Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 9065–9067
Tetrahedron Letters

A novel and facile iodine(III)-mediated approach for C(5)-acetoxylation of 6-hydroxyflavone and 6-hydroxyflavanones

Om Prakash,* Harpreet Kaur, Vijay Sharma, Vikas Bhardwaj and Rashmi Pundeer

Department of Chemistry, Kurukshetra University, Kurukshetra, Haryana, India

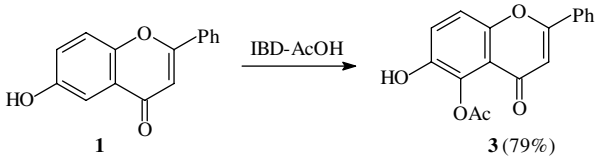
Received 3 August 2004; revised 27 September 2004; accepted 6 October 2004
Available online 22 October 2004

Abstract—Oxidation of 6-hydroxyflavone **1** and 6-hydroxyflavanones **2a–c** with iodobenzene diacetate (IBD) in acetic acid leads to regioselective acetoxylation, thereby providing a novel and convenient route for the synthesis of 5-acetoxylated products.
© 2004 Published by Elsevier Ltd.

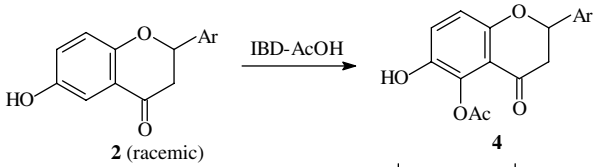
In recent years, considerable attention has been devoted to the use of hypervalent iodine reagents in organic synthesis.[1] Particularly, organoiodine reagents such as iodobenzene diacetate (IBD),[2] iodobis(trifluoro)acetate (IBTA)[3] and [hydroxy(tosyloxy)iodo] benzene (HTIB, Koser's Reagent)[4] have been used as versatile oxidizing agents. Some of the notable applications are: α-functionalization of carbonyl compounds,[5] oxidation of phenolic compounds,[6a–6f] generation of alkoxy,[7] aminyl[8] and azidyl radicals,[9] synthesis of heterocyclic compounds,[10] etc.

Previous investigations from our laboratory have shown that IBD, HTIB, etc. find interesting applications in flavonoids.[11–18] Various useful I(III) mediated transformations developed by us include (i) dehydrogenation of flavanones to flavones;[12] (ii) oxidative rearrangement of flavanonesto isoflavones[13] and 2-aryl-2,3-dihydrobenzofuran carboxylate;[14] (iii) C(3)-hydroxylation of flavanones to *cis*/*trans* 3-hydroxyflavanones;[15,16] (iv) C(3)-hydroxylation of flavones to flavonols[17] and (v) formation of iodonium ylides and *o*-iodoethers from 7-hydroxyflavone.[18] Continuing these studies and keeping in view the biogenetic and synthetic importance of nuclear oxidation of flavones and flavanones,[19] we have investigated hypervalent iodine oxidation of 6-hydroxyflavone **1** and 6-hydroxyflavanones **2**. The study was aimed at illustrating the application of iodine(III)-mediated phenolic oxidation for effecting nuclear oxygenation of **1** and **2**.

Thus, **1** was treated with IBD (1.1 equiv) in acetic acid with stirring at room temperature for 2 h. Work-up followed by column chromatographic separation (9:1 pet. ether–ethyl acetate) of the crude product afforded a yellow crystalline solid. Analysis of the spectral properties of the product (IR, ^{1}H NMR, ^{13}C NMR) and elemental analysis established the novel formation of 5-acetoxy-6-hydroxyflavone **3** (Eq. 1).[20] Encouraged by this result, the reaction was examined with 6-hydroxyflavanones **2a–c** under similar conditions. Interestingly, flavanones showed an analogous reactivity pattern and gave the corresponding 5-acetoxy-6-hydroxyflavanones **4a–c** as the sole products (Eq. 2).



