# SYNTHESIS OF A SERIES OF 2-INDOLYLMETHYLENE-LINKED COMPOUNDS BY THERMAL KNOEVENAGEL CONDENSATION UNDER CATALYST- AND SOLVENT-FREE CONDITIONS

**Tapas Halder[a], Nayim Sepay[a] and Asok K. Mallik[a]***

**Keywords:** Knoevenagel condensation, 3-methylindole-2-aldehyde, cyclic active methylene compounds, catalyst- and solvent-free reaction

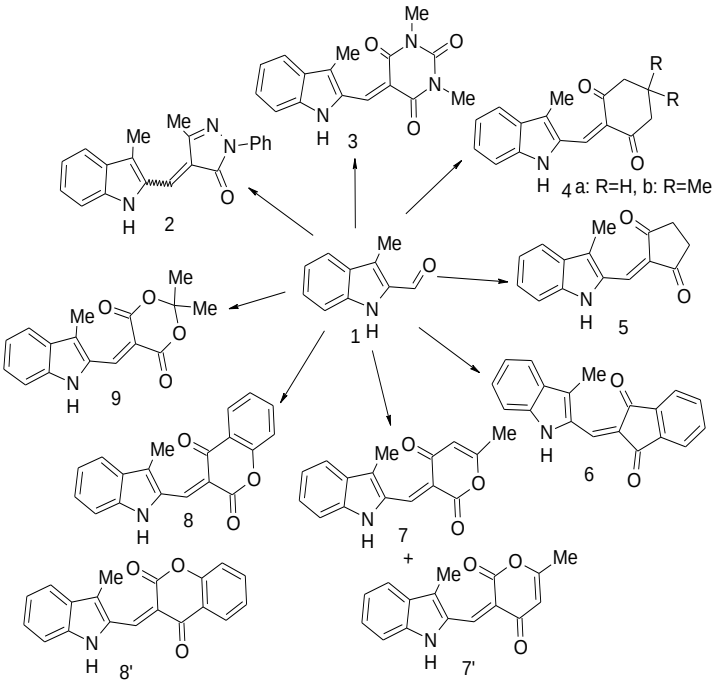
An efficient methodology has been developed by which a series of new 2-indolylmethylene-linked compounds can be readily synthesized by thermal Knoevenagel condensation of 3-methylindole-2-carboxaldehyde and cyclic active methylene compounds under catalyst- and solvent-free conditions.

* Corresponding Authors
E-Mail: mallikak52@yahoo.co.in
[a] Department of Chemistry, Jadavpur University, Kolkata-700 032, India

## Introduction

Indole derivatives are well-known for their versatile biological activities[1-3]. This has made the synthesis of compounds containing indole moiety an interesting target for synthetic organic chemists. The Knoevenagel condensation[4] of substituted aromatic aldehydes with active methylene compounds is an important and widely employed method for carbon-carbon bond formation in organic synthesis with numerous applications in the construction of different types of organic molecules of biological significance. The reactions are usually catalyzed by bases[5] such as aliphatic amines, ethylenediamine and piperidine or their corresponding ammonium salts, ammonia or sodium ethoxide in organic solvents. Lewis acids[6-9], zeolites[10], surfactants[11], different types of nanoparticles[12,13] have also been employed to catalyze the reactions. Moreover, the uses of ionic liquids[14], microwave[15,16] and ultrasound[17] are found in the recent literature to effect this condensation under eco-friendly conditions.

Organic reactions under solvent-free and catalyst-free[18-23] conditions have increasingly attracted interest of chemists, particularly from the viewpoint of green chemistry. Though a number of solvent-free methodologies are known for effecting Knoevenagel condensation[13,15,16,24], only a few catalyst-free reaction conditions are reported[25,26]. Considering the importance of synthesis of new compounds containing an indole moiety and effecting Knoevenagel condensation under catalyst- and solvent-free conditions, we undertook the present work where 3-methylindole-2-carboxaldehyde (**1**) (readily available from a well-known indole compound skatole)[27], with different active methylene compounds under the influence of heat only. The interesting results obtained in this study are presented herein.




**Scheme 1.** Synthesis of 2-indolyl-methylene-linked compounds.

## Experimentals

Melting points were recorded on a Köfler block. IR spectra were recorded on a Perkin Elmer FT-IR spectrophotometer (Spectrum BX II) in KBr pellets. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Bruker AV-300 (300 MHz) spectrometer. Analytical samples were routinely dried *in vacuo* at room temperature. Microanalytical data were recorded on two Perkin-Elmer 2400 Series II C, H, N analyzers. Mass spectra were measured with a Waters Xevo G2QTof HRMS spectrometer. TLC experiments were performed with silica gel G of SRL Pvt. Ltd make. Petroleum ether used had the boiling range of 60-80 °C.

