Research Article

Facile Iodine-Catalyzed Michael Addition of Indoles to α,α' -Bis(arylmethylene)cyclopentanones: An Efficient Synthesis of *E*-2-(3-Indolylphenylmethyl)-5-phenylmethylenecyclopentanones

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Iodine-catalyzed reaction of indoles with α,α' -bis(arylmethylene)cyclopentanones afforded one diastereomer of the corresponding Michael adducts, namely, *E*-2-(3-indolylphenylmethyl)-5-phenylmethylenecyclopentanones, in a good yield. The products form a new group of indole derivatives.

1. Introduction

The Michael reaction has attracted much attention as one of the most important C–C bond-forming reactions [1, 2]. Indole is a very good Michael donor through its 3-position, and the 3-indolyl system is one of the important building blocks for many biologically active compounds, both natural and unnatural [3]. Traditionally, the Michael addition of indole to α,β -unsaturated ketones as well as addition reactions of indole to other electron deficient olefins is known to be catalyzed by strong bases and Bronsted acids [4–8]. In recent years, it has been reported that these reactions can also be promoted by Lewis acids [9–20]. Following a recent report of iodine-catalyzed Michael addition of indole to some α,β -unsaturated ketones in ethanol [13], we studied the reaction between indole and α,α' -bis(arylmethylene)cyclohexanones under the same condition when we got bis(3-indolyl)methylarenes instead of any conjugate addition product [21]. A survey of the literature revealed that the Michael reaction between indoles and α,α' -bis(arylmethylene)cyclopentanones has not been studied so far. We, therefore, carried out this work under the iodine-catalyzed condition and obtained Michael adducts in good

yields (Scheme 1). The results of our study are presented herein.

2. Results and Discussion

In a preliminary study, α,α' -bis(phenylmethylene)cyclopentanone (**1a**) was treated with indole (**2a**) (mole ratio 1 : 1) in the presence of 10 mol% iodine as catalyst in dry dichloromethane at room temperature. The reaction was found to be complete within 4 h affording the conjugate addition product (**3a**) in 60% yield. The reaction using double the amount of indole also gave the same product in a comparable yield (62%). Encouraged by this result, we carried out the reaction by a variation of conditions, the results of which are given in Table 1.

It is evident from the results presented in Table 1 that the reaction gave the best yield of the product when dichloromethane was used as solvent and catalyst iodine was used to the extent of 10 mol% (Table 1, Entry 1). When ethanol was used as solvent, the solubility of the substrates at room temperature as well as at the reflux temperature was a problem.

SCHEME 1: Iodine-catalyzed Michael addition of indoles to α,α' -bis(arylmethylene) cyclopentanones.TABLE 1: Screening for optimum reaction conditions^a.

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield ^b (%)
1	10	Dichloromethane	4	60
2	10	Dichloromethane	2	40
3	10	Dichloromethane	6	63
4	10	Ethanol	4	0
5	10	Tetrahydrofuran	4	40
6	5	Dichloromethane	4	45
7	5	Dichloromethane	10	65
8	10	1,4-Dioxane	4	50

^a Conditions: **1a** (1 mmol), **2a** (1.1 mmol), and solvent (5 mL).^b Yield after column chromatography.

Under the optimized reaction condition, the generality of the process was investigated with a number of α,α' -bis(arylmethylene)cyclopentanones (**1**), and the results are summarized in Table 2. It was noted that **1** with an electron withdrawing or a weakly electron donating group in the phenyl ring underwent facile reaction at room temperature affording the corresponding product within 3–4 h, while **1** with an electron donating group in the phenyl ring failed to undergo any reaction (Table 2, Entries 8 and 9) even at reflux temperature. α,α' -Bis(furfurylidene)cyclopentanone behaved like the latter group of substrates (Table 2, entry 10). Analytical and spectral data of the products definitely showed that they were *E*-2-(3-indolyl)-2-arylmethyl-5-arylmethylenecyclopentanones (**3**) (HRMS of **3c** is shown in Figure 1). Another interesting point was that no bis(3-indolyl)methylarene formation was observed in this case. The reaction of **1** with one equivalent of 2-methylindole was then studied under similar conditions, which showed that this indole also reacted smoothly giving the corresponding products in a good yield (Table 2, Entries 5–7). Iodine-catalyzed reaction of α,α' -bis(arylmethylene)cyclohexanones with indole/2-methylindole in methylene chloride studied in this connection, however, gave bis(3-indolyl)methylarenes, just like that observed by the use of ethanol as solvent [21].