1 **3** (79%) (1)



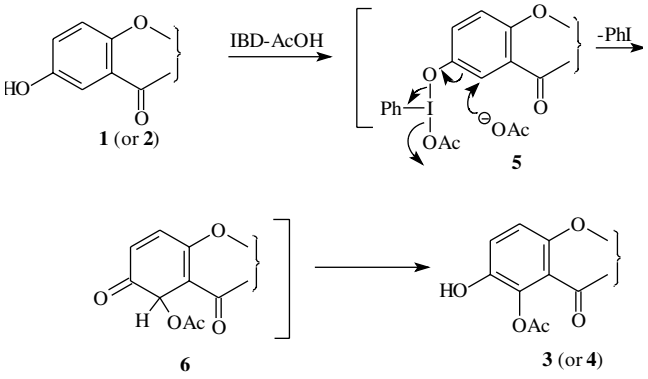
2 (racemic) **4**

2,4	Ar	Yield
a	C_6H_5	53%
b	C_6H_4Me-4	56%
c	C_6H_4OMe-4	63%

(2)

Keywords: Acetoxylation; 6-Hydroxyflavone; Iodobenzene diacetate; Regioselective; 6-Hydroxyflavanones.
* Corresponding author. Tel.: +91 1744 234366; fax: +91 1744 238277; e-mail addresses: chem@granth.kuk.ernet.in; oprakash11@yahoo.co.in

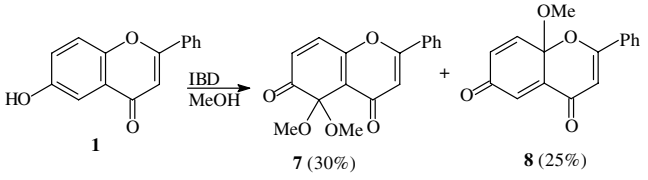
0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.10.037



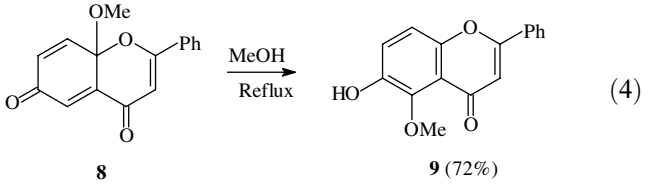
Scheme 1.

The oxidative conversion **1** → **3** (and **2** → **4**) probably involves the formation of O-I(III) intermediate **5** by ligand exchange between the phenolic hydroxyl group and $PhI(OAc)_2$ (Scheme 1). Nucleophilic attack of AcO^- at position C(5) and reductive elimination of iodobenzene from intermediate **5** gives the desired product (**3** or **4**).

To extend the scope of the newly developed approach for the alkoxylation[21] of **1** (and **2**), the reaction was carried out with various alcohols. However, the reaction did not follow a similar trend. For example, treatment of **1** with IBD–MeOH resulted in the formation of a mixture of 5,5-dihydro-4,6-dioxo-5,5-dimethoxy-2-phenyl-4*H*-benzo[*b*]pyran **7** (30%) (yellow orange crystals) and 6,8a-dihydro-4,6-dioxo-8a-methoxy-2-phenyl-4*H*-benzo[*b*]pyran **8** (25%) (bright yellow needles) (Eq. 3).[20] Refluxing the methanolic solution of **8** for 4 h led to the formation of 5-methoxy-6-hydroxyflavone **9** (Eq. 4).[21] This is an interesting observation as the overall outcome of this two step reaction sequence is 5-methoxylation of **1**.



(3)



(4)

Finally, noteworthy features of the present study are:

- The study, involving phenolic group oxidation using IBD–AcOH, offers a novel and facile route to **3** (and **4**). The 5-hydroxylated derivative of **4c** is a natural product, isolated from the plant *Artemesia campestris maritime*.[22]
- The enolizable ketonic moiety present in compounds **2a**–**c** remains unaffected under the reaction conditions which generally bring about reaction of enolizable ketones.[23]
- The lack of ylide formation in the case of **1** (and **2**) can be accounted for by the absence of the necessary skeletal structure required for this reaction (as observed in 7-hydroxyflavone).[18]
- There exists the possibility of using this reaction as a general approach for regioselective oxygenation of 6-hydroxyflavone and 6-hydroxyflavanones.

