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A convenient one-pot synthesis of 7-hydroxy-isoflavones from resorcinol with substituted phenylacetic acids☆

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Abstract—A mild and highly efficient one-pot synthesis of 7-hydroxy-isoflavones is reported. The acylation of resorcinol with various phenyl acetic acids in molten zinc chloride affords an intermediate deoxybenzoin which without isolation is subjected to cyclization with *N*,*N*-dimethylformamide in the presence of boron trifluoride diethyl etherate and methanesulfonyl chloride to afford the 7-hydroxy-isoflavone without the formation of any by-product.

1. Introduction

Flavonoids and isoflavonoids are a diverse group of phenolic compounds produced by various higher plants[1] to protect themselves from environmental stress and are present in foods such as beans, cabbage, soya beans, grains and hops.

They are structurally similar to mammalian oestrogen and oestradiol, and have oestrogenic properties. Compounds in this class show a wide variety of biological activities such as anti-viral, anti-inflammatory, anti-bacterial, anti-fungal and anti-cancer.[2] Other potential areas of benefit include diabetes, osteoporosis, heart disease and cognitive function.

The antioxidant properties[3] of these molecules have been implicated as a reason for the above activities. We therefore became interested in these molecules to design drugs for antidiabetic activity. This encouraged us to investigate a simple synthesis of 4*H*-1-benzopyran-4-one derivatives.

The literature synthesis for isoflavones in general involves two steps wherein a phenol is reacted in the presence of a Lewis acid with phenylacetic acid to generate an intermediate deoxybenzoin **2**,[4] which is then cyclized with a one carbon electrophile. A convenient approach is that of Baker et al.[5] who used oxalyl chloride and pyridine as the cyclizing agent, whereas others have used ethyl formate,[6] triethyl orthoformate,[7] or carbon disulfide.[8] Deoxybenzoins have been utilized as starting materials in some reported methods but need to be prepared prior to the cyclization.[9] Long cyclization periods are another disadvantage, for example, with $POCl_3$ and DMF.[10] Also, additional hydroxy groups have to be protected.[8]

During the synthesis of 7-hydroxy-isoflavone via the two-step procedure where we utilized the crude deoxybenzoin, obtained by electrophilic substitution of resorcinol with phenylacetic acid using $ZnCl_2$[4] followed by cyclization with DMF and $MeSO_2Cl$ in BF_3OEt_2,[11] a by-product was isolated in an appreciable yield (~35%). The structure of by-product **4** was established by spectral analysis. Elemental analysis[13] and the molecular ion peak (M+1) at 357 suggested a molecular formula $C_{23}H_{16}O_4$. In the IR spectrum, there was a band at 1627 cm^{-1} corresponding to an α,β-unsaturated carbonyl. In the proton NMR spectrum, the proton *peri* to the carbonyl at C-5 appeared as an *ortho* coupled doublet at δ 8.30. The proton at C-2 appeared as a singlet at δ 7.98. The presence of these two protons suggested an isoflavone skeleton. However, in comparison with an isoflavone structure, the by-product had no *meta* coupled doublet at δ 6.79 for the C-8 proton, which suggested the attachment of a benzyl ketone at C-8. A two- proton singlet at δ 3.91 suggested the

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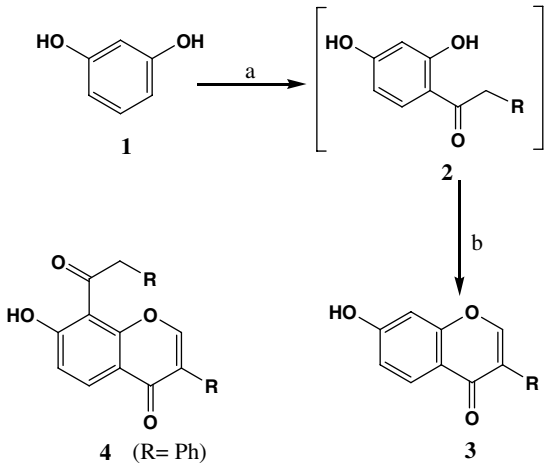

Scheme 1. Reagents and conditions: (a) $ZnCl_2$, RCH_2CO_2H, 120 °C and (b) DMF, BF_3OEt_2, 0 °C, $MeSO_2Cl$, 50–110 °C, 3 h.

Table 1. One-pot synthesis of 7-hydroxy-isoflavone derivatives **3a–e**

Product	R	Yield (%)	Mp (°C)
3a	C_6H_5	78	207–208
3b	*o*-$NO_2C_6H_4$	56	220–223
3c	*m*-ClC_6H_4	72	198–200
3d	*p*-$MeOC_6H_4$	65	210–213
3e	$C_{10}H_7$	68	215–217

presence of a benzylic methylene, which thus confirmed the structure of the by-product as 7-hydroxy-8-phenylacetyl-isoflavone (**4**, R = Ph). The isolation of **4** suggested the possibility of an acylation reaction of phenylacetic acid with activated phenols. Boron trifluoride is known to suppress the activity of phenols towards electrophilic substitution,[9] we therefore envisaged that the addition of BF_3OEt_2 during the course of the reaction would suppress the side reaction and also, on the other hand, would facilitate ring closure as the combination of two Lewis acids might enhance the activity.[12] This led us to study the reaction in a one-pot regime.

