

Note

Facile formation of bis(3-indolyl)methylarenes by iodine-catalyzed reaction of indole with α,α' -bis(arylmethylene)ketones and α -substituted arylmethyleneketones in dry ethanol

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Bis(3-indolyl)methylarenes are obtained in good yield by reaction of indole with α,α' -bis(arylmethylene)ketones and α -substituted arylmethyleneketones in dry ethanol using catalytic amount of molecular iodine at room temperature. A plausible mechanism for formation of these products has been suggested.

Keywords: α,α' -Bis(arylmethylene)ketones, α -substituted arylmethyleneketones, indole, bis(3-indolyl)methylarenes, molecular iodine

Indoles display a very wide range of biological activity¹. A good number of indole derivatives are in regular use as pharmaceuticals. These have made the chemistry of indoles to be one of the most active growth areas of heterocyclic chemistry^{1a,b,2}. Among the derivatives of indoles, 3-indolylketones **1** are important building blocks for synthesis of many natural products, e.g., hapalindoles³, a class of cytotoxic indole alkaloids. Development of methods for synthesis of **1** appears to be an important synthetic aspect.

In recent years a good number of methods have been developed for addition of indoles to α,β -unsaturated ketones^{4a-g} (**Scheme I**) as well as to olefinic moieties conjugated with electron withdrawing groups^{4h,i} other than carbonyl exclusively at the 3-position of this heterocycle. In each case, very good yield of the conjugate addition product has been reported.

E-3-Benzylidenechromanones **2** and *E*-3-benzylideneflavanones **3** are compounds which possess α,β -unsaturated ketone moiety. Recently, some reactions of *E*-3-benzylidenechromanones **2** and *E*-3-benzylideneflavanones **3** (**Figure 1**) have been studied by this group⁵. The availability of these

compounds generated interest for undertaking the conjugate addition of indoles using them as substrate with a view to getting new compounds incorporating both indole and chromanone moieties. However, attempts in this direction have been unsuccessful and both **2** and **3** have been found to be inert towards reaction with indole under iodine-catalysed conditions^{4e,f} even upto 70°C (with or without using ethanol as solvent).

The reaction of arylmethyleneketones of the type **4-6** (**Figure 2**) with indole in ethanol under iodine-catalysed condition at RT was then studied.

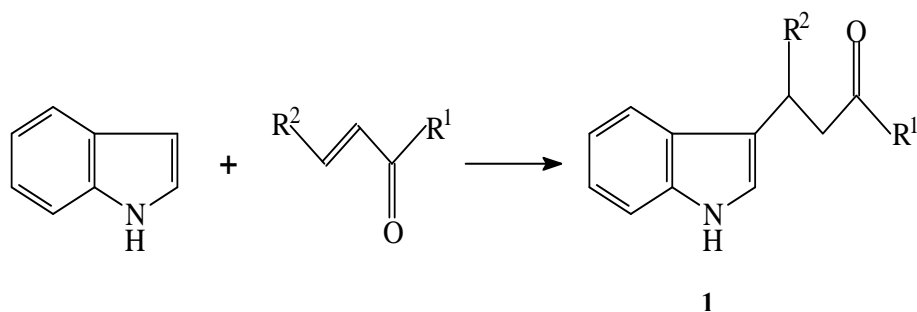
It was noted with much interest that under this condition all of **4-6** produced bis(3-indolyl)methylarenes **7** (**Scheme II**), instead of any conjugated addition product. This was the case even when 1 mole of indole was used per arylmethylene moiety in the substrate (yield of **7**: 29-34%). The yield of this product was found to improve by doubling the amount of indole and the results obtained under this condition are presented in **Table I**. The curious repetition of the reaction using indole and chalcone^{4e}, however, gave the reported conjugate addition product (**1**, R¹ = R² = Ph).

For the formation of the bis(3-indolyl)methylarenes **7**, the plausible mechanism is delineated in **Scheme III**.

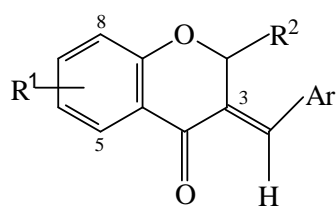
Thus, herein is reported a unique method by which α,α' -bis(arylmethylene)ketones and α -substituted arylmethyleneketones can be converted directly to bis(3-indolyl)methylarenes **7** in good yield. It may be mentioned here that all the reported methods for synthesis of **7**, including the current ones^{6,7}, use no starting material other than aromatic aldehydes.