Acknowledgement

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

References and notes

1. (a) Varvoglis, A. *The Organic Chemistry of Polycoordinated Iodine*; VCH: New York, 1992; (b) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic: London, 1997; (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523.
2. (a) Varvoglis, A. *Chem. Soc. Rev.* **1981**, *10*, 377; (b) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244; (c) Ramsden, C. A. *Chem. Soc. Rev.* **1994**, *23*, 111.
3. (a) Moreno, I.; Tellitu, I.; Etayo, J.; SanMartin, R.; Domenguez, E. *Tetrahedron* **2001**, *57*, 5403; (b) Kita, Y.; Takada, T. *J. Org. Chem.* **1995**, *60*, 6499.
4. (a) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365; (b) Koser, G. F. *Aldrichim. Acta* **2001**, *34*, 89.
5. (a) Moriarty, R. M.; Prakash, O. *Acc. Chem. Res.* **1986**, *19*, 244; (b) Prakash, O.; Saini, N.; Tanwar, M. P.; Moriarty, R. M. *Contemp. Org. Synth.* **1995**, *2*, 121; (c) Moriarty, R. M.; Prakash, O. *Org. React.* **1999**, *54*, 273.
6. (a) Kita, Y.; Tohma, H.; Yakura, T. *Trends Org. Chem.* **1992**, *3*, 113; (b) Moriarty, R. M.; Prakash, O. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: New York, 2001; 57, p 327; (c) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891; (d) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1.* **1994**, 2047; (e) McKillop, A.; McLaren, L.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1386; (f) Wipf, P.; Kim, Y. *J. Org. Chem.* **1993**, *58*, 1649.
7. Ellwood, C. W.; Pattenden, N. G. *Tetrahedron Lett.* **1991**, *32*, 1591.
8. Rawal, V. H.; Iwasa, S. *Tetrahedron Lett.* **1996**, *37*, 2441.
9. Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406.
10. Moriarty, R. M.; Prakash, O. *Adv. Heterocycl. Chem.* **1998**, *69*, 1–84, Chapter 1.
11. Prakash, O. *Aldrichim. Acta* **1995**, *28*, 63.
12. Prakash, O.; Pahuja, S.; Moriarty, R. M. *Synth. Commun.* **1990**, *20*, 1417.
13. Prakash, O.; Pahuja, S.; Goyal, S.; Sawhney, S. N.; Moriarty, R. M. *Synlett* **1990**, 337.
14. Prakash, O.; Tanwar, M. P. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1168.
15. Prakash, O.; Pahuja, S.; Sawhney, S. N. *Indian J. Chem.* **1991**, *30B*, 1023.
16. Moriarty, R. M.; Prakash, O. *J. Org. Chem.* **1985**, *50*, 151.
17. Prakash, O.; Pahuja, S.; Tanwar, M. P. *Indian J. Chem.* **1994**, *33B*, 272.

