A New and Facile Iodine(III)-Mediated Approach for the Regioselective Alkoxylation of 2,5-Dihydroxyacetophenone

Om Prakash,* Rashmi Pundeer, Harpreet Kaur

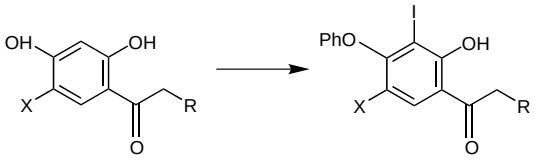
Chemistry Department, Kurukshetra University, Kurukshetra, Haryana 136119, India
Fax +91(1744)238277; E-mail: oprakash50@sify.com

Received 21 July 2003; revised 25 September 2003

Abstract: Oxidation of 2,5-dihydroxyacetophenone with iodobenzene diacetate (IBD) in different alcohols leads to regioselective alkoxylation, thereby providing a new and convenient route for the synthesis of 6-alkoxy-2,5-dihydroxyacetophenones.

Key words: hypervalent iodine, regioselective alkoxylation, 2,5-dihydroxyacetophenone , iodobenzene diacetate , oxidations

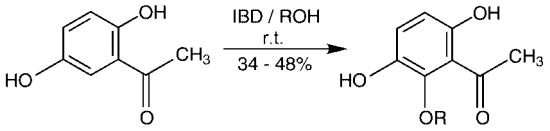
In connection with our ongoing studies on the use of organoiodine(III) reagents in organic synthesis,[1,2] we have earlier reported that hypervalent iodine oxidation of *m*-dihydric phenolic compounds bearing electron-withdrawing ketonic moieties such as $COCH_2R$ leads to a novel route for the synthesis of *o*-iodo ethers (Scheme 1).[3] The reaction, providing a unique application of organohypervalent iodine reagents, occurs via rearrangement of iodonium ylides leaving the enolizable ketone moiety intact. In continuation of these encouraging studies, we have now examined the oxidation of 2,5-dihydroxyacetophenone (**1**) with iodobenzene diacetate [IBD or $PhI(OAc)_2$] in different alcohols.



Scheme 1

The aim was to ascertain the influence of the change of position of the phenolic hydroxy group[1] on the course of this reaction and hopefully to develop a new and facile approach for the synthesis of 6-alkoxy-2,5-dihydroxyacetophenones **2** which have potential use in synthesis. Thus, **1** was treated with IBD (1.1 equiv) in methanol at room temperature. The usual work-up, followed by column chromatographic separation of the crude

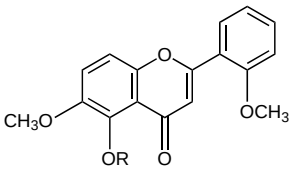
product afforded 2,5-dihydroxy-6-methoxyacetophenone (**2a**) in 48% yield. To test the scope of this method, **1** was subjected to oxidation with IBD in several alcohols, namely, ethanol, propan-1-ol, propan-2-ol, butan-1-ol, 2-methoxyethanol and 2-ethoxyethanol. The reaction, indeed, gave the corresponding 6-alkoxy derivatives **2a**–**g** in moderate yields (Scheme 2).



2a, R=CH_3
2b, R=C_2H_5
2c, R=*n*-C_3H_7
2d, R=*i*-C_3H_7
2e, R=*n*-C_4H_9
2f, R=$CH_2CH_2OCH_3$
2g, R=$CH_2CH_2OCH_2CH_3$

Scheme 2

It is worthwhile to note that compounds **2a**–**g** accessible through the present study are useful precursors for the synthesis of several unusually oxygenated synthetic and natural flavone derivatives. For example, **2a** has recently been used as a key starting material in the synthesis of 5-hydroxy-6,2′-dimethoxyflavone (**3a**) and 5,6,2′-trimethoxyflavone (**3b**), isolated from the farinose leaf exudates of *Primula denticulata*[4] species and *Sargentia greggi*,[5] respectively (Figure 1). However, apart from the single report of Wollenweber et al.[6] on the Elbs oxidation of 2-hydroxy-6-methoxyacetophenone leading to the formation of **2a** (38% yield), no efforts have been made to develop general synthetic approach(s) for **2**.

