Diastereoselective Tandem Michael Additions of Indoles to 3-Nitrocoumarin Derivatives and Methyl Vinyl Ketone

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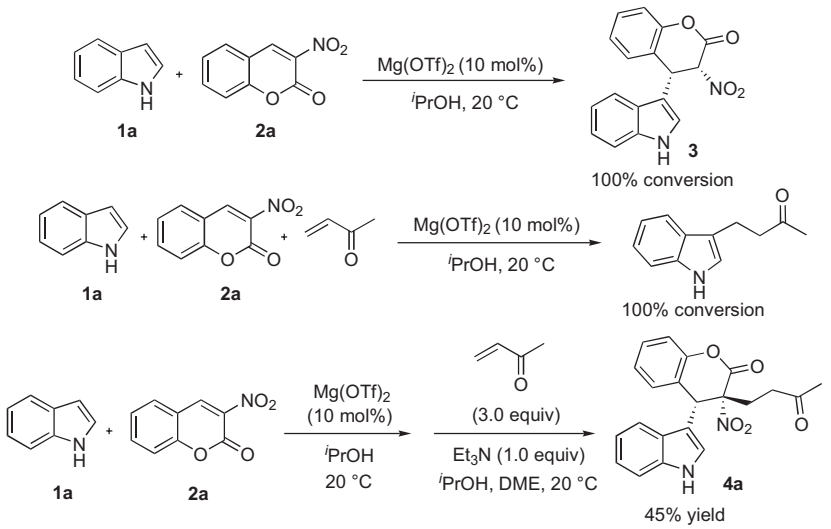
Abstract: Tandem Michael additions of indole derivatives to 3-nitrocoumarins **2**, followed by MVK, in one pot, has been developed for the synthesis of multi-functionalized 3,4-dihydrocoumarins bearing a quaternary stereocenter. The reaction proceeds with high diastereoselectivities in good to excellent yields.

Key words: α,β-unsaturated nitroesters, tandem Michael additions, one-pot reactions, 3,4-dihydrocoumarins

One-pot tandem reactions have received increasing attention in organic synthesis due to their unique characteristics such as simplicity, economy, and environmental friendliness.[1] While studying Lewis acid catalyzed organic transformation,[2] we recently found that indole[3] could react smoothly with nitroolefin **2a** to give the corresponding Michael adduct in high yield in the presence of a catalytic amount of $Mg(OTf)_2$.[4] Further study led us to a one-pot two-step Michael addition of indole to nitroolefin **2a** and MVK, providing an easy access to multi-functionalized 3,4-dihydrocoumarins[5] with high stereoselectivity in good to excellent yield. In this communication, we wish to report the preliminary results.

Conjugated additions to α,β-unsaturated nitroesters by a wide range of nucleophiles,[6] including carbon, nitrogen, oxygen, and sulfide nucleophiles, have been reported. Most of them were promoted by strong Brönsted acids or bases, or heating. The application of Lewis acids as mild promoters in these Michael reactions is rare. To the best of our knowledge, only three examples have been reported: the copper(I)-catalyzed conjugate addition of R_2Zn to 3-nitrocoumarins with up to 20:1 diastereoselectivity;[7] the zinc(II)-catalyzed radical conjugate addition to α,β-unsaturated nitro esters and amides with up to 2.6:1 diastereoselectivity;[8] and the cerium(III)-catalyzed conjugate addition of indole to 2-nitroacrylic acid ethyl ester, which was not diastereoselective.[9] Therefore, we were interested in developing a stereoselective Lewis acid catalyzed Michael addition to α,β-unsaturated nitroesters, a potential access to non-natural amino acids.

Initially, we found that the reaction of indole with coumarin **2a** proceeded well to give the desired Michael addition product **3** with 100% conversion in the presence of $Mg(OTf)_2$ in *i*-PrOH at 20 °C (Scheme 1). Considering that the addition of indole to α,β-unsaturated α-nitro ester first formed an enolate, we envisioned that the enolate



Scheme 1 Highly diastereoselective sequential Michael additions

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could possibly be further trapped by an active Michael acceptor such as MVK. Therefore, we tried a three-component reaction by mixing indole, coumarin **2a**, and MVK in one pot using $Mg(OTf)_2$ as a catalyst in *i*-PrOH at 20 °C. Unfortunately, the only adduct isolated resulted from addition of indole to MVK, suggesting that the reaction of indole with MVK was faster than that with 3-nitrocoumarin.

