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A CONVENIENT SYNTHESIS OF 3-SUBSTITUTED 1H-INDOLES

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Abstract: A convenient synthesis of 3-substituted 1H-indoles via functionalization of enamines, which serve as intermediates in the Leimgruber-Batcho approach, followed by reductive cyclization is described.

The Leimgruber-Batcho indole synthesis is one of the primary methods for the synthesis of 1H-indoles unsubstituted in 2 and 3 positions.[1] We reasoned that this method could be extended to a general synthesis of 3-substituted 1H-indoles by functionalizing the intermediate enamines used in this synthesis. Such a strategy has received only limited attention.[2] In this paper we describe our results on this approach.

Our initial interest was in the synthesis of substituted 1H-indole-3-carboxylic acids because they serve as important intermediates in the synthesis of serotonin antagonists.[3] We envisioned that carbomethoxylation of enamines **I** to **II** would be the key step, which would be followed by the reductive cyclization of **II** to the desired 3-carbomethoxy-1H-indoles **III** (Scheme 1).

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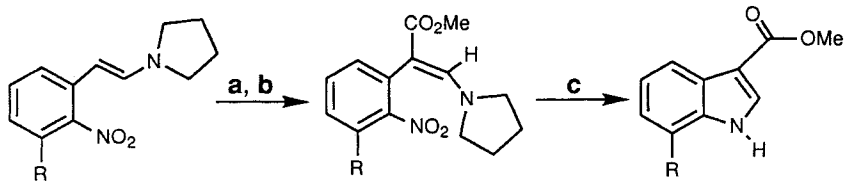


I **II** **III**

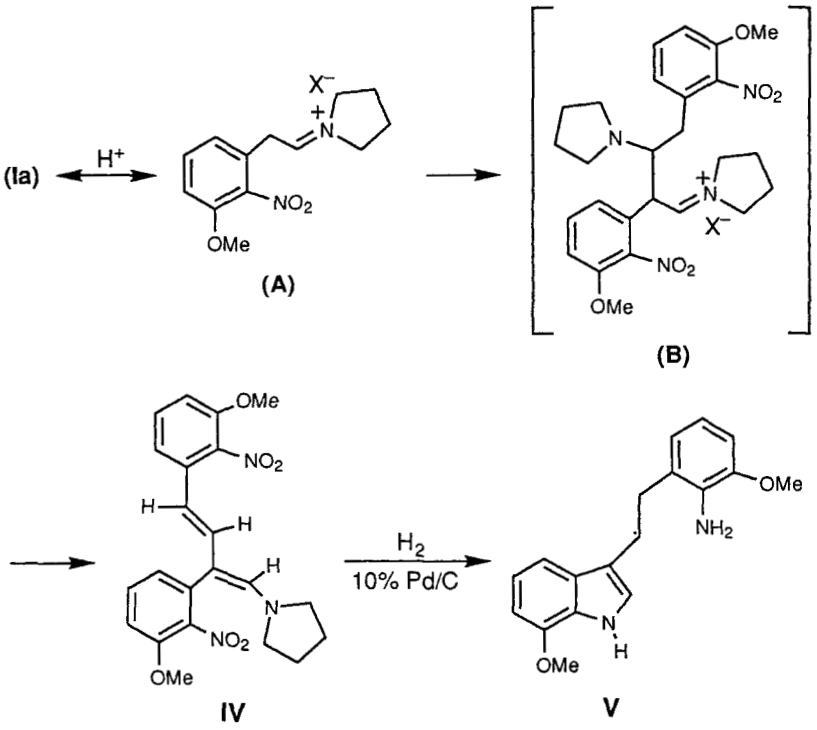
Ia : R = OMe **IIa** : R = OMe **IIIa** : R = OMe
Ib : R = H **IIb** : R = H **IIIb** : R = H

a) $COCl_2$, Et_3N, Toluene, –20 °C to RT, b) MeOH, –10 °C to RT,
c) H_2, 10% Pd/C, MeOH, EtOAc, CH_3CO_2H, RT.

(Scheme 1)

Carboxylation of enamines, derived from cyclohexanone, with ethyl chloroformate in refluxing chloroform in the presence of N,N-diethylaniline is documented in the literature.[4] When these conditions were applied to **Ia**, no carboxylated product could be detected. Spectral and analytical data suggested the product to be dienamine **IV**. Next we turned our attention to study the carboxylation of **Ia** using phosgene as an electrophile.[5] Treatment of **Ia** with a solution of phosgene in toluene, followed by quenching the reaction mixture with methanol, yielded the desired carbomethoxylated enamine **IIa** in 73% yield. Hydrogenation of **IIa** in the presence of 10% Pd/C furnished the desired methyl 7-methoxy-1H-indole-3-carboxylate **IIIa** in 65% yield. This approach was also successfully utilized to prepare methyl 1H-indole-3-carboxylate **IIIb** via carbomethoxylation of **Ib** to **IIb** in 78% yield, followed by hydrogenation of **IIb** to **IIIb** in 69% yield. The E configuration in **IIa** and **IIb** was assigned based on NOE experiments.

