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Regioselective Friedel–Crafts acetylation of 5-hydroxyindole derivatives: synthesis of 4H–pyranoindol–4–one derivatives

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Abstract. The Friedel-Crafts acetylation of 5–hydroxyindole derivatives 1a–c regioselectively produced 6–acetyl–5–hydroxy–indole derivatives 2a–c which were condensed with cinnamic acid using $POCl_3$ and dry pyridine to afford 5–cinnamoyloxy–6–acetyl–indoles 3a–c. These upon Baker–Venkataraman transformation furnished 6–cinnamoylacetyl–5–hydroxyindoles 4a–c which were cyclised separately with AcOH/HCl and Ac_2O/AcONa to 4H–pyrano–(2,3–*f*)indol–4–one derivatives 5a–c and 6a–c respectively.

Keywords. Friedel-Crafts acetylation of 5–hydroxyindole derivatives; Baker-Venkataraman transformation; 4H–pyrano(2,3–*f*)indol–4–one derivatives.

1. Introduction

Indoles (Shen *et al* 1963; Glennon 1987, 1988) and γ-pyrones (Cairns *et al* 1972; Atwell *et al* 1990) are important heterocycles owing to their widespread use in biological and pharmaceutical fields. The literature survey revealed that 4H–pyranoindol–4–ones, reported so far carry the fusion of γ-pyrone ring on the side b of the indole moiety. Practically there are no reports on the γ-pyranoindoles involving the fusion of γ-pyrone ring to the benzenoid part of the indole moiety. Hence, it was thought of considerable interest to build the γ-pyrone ring on the benzenoid part of the indole nucleus to produce hitherto unknown title compounds.

2. Results and discussion

The starting materials of choice for the synthesis of title compounds were 6–acetyl–5–hydroxyindoles (2a–c) and these were obtained by the Friedel–Crafts acetylation of 5–hydroxy–indoles 1a–c with acetyl chloride and anhydrous aluminium chloride in freshly distilled nitrobenzene. Though there were two reactive sites (C–4 and C–6 ortho to C–5 OH), the acetyl group regioselectively entered at C–6 position which is also in conformity with the earlier report (Suehiro and Niitsu 1971).

The IR spectrum of 1–phenyl–2–methyl–3,6–diacetyl–5–hydroxyindole (2a) showed diffused stretching bond at 2720 cm^{-1} due to C–5 OH. The shift of OH band

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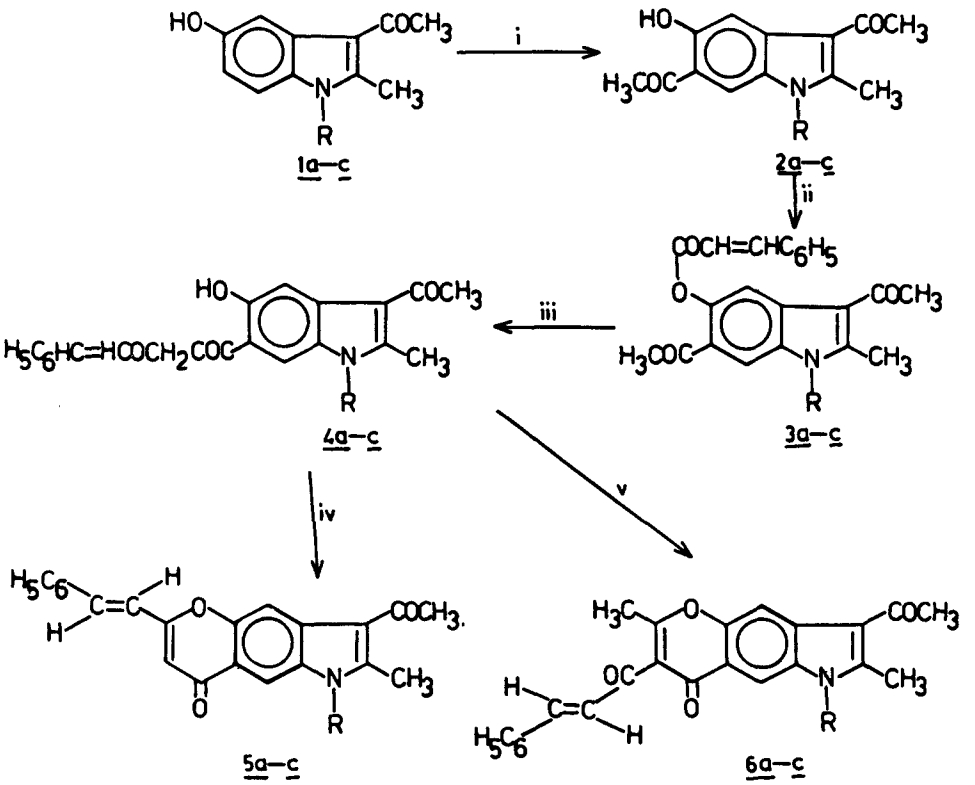
to such a lower field was due to the strong intramolecular hydrogen bonding between OH and C–6 $COCH_3$ (Nakanishi and Solomon 1977). A strong stretching band due to C–6 and C–3 acetyl groups was observed at 1625 cm^{-1}. Its PMR spectrum showed singlets at δ 7·30 and 7·52 corresponding to C–7 and C–4 protons confirming the entry of acetyl group at C–6 position.