Alternatively, we investigated one-pot tandem Michael additions: after the first Michael reaction of indole with **2a** in the presence of $Mg(OTf)_2$ in *i*-PrOH at 20 °C was complete, MVK was added directly as the second Michael acceptor. Fortunately, by screening reaction conditions, we were pleased to find that the addition of one equivalent of triethylamine in the second step promoted the reaction in DME–*i*-PrOH (1:1). In this case, the adduct **4a** was isolated as a single *cis* diastereomer in 45% yield. Without DME, a precipitate appeared and **4a** was not obtained. The *cis* configuration was determined by ^{1}H NMR spectroscopy and was further confirmed by X-ray crystallographic analysis of compound **4a** (Figure 1).

To further improve the yield, several bases were screened. As shown in Table 1, no desired product was observed in the presence of one equivalent of *n*-Bu_3P. Reduction of *n*-Bu_3P to 0.4 equivalents, increased the yield of **4a** to 67%. Further lowering the amount of *n*-Bu_3P resulted in low conversion even after long reaction time. Using Ph_3P as a base instead of *n*-Bu_3P, resulted in a higher yield (Table 1, entry 4). Compared with $Mg(OTf)_2$, $Zn(OTf)_2$ gave a similar result (Table 1, entry 5), but $Cu(OTf)_2$ afforded **4a** in only 45% yield (Table 1, entry 6). Reduction of the loadings of both Lewis acid and base improved the yield greatly. For example, using 2 mol% $Mg(OTf)_2$ and 20 mol% *n*-Bu_3P gave **4a** in 84% yield (Table 1, entry 7),

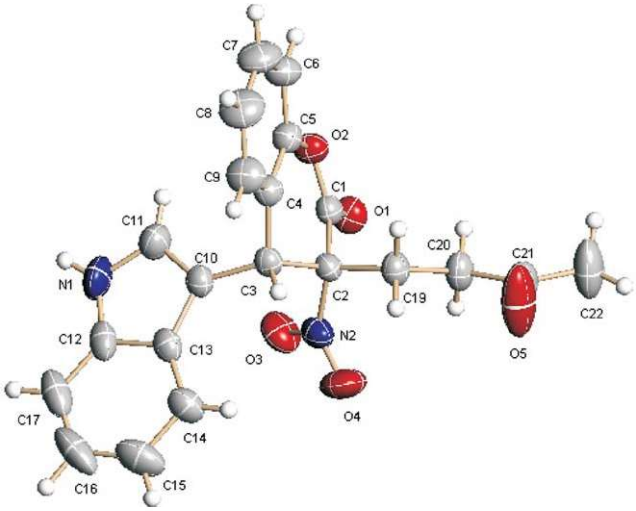
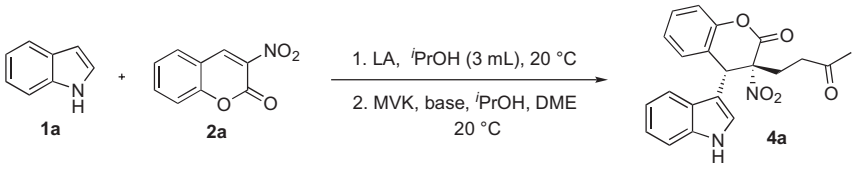


Figure 1 Single-crystal X-ray structure of compound **4a**

replacement of *n*-Bu_3P with Ph_3P increased the yield to 91% (Table 1, entry 8).

