75.26; H, 5.40; N, 4.34; O 15.00.

8b: Solid, m.p. 125–126°C; IR (KBr) v_{max} (cm^{-1}): 3665, 1695, 1593, 1484 and 1244; ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.18 (3H, s), 3.78 (3H, s), 6.62 (1H, d, $J=2.0$ Hz), 6.84 (1H, dd, $J=7.8, 2.0$ Hz), 7.23 (1H, d, $J=7.8$ Hz), 7.38 (1H, d, $J=2.2$ Hz), 7.75 (2H, t, $J=7.8$ Hz), 8.18 (2H, m) and 8.43 (1H, brs, NH); ^{13}C NMR (75 MHz, CDCl$_3$) δ: 16.50, 56.02, 102.20, 108.42, 112.35, 120.01, 122.36, 123.42, 130.60, 131.74, 132.27, 132.63, 132.80, 140.02, 135.04, 135.06, 143.20, 151.24, 184.82 and 186.04; EIMS m/z (%): 317 (M$^+$, 80), 303 (78), 285 (8), 258 (4), 217 (10). 178 (12), 136 (24), 104 (42) and 76 (50). Anal. calcd for C$_{20}$H$_{15}$NO$_3$: C, 75.70; H, 4.76; N, 4.41; O, 15.12. Found: C, 75.54; H, 4.72; N, 4.59; O, 15.15.