3,6–Diacetyl–5–hydroxyindoles (2a–c) were condensed with cinnamic acid in dry pyridine using phosphorus oxychloride as condensing agent (Wadodkar and Marathey 1972) to produce 3,6–diacetyl–5–cinnamoyloxyindole derivatives (3a–c) which were further subjected to Baker–Venkataraman transformation (Baker 1933; Mahal and Venkataraman 1933) with dry pyridine and KOH to afford 6–cinnamoylacetyl–5–hydroxyindole derivatives (4a–c). Cyclodehydration of these 6–cinnamoylacetyl–5–hydroxyindoles (4a–c) with glacial acetic acid containing few drops of conc HCl (Gaddad and Wadodkar 1985) afforded the desired 2–styryl–4H–pyrano (2,3–*f*) indol–4–one derivatives (5a–c). When acetic anhydride and freshly fused sodium acetate were used as cyclising agent (Sammes and Wallace 1975) for (4a–c), 2–methyl–3–cinnamoyl–4H–pyrano(2, 3–*f*)indol–4–one derivatives (6a–c) were obtained (scheme 1).



Scheme 1.

The analytical and spectral data of these compounds confirmed the structures assigned. The IR spectrum of 2–styryl–6–phenyl–7–methyl–8–acetyl–4H–pyrano (2,3–*f*)indol–4–one (5a) exhibited stretching bands at 1630 cm^{-1} due to the carbonyls of γ–pyrone ring and C–8 acetyl function respectively. Its PMR showed singlets at δ6·39 and 8·44 corresponding to C–3 proton of γ–pyrone ring and C–5 proton (Mathis and Goldstein 1964) respectively. The orientation of vinylic proton in the styryl group was *trans* which was evident from the coupling constant ($J = 12$ Hz) for α–vinylic proton displayed at δ7·24 as doublet. The β-vinylic proton was found merged in the aromatic proton signals (multiplet from δ7·38 to 7·86). The mass spectrum of (5a) showed molecular ion peak at *m/z* 419. The cleavage of methyl from C–8–$COCH_3$ of the molecular ion resulted in a base peak at *m/z* 404. The successive loss of CO and $HC\equiv C-CH=CHC_6H_5$ from the base peak produced peaks at *m/z* 376 and 248 respectively. The peaks observed at *m/z* 291 and 276 were obtained from M^+ by the successive loss of $HC\equiv C-CH=CHC_6H_5$ and CH_3 respectively. The peak at *m/z* 248 might have been obtained from fragment *m/z* 276 by the loss of CO.

The IR spectrum of 2,7–dimethyl–2–cinnamoyl–6–phenyl–8–acetyl–4H–pyrano (2,3–*f*)indol–4–one(6a) displayed carbonyl stretching absorption bands due to γ–pyrone, C–3 cinnamoyl and C–8 acetyl groups at 1650 cm^{-1}, 1635 cm^{-1} and 1615 cm^{-1} respectively. A doublet displayed at δ8·32 with $J = 12$ Hz for β-vinylic proton of cinnamoyl group in the PMR spectra of (6a) indicated trans-orientation of vinylic protons. The α–vinylic proton signal merged with aromatic protons' signals appeared as multiplet from δ7·22 to 7·9. The mass spectrum of this compound showed molecular ion peak at *m/z* 461, which was also base peak. The successive loss of C_6H_5, $CH\equiv CH$ and CO from M^+ produced peaks at *m/z* 384, 358 and 330 respectively. The peaks observed at *m/z* 446, 418 and 248 were obtained by the successive loss of CH_3, CO and $H_3C-C\equiv COCH=CHC_6H_5$ respectively from M^+. The molecular ion might have also lost $H_3C-C\equiv C-COCH=CHC_6H_5$, CH_3 and CO successively to generate fragments at *m/z* 291, 276 and 248 respectively.

3. Experimental

Melting points were taken in open capillary tubes and are uncorrected. IR spectra were obtained on a Perkin-Elmer 881. PMR spectra were recorded on GE NMR–300 MHz and mass spectra on Autospec EI spectrometer. 1–Substituted–2–methyl–3–acetyl–5–hydroxyindoles (1a–c) were prepared by the reported procedure (Grinev *et al* 1966). General procedures for the synthesis of various new compounds mentioned in the present paper have been described below.