**Preparation of 3-methylindole-2-carboxaldehyde (1)**

This compound was prepared by a known procedure.[26] A solution of 3-methylindole (1.64 g, 12.5 mmol) in DMF (1 mL) was added drop wise to a complex obtained from $POCl_3$ (2.3 g, 15 mmol) and DMF (7.76 g, 105 mmol). The reaction mixture was heated at 100 ° C for 3h. The crude product so obtained was cooled and subjected to column chromatography over silica gel (Spectrochem Pvt. Ltd., India, 100-200 mesh) using a mixture of petroleum ether and ether (19:1) as eluent gave first 3-methylindole-1-carboxaldehyde as a colourless oil. Further elution of the column with a mixture of petroleum ether and ether (17:3) gave **1** (0.42 g, 21 %) which was crystallised from petroleum ether as colourless needles, m.p. 138-140 °C (lit.[26] 139-140 °C), **1**H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, indole-3-$CH_3$), 7.14-7.19 (m, 1H), 7.38 (br. d, 1H), 7.71 (d, J=8.1 Hz, 1H), 8.80 (br. s, 1H, indole-3-$CH_3$), 10.04 (s, 1H, -CHO).

**Synthesis of 2-9**

An intimate mixture of 3-methylindole-2-carboxaldehyde (**1**, 1 mmol) and an active methylene compound (1 mmol) was taken in a round-bottomed flask fitted with an air condenser, and it was heated in an oil bath at a temperature between 80-120°C for a time period of 10-40 min (*vide* Table 1). The reaction vessel was then cooled and the reaction mixture was subjected to column chromatography over silica gel. The pure product thus obtained was crystallized from dichloromethane-petroleum ether.

**3-Methyl-4-((3-methyl-1*H*-indol-2-yl)methylene)-1-phenyl-1*H*-pyrazol-5(4*H*)-one (2)**

Brick red crystals, IR (KBr): ν/$cm^{-1}$ = 1672, 1578, 1330, 1216, 740. $^1$H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, pyrazolone-$CH_3$), 2.61 (3H, s, indole-3-$CH_3$), 7.11 (1H, t, J=7.4 Hz), 7.23 (t, J=7.0 Hz,1H), 7.37 (t, J=8.3 Hz,1H), 7.43-7.48 (m, 4H), 7.62 (d, J=7.9 Hz, 1H), 7.98 (d, J=8.0 Hz,1H), 7.99 (s, 1H, indole-2-CH=), 13.12 (br. s, 1H, indole-NH). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 9.8 (indole-3-$CH_3$), 13.1 (pyrazolone-$CH_3$), 112.9, 119.7, 120.4, 120.9, 125.3, 127.4, 128.2, 128.4, 128.9, 130.9, 131.7, 138.4, 139.2, 150.8, 163.8 (pyraozolone-C=O). HRMS *m/z* Calcd. for $C_{20}H_{18}N_3O$ $(M+H)^+$: 315.1450; Found: 316.1450. Anal. Calcd. for $C_{20}H_{17}N_3O$: C, 76.17; H, 5.43; N 13.32. Found: C, 75.92; H, 5.51; N, 13.15.

**1,3-Dimethyl-5-((3-methyl-1*H*-indol-2-yl)methylene)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3)**

Yellow crystals, $^1$H NMR (300 MHz, $CDCl_3$): δ 2.68 (s, 3H, indole-3-$CH_3$), 3.42 (s, 3H, barbiturate-$CH_3$), 3.46 (s, 3H, barbiturate-$CH_3$), 7.12 (br. t, J= 7.1 Hz, 1H), 7.40-7.44 (m, 2H), 7.66 (d, J=8.2, 1H), 8.67 (s, 1H, indole-2-CH=), 12.43 (br. s, 1H, indole-N-H). $^{13}$C NMR (75 MHz, $CDCl_3$): 10.0 (indole-3-$CH_3$), 28.5 (barbiturate-$CH_3$), 28.9 (barbiturate-$CH_3$), 108.1, 112.8, 120.7, 121.5, 128.2, 129.5, 130.3, 132.8, 139.6, 140.8, 151.2 (C=O), 163.1(C=O), 163.3 (C=O). HRMS *m/z* Calcd. for $C_{16}H_{16}N_3O_3$ $(M+H)^+$: 298.1192; Found: 298.0818. Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N 14.13. Found: C, 64.72; H, 5.31; N, 14.25.