Under the optimal conditions, we examined a series of substituted indoles and pyrrole with several 3-nitrocoumarins in tandem Michael addition reactions. Both *N*-Me and 2-Me indoles gave the expected product in 91% and 86% yield, respectively (Table 2, entries 2 and 3). The electronic character of the aromatic ring of indole affected the yields. For example, 5-methoxyindole, 5-methylindole and 6-benzoxyindole gave 89%, 87%, and 85% yield, respectively (Table 2, entries 5, 6, and 8) but 5-bromoindole gave a slightly lower yield (81%, Table 2, entry 7). In contrast, 4-methoxyindole afforded an even lower yield (61%, Table 2, entry 4), probably owing to steric hindrance. Pyrrole was also a good substrate for this

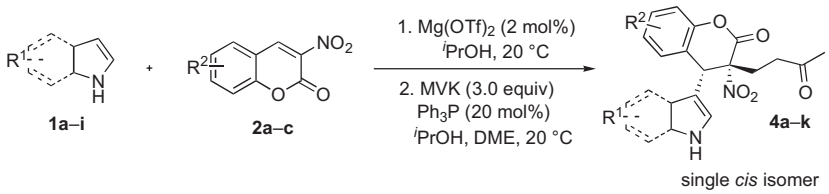
Table 1 Optimization of Reaction Conditions

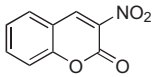
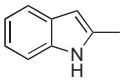
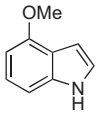
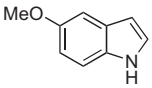
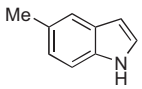
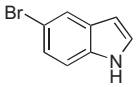
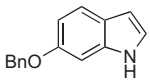
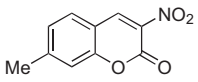
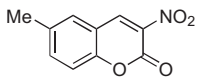


Entry	Lewis acid (mol%)	Base (mol%)	Yield (%)[a,b]
1	$Mg(OTf)_2$ (10)	Et_3N (100)	45
2	$Mg(OTf)_2$ (10)	*n*-Bu_3P (100)	0
3	$Mg(OTf)_2$ (10)	*n*-Bu_3P (40)	67
4	$Mg(OTf)_2$ (10)	Ph_3P (40)	77
5	$Zn(OTf)_2$ (10)	Ph_3P (40)	76
6	$Cu(OTf)_2$ (10)	Ph_3P (40)	45
7	$Mg(OTf)_2$ (2)	*n*-Bu_3P (20)	84
8	$Mg(OTf)_2$ (2)	Ph_3P (20)	91

[a] Reactions were performed on 0.5 mmol scale with MVK (3.0 equiv).
[b] Isolated yield.

Table 2 One-Pot Sequential Michael Additions[10]



Entry	Indole	3-Nitrocoumarin	Chromanone[a,b]	Yield (%)[c]
1	 **1a**	 **2a**	**4a**	91
2	 **1b**	**2a**	**4b**	91
3	 **1c**	**2a**	**4c**	86
4	 **1d**	**2a**	**4d**	61
5	 **1e**	**2a**	**4e**	89
6	 **1f**	**2a**	**4f**	87
7	 **1g**	**2a**	**4g**	81
8	 **1h**	**2a**	**4h**	85
9	 **1i**	**2a**	**4i**	65
10	**1a**	 **2b**	**4j**	88
11	**1a**	 **2c**	**4k**	96

[a] Reactions were performed on a 0.5 mmol scale.
[b] All products were characterized by NMR, IR, mass spectrometry.
[c] Isolated yields.

reaction and 65% yield could be obtained (Table 2, entry 9). 7-Methyl-3-nitrocoumarin and 6-methyl-3-nitrocoumarin worked well in this reaction to give high yields (88% and 96%, respectively, Table 2, entries 10 and 11). Noticeably, only one isomer was isolated in all cases, indicating that diasteroselectivity for this reaction was excellent.

In summary, we have developed tandem Michael additions of indole derivatives to 3-nitrocoumarins and MVK in one pot, affording a facile synthesis of multi-functionalized 3,4-dihydrocoumarins with high diastereoselectivities. High yields, mild reaction conditions, simple procedure, and in particular the indole framework produced make this synthetic method potentially useful.