3.1 *1–Phenyl–2–methyl–3,6–diacetyl–5–hydroxyindole (2a)*

To a suspension of 1–phenyl–2–methyl–3–acetyl–5–hydroxy–indole 1a (3·939 g, 0·015 mol) in freshly distilled nitrobenzene (50 ml) was added acetyl chloride (2·36 g, 0·0375 mol) in portions as rapidly as it dissolved. The reaction mixture was heated for three hours on a steam bath and left overnight. It was poured into ice water (200 ml) containing conc.HCl (40 ml) and then subjected to steam distillation to remove nitrobenzene. The solid mass that separated on cooling to room temperature was filtered and recrystallised from dioxane to afford the desired 1–phenyl–2–methyl–3,6–diacetyl–5–hydroxyindole.

Table 1. Characterisation data of compounds.

Compd.	Yield (%)	MP (°C)	Mol. formula	Found (Calc). (%) C	H	N
2a	59	197–98	$C_{19}H_{17}NO_3$	74·4 (74·3)	5·5 (5·6)	4·7 (4·6)
2b	53	237–38	$C_{19}H_{16}ClNO_3$	66·7 (66·8)	4·7 (4·7)	4·2 (4·1)
2c	58	221–22	$C_{20}H_{19}NO_3$	74·9 (74·8)	5·9 (5·9)	4·5 (4·4)
3a	82	211–12	$C_{28}H_{23}NO_4$	76·9 (76·9)	5·4 (5·3)	3·4 (3·2)
3b	83	207–08	$C_{28}H_{22}ClNO_4$	71·3 (71·3)	4·8 (4·7)	3·1 (3·0)
3c	80	200–01	$C_{29}H_{25}NO_4$	77·1 (77·1)	5·7 (5·6)	3·3 (3·1)
4a	69	241–42	$C_{28}H_{23}NO_4$	76·9 (76·9)	5·4 (5·3)	3·3 (3·2)
4b	72	312–13	$C_{28}H_{22}ClNO_4$	71·4 (71·3)	4·8 (4·7)	3·1 (3·0)
4c	70	277–78	$C_{29}H_{25}NO_4$	77·2 (77·1)	5·7 (5·6)	3·3 (3·1)
5a	72	295–96	$C_{28}H_{21}NO_3$	80·3 (80·2)	5·2 (5·1)	3·5 (3·3)
5b	64	318–19	$C_{28}H_{20}ClNO_3$	74·0 (74·1)	4·5 (4·4)	3·2 (3·1)
5c	67	308–09	$C_{29}H_{23}NO_3$	80·4 (80·3)	5·4 (5·3)	3·4 (3·2)
6a	76	248–49	$C_{30}H_{23}NO_4$	78·2 (78·1)	4·9 (5·0)	3·2 (3·0)
6b	59	315–16	$C_{30}H_{22}ClNO_4$	72·8 (72·7)	4·5 (4·5)	3·0 (2·8)
6c	61	300–01	$C_{31}H_{25}NO_4$	78·4 (78·3)	5·4 (5·3)	3·1 (3·0)

Solvents used for crystallisation were benzene for 6a and 6c, DMF for 4b, 4c, 5a, 5b and 6b and dioxan for rest of the compounds.

IR(Nujol); νcm^{-1}; 2720 (OH, diffused); 1625 (acetyl carbonyl). PMR ($CDCl_3$/TMS):δ: 2·52(*s*, 3H, C–3 $COCH_3$); 2·58(*s*, 3H, C–6 $COCH_3$); 2·70 (*s*, 3H, C–2 CH_3); 7·30 (*s*, 1H, C–7H); 7·52 (*s*, 1H, C–4H); 7·35–7·75 (*m*, 5H, ArH); 12·1 (*s*, 1H, OH).

3.2 *1–Phenyl–2–methyl–3,6–diacetyl–5–cinnamoyloxyindole (3a)*

To a stirred solution of 1–phenyl–2–methyl–3,6–diacetyl–5–hydroxyindole 2a (1·537g, 0·005 mol) and cinnamic acid (0·815g, 0·0055 mol) in dry pyridine (20 ml) was added dropwise phosphorus oxychloride (0·3 ml) with constant stirring and external cooling. The reaction mixture was stirred further for two hours at 50–60° and then poured into crushed ice (50 g). It was neutralised with dilute HCl to remove pyridine

and the separated solid was filtered, successively washed with water, aqueous sodium carbonate (10%) and water. The dried sample was crystallised from dioxane as colourless needles.