Experimental Section

Melting points were recorded on a Kofler block and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 397 spectrometer. ¹H NMR spectra were recorded in CDCl₃ on Bruker DPX-300 (300 MHz) spectrometer using TMS as an internal standard and EI mass spectra were recorded on JEOL JMS D-300 and Shimadzu QP-1000 spectrometers. Column chromatography was performed with silica gel (100-200 mesh) and TLC with silica gel G from SRL Pvt. Ltd. Petroleum ether had the boiling range 60-80°C.



Scheme I



2: $R^1 = H$ or 6-Me, $R^2 = H$
3: $R^1 = H$ or 6-Me or 7-OMe, $R^2 = \text{Aryl}$

Figure 1

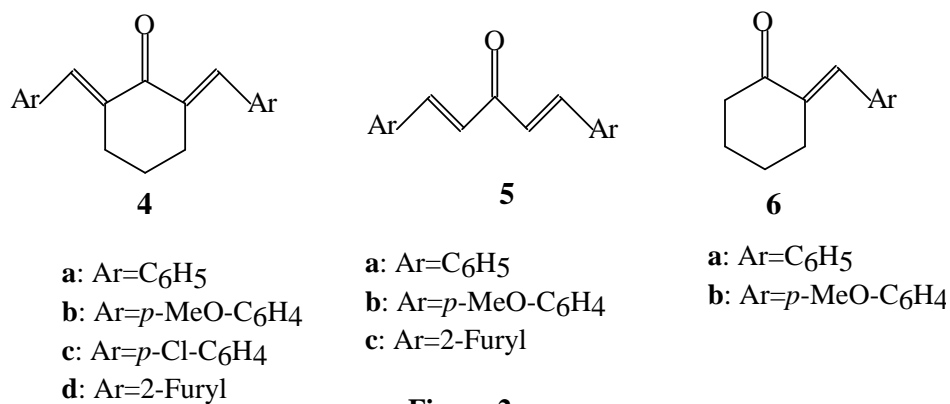
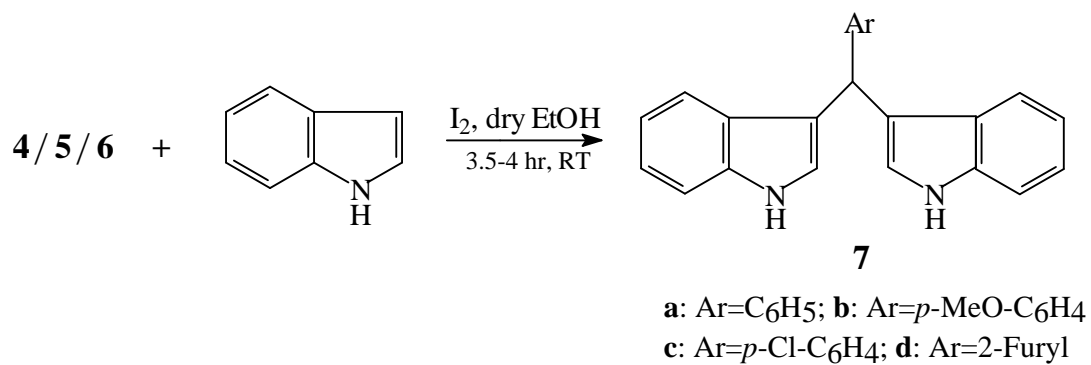


Figure 2



Scheme II

General procedure for synthesis of α,α' -bis(aryl-methylene)ketones and α -substituted aryl-methyleneketones: A mixture of cyclohexanone/acetone (10 mmol) and aromatic aldehyde (20 mmol or 10 mmol) was added in two equal portions to 5% sodium hydroxide solution in ethanol-water (4:5, 45 mL), under stirring. A flocculent precipitate was formed within 2-3 min after addition of the first