We propose that the formation of dienamine **IV** from **Ia** is catalyzed by HCl generated from the decomposition of ethyl chloroformate in this reaction. Dienamine **IV** was also prepared by treatment of **Ia** with 0.5 equivalents of p-toluenesulfonic acid in toluene at 90 °C in 52% yield. A possible mechanism of the formation of **IV** is depicted in Scheme 2. Protonation of **Ia** under thermodynamic conditions[6] would lead to iminium ion (**A**). Reaction of iminium ion (**A**) with another molecule of **Ia** would give intermediate (**B**), which upon elimination of pyrrolidino group would yield the observed product **IV**. The 1Z, 3E configuration in **IV** was assigned based on NOESY experiments.



(Scheme 2)

The utility of functionalized enamines in the synthesis of 3-substituted 1H-indoles was further demonstrated by hydrogenating **IV** in the presence of 10% Pd/C to furnish **V** in 58% yield.

In summary, functionalization of enamines followed by hydrogenation provided a convenient synthesis of 3-substituted 1H-indole derivatives. This approach represents a new application of the Leimgruber-Batcho synthesis.

EXPERIMENTAL

Melting points were determined on a Büchi 535 melting point apparatus. IR spectra were recorded on a BioRad FTS-40 FTIR spectrophotometer. NMR spectra were recorded on a Bruker AC 300 NMR spectrometer. Microanalyses were performed on a EA 1108

elemental analyzer from Carlo Erba instruments. Enamines **Ia**[7] and **Ib**[8] were prepared by known methods.

General method of carbomethoxylation of enamines Ia and Ib:

To a stirred solution of enamine (10 mmol) and triethylamine (11 mmol) in dry toluene (10 mL), cooled to –20 °C, was added a 1.93 M solution of phosgene in toluene (5.3 mL; 10.2 mmol) dropwise over a period of 10 minutes. The cooling bath was removed, and the mixture was warmed to room temperature. After stirring at room temperature for 2 h, the mixture was cooled to –10 °C, and to it was added triethylamine (11 mmol) and methanol (5 mL). After stirring for 1 h at room temperature the reaction mixture was diluted with toluene (80 mL) and was washed with water (2X 40 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated in vacuo. The product was purified on silica gel using a 70:30, followed by 50:50 mixture of hexane and ethyl acetate as an eluant.

Methyl (E)-2-(3-methoxy-2-nitrophenyl)-3-(1-pyrrolidinyl)-2-propenoate (IIa): Yield 73%; m.p. 179–181 °C; IR (KBr, cm^{-1}) 1592, 1681; NMR ($CDCl_3$, δ) 1.72 (m, 4H, 2 x CH_2), 3.15 (bm, 4H, 2 x NCH_2), 3.6 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.87 (d, 1H, J=7.5 Hz, Ar-H), 6.92 (d, 1H, J=7.5 Hz, Ar-H), 7.27 (dd, 1H, J=7.5 & 15 Hz, Ar-H), 7.72 (s, 1H, =CH-N); Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.99, H, 6.03, N, 9.02.

Methyl (E)-2-(2-nitrophenyl)-3-(1-pyrrolidinyl)-2-propenoate (IIb): Yield 78%; m.p. 83–86 °C; IR (KBr, cm^{-1}) 1595, 1690; NMR ($CDCl_3$, δ) 1.75 (m, 4H, 2 x CH_2), 3.05 (bm, 4H, 2 x NCH_2), 3.6 (s, 3H, OCH_3), 7.25 (m, 1H, Ar-H), 7.35 (m, 1H, Ar-H), 7.5 (m, 1H, Ar-H), 7.8 (s, 1H, =CH-N), 7.85 (dd, 1H, J=7.5 Hz, Ar-H); Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.73, H, 5.88, N, 10.11.

Hydrogenation of Carbomethoxylated enamines IIa and IIb:

A suspension of carbomethoxylated enamine (2 mmol) and 10% Pd/C (0.08 g) in methanol (10 mL), ethyl acetate (2 mL) and acetic acid (0.5 mL) was hydrogenated at room temperature and 40 psi overnight (14 h). The reaction mixture was filtered over Celite and concentrated in vacuo. The crude mixture was purified by silica gel chromatography using a mixture of hexane and ethyl acetate (70:30 for **IIIa** and 80:20 for **IIIb**).

