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## FACILE SYNTHESIS OF INDOLINES BY A TANDEM NITRO-REDUCTION AZA MICHAEL ADDITION REACTION

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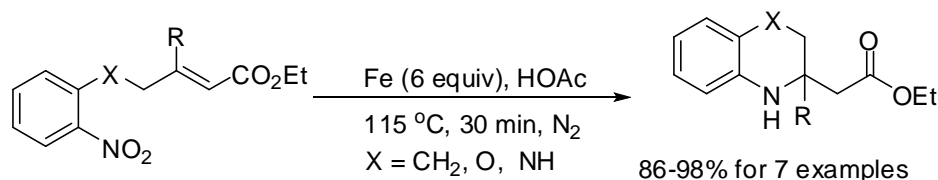
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**Abstract** –A diverse array of substrates are conveniently prepared by coupling diazonium salts to ethyl vinyl ether and subjecting the resultant aldehyde intermediate to a Wittig reaction to provide  $\alpha,\beta$ -unsaturated esters with only one purification step. The cyclisation of 4-aryl-but-2-enoates is carried out in the presence of stoichiometric amounts of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  and thus this one-pot strategy also permitted the expeditious synthesis of indolines in good yield.

### INTRODUCTION

Compounds with biological activity that have found applications as pharmaceuticals and agricultural chemicals are often derived from nitrogen-heterocyclic structures, which also appear frequently in natural products.<sup>1,2</sup> Nitrogen-heterocycles pertinent to this work include indoline structures and a variety of synthetic methodologies for the synthesis of these structures have been summarized in many reviews.<sup>3,4</sup> Despite the wide availability of synthetic methods, there still exists a need to develop more efficient procedures, particularly those that allow the synthesis of indoline intermediates with pendant functional groups which could later be exploited for the preparation of other complex azapolycyclic ring-systems. The intramolecular *aza*-Michael reaction offers a direct and atom-economical means of efficiently synthesizing nitrogen heterocycles. It is known that in the presence of triphenylphosphine, that azide functional group bearing acyclic  $\alpha,\beta$ -unsaturated carbonyl and cyano compounds spontaneously cyclise upon reduction to afford pyrrolidines or piperidines in good yields.<sup>5</sup> Furthermore, carbamates and sulfonamides can undergo intermolecular cyclisations with  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of a simple base such as sodium *tert*-butoxide or sodium hydrogen carbonate<sup>6-10</sup> (Scheme 1). In 2000 Bunce and co-workers demonstrated that the exploitation of a nitro group in a tandem

reduction-intramolecular Michael addition protocol could efficiently provide nitrogen heterocycles such as 2-(tetrahydroquinolin-2-yl)-, 2-(3,4-dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)- and 2-(tetrahydroquinoxalin-2-yl) acetates in good yield when simply employing iron powder in glacial acetic (Scheme 1).<sup>11</sup>



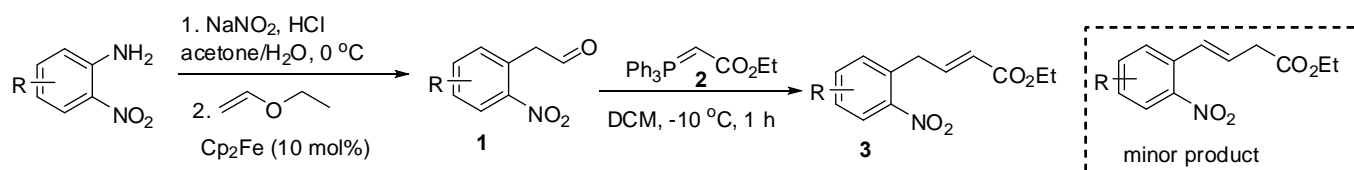
**Scheme 1.** Tandem reduction-intramolecular Michael addition

Thus, proof of concept had been established for the synthesis of aryl fused 6 membered ring nitrogen heterocycles and our curiosity was aroused as to whether analogous 5 membered compounds could be conveniently accessed in a similar manner. The availability of a convenient approach for the synthesis of the requisite precursor for the domino reaction would render this approach synthetically useful for its application in a longer multistep synthesis. In this regard, herein, we report the application of a domino nitro reduction-intramolecular *aza*-Michael strategy which occurs in a one-pot fashion upon when 4-(2-nitrophenyl)but-2-enoate derivatives are reduced in the presence of zinc powder to afford substituted indoline derivatives.