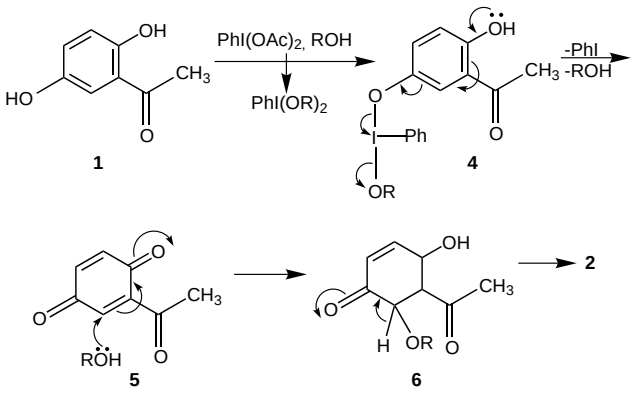


3a, R=H
3b, R=CH_3

Figure 1 Structures of flavones **3a**,**b**

Mechanistically, a plausible pathway for the transformation **1** → **2** probably involves the formation of O–I(III) intermediate **4** by the ligand exchange between the phenolic hydroxyl group and $PhI(OR)_2$[7] (generated from IBD-ROH). The reductive elimination of iodobenzene leads to **5** which on attack by an alcohol gives the corresponding 6-alkoxy-2,5-dihydroxyacetophenones **2** (Scheme 3).

SYNTHESIS 2003, No. 18, pp 2768–2770
Advanced online publication: 05.11.2003
DOI: 10.1055/s-2003-42461; Art ID: T07103SS



Scheme 3

The structure of all new alkoxy derivatives **2c**, **2f** and **2g** were confirmed by spectral data (IR, ^{1}H NMR and MS) and elemental analysis, whereas the products **2a**, **2b**, **2d** and **2e** already known in literature were identified by comparison of their melting points, IR and ^{1}H NMR spectra.

In conclusion, the new I(III)-mediated approach not only reports a first convenient method for the regioselective alkoxylation of 2,5-dihydroxyacetophenone, but also offers an alternative simple synthesis of natural flavones **3a** and **3b** via **2a**.

Melting points were taken in open capillaries and are not corrected. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument using TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer 1800 IR spectrophotometer. Mass spectra were recorded on a 70 eV mass spectrometer. 2,5-Dihydroxyacetophenone was prepared according to the literature method starting from hydroquinone.[8]

Alkoxylation of 2,5-Dihydroxyacetophenone (1); General Procedure

To a suspension of 2,5-dihydroxyacetophenone (**1**; 1.52 g, 10 mmol) in the appropriate alcohol (15 mL) was added IBD (4.31 g, 11 mmol) in portions. The reaction mixture was stirred at r.t. and the progress of the reaction was monitored by TLC. After stirring for 2 h,[9] the solvent was evaporated in vacuo to give a crude product containing a mixture of 6-alkoxy derivative, iodobenzene and the starting material. Pure 6-alkoxy-2,5-dihydroxyacetophenone **2** was obtained by column chromatographic separation on a column of silica gel using EtOAc–petroleum ether (bp 35–60 °C) as eluent.

6-Methoxy-2,5-dihydroxyacetophenone (2a)
Yield: 870 mg (48%); mp 86–87 °C (Lit.[10] mp 90 °C).

6-Ethoxy-2,5-dihydroxyacetophenone (2b)
Yield: 900 mg (46%); mp 100 °C (Lit.[10] mp 103 °C).

6-Propoxy-2,5-dihydroxyacetophenone (2c)
Yield: 880 mg (42%); mp 66–68 °C.

IR (Nujol): 3300 (O–H), 1633 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.08 (t, *J* = 7.5 Hz, 3 H, $OCH_2CH_2CH_3$), 1.81–1.91 (m, 2 H, $OCH_2CH_2CH_3$), 2.73 (s, 3 H, $COCH_3$), 3.84 (t, *J* = 7.5 Hz, 2 H, $OCH_2CH_2CH_3$), 5.10 (s, 1 H, C5-OH), 6.70 (d, *J* = 9.0 Hz, 1 H, H-3), 7.21 (d, *J* = 9.0 Hz, 1 H, H-4), 11.82 (s, 1 H, C2-OH).

HRMS: *m*/*z* calcd for $C_{11}H_{14}O_4$: 210.089209; found: 210.089648.

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.66. Found: C, 63.02; H, 6.73.

6-Isopropoxy-2,5-dihydroxyacetophenone (2d)
Yield: 780 mg (37%); mp 90 °C (Lit.[10] mp 90–92 °C).

