Iranian Journal of Organic Chemistry Vol. 3, No. 3 (2011) 695-697

Efficient synthesis of 1,3-dihydro-2*H*-indole-2-one derivatives

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Received: July 2011; Revised: July 2011; Accepted: July 2011

Abstract: A facile efficient method for synthesis of 1,3-dihydro-2*H*-indole-2-one derivatives using reaction of isatin in precence of NaH and methyl ketons under solvent free condition is described. In these reactions, synthesis of 1,3-dihydro-2*H*-indole-2-one is possible under solvent free condition and without using any catalyst.

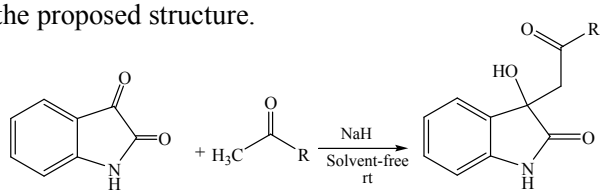
Keywords: Isatin, Indole, Methyl ketones.

Introduction

Indole moiety has been found in a wide variety of pharmacologically and biologically active compounds [1]. Many bisindole alkaloids are recognized as one of the rapidly growing groups of sponge metabolites because of their broad spectrum of biological properties [2–5] For example, Nortopsentins A–C, having 2,4-bis(3'-indolyl)-imidazole moieties, exhibit in vitro cytotoxicity against P388 cells [6]; Hamacanthin B, having a characteristic 3,5-bis(3'-indolyl) pyrazinone skeleton, exhibits cytotoxic activities against a wide range of human tumor cell lines with GI50 values at micromolar concentration [7]. Here, we describe an efficient synthesis of 1,3-dihydro-2*H*-indole-2-one derivatives from reaction of isatin in the presence of NaH and methyl ketones under solvent-free condition.

Results and discussion

As indicated in Scheme **1**, the reaction of isatin **1** in the presence NaH and methyl ketone **2** under solvent-free conditions proceeds smoothly at room temperature to produce 1,3-dihydro-2*H*-indole-2-one derivatives **3** in 95% yields (Scheme 1).
The products were characterized based on their IR, ^{1}H NMR, and ^{13}C NMR. The mass spectra of compounds **3a-3e** displayed molecular ion peaks at appropriate *m/z* values. ^{1}H NMR spectrum of **3a** exhibited one singlet at δ 2.09 for CH_3, AB system for CH_2 at δ 3.25 ($^2J_{HH}$ =16.8 Hz) and one singlet at δ 5.08 for OH proton along with multiplets for isatin moiety. For NH proton of isatin one broad singlet peak is demonestered at δ 9.33. The proton-decoupled ^{13}C NMR spectra of **3a** showed 11 distinct resonances in agreement with the proposed structure.



Scheme 1: The reaction of isatin, methylketones in presence of NaH.

The following mechanism (Scheme **2**) may be invoked for the formation of compounds **3**. Conceivably, the starting point of the reaction is the formation of isatin anion **4**, which undergoes proton transfer with methyl ketone **2** which produced isatin and carbanion **5**. This carbanion performs nucleophilic addition reaction with isatin to produce **6**. Intermediate **6** is converted to **3** by protonation.

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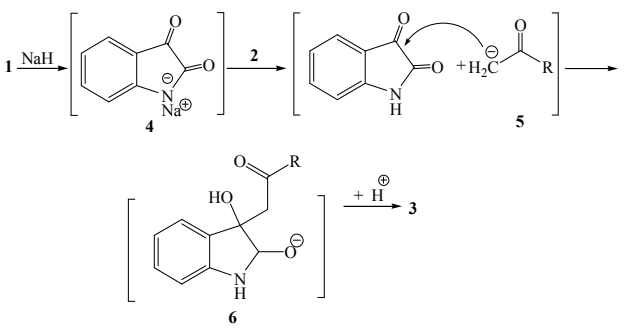

Scheme 2: Proposed mechanism for the formation of **3**.

Conclusion

In conclusion, we report a novel transformation involving isatin, methyl ketones and NaH, which affords 1,3-dihydro-2*H*-indole-2-one derivatives. The advantage of the present procedure is that the reaction is performed under solvent free condition by simple mixing of the starting materials. The procedure described here provides an facile and efficient method for the preparation of 1,3-dihydro-2*H*-indole-2-one.

Experimental

All chemicals obtained from Fluka and were used without further purification. M.p.: Electrothermal-9100 apparatus. IR Spectra: Bruker IR-460 spectrometer. ^{1}H NMR and ^{13}C NMR spectra: Bruker DRX-400 AVANCE instrument; in $CDCl_3$ at 400 and 100 MHz, respectively; δ in ppm, J in Hz. EI-MS (70 eV): Finnigan-MAT-8430 mass spectrometer, in m/z. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyzer. The results agreed favorably with the calculated values.