**2-((3-Methyl-1*H*-indol-2-yl)methylene)cyclohexane-1,3-dione (4a)**

Red crystals, $^1$H NMR (300 MHz, $CDCl_3$): δ 2.05-2.13 (m, 2H), 2.66 (s, 3H, indole-3-$CH_3$), 2.66-2.73 (m, 2H), 2.75-2.82 (m, 2H), 7.09-7.15 (m, 1H), 7.38-7.42 (m, 2H), 7.65 (d, J=8.1Hz, 1H), 8.44 (s, 1H, indole-2-CH=), 12.38 (br. s, 1H, indole-NH). HRMS *m/z* Calcd. for $C_{16}H_{16}NO_2$ $(M+H)^+$: 254.1181; Found: 254.1168. Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.57; H, 6.34; N, 5.51. Found: C, 76.02; H, 6.21; N, 5.34.

**5,5-Dimethyl-2-((3-methyl-1*H*-indol-2-yl)methylene)-cyclohexane-1,3-dione (4b)**

Orange crystals, $^1$H NMR (300 MHz, $CDCl_3$): δ 1.13 (s, 6H, 2×$CH_3$ of dimidone moiety), 2.60-2.67 (m, 4H, 2×$CH_2$ of dimidone moiety), 2.67 (s, 3H, indole-3-$CH_3$), 7.10 (br. t, J=7.5 Hz,1H), 7.38-7.44 (m, 2H), 7.64 (br. d, J = 8.1 Hz, 1H), 8.42 (s, 1H, indole-2-CH=), 12.41 (br. s, 1H, indole-NH). Anal. Calcd. for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N 4.98. Found: C, 76.58; H, 6.64; N, 5.15.

**2-((3-Methyl-1*H*-indol-2-yl)methylene)cyclopentane-1,3-dione (5)**

Orange crystals, IR (KBr): ν /$cm^{-1}$ = 1650, 1626, 1562, 1523, 1323, 1201, 1128, 1054, 746, 712. **1**H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, indole-3-$CH_3$), 2.80 (s, 4H, 2×$CH_2$ of cyclopenta-1,3-dione moity), 7.09-7.13 (m, 1H), 7.44 (br. s, 2H), 7.64 (d, J=8.3, 1H), 7.91 (s, 1H, indole-2-CH=), 12.64 (br. s, 1H, indole-NH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 10.0 (indole-3-$CH_3$), 34.3 ($CH_2$ of cyclopenta-1,3-dione moiety), 34.5 ($CH_2$ of cyclopenta-1,3-dione moiety), 113.1, 121.0, 121.6, 122.4, 128.7, 130.3, 132.5, 133.4, 134.2, 140.0, 203.2 (C=O), 205.2 (C=O). Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N 5.85. Found: C, 74.99; H, 5.61; N, 5.58.

**2-((3-Methyl-1*H*-indol-2-yl)methylene)-1*H*-indene-1,3(2*H*)-dione (6)**

Red crystals, IR (KBr): ν /$cm^{-1}$ = 1665, 1596, 1554, 1498, 1325, 1262, 1158, 991, 755. **1**H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, indole-3-$CH_3$), 7.11 (t, J=7.5 Hz, 1H), 7.40 (t, J=7.5 Hz, 1H), 7.47 (d, J=8.1 Hz, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.76-7.80 (m, 2H), 7.95-7.99 (m, 2H), 7.99 (s, 1H, indole-2-CH=), 12.31 (br. s, 1H, indole-NH); $^{13}$C NMR (75 MHz, $CDCl_3$): δ 9.8 (indole-3-$CH_3$), 112.6, 120.5, 121.1, 122.5, 122.8, 128.5, 128.7, 129.5, 130.8, 131.6, 134.7, 135.1, 139.2, 140.3, 141.5, 162.3, 190.3 (C=O), 191.9 (C=O). Anal. Calcd. for $C_{19}H_{13}NO_2$: C, 79.43; H, 4.56; N 4.88. Found: C, 79.72; H, 4.51; N, 5.15.