## RESULTS AND DISCUSSION

The synthesis of the target precursor begins with diazotization of commercially available substituted 2-nitroanilines that are subsequently coupled to ethyl vinyl ether in the presence of  $\text{Cp}_2\text{Fe}$  following the protocol described by Buchwald and Chernyak.<sup>12</sup> The coupling reaction can be considered as the synthetic equivalent of an  $\alpha$ -arylation with acetaldehyde enolate to provide substituted 2-(2-nitrophenyl)acetaldehyde derivatives.

Next, the crude reaction mixture containing 2-(2-nitrophenyl)acetaldehyde was employed directly in the synthesis of the  $\alpha,\beta$ -unsaturated esters via a Wittig reaction with phosphonium ylide **2** under neutral conditions (Scheme 2).

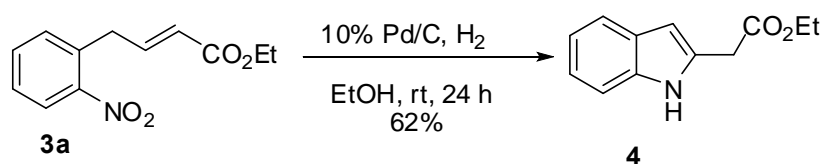


Yield over 2 steps. **3a**: 56%, **3b**: 52%, **3c**: 55%, **3d**: 57%, **3e**: 43%, **3f**: 51%, **3g**: 59%

**Scheme 2.** Synthesis of 4-(2-nitrophenyl)but-2-enoate derivatives

Synthesis of the  $\alpha,\beta$ -unsaturated carbonyl compound in which the neighboring methylene carbon is also a benzylic position is often troublesome due to the possibility for double bond migration.<sup>13</sup> A small amount of undesired isomer was isolated by column chromatography, but in general, the synthesis of **3a-g** proceeded smoothly to afford the  $\alpha,\beta$ -unsaturated esters in modest yields and with predominantly *E*-selectivity (>96%) as determined by <sup>1</sup>H NMR spectroscopy.

Reduction of **3a** under a hydrogen atmosphere in the presence of a catalytic amount of Pd/C gave substituted indole **4** in good yield.