The Michael addition products **3** contain two adjacent stereogenic centres. It was an interesting observation that out

of their two diastereomeric *dl*-pairs only one was formed. However, the configuration of the diastereomer formed could not be ascertained as none of **3a–g** formed good quality crystals from common organic solvents. *E*-Configuration has been suggested for them by considering that one of the phenylmethylene units of **1** remains completely unchanged during the reaction.

3. Conclusions

We have developed a simple and efficient method for Michael addition of indoles to α,α' -bis(arylmethylene)cyclopentanones using iodine as catalyst. The method is clean, and the products were obtained in a good yield without the formation of any side product. The Michael addition products **3a–g** are new compounds and may have potential biological activities.

4. Experimental Section

4.1. General. ¹H and ¹³C NMR spectra were obtained with a Bruker AV-300 (300 MHz) spectrometer in CDCl₃ with TMS as an internal standard. IR spectra were recorded with a Perkin Elmer FT-IR Spectrophotometer (Spectrum BX II) as KBr pellets. Mass Spectra were recorded on Micro

4.3.2. *E*-2-(3-Indolyl-*p*-methylphenylmethyl)-5-*p*-methylphenyl-methylenecyclopentanone (**3b**). (Entry 2 in Table 2): White solid; IR (KBr): 3380 (N–H), 3000 (ArC–H), 1698 (C=O), 1608, 1590 (C=C), 1496, 1426, 1238, 1165 cm^{−1}; ¹H NMR (300 MHz, CDCl₃): δ 8.06 (br. s, 1H, N–H), 6.93–7.40 (m, 14H, Ar–H and C=C–H), 5.02 (d, 1H, *J* = 3.6 Hz, H-β), 3.18–3.22 (m, 1H, H-2), 2.70–2.73 (m, 2H, H-4), 2.37 (s, 3H, CH₃), 2.22–2.31 (m, 4H, H-3 and CH₃),

FIGURE 1: HRMS of compound **3c**.

1.81–1.89 (m, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.01 (C=O), 140.50, 136.42, 135.63, 135.33, 132.64, 130.54, 129.35, 129.09, 128.88, 128.70, 128.09, 127.19, 122.93, 121.51, 119.88, 119.18, 117.13, 110.8, 52.98 (C- β), 41.82 (C-2), 27.42 (C-4), 24.42 (C-3), 21.38 (CH_3), 20.93 (CH_3); Anal.

Calcd for $C_{29}H_{27}NO$: C, 85.89; H, 6.71; N, 3.45; Found C, 85.71; H, 6.53; N, 3.41.

4.3.3. *E*-2-(3-Indolyl-*p*-chlorophenylmethyl)-5-*p*-chlorophenyl-methylenecyclopentanone (**3c**). (Entry 3 in Table 2): White

solid; IR (KBr): 3495 (N–H), 2910 (ArC–H), 1707 (C=O), 1620, 1600 (C=C), 1495, 1460, 1420, 1240, 1160, 1100 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 8.11 (br. s, 1H, N–H), 6.95–7.42 (m, 14H, Ar–H and C=C–H), 5.06 (d, 1H, J = 3.6 Hz, H- β), 3.19–3.25 (m, 1H, H-2), 2.70–2.79 (m, 2H, H₂-4), 2.30–2.35 (m, 1H, H-3), 1.75–1.83 (m, 1H, H-3); ^{13}C NMR (75 MHz, CDCl_3): δ 206.91 (C=O), 140.07, 136.46, 136.34, 135.31, 133.88, 132.14, 131.62, 131.57, 130.64, 128.9, 128.20, 126.91, 122.30, 121.53, 119.72, 119.45, 117.89, 110.98, 52.76 (C- β), 41.19 (C-2), 27.45 (C-4), 23.79 (C-3); HRMS observed for $(\text{M} + \text{Na})^+$ at 468.0894. Calculated for $\text{C}_{27}\text{H}_{21}\text{NOCl}_2$ $[\text{M} + \text{Na}]^+$ at 468.0898.

