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# SYNTHESIS OF SOME NOVEL INDOLINE DERIVATIVES

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**ABSTRACT**

Two indoline derivativesi.e2-(4-nitroindolin-3-yl)acetic acid and ethyl 2-(4-aminoindolin-3-yl)acetate were synthesised from 2-methyl-3-nitroaniline by using multistep synthesis. The final indoline products obtained in good yields.

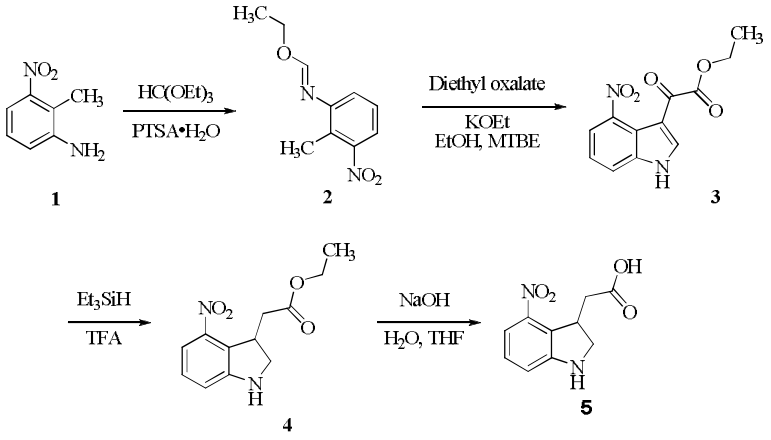
## Introduction

Indoline frame works are an important part in numerous biologically active natural and non naturalproducts[1] and as organic dyes for dye-sensitized solar cells.[2] Indoline and other related ring systems possess several interesting biological activities. The indolines are also interesting structural scaffolds and have, for example, been evaluated as 5-$HT_{2C}$ receptor agonists for the treatment of obesity.[3] Factor Xa (FXa) is well known to play a pivotal role in blood coagulation; hence, an FXa inhibitor is a promising drug candidate for prophylaxis and treatment of thromboembolic diseases. Some indoline derivatives have been found to show very good FXa inhibitory activities.[4]Indoline derivatives have also been found to show an antagonistic effect on progesterone receptors.[5] In addition, indolines have been evaluated for antimicrobial activity.[6]

Indolines have been synthesized using different strategies, such as via the Pd- or Cu-catalyzed cyclization of amine, amide, or carbamate,[7] the radical cyclization of O-bromo phenethylamine[8] (type A), Pd-catalyzed intermolecular 1,2-carboamination from N-arylureas and 1,3-dienes(type B),[9]Pd-catalyzed domino Amidation from O-triflyloxyphenethyl carbonates using amide (type C),[10] Pd-catalyzed C−C/C−N coupling of bromo alkyl-amines (type D),[11]intramolecular Diels−Alder reaction of 2-amino furans (type E),[12] and the Pd-catalyzed C−H activation of arylethylamines (type F).[13] A more versatile route for the synthesis of indoline was reported via aryneannulation[14] and via solid-phase organic synthesis using selenenylbromide resin.[15] Owing to the biological importance of indolines and in continuation of our work on the synthesis of biologically important heterocyclic compounds, Here we reported the synthesis of some indoline derivatives.

## Results and Discussion

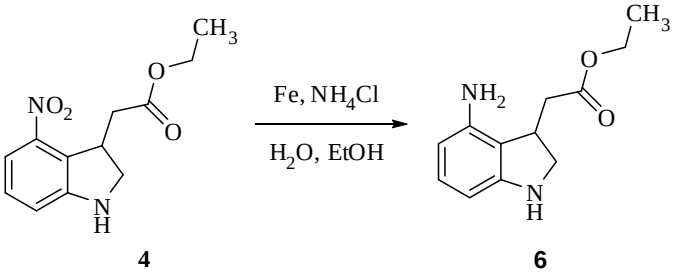
2-methyl-3-nitroaniline (**1**) react with $HC(OEt)_3$ in the presence of $PTSA{\bullet}H_2O$ to afford compound (E)-ethyl *N*-2-methyl-3-nitrophenylformimidate **2**. The compound **2** react with Diethyl oxalate in the presence of potassium ethoxide to afford compound ethyl 2-(4-nitro-1*H*-indol-3-yl)-2-oxoacetate **3**. The compound **3** react with triethylsilyl hydride to afford keto reduced compound ethyl 2-(4-nitroindolin-3-yl)acetate **4.** The compound **4** undergo ester hydrolysis to afford 2-(4-nitroindolin-3-yl)acetic acid **5** as shown in scheme 1.