*General Procedure for the Preparation of Compounds **3a-3e**:*

A mixture of isatin **1** (2 mmol, 0.29g) and NaH was grated and stirred for 20 minutes, then methyl ketone **2** (2 mmol) was added (0.1 g, 2 mmol) to the mixture at room temperature. The reaction mixture was stirred for 2 h. Upon completion that monitored by TLC (EtOAc–hexane 2:1), resulting precipitate was washed by acetonitril (CH_3CN) (15 mL) and then precipitate was separated by filtration. The resulting solution was purified by column chromatography (SiO_2; hexan/AcOEt 3:1) to afford the pure compound.

*3-Hydroxy-3-(2-oxopropyl)-1,3-dihydro-2H-indol-2-one (**3a**):*

Pale yellow powder, yield: 0.37 g (90%), m.p.: 162-164°C, IR (KBr): ν = 1734 (C=O), 2957 (CH), 3350 (OH) cm $^{-1}$. EI-MS: 205 (60, M+), 162 (90), 148 (70), 119 (85), 92 (85), 43 (100). Anal. Calc. for $C_{11}H_{11}NO_3$ (205.21): C 64.38, H 6.83%; found: C 64.35, H 6.80 %. ^{1}H NMR: 2.09 (s, CH_3), 3.25 (AB q, J_{AB}= 16.8 Hz, CH_2), 5.08 (s, OH), 6.90 (d, J= 8 Hz, CH), 6.96 (t, J= 7.6 Hz, CH), 7.22 (t, J= 7.6 Hz, CH), 7.33 (d, CH, J = 8 Hz), 9.33 (bs, NH) . ^{13}C NMR: 29.9 (CH_3), 49.8 (CH_2), 73.3 (C), 109.6 (CH), 121.6 (CH), 123.8 (CH), 129.2 (CH), 131.3 (C), 142.6 (C), 177.8 (C=O), 204.8 (C=O).

*3-Hydroxy-3-(2-oxobutyl)-1,3-dihydro-2H-indol-2-one (**3b**):*

Yellow powder, yield: 0.42 g (95%), m.p: 128-130°C, IR (KBr): ν = 1750 (C=O), 2937 (CH), 3400 (OH) cm $^{-1}$. EI-MS: 219 (70, M+), 190 (85), 162 (75), 148 (85), 119 (85), 92 (85), 57 (95), 29 (100). Anal. Calc. for $C_{12}H_{13}NO_3$ (219.24): C 65.74, H 5.98%; found: C 64.70, H 5.95 %. ^{1}H NMR: 0.95 (t, J= 7.6 Hz, CH_3), 2.5 (q, J= 7.6 Hz, CH_2), 3.25 (AB q, J_{AB}= 16.8 Hz, CH_2), 5.08 (s, OH), 6.90 (d, J= 8 Hz, CH), 6.96 (t, J= 7.6 Hz, CH), 7.22 (t, J= 7.6 Hz, CH), 7.33 (d, CH, J = 8 Hz), 9.33 (bs, NH) . ^{13}C NMR: 14.3 (CH_3), 37.3 (CH_2), 47.8 (CH_2), 74.6 (C), 110.6 (CH), 123.0 (CH), 124.0 (CH), 129.9 (CH), 130.3 (C), 140.9 (C), 179.0 (C=O), 210.1 (C=O).

*3-Hydroxy-3-(2-oxo-2-phenylethyl)-1,3-dihydro-2H-indol-2-one (**3c**):*

Pale yellow powder, yield: 0.48 g (90%), m.p: 171-173°C, IR (KBr): ν = 1734 (C=O), 2957 (CH), 3350 (OH) cm $^{-1}$. EI-MS: 267 (60, M+), 162 (90), 148 (70), 119 (85), 92 (85), 105 (100). Anal. Calc. for $C_{16}H_{13}NO_3$ (267.28): C 71.90, H 4.90%; found: C 71.90, H 4.91 %. ^{1}H NMR: 3.82 (AB q, J_{AB}= 17.6 Hz, CH_2), 6.06 (s, OH), 6.81 (d, J= 8 Hz, CH), 6.85 (t, J= 8 Hz, CH), 7.16 (t, J= 8 Hz, CH), 7.27 (d, CH, J = 8 Hz),7.49 (t, J= 8 Hz, 2CH), 7.62 (t, J= 7.8 Hz, CH), 7.88 (d, J= 7.8 Hz, 2CH), 10.26 (bs, NH) . ^{13}C NMR: 46.2 (CH_2), 73.4 (C), 109.6 (CH), 121.6 (CH), 124.0 (CH), 128.3 (2CH), 129.2 (2CH), 129.4(CH), 132.2 (C),133.9 (CH), 136.6 (C), 143.4 (C), 178.7 (C=O), 196.9 (C=O).