**(*E* and *Z*)-6-Methyl-3-((3-methyl-1*H*-indol-2-yl)methyl-ene)-2*H*-pyran-2,4(3*H*)-dione (7 and 7′)**

Orange crystals, **1**H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, pyrone-6-$CH_3$), 2.68 and 2.70 (each s, 3H (total), indole-3-$CH_3$), 5.86 and 5.90 (each s, 1H (total), pyrone-H-5), 7.09-7.13 (m, 1H), 7.42 and 7.43 (each br. s, 2H (total)), 7.65 and 7.67 (each d, J=7.5 Hz, 1H (total)), 8.61 and 8.75 (each s, 1H (total), indole-2-CH=), 12.10 and 13.16 (each br.

s, 1H (total), indole-NH) [Characteristic peaks: δ 2.68, 5.86, 8.60, 13.16 (major isomer *ca*. 72 %), δ 2.70, 5.90, 8.75, 12.10 (minor isomer *ca*. 28 %)].

**(*E* and *Z*)-3-((3-methyl-1*H*-indol-2-yl)methylene)chrom an-2,4-dione (8 and 8′)**

Red crystals, $^1$H NMR (300 MHz, $CDCl_3$): δ 2.74 and 2.76 (each s, 3H (total), indole-3-$CH_3$), 7.14 (br. t, *J* = 6.6 Hz, 1H), 7.26-7.35 (m, 2H,), 7.45-7.50 (m, 2H), 7.63-7.70 (m, 2H), 8.14-8.20 (m, 1H), 8.83 and 8.95 (each s, 1H (total), indole-2-CH=), 12.25 (br. s, 1H, Indole-NH), 13.11 (br. s, 1H (total), indole-NH) [Characteristic peaks: δ 2.74, 8.83, 13.11 (major isomer *ca*. 75 %), δ 2.76, 8.86, 12.20 (minor isomer *ca*. 25 %)]. $^{13}$C NMR (75 MHz, $CDCl_3$): 10.3 (indole-3-$CH_3$), 113.0, 113.3, 117.2, 117.4, 120.9, 121.0, 121.2, 122.0, 124.5, 124.8, 127.4, 128.2, 128.8, 131.0, 132.4, 135.2, 135.6, 135.8, 136.2, 140.2, 141.0, 141.7, 143.4, 154.5, 154.9, 163.7, 164.4, 180.4 (very much characteristic of a mixture). HRMS *m/z* Calcd. for $C_{19}H_{14}NO_3$ $(M+H)^+$: 304.0974; Found: 304.1276.

**2,2-Dimethyl-5-((3-methyl-1*H*-indol-2-yl)methylene)-1,3-dioxane-4,6-dione (9)**

Red crystals, $^1$H NMR (300 MHz, $CDCl_3$): δ 1.80 ( s, 6H**,** 2×$CH_3$ of the Meldrm's acid moiety), 2.67(s, 3H, indole-3-$CH_3$), 7.11-7.17 (m, 1H), 7.42-7.44 (m, 2H), 7.67 (d, J= 8.2 Hz, 1H), 11.86 (br. s, 1H, indole NH). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 10.0 (indole-3-$CH_3$), 27.4 (2×$CH_3$ of Meldrum's acid moiety), 103.5, 104.4, 112.9, 121.0, 121.7, 128.1, 129.6, 129.9, 133.4, 140.1, 141.3, 163.8 (C=O), 164.1 (C=O); HRMS *m/z* Calcd. for $C_{16}H_{16}NO_4$ $(M+H)^+$: 286.1079; Found: 286.1092.

**9-(3-Methyl-1*H*-indol-2-yl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (10)**

Colorless crystals, m.p. 286-287 °C $^1$H NMR (300 MHz, $CDCl_3$): δ 2.01-2.10 (m, 4H), 2.11 (s, 3H, indole-3-$CH_3$), 2.25-2.44 (m, 4H), 2.53-2.71 (m, 4H), 4.94 (s, 1H), 7.00 (t, 1H, J= 7.7 Hz), 7.08 (t, 1H, J= 7.4 Hz), 7.26 (d, 1H, merged with $CHCl_3$ signal), 7.42 (d, 1H, J=7.5 Hz), 8.36 (br. s, 1H, indole NH) Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03, Found: C, 75.89; H, 6.21; N, 4.24.