6-*n*-Butoxy-2,5-dihydroxyacetophenone (2e)
Yield: 760 mg (34%); mp 61 °C (Lit.[10] mp 62.5–63.5 °C).

6-(2-Methoxyethoxy)-2,5-dihydroxyacetophenone (2f)
Yield: 1.01 g (45%); mp 36 °C.

IR (Nujol): 3312 (O–H), 1635 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.73 (s, 3 H, $COCH_3$), 3.56 (s, 3 H, $OCH_2CH_2OCH_3$), 3.73–3.76 (m, 2 H, $OCH_2CH_2OCH_3$), 4.06–4.09 (m, 2 H, $OCH_2CH_2OCH_3$), 6.70 (d, *J* = 9.0 Hz, 1 H, H-3), 7.13 (d, *J* = 9.3 Hz, 1 H, H-4), 12.02 (s, 1 H, C2-OH).

HRMS: *m*/*z* calcd for $C_{11}H_{14}O_5$: 226.084124; found: 226.084011.

Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.19. Found: C, 58.52; H, 6.26.

6-(2-Ethoxyethoxy)-2,5-dihydroxyacetophenone (2g)
Yield: 940 mg (39%); mp 34 °C.

IR (Nujol): 3300 (O–H), 1637 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.34 (t, *J* = 7.0 Hz, 3 H, $OCH_2CH_2OCH_2CH_3$), 2.74 (s, 3 H, $COCH_3$), 3.66–3.80 (m, 4 H, $OCH_2CH_2OCH_2CH_3$), 4.07–4.10 (m, 2 H, $OCH_2CH_2OCH_2CH_3$), 6.70 (d, *J* = 8.8 Hz, 1 H, H-3), 7.13 (d, *J* = 8.9 Hz, 1 H, H-4), 12.03 (s, 1 H, C2-OH).

HRMS: *m*/*z* calcd for $C_{12}H_{16}O_5$: 240.099774; found: 240.099643.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 60.00; H, 6.66. Found: C, 59.86; H, 6.79.

Acknowledgment

We are thankful to DRDO (ERIP/ER/0103294/M/01), New Delhi for financial assistance.

References

(1) (a) Prakash, O.; Kaur, H.; Batra, H.; Rani, N.; Singh, S. P. *J. Org. Chem.* **2001**, *66*, 2019. (b) Prakash, O.; Rani, N.; Sharma, P. K. *Synlett* **1994**, 221. (c) Prakash, O. *Aldrichimica Acta* **1995**, *28*, 63.
(2) (a) Moriarity, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365. (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: New York, **1997**. (c) Varma, R. S.; Dhaiya, R.; Saini, R. K. *Tetrahedron Lett.* **1997**, *38*, 7029. (d) Ochiai, M. In *Chemistry of Hypervalent Compounds*; Akiba, K., Ed.; VCH Publishers: Weinheim, **1999**, Chap. 13, 359–387. (e) Koser, G. F. *Aldrichimica Acta* **2002**, *34*, 89. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.
(3) (a) Prakash, O.; Tanwar, M. P.; Goyal, S.; Pahuja, S. *Tetrahedron Lett.* **1992**, *33*, 6519. (b) Prakash, O.; Sharma, V.; Tanwar, M. P. *Can. J. Chem.* **1999**, *77(7)*, 1191.
(4) Wollenweber, E. *Biology and Chemistry of Plant Trichomes*; Rodriguez, E.; Healey, P. L.; Mehta, I., Eds.; Plenum Press: New York, **1984**, 53.
(5) Meyer, B. N.; Wall, M. E.; Wani, M. C.; Taylor, H. L. *J. Nat. Prod.* **1985**, *48*, 952.
(6) Wollenweber, E.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1990**, *29*, 633.

(7) (a) Schardt, B. C.; Hill, C. L. *Inorg. Chem.* **1983**, *22*, 1563. (b) Makarchenko, S. S.; Merkushev, E. B.; Shakirov, M. M.; Rezvukhin, A. I. *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk* **1978**, 125; *Chem. Abstr.* **1978**, *89*, 162876.
(8) Amin, G. C.; Shah, N. M. *Org. Synth., Coll. Vol. 3*; Wiley: New York, **1955**, 280.
(9) There was no significant increase in the yields by running the reaction for longer time or by adding more IBD.
(10) Farina, F.; Valderrama, J. *Synthesis* **1971**, 315.