IR (Nujol):$\nu\, cm^{-1}$; 1710(C–5 ester carbonyl); 1660(C–6 acetyl carbonyl); 1620(C–3 acetyl carbonyl).
PMR ($CDCl_3$/TMS):δ:2·52(*s*, 3H, C–3 $COCH_3$); 2·62(*s*, 3H, C–6 $COCH_3$); 2·72(*s*, 3H, C–2 CH_3); 6·76(*d*, $J = 12$ Hz, 1 H, α–vinylic H); 7·96(*d*, $J = 12$ Hz, 1H, β–vinylic H); 7·84(*s*, 1H, C–4H); 7·30–7·70(*m*, 11H, ArH).

3.3 *1–Phenyl–2–methyl–3–acetyl–6–cinnamoylacetyl–5–hydroxyindole (4a)*

A mixture of 1–phenyl–2–methyl–3,6–diacetyl–5–cinnamoyloxyindole 3a (1·312 g, 0·003 mol), powered potassium hydroxide (0·505 g, 0·009 mol) and dry pyridine (20 ml) was stirred for two hours at room temperature. The reaction mixture was then poured into crushed ice and neutralised with dil.HCl. The separated solid was filtered, washed with sodium bicarbonate solution (10%), water and crystallised from dioxane as orange needles.

IR (Nujol):$\nu\, cm^{-1}$:1625(C–3 acetyl and C–6 cinnamoylacetyl carbonyls).
PMR (DMSO–d_6/TMS):δ:2·63(*s*, 3H, C–3 $COCH_3$); 2·73(*s*, 3H, C–2 CH_3); 3·7(*s*, 2H, CH_2); 6·95(*s*, 1H, C–7H); 7·1(*d*, $J = 12$ Hz, 1H, α–vinylic H); 7·46–7·96(*m*, 12H, ArH and β–vinylic H); 11·06(*s*, 1H, OH).

3.4 *2–Styryl–6–phenyl–7–methyl–8–acetyl–4H–pyrano (2,3–f)indol–4–one (5a)*

To a suspension of 1–phenyl–2–methyl–3–acetyl–6–cinnamoylacetyl–5–hydroxyindole derivative 4a (0·437 g, 0·001 mol) in glacial acetic acid (10 *ml*) was added 1 drop of conc·HCl and the mixture was heated at reflux for one hour. After attaining room temperature, the reaction mixture was poured into ice-cold water (20 *ml*). The separated solid was filtered, washed with water, dried and crystallised from dimethyl formamide as yellow granules.

IR(Nujol):$\nu\, cm^{-1}$; 1630(γ–pyrone); 1610(C–8 acetyl).
PMR: (DMSO–d_6/TMS):δ; 2·6(*s*, 3H, C–8 $COCH_3$); 2·7(*s*, 3H, C–7 CH_3); 6·39(*s*, 1H, C–3H); 8·44(*s*, 1H, C–5H); 7·24(*d*, $J = 12$ Hz, 1H, α–vinylic H); 7·38–7·86(*m*, 12H, ArH and β–vinylic H).
Mass spectra:*m/z*(%); 419 ($[M]^+$,92); 404($[M-CH_3]^+$, 100); 376($[M-COCH_3]^+$, 12); 291($[M-C_{10}H_8]^+$, 13); 276($[M-C_{11}H_{11}]^+$, 10); 248($[M-C_{12}H_{11}O]^+$, 8).

3.5 *2,7–Dimethyl–3–cinnamoyl–6–phenyl–8–acetyl–4H–pyrano(2,3–f)indole–4–one (6a)*

A mixture of 1–phenyl–2–methyl–3–acetyl–6–cinnamoylacetyl–5–hydroxyindole 4a (0·437 g, 0·001 mol), freshly fused soldium acetate (2·5 g) and acetic anhyride (10 ml) was heated at 150–60° in an oil bath for two hours. It was cooled to room temperature and poured into crushed ice (25 g). The separated solid was filtered, washed with water and crystallised from benzene as colourless flakes.

IR (Nujol):$\nu\, cm^{-1}$; 1650(γ–pyrone); 1635(C–3 cinnamoyl); 1615(C–8 acetyl).

PMR ($CDCl_3$/TMS):δ: 2·58(*s*, 3H, C–2 CH_3); 2·63 (*s*, 3H, C–8 $COCH_3$); 2·77(*s*, 3H, C–7 CH_3); 8·32(*d*, J = 12 Hz, 1H, β–vinylic H); 7·22–7·9(*m*, 13H, ArH and α-vinylic H).

Mass spectra:m/z(%); 461($[M]^+$, 100); 466($[M-CH_3]^+$, 37); 418($[M-COCH_3]^+$, 28); 384($[M-C_6H_5]^+$, 50); 358($[M-C_8H_7]^+$, 13); 330($[M-C_9H_7O]^+$, 3); 291 ($[M-C_{12}H_{10}O]^+$, 24); 276($[M-C_{13}H_{13}O]^+$, 15); 248($[M-C_{14}H_{13}O_2]^+$, 12).

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