## Results and Discussion

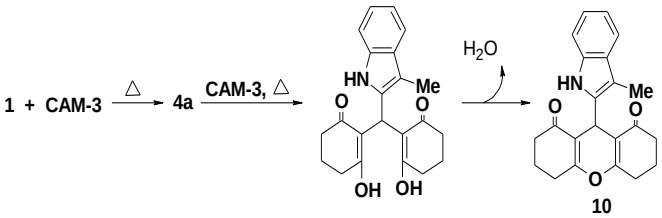
Our present method involves subjecting of an intimate mixture of 3-methylindole-2-carboxaldehyde (**1**) and a cyclic active methylene compound (1:1 mole ratio) directly to heat. A range of structurally diverse cyclic active methylene compounds, *viz.*, 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one (**CAM-1,** $pK_a$ = 6.90)[28], 1,3-dimethylbarbituric acid (**CAM-2,** $pK_a$ = 4.68)[29], cyclohexan-1,3-dione (**CAM-3,** pKa = 10.3)[30], 5,5-dimethylcyclohexan-1,3-dione (dimedone) (**CAM-4,** $pK_a$ = 11.2)[30], cyclopentan-1,3-dione (**CAM-5,** $pK_a$ = 4.4)[31], indan-1,3-dione (**CAM-6,** $pK_a$ = 7.82)[32], 6-methyl-4-hydroxy-2-pyrone (**CAM-7,** $pK_a$ = 4.94)[33], 4-hydroxycoumarin (**CAM-8,** $pK_a$ = 4.14)[34] and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (**CAM-9,** $pK_a$ = 7.3)[30] were taken to get the condensation products **2-9**, all of which are new compounds. The time and temperature for the reaction of **1** with each of the above cyclic active methylene compounds were optimized and the results are shown in Table 1. It is interesting to note that when 3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one was used, only one geometrical isomer of the condensation product was obtained. However, as the product did not give good quality crystals, settlement of its configuration by x-ray crystallography could not be done.

**Table 1.** Optimised reaction conditions for synthesis of **2-9**.

| Methylene compound | Time (min) | Temp. (°C) | Product | Yield (%) | m.p. (°C) |
|---|---|---|---|---|---|
| CAM-1 | 20 | 120 | 2 | 65 | 154-155 |
| CAM-2 | 40 | 120 | 3 | 90 | 208-209 |
| CAM-3 | 20 | 80 | 4a§ | 25 | 94-96 |
| CAM-4 | 20 | 95 | 4b | 31 | 104-105 |
| CAM-5 | 20 | 115 | 5 | 79 | 184-185 |
| CAM-6 | 20 | 120 | 6 | 91 | 252-253 |
| CAM-7 | 20 | 120 | 7+7′ | 45 | 186-190 |
| CAM-8 | 140 | 120 | 8+8′ | 83 | 211-215 |
| CAM-9 | 20 | 110 | 9 | 89 | 193-194 |

§ In this case, another product (**10**) was also obtained (Scheme 2).

In the condensation reaction of **1** with each of **CAM-7** and **CAM-8**, a mixture of two products were obtained in approx. 4:1 ratio, which were found to be inseparable by column chromatography. When the results of the reactions of **1** with cyclic 1,3-diones were analyzed, it was observed that Knoevenagel condensation products were formed in better yields from the 5-membered 1,3-diones as compared to the six-membered 1,3-diones. From the reaction mixture using **CAM-3** some amount of the new xanthene-1,8(2*H*)-dione derivative **10** could be isolated in low yield (16%, based on amount of **1** taken), which indicated the occurrence of a facile Michael reaction on **4a** under the applied reaction conditions (Scheme 2). It may, therefore, be expected that development of a method for synthesis of **10** or its analogs may be possible by use of **1** and cyclohexan-1,3-diones in 1:2 mole ratio. Furthermore, we wish to report here that attempted reaction of **1** with the acyclic 1,3-dione acetylacetone ($pK_a$ = 13.3)[30] (120 °C, 3 h) did not afford any Knoevenagel condensation product. The $pK_a$ values of the active methylene compounds as quoted above indicate that the acidity of these compounds possibly plays an important role on the ease of their Knoevenagel condensation with **1**.




**Scheme 2.** Formation of 9-(3-methyl-1*H*-indol-2-yl)-3,4,5,6,7,9-hexahydro-1*H*-xanthene-1,8(2*H*)-dione (**10**)

The formatiom of 2-9 is expected to follow a path typical for acid-catalyzed Knoevenagel condensation. Possibly, the enol forms of the cyclic active methylene compounds are acting as acid catalysts.

## Conclusions

We have developed a simple and efficient method for synthesis of a series of new 2-indolylmethylene-linked compounds by Knoevenagel condensation of 3-methylindole-2-carboxaldehyde and cyclic active methylene compounds under catalyst- and solvent-free conditions. Yields of the products were found to be moderate to very good in majority of cases.

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## Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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