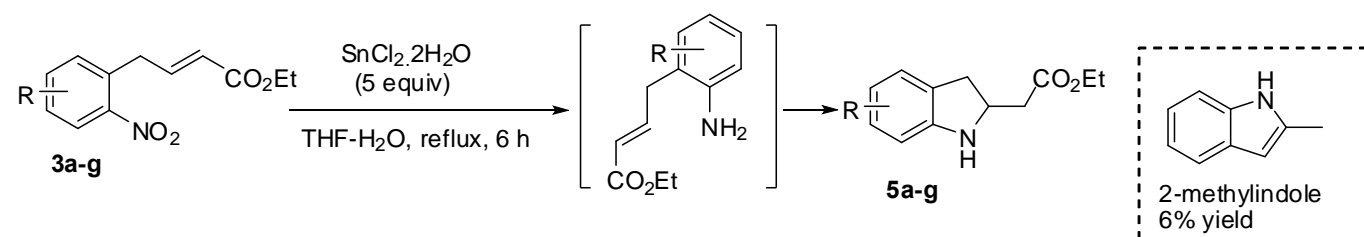


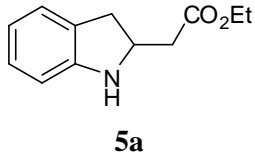
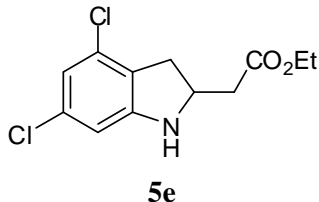
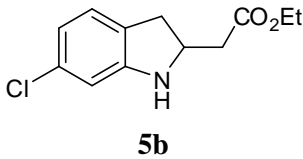
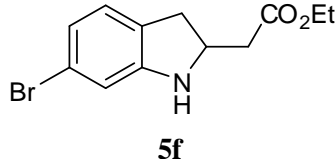
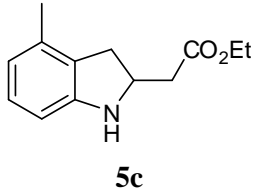
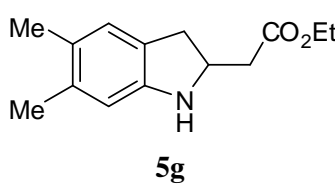
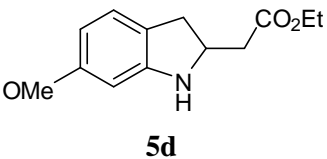
**Scheme 3.** Nitro-reduction, cyclisation-dehydrogenation reaction

The spectral data for **4** were identical with those reported for the compound that was obtained by using a different synthetic route.<sup>14</sup> Evidently, the nitro group is reduced faster than the alkene function resulting in formation of a substituted aniline, which then undergoes an intramolecular Michael addition reaction to give a cyclic precursor to **4**. The formation of indole **4** from the intermediate indoline requires a Pd-catalyzed dehydrogenation reaction to take place. The highly efficient Pd-catalyzed aromatization of indolines are known.<sup>15</sup>

Substrates **3a-g** were subjected to the tandem reduction-*aza*-Michael reaction using SnCl<sub>2</sub>·2H<sub>2</sub>O as the reducing agent (Table 1). Perhaps unsurprisingly, substituted indolines **5a-g** were obtained in good yield. In the case of **3a**, a small amount of a white solid was also isolated from the reaction mixture, which was found to be 2-methylindole. This was confirmed by the <sup>1</sup>H NMR spectra displaying two clear singlet resonance at 2.48 ppm (CH<sub>3</sub>) and 6.26 ppm (CH), integrating in a 3 : 1 ratio, corresponding to the methyl and methine protons.<sup>16</sup>

We were pleased to find that in general, yields were modest to good irrespectively of the electronic or steric nature of the aryl substituent (entries 1-6). It appears that the intramolecular *aza*-Michael reaction occurs spontaneously post nitro reduction and therefore allowing the obtainment of the indoline product in a one-pot fashion. Cyclisation is easily confirmed by absence of the olefinic hydrogen signals and the appearance of a methine double doublet at ~3.30 ppm in the <sup>1</sup>H NMR spectra. The purity of the compounds was confirmed by <sup>1</sup>H, <sup>13</sup>C NMR spectra and high resolution mass spectrometry.

**Table 1.** Evaluation of substituted 4-(2-nitrophenyl)but-2-enoate derivatives

Entry	Substrate	Product	Yield/%	Entry	Substrate	Product	Yield/%
1	<b>3a</b>	 <b>5a</b>	62	5	<b>3e</b>	 <b>5e</b>	70
2	<b>3b</b>	 <b>5b</b>	69	6	<b>3f</b>	 <b>5f</b>	57
3	<b>3c</b>	 <b>5c</b>	65	7	<b>3g</b>	 <b>5g</b>	60
4	<b>3d</b>	 <b>5d</b>	59				

In summary, we have developed a convenient methodology for the synthesis of a variety of indolines in 3 synthetic steps that require only two purifications by column chromatography. The key cyclisation step is realized in the form of a domino type reaction in which nitro reduction is immediately followed by intramolecular aza-Michael reaction to  $\alpha,\beta$ -unsaturated esters. Work is ongoing in our group to expand this approach towards the development of new strategies for the synthesis of medium sized benzo-fused nitrogen heterocycles.