1 2 3 4 5

Scheme 1. Synthesis of 2-(4-nitroindolin-3-yl)acetic acid

The compound **4** undergo nitro reduction in the presence of Iron to afford ethyl 2-(4-aminoindolin-3-yl)acetate **6** as shown in scheme 2.




4 6

Scheme 2. Synthesis of ethyl 2-(4-aminoindolin-3-yl)acetate

**Conclusion**

In conclusion we have developed new heterocyclic systemindoline derivatives from 2-methyl-3-nitroaniline. Overall, the synthetic strategy described here could be useful in constructing library of small molecules based on indoline framework. Additionally, the indoline heterocyclic framework presented here could be an attractive template for the identification of novel and potential biologically active compounds.

**1. Experimental**

Reagents were purchased from commercial sources and were used as received. $^{1}$H NMR spectra were obtained on a Bruker AVANCE 400 spectrometer at 400 MHz or Bruker AVANCE 300 spectrometer at 300 MHz with tetramethylsilane used as an internal reference. $^{13}$C NMR spectra were obtained on a Bruker AVANCE 300 spectrometer at 75 MHz with the solvent peak used as the reference. Thin-layer chromatography (TLC) was performed using Whatman No. 4500-101 (Diamond No. MK6F silica-gel 60 Å) plates. Visualization of TLC plates was performed using UV light (254 nm).

**Synthesis of (E)-ethyl *N*-2-methyl-3-nitrophenylformimidate (2):**

A stirred mixture of 2-methyl-3-nitroaniline (**1,** 500 g, 3.29 mol), $HC(OEt)_3$ (820 mL, 4.93 mol,), and PTSA•$H_2O$ (2.00 g) was heated at 120 °C for 15 h. When TLC analysis showed consumption of the starting material, the reaction mixture was distilled under high vacuum to afford **2** (708 g, 97%) as a yellow solid.$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.93 (s, 1H), 7.62 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.21 (dd, *J* = 7.8, 0.9 Hz, 1H), 4.30 (q, *J* = 6.9 Hz, 2H), 3.33 (s,2H), 2.50 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H).

**Synthesis of ethyl 2-(4-nitro-1*H*-indol-3-yl)-2-oxoacetate (3):**

A solution of KOEt(542 g, 6.44 mol) in EtOH (2.0 L) was stirred for 30 min at room temperature. MTBE (3.0 L) and diethyl oxalate (1312.8 g, 9.66 mol) were added and the reaction mixture was stirred at room temperature for 15 min. **2** (670 g, 3.22 mol) was added and the reaction mixture was stirred at 80 °C for 24 h. When TLC analysis showed complete consumption of the starting material, the reaction mixture was concentrated under pressure and the residue was poured into ice-cold water (3.5 L). The precipitated solids were filtered, triturated with 10% MeOH in EtOAc, and dried under reduced pressure to afford **3** (382 g, 45%) as a yellow solid.$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.58 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J*= 8.1 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H).

**Synthesis of ethyl 2-(4-nitroindolin-3-yl)acetate (4):**

A stirred solution of **3** (120 g, 0.46 mol) in TFA (3.0 L) was charged with $Et_3SiH$ (220 mL, 1.37 mol) dropwise at 0°C over 30 min and the reaction mixture was stirred at room temperature for 12 h. When TLC analysis showed complete consumption of the starting material, the reaction mixture was poured into ice-cold water (2.5 L) and basified to pH ≈12 with solid $Na_2CO_3$ and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 1.5 L). The combined organic layers were washed with brine (2 × 1.0 L), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to afford **4** (60.3 g, 52%) as an orange solid.$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.49 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.17 (t, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 4.35−4.27 (m, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.07 (bs, 1H), 3.80−3.73 (m, 1H), 3.53 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.74−2.54 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

**Synthesis of 2-(4-nitroindolin-3-yl)acetic acid (5):**

A stirred solution of **4** (60.0 g, 0.24 mol) in THF (300 mL) was charged with a solution of NaOH (19.2 g, 0.479 mol) in $H_2O$ (300 mL) at room temperature and the reaction mixture was stirred at the same temperature for 14 h. When TLC analysis showed complete consumption of the starting material, THF was removed under reduced pressure; the residue was acidified to pH ≈8 with citric acid and extracted with EtOAc (2 × 1.0 L). The combined organic layers were concentrated under reduced pressure and the residue was triturated with hexanes to afford **5** (44.2 g, 83%, 94.7% AUC by HPLC) as a yellow solid.$^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 12.32 (bs, 1H), 7.79 (d, *J* = 6.0 Hz, 1H), 7.28−7.15 (m, 1H), 6.84 (d, *J* = 5.7 Hz, 1H), 6.22 (bs, 1H), 4.06 (t, *J* = 6.9 Hz, 1H), 3.60 (t, *J* = 6.6 Hz, 1H), 3.30 (t, *J* = 6.9 Hz, 1H), 2.49−2.32 (m, 2H).$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 173.51, 155.11, 145.55, 129.61, 127.10, 114.19, 111.97, 52.46, 37.10, 27.13.MS (MM) *m/z*223 $[M + H]^+$.