4.3.4. *E*-2-(3-Indolyl-*p*-bromophenylmethyl)-5-*p*-bromophenylmethylenecyclopentanone (**3d**). (Entry 4 in Table 2): White solid; IR (KBr): 3371 (N–H), 2955 (ArC–H), 1692 (C=O), 1611, 1583 (C=C), 1487, 1404, 1290, 1152, 1073 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 8.08 (br. s, 1H, N–H), 6.94–7.53 (m, 14H, Ar–H and C=C–H), 5.05 (d, 1H, J = 3.6 Hz, H- β), 3.19–3.27 (m, 1H, H-2), 2.69–2.77 (m, 2H, H₂-4), 2.30–2.37 (m, 1H, H-3), 1.57–1.82 (m, 1H, H-3); ^{13}C NMR (75 MHz, CDCl_3): δ 206.88 (C=O), 140.63, 136.50, 134.33, 131.93, 131.87, 131.67, 131.2, 131.09, 126.93, 123.72, 122.36, 121.57, 120.34, 119.75, 119.52, 117.86, 111.02, 52.86 (C- β), 41.26 (C-2), 27.36 (C-4), 23.83 (C-3); Anal. Calcd for $\text{C}_{27}\text{H}_{21}\text{NOBr}_2$ (535.27): C, 60.58; H, 3.95; N, 2.62; Found C, 60.43; H, 3.77; N, 2.85.

4.3.5. *E*-2-[3-(2-Methyl)indolyl-phenylmethyl]-5-phenylmethylenecyclopentanone (**3e**). (Entry 5 in Table 2): White solid; IR (KBr): 3401 (N–H), 3024 (ArC–H), 2952, 1705 (C=O), 1622 (C=C), 1459, 1448, 1302, 1187, 741 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.75 (br. s, 1H, N–H), 6.91–7.62 (m, 15H, Ar–H and C=C–H), 4.85 (d, 1H, J = 6.0 Hz, H- β), 3.52–3.55 (m, 1H, H-2), 2.73–2.78 (m, 2H, H₂-4), 2.43 (s, 3H, Me), 2.31–2.39 (m, 1H, H-3), 1.85–1.90 (m, 1H, H-3); ^{13}C NMR (75 MHz, CDCl_3): δ 205.36 (C=O), 140.46, 135.28, 134.90, 132.65, 128.65, 128.49, 127.80, 120.61, 120.39, 118.95, 112.72, 109.95, 53.19 (C- β), 39.86 (C-2), 25.64 (C-4), 20.90 (C-3), 12.48 (Me); Anal. Calcd for $\text{C}_{28}\text{H}_{25}\text{NO}$ (391.50): C, 85.90; H, 6.44; N, 3.58; Found C, 85.68; H, 6.50; N, 3.49.

4.3.6. *E*-2-[3-(2-Methyl)indolyl-*p*-methylphenylmethyl]-5-*p*-methylphenylmethylenecyclopentanone (**3f**). (Entry 6 in Table 2): White solid; yield; IR (KBr): 3410 (N–H), 3022 (ArC–H), 2940, 1715 (C=O), 1612 (C=C), 1495, 1430, 1240, 1012, 750 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 7.74 (br. s, 1H, N–H), 6.82–7.25 (m, 13H, Ar–H and C=C–H), 4.88 (d, 1H, J = 4.2 Hz, H- β), 2.78–2.82 (m, 1H, H-2), 2.35 (s, 3H, Me), 2.27–2.31 (m, 2H, H₂-4), 2.25 (s, 6H, 2Me), 2.13–2.19 (m, 1H, H-3), 1.66–1.70 (m, 1H, H-3); Anal. Calcd for $\text{C}_{30}\text{H}_{29}\text{NO}$ (419.56): C, 85.88; H, 6.97; N, 3.34; Found C, 86.01; H, 7.11; N, 3.29.

4.3.7. *E*-2-[3-(2-Methyl)indolyl-*p*-chlorophenylmethyl]-5-*p*-chlorophenylmethylenecyclopentanone (**3g**). (Entry 7 in Table 2): White solid; IR (KBr): 3396 (N–H), 3052 (ArC–H), 2953, 1706 (C=O), 1623 (C=C), 1490, 1459, 1237, 1091, 742 cm^{-1} ;

^1H NMR (300 MHz, CDCl_3): δ 7.78 (br. s, 1H, N–H), 7.17–7.40 (m, 11H, Ar–H and C=C–H), 7.65 (t, 1H, J = 6.9 Hz), 6.94 (t, 1H, J = 7.8 Hz), 4.74 (d, 1H, J = 6.6 Hz, H- β), 3.47–3.51 (m, 1H, H-2), 2.42 (s, 3H, Me), 2.70–2.75 (m, 2H, H₂-4), 2.26–2.30 (m, 1H, H-3), 1.81–1.85 (m, 1H, H-3); Anal. Calcd for $\text{C}_{28}\text{H}_{23}\text{NCl}_2\text{O}$ (460.39): C, 73.05; H, 5.04; N, 3.04; Found C, 73.22; H, 4.90; N, 3.17.

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