## EXPERIMENTAL

### General Method for the Synthesis of Indoline Derivatives

To a solution of the substrate **5a-g** (2 mmol) in THF (10 mL) and distilled water (4.5 mL) was added

SnCl<sub>2</sub>·2H<sub>2</sub>O (8 mmol). The reaction mixture was heated under reflux for 6 h. The reaction was monitored by TLC analysis. After cooling to room temperature, the solution was poured onto ice and treated with a solution of 5% NaHCO<sub>3</sub> in water (20 mL) until the pH was between 7-8. EtOAc (20 mL) was then added and the white precipitate was filtered off. The product was then extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was removed under reduced pressure to leave the crude product, which was further purified by column chromatography.

**Ethyl 2-(indolin-2-yl)acetate (5a):** The product was obtained as a pale yellow oil; R<sub>f</sub> = 0.5 (Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (thin film, cm<sup>-1</sup>): 3351, 2942, 1623, 1456, 1310, 1254, 1262, 1157, 1044, 925, 865, 761;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>): 7.12 (1H, d, *J* = 7.6 Hz), 7.09 (1H, t, *J* = 7.6 Hz), 6.79 (1H, t, *J* = 7.6 Hz), 6.73 (1H, d, *J* = 7.6 Hz), 5.67 (1H, br s), 4.28-4.31 (1H, m), 4.22 (2H, q, *J* = 7.2 Hz), 3.26 (1H, dd, *J* = 8.4, 15.2 Hz), 2.77-2.68 (3H, m), 1.32 (3H, t, *J* = 7.2 Hz);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>): 172.1, 148.3, 128.8, 127.7, 124.8, 120.3, 110.9, 60.8, 56.0, 40.2, 35.7, 14.2; MS *m/z* (EI): calcd. for C<sub>12</sub>H<sub>15</sub>NO<sub>2</sub> 205.1103, found 205.1109.

**Ethyl 2-(6-chloroindolin-2-yl)acetate (5b):** The product was obtained as a pale yellow oil; R<sub>f</sub> = 0.4 (Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (thin film, cm<sup>-1</sup>): 3354, 2942, 1624, 1456, 1316, 1268, 1152, 1043, 934;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>): 7.01 (1H, d, *J* = 7.6 Hz), 6.72 (1H, d, *J* = 7.6 Hz), 6.56 (1H, s), 5.82 (1H, br s, NH), 4.23-4.30 (1H, m), 4.21 (2H, q, *J* = 7.2 Hz), 3.27 (1H, dd, *J* = 8.5, 15.0 Hz), 2.76-2.68 (3H, m), 1.32 (3H, t, *J* = 7.2 Hz);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>): 172.4, 143.3, 133.5, 124.7, 122.8, 120.5, 110.3, 60.5, 56.2, 40.5, 35.9, 14.4; MS *m/z* (EI): calcd. for C<sub>12</sub>H<sub>14</sub>ClNO<sub>2</sub> 239.0713, found 239.0709.

**Ethyl 2-(4-methylindolin-2-yl)acetate (5c):** The product was obtained as a pale yellow oil; R<sub>f</sub> = 0.47 (Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (KBr disc, cm<sup>-1</sup>): 3359, 2951, 1635, 1447, 1376, 1312, 1269, 1174, 1159, 1061, 1040;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>): 7.06-7.02 (2H, m), 6.58 (1H, s), 5.71 (1H, br s, NH), 4.23-4.30 (1H, m), 4.22 (2H, q, *J* = 7.2 Hz), 3.29 (1H, dd, *J* = 8.5, 15.0 Hz), 2.79-2.68 (3H, m), 2.25 (3H, s), 1.35 (3H, t, *J* = 7.2 Hz);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>): 170.9, 151.3, 135.2, 127.9, 122.6, 118.5, 112.0, 60.0, 55.5, 40.0, 34.5, 18.6, 14.5; MS *m/z* (EI): calcd. for C<sub>13</sub>H<sub>17</sub>NO<sub>2</sub> 219.1259, found 219.1252.