**Synthesis of (E)-ethyl *N*-2-methyl-3-nitrophenylformimidate (2):**

A stirred mixture of 2-methyl-3-nitroaniline (**1**, 500 g, 3.29 mol), $HC(OEt)_3$ (820 mL, 4.93 mol), and *p*-TsOH•$H_2O$ (2.00 g) was heated at 120 °C for 15 h. When TLC analysis showed consumption of the starting material, the reaction mixture was distilled under high vacuum to afford **2** (708 g, 97%) as a yellow solid.$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.93 (s, 1H), 7.62 (dd, *J* = 8.1,

0.9 Hz, 1H), 7.36 (t, *J* = 7.9 Hz, 1H), 7.21 (dd, *J* = 7.8, 0.9 Hz, 1H), 4.30 (q, *J* = 6.9 Hz, 2H), 3.33 (s,2H), 2.50 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H).

**Synthesis of ethyl 2-(4-nitro-1*H*-indol-3-yl)-2-oxoacetate (3):**

A solution of KOEt(542 g, 6.44 mol) in EtOH (2.0 L) was stirred for 30 min at room temperature. MTBE (3.0 L) and diethyl oxalate (1312.8 g, 9.66 mol) were added and the reaction mixture was stirred at room temperature for 15 min. **2** (670 g, 3.22 mol) was added and the reaction mixture was stirred at 80 °C for 24 h. When TLC analysis showed complete consumption of the starting material, the reaction mixture was concentrated under pressure and the residue was poured into ice-cold water (3.5 L). The precipitated solids were filtered, triturated with 10% MeOH in EtOAc, and dried under reduced pressure to afford **3** (382 g, 45%) as a yellow solid.$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 8.58 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J*= 8.1 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.30 (t, *J* = 7.0 Hz, 3H).

**Synthesis of ethyl 2-(4-nitroindolin-3-yl)acetate (4):**

A stirred solution of **3** (200 g, 0.76 mol) in TFA (2.0 L) was charged with $Et_3SiH$ (245 mL, 1.52 mol) dropwise at 0 °C over 30 min and the reaction mixture was stirred at room temperature for 12 h. When TLC analysis showed complete consumption of the starting material, the reaction mixture was poured into ice-cold water (2.5 L) and basified to pH ≈12 with solid $Na_2CO_3$. The aqueous phase was extracted with $CH_2Cl_2$ (2 × 1.5 L). The combined organic layers were washed with brine (1 × 1.0 L), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure to afford **4** (78.0 g, 41%) as an orange solid.$^{1}$H NMR (300 MHz, DMSO-$d_6$): δ 7.49 (dd, *J* = 8.2, 0.7 Hz, 1H),7.17(t, *J*=8.1 Hz, 1H), 6.85 (d, *J* = 7.8 Hz,1H), 4.35−4.27(m,1H), 4.17 (q, *J*=7.1Hz,2H), 4.07 (bs, 1H), 3.80−3.73(m,1H), 3.53 (dd, *J* = 9.6, 1.8 Hz, 1H), 2.74−2.54 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