18. (a) Mallik, U. K.; Mallik, A. K. *Indian J. Chem.* **1992**, *31B*, 696; (b) Prakash, O.; Sharma, V., unpublished results.
19. (a) Seshadri, T. R. *Proc. Indian Acad. Sci.* **1948**, *28A*, 1; (b) Sawhney, P. L.; Seshadri, T. R.; Thiruvengadam, T. R. *Proc. Indian Acad. Sci.* **1951**, *33A*, 11; (c) Seshadri, T. R.; Viswanadham, N. *Proc. Indian Acad. Sci.* **1951**, *33A*, 148; (d) Balakrishna, K. J.; Rao, N. P.; Seshadri, T. R. *Proc. Indian Acad. Sci.* **1951**, *33A*, 151.
20. Compound **3**: Yield: 79%; mp 183–184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.38 (s, 3H, OCOC*H*$_3$), 6.75 (s, 1H, C(3)-*H*), 7.02–7.05 (d, 1H, C(7)-*H*, J = 9.0 Hz), 7.37–7.40 (d, 1H, C(8)-*H*, J = 9.0 Hz), 7.51–7.61 (m, 3H, aromatic protons), 7.90–7.93 (m, 2H, C(7), C(8)-*H*), 12.81 (s, 1H, C(6)-O*H*, D_2O exchangeable); ^{13}C NMR ($CDCl_3$, 75 MHz, δ): 105.65, 106.75, 111.69, 126.54, 129.22, 131.03, 132.31, 133.53, 151.80, 153.85, 165.11, 168.96, 183.67; IR (Nujol, ν_{max}): 3433 (O–H str.), 1750 (C=O str.), 1656 (C=O str.), 1621 (C=C str.) cm^{-1}.
4a: Yield: 53%; mp 86–88 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.27 (s, 3H, OCOC*H*$_3$), 2.79–3.13 (m, 2H, C(3)-*H*), 5.40 (dd, 1H, C(2)-*H*, J = 13.2 Hz, 3.0 Hz), 6.45 (d, 1H, C(7)-*H*, J = 9.0 Hz), 7.13 (d, 1H, C(8)-*H*, J = 9.0 Hz), 7.33–7.39 (m, 5H, C(2)-Ph), 11.73 (s, 1H, C(6)-O*H*, D_2O exchangeable); IR (KBr, ν_{max}): 3467 (O–H str.), 1768 (C=O str.), 1653 (C=O str.).
4b: Yield: 56%; mp 110–112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.26 (s, 3H, OCOC*H*$_3$), 2.31 (s, 3H, C(3)-C*H*$_3$), 2.76–3.13 (m, 2H, C(3)-*H*), 5.36 (dd, 1H, C(2)-*H*, J = 13.2 Hz, 3.0 Hz), 6.43 (d, 1H, C(7)-*H*, J = 9.0 Hz), 7.11 (d, 1H, C(8)-*H*, J = 9.0 Hz), 7.18 (d, 2H, C(3)-*H*, C(5)-*H*, J = 7.5 Hz), 7.28 (d, 2H, C(2)-*H*, C(6)-*H*, J = 8.1 Hz), 11.74 (s, 1H, C(6)-O*H*, D_2O exchangeable); IR (KBr, ν_{max}): 3466 (O–H str.), 1762 (C=O str.), 1652 (C=O str.).
4c: Yield: 63%; mp 144–146 °C; ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.26 (s, 3H, OCOC*H*$_3$), 2.75–3.14 (m, 2H, C(3)-*H*), 3.77 (s, 3H, C(4)-OC*H*$_3$), 5.34 (dd, 1H, C(2)-*H*, J = 13.5 Hz, 3.0 Hz), 6.43 (d, 1H, C(7)-*H*, J = 9.0 Hz), 6.88–6.91 (d, 2H, C(3)-*H*, C(5)-*H*, J = 9.0 Hz), 7.11 (d, 1H, C(8)-*H*, J = 9.0 Hz), 7.32 (d, 2H, C(2)-*H*, C(6)-*H*, J = 8.4 Hz), 11.74 (s, 1H, C(6)-O*H*, D_2O exchangeable); IR (KBr, ν_{max}): 3508 (O–H str.), 1762 (C=O str.), 1652 (C=O str.).
All the products gave satisfactory elemental analyses.
21. Prakash, O.; Pundeer, R.; Kaur, H. *Synthesis* **2003**, 2768.
22. Rauter, A. P.; Branco, I.; Tostao, Z.; Pais, M. S.; Gonzalez, A. G.; Bermejo, F. *Phytochemistry* **1989**, *28*, 2173.
23. (a) Mizukami, F.; Ando, M.; Tanaka, T.; Imamura, J. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 335; (b) Andews, I.-P.; Lewis, N. J.; McKillop, A.; Wells, A. S. *Heterocycles* **1994**, *38*, 713; (c) Podolesov, B. *J. Org. Chem.* **1984**, *49*, 2644.