**Ethyl 2-(6-methoxyindolin-2-yl)acetate (5d):** The product was obtained as a pale yellow oil; R<sub>f</sub> = 0.35 (Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (thin film, cm<sup>-1</sup>): 3335, 2942, 1628, 1476, 1311, 1275, 1172, 1169, 1108, 972;  $\delta_{\text{H}}$  (400 MHz, CDCl<sub>3</sub>): 7.11 (1H, d, *J* = 7.6 Hz), 6.14 (1H, d, *J* = 7.6 Hz), 6.02 (1H, s), 5.51 (1H, br s, NH), 4.23-4.30 (1H, m), 4.22 (2H, q, *J* = 7.2 Hz), 3.72 (3H, s), 3.27 (1H, dd, *J* = 8.5, 15.0 Hz), 2.74-2.67 (3H, m), 1.33 (3H, t, *J* = 7.2 Hz);  $\delta_{\text{C}}$  (100 MHz, CDCl<sub>3</sub>): 173.3, 153.7, 145.3, 124.1, 123.8, 124.5, 115.0, 61.5, 56.2, 55.2, 40.2, 35.8, 14.4; MS *m/z* (EI): calcd. for C<sub>13</sub>H<sub>17</sub>NO<sub>3</sub> 235.1208, found 235.1212.

**Ethyl 2-(4,6-dichloroindolin-2-yl)acetate (5e):** The product was obtained as a pale yellow oil; R<sub>f</sub> = 0.4

(Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (thin film,  $\text{cm}^{-1}$ ): 3364, 2947, 1624, 1510, 1456, 1312, 1268, 1158, 1063, 967, 940;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ): 6.64 (1H, s), 6.32 (1H, s), 5.74 (1H, br s, NH), 4.21-4.30 (1H, m), 4.21 (2H, q,  $J = 7.2$  Hz), 3.25 (1H, dd,  $J = 8.5, 15.0$  Hz), 2.76-2.70 (3H, m), 1.31 (3H, t,  $J = 7.2$  Hz);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ): 172.4, 150.1, 136.3, 132.5, 124.7, 122.8, 111.3, 60.1, 56.6, 40.2, 36.1, 14.5; MS  $m/z$  (EI): calcd. for  $\text{C}_{12}\text{H}_{13}\text{Cl}_2\text{NO}_2$  273.0323, found 273.0317.

**Ethyl 2-(6-bromoindolin-2-yl)acetate (5f)**: The product was obtained as a pale yellow oil;  $R_f = 0.4$  (Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (thin film,  $\text{cm}^{-1}$ ): 1721, 1625, 1473, 1441, 1394, 1380, 1379, 1328, 1299, 1255, 1252, 1175, 1055, 1027, 904;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ): 7.03 (1H, d,  $J = 7.6$  Hz), 6.70 (1H, d,  $J = 7.6$  Hz), 6.59 (1H, s), 5.70 (1H, br s, NH), 4.21 (2H, q,  $J = 7.2$  Hz), 3.27 (1H, dd,  $J = 8.5, 15.0$  Hz), 2.76-2.68 (3H, m), 1.32 (3H, t,  $J = 7.2$  Hz);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ): 172.1, 143.5, 133.2, 124.7, 122.5, 121.5, 113.5, 60.5, 56.1, 40.5, 35.8, 14.4; MS  $m/z$  (EI): calcd. for  $\text{C}_{12}\text{H}_{14}\text{BrNO}_2$  283.0208, found 283.0211.