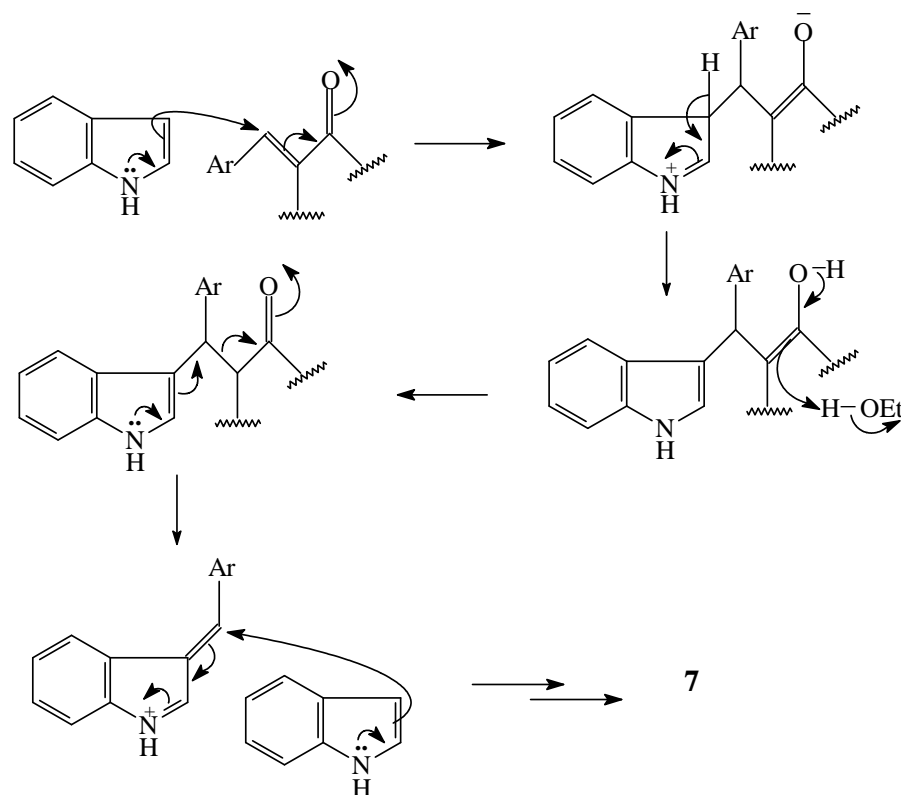
portion. After allowing the reaction to continue for 15 min, the remaining portion of the said mixture was added. Stirring was continued for 2 hr and then the precipitated material was collected by filtration. The crude product so obtained was purified by recrystallization from ethanol. The identity of the pure product obtained was established from the reported melting point or spectral characterization data. The spectral characterization data of **4d** (m.p. 143-44°C), one of the compounds of this group, are as follows: IR (KBr): 3145, 1644 (C=O), 1592, 1546, 1472, 1286, 1149, 1027 and 750 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.56 (4H, br.s), 6.66 (2H, d, $J=3.2$ Hz), 6.52 (2H, dd, $J=3.2$ and 1.6 Hz), 3.01 (4H, t, $J=5.4$ Hz) and 1.93-1.84 (2H, m).

General procedure for the reaction of α,α' -bis(arylmethylene)ketones and α -substituted aryl-methyleneketones with indoles: A mixture of an appropriate arylmethyleneketone (0.5 mmol) and indole (1 or 2 mmol) was dissolved in dry ethanol at RT and to the solution molecular iodine (0.025 g, 0.1 mmol) was added under stirring. When the starting materials disappeared almost completely (after 3.5-4.0 hr, checked by TLC), the reaction

Table I — Results of bis(3-indolyl)methylarene formation[†]

Entry	Starting aryl-methyleneketone	Reaction time (hr)	Isolated product	Yield (%)	Ref.
1	4a	3.5	7a	56	6a
2	5a	4	7a	55	6b
3	6a	3.5	7a	52	6a
4	4b	4	7b	58	6b
5	5b	4	7b	56	6b
6	6b	4	7b	59	6b
7	4c	3.5	7c	62	6c
8	4d	4	7d	54	6b
9	5c	4	7d	63	6b

[†] The products were characterised from their spectral data.



Scheme III

mixture was diluted with water and the reaction product was extracted with chloroform (50 mL). The chloroform extract was washed with sodium thiosulphate solution and water (each 2×25 mL) and then dried over anhydrous sodium sulphate. The concentrate of the chloroform extract was chromatographed over silica gel using petroleum ether-ethyl acetate (9:1) as eluent to obtain the pure product. All the bis(3-indolyl)methylarenes **7** produced are known compounds⁶ (**Table I**) and they were characterised from their physical and spectral (IR, ¹H NMR and MS) data. The spectral characterization data of **7d** (m.p. 117-18°C), one of the bis(3-indolyl)methylarenes are as follows : IR (KBr): 3479 (N-H), 1638, 1217 and 771 cm⁻¹; ¹H NMR (CDCl₃): δ 7.98 (2H, br.s), 7.48 (2H, d, *J*=8.1 Hz), 7.38 (2H, d, *J*=8.1 Hz), 7.35 (1H, d, *J*=1.6 Hz), 7.12 (2H, t, *J*=7.8 Hz), 7.04 (2H, t, *J*=7.8 Hz), 6.89 (2H, br.s), 6.29-6.31 (1H, m), 6.06 (1H, d, *J*=3 Hz), 5.95 (1H, s); EIMS: *m/z*(%) 313(87.5) (M+H)⁺, 312(50.2) (M⁺), 284 (37.5), 196 (21.3), 168 (23.7), 142 (28.7), 97 (25), 43 (100). Anal. Calcd. for C₂₁H₁₆N₂O: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.25; H, 5.32; N, 8.49%.

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