*3-Hydroxy-3-(2-oxopentyl)-1,3-dihydro-2H-indol-2-one (**3d**):*

Yellow wish oil, yield: 0.44 g (95%), IR (KBr): ν = 1734 (C=O), 2957 (CH), 3350 (OH) cm $^{-1}$. EI-MS: 233 (60, M+), 162 (90), 148 (70), 119 (85), 92 (85), 105 (100). Anal. Calc. for $C_{13}H_{15}NO_3$ (233.26): C 66.94, H 6.48%; found: C 66.92, H 6.48 %. ^{1}H NMR: 0.80 (t, J= 7.5 Hz, CH_3), 1.39 (sixtet, J= 7.5 Hz, CH_2), 2.41 (t, J= 7 Hz, CH_2), 3.18 (AB q, J_{AB}= 17.6 Hz, CH_2), 6.06 (s,

OH), 6.90 (d, *J*= 8 Hz, CH), 6.96 (t, *J*= 7.6 Hz, CH), 7.22 (t, *J*= 7.6 Hz, CH), 7.33 (d, CH, *J* = 8 Hz), 9.33 (bs, NH) . ^{13}C NMR: 13.6 (CH_3), 17.20 (CH_2), 27.03 (CH_2), 45.9 (CH_2), 90.24 (C), 109.6 (CH), 121.6 (CH), 123.8 (CH), 129.2 (CH), 131.3 (C), 142.6 (C), 177.8 (C=O), 204.8 (C=O).

*3-Hydroxy-3-(4-methyl-2-oxopentyl)-1,3-dihydro-2H-indol-2-one (**3e**):*

Yellow wish oil, yield: 0.51 g (95%), IR (KBr): ν = 1708 (C=O), 2958 (CH), 3291 (OH) cm $^{-1}$. EI-MS: 247 (60, M^+), 204 (80), 190 (70), 162 (55), 148 (67), 92 (85),57 (95), 43 (100). Anal. Calc. for $C_{14}H_{17}NO_3$ (247.29): C 68.00, H 6.93%; found: C 68.05, H 6.95 %. ^{1}H NMR: 0.83 (d, *J*= 6.4 Hz, CH_3), 0.84 (d, *J*= 6.8 Hz, CH_3), 2.06 (m, CH), 2.30 (d, *J*= 6.8 Hz, CH_2), 3.10 (AB q, J_{AB}= 17.2 Hz, CH_2), 4.96 (bs, OH), 6.90 (d, *J*= 7.6 Hz, CH), 7.01 (t, *J*= 6.8 Hz, CH), 7.22 (t, *J*= 6.8 Hz, CH), 7.33 (d, CH, *J* = 7.2 Hz), 9.01 (bs, NH) . ^{13}C NMR: 22.4 ($2CH_3$), 24.3 (CH), 48.6 (CH_2), 52.8 (CH_2), 74.6 (C), 110.8 (CH), 123.0 (CH), 124.0 (CH), 129.9 (CH), 130.3 (C), 140.9 (C), 179.1 (C=O), 209.5 (C=O).

References

[1] Houlihan, W. J.; Remers, W. A., Brown, R. K.; *Indoles*: Part I; Wiley: New York, NY. **1992**.

[2] Sundberg, R. J.; *The Chemistry of Indoles*; Academic Press: New York **1996**.

[3] (a) Casapullo, A.; Bifulco, G.; Bruno, I.; Riccio, R. J.; *Nat. Prod*. **2000**, *63*, 447; (b) Bao, B.; Sun, Q.; Yao, X.; Hong, J.; Lee, C. O.; Sim, C. J.; Im, K. S.; Jung, J. H. J. *Nat. Prod*. **2005**, *68*, 711.

[4] Skibo, E. B.; Xing, C.; Dorr, R. T.; *J. Med. Chem.,* **2001**, *44*, 3545.

[5] (a) Gupta, L.; Talwar, A.; Palne, N. S.; Gupta, S.; Chauhan, P. M. S.; *Bioorg. Med. Chem. Lett*., **2007**, *17*, 4075; (b) Kaniwa, K.; Arai, M.; Li, A. X.; Ishibashi, M. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 4254.

[6] (a) Sakemi, S.; Sun, H. H. *J. Org. Chem*. **1991**, *56*, 4304; (b) Kawasaki, I.; Yamashita, M.; Ohta, S. *Chem. Pharm. Bull*. **1996**, *44*, 1831.

[7] (a) Kouko, T.; Matsumura, K.; Kawasaki, T. *Tetrahedron* **2005**, *61*, 2309; (b) Higuchi, K.; Takei, R.; Kouko, T.; Kawasaki, T. *Synthesis* **2007**, 669.