**Ethyl 2-(5,6-dimethylindolin-2-yl)acetate (5g)**: The product was obtained as a pale yellow oil;  $R_f = 0.37$  (Hexanes/EtOAc, 7:3);  $\nu_{\max}$  (thin film,  $\text{cm}^{-1}$ ): 3080, 2979, 2939, 2885, 2861, 1653, 1619, 1150, 1045;  $\delta_{\text{H}}$  (400 MHz,  $\text{CDCl}_3$ ): 7.24 (1H, s), 6.90 (1H, s), 4.96 (1H, br s, NH), 4.25-4.29 (1H, m), 4.20 (2H, q,  $J = 7.2$  Hz), 3.32 (1H, dd,  $J = 8.5, 15.0$  Hz), 2.77-2.65 (3H, m), 2.22 (3H, s), 2.17 (3H, s), 1.32 (3H, t,  $J = 7.2$  Hz);  $\delta_{\text{C}}$  (100 MHz,  $\text{CDCl}_3$ ): 171.0, 137.3, 135.2, 131.9, 127.6, 126.5, 115.4, 60.3, 56.1, 40.0, 34.2, 20.2, 19.4, 14.4; MS  $m/z$  (EI): calcd. for  $\text{C}_{14}\text{H}_{19}\text{NO}_2$  233.1416, found 233.1420.

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## REFERENCES

1. T. Naito, [Chem. Pharm. Bull.](#), 2008, **56**, 1367.
2. J. P. Michael, [J. Nat. Prod. Rep.](#), 1996, **13**, 73.
3. D. Liu, G. Zhao, and L. Xiang, [Eur. J. Org. Chem.](#), 2010, 3975.
4. N. G. Kozlov, K. N. Gusak, and A. P. Kadutskii, [Chem. Heterocycl. Compd.](#), 2010, **46**, 505.
5. N. Knouzi, M. Vaultier, L. Toupet, and R. Carrie, [Tetrahedron Lett.](#), 1987, **28**, 1757.
6. S. Fustero, J. Moscardo, M. Sanchez-Rosello, E. Rodriguez, and P. Barrio, [Org. Lett.](#), 2010, **12**, 5494.
7. M. Gärtner, R. Weihofen, and G. Helmchen, [Chem. Eur. J.](#), 2011, **17**, 7605.

8. C. Enkisch and C. Schneider, [\*Eur. J. Org. Chem.\*, 2009, 5549.](#)
9. P. Wipf and Y. Kim, [\*Tetrahedron Lett.\*, 1992, \*\*33\*\*, 5477.](#)
10. D. Bland, G. Chambournier, V. Dragan, and D. J. Hart, [\*Tetrahedron\*, 1999, \*\*55\*\*, 8953.](#)
11. R. A. Bunce, D. M. Herron, and M. L. Ackerman, [\*J. Org. Chem.\*, 2000, \*\*65\*\*, 2847.](#)
12. N. Chernyak and S. L. Buchwald, [\*J. Am. Chem. Soc.\*, 2012, \*\*134\*\*, 12466.](#)
13. N. D. F. Moreira, T. T. de Oliveira, T. J. Nagem, and J. G. Taylor, [\*Heterocycl. Commun.\*, 2011, \*\*17\*\* \(5-6\), 203.](#)
14. M. A. Guerrero and L. D. Miranda, [\*Tetrahedron Lett.\*, 2006, \*\*47\*\*, 2517.](#)
15. R. Bader, R. J. Bridgwater, and P. R. Freeman, [\*J. Am. Chem. Soc.\*, 1961, \*\*83\*\*, 3319.](#)
16. S. Cho, J. H. Kim, T.-J. Kim, and S. C. Shim, [\*Tetrahedron\*, 2001, \*\*57\*\*, 3321.](#)