Acknowledgment

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(10) **Typical Procedure**: To a stirred solution of $Mg(OTf)_2$ (0.01 mmol) and 3-nitrocoumarin **2** (0.50 mmol) in *i*-PrOH (3 mL) at 20 °C in air was added indole derivative **1** (0.51 mmol). After the reaction was complete (ca. 3–12 h, monitored by TLC), MVK (124 μL, 1.50 mmol) and Ph_3P (26.2 mg, 0.10 mmol) were added in turn, then DME (3 mL) was added in ca. five minutes. The resulting mixture was stirred for the required time (TLC), concentrated, and purified by flash chromatography on silica gel (PE–EtOAc, 2:1) to give the product **4**.
Selected spectral data:
4a: IR (neat): 3418, 1773, 1710, 1554, 1458, 1356, 1226, 1169, 747 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.43 (br s, 1 H), 7.40–7.33 (m, 3 H), 7.25–7.20 (m, 2 H), 7.14–7.07 (m, 4 H), 4.98 (s, 1 H), 2.86–2.73 (m, 2 H), 2.66–2.44 (m, 2 H), 2.09 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.75, 161.25, 149.76, 135.81, 129.64, 128.56, 126.70, 125.60, 124.70, 122.83, 122.60, 120.41, 117.88, 116.78, 111.72, 107.69, 92.98, 43.96, 38.12, 29.87, 28.42. LRMS-EI: *m*/*z* (%) = 378 (M^+), 274 (100). Anal. Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.79; N, 7.40. Found: C, 66.67; H, 4.84; N, 7.40.
4b: IR (neat): 3052, 2926, 1774, 1718, 1554, 1487, 1456, 1338, 1226, 1166, 742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.32 (m, 3 H), 7.28–7.20 (m, 2 H), 7.13–7.07 (m, 3 H), 6.97 (s, 1 H), 4.97 (s, 1 H), 3.78 (s, 3 H), 2.80–2.71 (m, 2 H), 2.60–2.44 (m, 2 H), 2.08 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.62, 161.22, 149.75, 136.66, 129.56, 128.99, 128.52, 127.41, 125.54, 122.90, 122.37, 120.00, 117.89, 116.75, 109.78, 105.91, 93.04, 43.81, 38.11, 33.07, 29.83, 28.40. LRMS-ESI: *m*/*z* = 393 (M + H^+). HRMS: *m*/*z* calcd for $C_{22}H_{20}N_2O_5Na$ (M + Na^+): 415.1270; found: 415.1267.

4c: IR (neat): 3418, 1770, 1716, 1587, 1556, 1509, 1455, 1360, 1264, 1237, 1169, 1091, 735 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 11.27 (s, 1 H), 7.41–7.30 (m, 3 H), 7.05–6.94 (m, 3 H), 6.73–6.61 (m, 2 H), 5.44 (s, 1 H), 3.52 (s, 3 H), 3.00–2.49 (m, 4 H), 2.05 (s, 3 H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 206.94, 161.87, 150.40, 137.42, 136.24, 130.01, 129.87, 125.64, 121.95, 121.13, 119.26, 119.20, 116.90, 111.76, 103.26, 92.88, 44.23, 38.33, 30.34, 28.41, 12.27. LRMS-ESI: *m*/*z* = 393 ($M + H^+$). HRMS: *m*/*z* calcd for $C_{22}H_{20}N_2O_5Na$ ($M + Na^+$): 415.1270; found: 415.1265.

4d: IR (neat): 3421, 1767, 1716, 1554, 1509, 1361, 1264, 1092, 736 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.50 (br s, 1 H), 7.34–7.30 (m, 1 H), 7.20–7.05 (m, 4 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.87 (d, *J* = 1.8 Hz, 1 H), 6.53 (d, *J* = 8.1 Hz, 1 H), 5.86 (br s, 1 H), 3.88 (br s, 3 H), 2.94–2.48 (m, 4 H), 2.08 (s, 3 H). ^{13}C NMR (75 MHz, acetone-d_6): δ = 205.15, 161.57, 154.03, 149.97, 137.47, 128.96, 128.48, 125.23, 124.71, 123.42, 122.72, 117.42, 116.20, 107.21, 105.25, 99.92, 94.32, 54.42, 42.54, 37.47, 28.85, 27.69. LRMS-ESI: *m*/*z* = 409 ($M + H^+$). HRMS: *m*/*z* calcd for $C_{22}H_{20}N_2O_5Na$ ($M + Na^+$): 431.1219; found: 431.1217.

Spectral data for compound **3**: ^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H), 7.46–7.04 (m, 9 H), 5.84 (d, *J* = 9.3 Hz, 1 H), 5.40 (d, *J* = 9.3 Hz, 1 H).