**Synthesis of ethyl 2-(4-aminoindolin-3-yl)acetate (6):**

A solution of **4** (92.0 g, 0.37 mol), Fe powder (103 g, 1.85 mol), and $NH_4Cl$ (192 g, 3.70 mol) in a mixture of EtOH/$H_2O$ (8:1, 900 mL) was heated at 90 °C for 3 h. When TLC analysis showed complete consumption of the starting material, the reaction mixture was filtered through a bed of diatomaceous earth and the filtrate was dissolved in EtOAc (1.0 L) and $NaHCO_3$ solution (1.0 L). The organic layer was separated, washed with brine (1 × 1.0 L), dried over anhydrous $Na_2SO_4$, and concentrated under reduced pressure. The residue was purified by alumina column chromatography (10% to 30% EtOAc in *n*-hexanes) to afford **6** (52.0 g, 59%, >95% purity by $^{1}$H NMR) as a brown solid.$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.00−6.94 (m, 2H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.35 (d, *J* = 7.5 Hz, 1H), 4.56 (bs, 2H), 4.15 (q, *J* = 14.1, 7.2 Hz, 2H), 3.86 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).$^{1}$H NMR (400 MHz, DMSO-$d_6$): δ 10.66 (s, 1H), 6.98 (d, *J* = 2.1 Hz, 1H), 6.75 (t, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 8.1 Hz, 1H), 6.17 (d, *J* = 7.5 Hz, 1H), 4.91 (bs, 2H), 4.07 (q, *J* = 14.1 Hz, 7.2 Hz, 2H), 3.82 (s, 2H), 1.18 (t, *J* = 7.2 Hz, 3H).$^{13}$C NMR (75 MHz, $CDCL_3$): δ 173.88, 173.87, 141.01, 138.25, 123.32, 122.73, 116.65, 107.36, 105.87, 103.00, 61.37,33.33, 14.20.MS (MM) *m/z* 219 $[M + H]^+$.

**References**


1. (a) Ontoria, J. M.; DiMarco, S.; Conte, I.; DiFrancesco, M. E.; Gardelli, C.; Koch, U.; Matassa, V. G.; Poma, M.; Steinkuhler, C.; Volpari, C.; Harper, S. *J.Med.Chem.***2004**, *47*, 6443. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.***2003**, *103*, 893. (c) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.***1997**, *97*, 787. (d) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.***1990**, *33*, 1929. (e) Glennon, R. A. *J. Med. Chem.***1987**, *30*, 1.
2. (2) Kuang, D.; Uchida, S.; Humphry-Baker, R.; Zakeeruddin, S. M.; Gratzel, M. *Angew. Chem., Int.Ed.***2008**, *47*, 1923.
3. J. M. Bentley, S. P. Vickers, D. R. Adams, D. Bebbington, K. R. Benwell, M. J. Bickerdike, J. E. P. Davidson, C. E. Dawson, C. T. Dourish, M. A. J. Duncton, S. Gaur, A. R. George, P. R. Giles, R. J. Hamlyn, G. A. Kennett, A. R. Knight, C. S. Malcolm, H. L. Mansell, A. Misra, N. J. T. Monck, R. M. Pratt, K. Quirk, J. R. A. Roffey, S. P. Vickers, I. A. Cliffe, *Bioorg. Med. Chem. Lett.***2004**, *14*, 2367.
4. T. Noguchi, N. Tanaka, T. Nishimata, R. Goto, M. Hayakawa, A. Sugidachi, T. Ogawa, F. Asai, T. Ozeki, K. Fujimoto, *Chem. Pharm. Bull.***2007**, *55*, 393.
5. A. Fensome, W. R. Adams, A. L. Adams, T. J. Berrodin, J. Cohen, C. Huselton, A. Illen-berger, J. C. Kern, V. A. Hudak, M. A. Marella, E. G. Melenski, C. C. McComas, C.A. Mugford, O. D. Slayden, M. Yudt, Z. Zhang, P. Zhang, Y. Zhu, R. C. Winneker, J. E. Wrobel, *J. Med. Chem.* 2008, *51*, 1861.
6. A. H. Abdel-Rahman, E. M. Keshk, M. A. Hanna, S. M. El-Bady, *Bioorg. Med. Chem.***2004**, *12*, 2483.
7. (a) Omar-Amrani, R.; Schneider, R.; Fort, Y. *Synthesis* **2004**, 2257. (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.***1999**, *1*, 35. (c) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron***1996**, *52*, 7525.

8. (a) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.***2001**, *3*, 1009. (b) Viswanathan, R.; Smith, C. R.; Prabhakaran, E. N.; Johnston, J. N. *J.Org.Chem.***2008**, *73*, 3040.
9. Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J.Am.Chem.Soc.***2008**, *130*, 10066.
10. Ganton, M. D.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 4777.
11. Thansandote, P.; Raemy, M.; Rudolph, A.; Lautens, M. *Org. Lett*.**2007**, *9*, 5255.
12. (a) Padwa, A.; Brodney, M. A.; Dimitroff, M. *J. Org. Chem.***1998**, *63*, 5304. (b) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J.Org.Chem.***1999**, *64*, 3595.
13. (a) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J.Am.Chem.Soc.***2009**, *131*, 10806. (b) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew.Chem.,Int.Ed.***2008**, *47*, 6452.
14. Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J.Am.Chem.Soc.***2008**, *130*, 1558.
15. Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J.Am.Chem.Soc.***2000**, *122*, 2966.