Methyl 7-methoxy-1H-indole-3-carboxylate (IIIa): Yield 65%; m.p. 106–107 °C; IR (KBr, cm^{-1}) 1691; NMR ($CDCl_3$, δ) 3.9 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.72 (d, 1H, J=7.5 Hz, Ar-H), 7.18 (dd, 1H, J=7.5 Hz, Ar-H), 7.75 (d, 1H, J=7.5 Hz, Ar-H), 7.88 (d, 1H, J=3 Hz, N-CH), 8.8 (bs, 1H, NH); Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.35, H, 5.56, N, 6.70.

Methyl 1H-indole-3-carboxylate (IIIb): Yield 69%; m.p. 149–151 °C (Lit., 144–149 °C)[9]; IR (KBr, cm^{-1}) 1667; NMR ($CDCl_3$, δ) 3.92 (s, 3H, OCH_3), 7.27 (m, 2H, Ar-H), 7.41 (m, 1H, Ar-H), 7.9 (d, 1H, J=3 Hz, N-CH), 8.2 (m, 1H, Ar-H), 8.8 (bs, 1H, NH); Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.74, H, 5.22, N, 7.75.

(1Z, 3E)-1-[2,4-bis(3-methoxy-2-nitrophenyl)-1,3-butadienyl]-pyrrolidine (IV):

To a solution of enamine **Ia** (2 mmol) in toluene (3 mL) was added p-toluenesulfonic acid monohydrate (1 mmol), and the mixture was heated at 90 °C for 6 h. Toluene was evaporated in vacuo. The residue was treated with methanol (4 mL). The solid was filtered and washed with hexane (5 mL).

IV: Yield 52%; m.p. 198–200 °C; NMR ($CDCl_3$, δ) 1.7 (bm, 4H, 2 x CH_2), 2.95 (m, 2H, CH_2), 3.12 (m, 2H, CH_2), 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 5.3 (d, 1H, J=15 Hz, 4-CH), 6.6 (s, 1H, =CH-N), 6.65 (d, 1H, J= 7.5 Hz, Ar-H), 6.82 (d, 1H, J= 15 Hz, 3-CH), 6.9 (dd, 1H, J= 7.5 Hz, Ar-H), 6.98 (dd, 1H, J= 7.5 Hz, Ar-H), 7.05 (d, 1H, J= 7.5 Hz, Ar-H), 7.2 (dd, 1H, J= 7.5 Hz, Ar-H), 7.37 (dd, 1H, J= 7.5 Hz, Ar-H); Anal. Calcd for $C_{22}H_{23}N_3O_6$: C, 62.11; H, 5.45; N, 9.88. Found: C, 61.77, H, 5.45, N, 9.65.

2-Methoxy-6-[2-(7-methoxy-1H-indol-3-yl)ethyl]-benzenamine (V):

A suspension of dienamine **IV** (1.18 mmol) and 10% Pd/C (0.05 g) in methanol (10 mL) and acetic acid (0.4 mL) was hydrogenated at room temperature and 40 psi overnight (14 h). The reaction mixture was filtered over Celite and concentrated in vacuo. The crude mixture was purified by silica gel chromatography using a mixture of hexane and ethyl acetate (75:25 followed by 60:40).

V: Yield 58%; m.p. 74–77 °C; NMR ($CDCl_3$, δ) 2.87 (m, 2H, CH_2), 3.06 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.65 (d, 1H, J= 7.5 Hz, Ar-H), 6.68-6.8 (m, 3H, Ar-H), 6.9 (d, 1H, J= 3 Hz, N-CH), 7.02 (dd, 1H, J= 7.5 Hz, Ar-H), 7.22 (d, 1H, J= 7.5 Hz, Ar-H), 8.15 (bs, 1H, NH); Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.88, H, 7.09, N, 9.20.

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REFERENCES

1. Clark, R.D., Repke, D.B., Heterocycles, 1984, **22**, 195.
2. Hengartner, U., Batcho, A.D., Blount, J.F., Leimgruber, W., Larscheid, M.E., Scott, J.W., J. Org. Chem., 1979, **44**, 3748.
3. Dixon, A.K.; Giger, R.K.A., Eur. Pat. Appl. EP 491 664 A1, 24 June 1992.
4. a) Brizzolara, A.A. Ph.D. Thesis, Columbia University, 1960 (unpublished results). b) Szmuszkovicz, J., Adv. Org. Chem., 1963, **4**, 1.
5. Halleux, A.; Viehe, H.G., J. Chem. Soc. (C), 1970, 881.
6. Alt, G.H.; Cook, A.G., in "Enamines- Synthesis, Structure, and Reactions", Ed. Cook, A.G., Marcel Dekker, Inc., New York, 1988; pp 181–246.
7. Repke, D.B.; Grotjahn, D.B.; Shulgin, A.T., J. Med. Chem., 1985, **28**, 892.
8. Batcho, A.D.; Leimgruber, W., U.S. Patent 3 976 639, 24 August 1976.
9. Mills, K.; Khawaja, I.K.A.; Al-Saleh, F.S.; Joule, J.A., J. Chem. Soc. Perkin I, 1981, 636.

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