The one-pot procedure began with the reaction of an appropriately substituted phenylacetic acid with resorcinol in the presence of zinc chloride[4] via the formation of an intermediate deoxybenzoin **2** followed by cyclization to the corresponding isoflavone **3** on treatment with BF_3OEt_2, DMF and $MeSO_2Cl$ (Scheme 1). BF_3OEt_2 is believed to form a complex with the *ortho*-hydroxyaryl-ketones, which deactivates the aromatic ring, preventing ring acylation and consequent polymerization.[11] The use of two Lewis acids, namely, zinc chloride and boron trifluoride diethyl etherate, proved beneficial in this procedure, as by-product **4** was not formed. A series of 7-hydroxy-isoflavones **3** was prepared in good yields using this procedure (Table 1).[14]

2. General experimental procedure

To molten anhydrous $ZnCl_2$ (99 mmol), phenylacetic acid (108 mmol) was added with vigorous stirring and heating at about 120–130 °C followed by the slow addition of resorcinol (90 mmol). After completion (TLC), the reaction mixture was cooled to room temperature, followed by the addition of DMF (60 mL), and BF_3OEt_2 (363 mmol) at 0 °C. To this mixture was added a solution of $MeSO_2Cl$ (272 mmol) in DMF (10 mL) at 50 °C and the temperature was raised to ~110 °C for 90 min. The reaction mixture was cooled and poured into ice water. The separated oil was extracted with ethyl acetate, the organic layer washed with water, dried and the solvent removed. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane (50:50) or chloroform/methanol (98:2) (Table 1).[14]

In conclusion, our procedure provides an easy access to 7-hydroxy-isoflavones in 56–78% yields in one-pot from resorcinol and substituted phenylacetic acids without the isolation of the deoxybenzoin intermediate. Using the combination of two Lewis acids avoids the formation of any by-product.

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References and notes

1. Dixon, R. A.; Steele, C. L. *Trends Plants Sci.* **1999**, *4*, 394–400.
2. (a) Vrijsen, R.; Everaert, L.; Boeye, A. *J. Gen. Virol.* **1988**, *69*, 1749–1751; (b) Ito, M.; Ishmoto, S.; Nishida, Y.; Shiramizu, T.; Yumoki, H. *Agric. Biol. Chem.* **1986**, *50*, 1073–1074; (c) Miski, M.; Ulubelen, A.; Johansson, C.; Mabry, T. J. *J. Nat. Prod.* **1983**, *46*, 874–875.
3. (a) Ruiz-Larrea, M. B.; Mohan, A. R.; Paganga, G.; Miller, N. J.; Bolwell, G. P.; Rice-Evans, C. A. *Free Radical Res.* **1997**, *26*, 63–70; (b) Wagner, J. D.; Cefalu, W. T.; Anthony, M. S.; Litwak, K. N.; Zhang, L.; Clarkson, T. B. *Metabolism* **1997**, *46*, 698–705.
4. Dohme, A. R. L.; Cox, E. H.; Miller, E. *J. Am. Chem. Soc.* **1926**, *48*, 1688–1693.
5. Baker, W.; Chadderton, J.; Harborne, J.; Ollis, W. D. *J. Chem. Soc.* **1953**, 1852–1864.
6. Mahal, H. S.; Rai, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1120–1122.
7. Sathe, V. R.; Venkataraman, K. *Curr. Sci. India* **1949**, *18*, 373.
8. Kim, Y. W.; Brueggemeier, R. W. *Tetrahedron Lett.* **2002**, *43*, 6113–6115.
9. Wahala, K.; Hase, T. A. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 3005–3008.
10. Kagal, S. A.; Nair, P. M.; Venkataraman, K. *Tetrahedron Lett.* **1962**, *14*, 593–597.
11. Bass, R. J. *J. Chem. Soc., Chem. Commun.* **1976**, 78–79.
12. Jung, M. E.; Ho, D.; Chu, V. H. *Org. Lett.* **2005**, *7*, 1649–1651.
13. Elemental analysis and physical data of **4**: Found: C, 77.14; H, 4.88; O, 17.98% $C_{23}H_{16}O_4$ requires: C, 77.31; H, 4.48; O, 17.92%; IR (KBr): 3206, 2363, 1627, 1581, 1470, 1384, 1267, 1099, 858, 703 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): δ 10.15 (s, 1H, Ar–OH), 8.30 (d, 1H, ArH, $J = 8.9$ Hz), 7.98 (s, 1H, =CH), 7.56–7.55 (m, 2H, ArH), 7.46–7.25 (m, 8H, ArH), 7.13 (dd, 1H, ArH, $J = 8.7$, 2.1 Hz), 3.91 (s, 2H, $-CH_2C_6H_5$); ^{13}C NMR (75.47 MHz, $CDCl_3$): δ 167.8, 153.6, 151.8, 130.2, 128.0, 127.6, 127.0, 126.5, 126.3, 121.1, 118.1, 109.5, 40.1; ESMS m/z (%): 357 (100, $[M+H]^+$).

14. Physical and spectral data of compounds (**3a**–**e**): Compound **3a**: IR (KBr): 3258, 2366, 1625, 1454, 1385, 1266, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3 + DMSO/d_6$): δ 10.17 (s, 1H, Ar–OH), 8.01 (d, 1H, ArH, $J = 8.7$ Hz), 7.89 (s, 1H, =CH), 7.46 (d, 2H, ArH, $J = 6.6$ Hz), 7.37–7.28 (m, 2H, ArH), 7.23–7.18 (m, 1H, ArH), 6.86 (d, 1H, ArH, $J = 8.7$ Hz), 6.79 (d, 1H, ArH, $J = 1.4$ Hz); ESMS m/z (%): 239 (100, $[M+H]^+$), 238 (30, $[M]^+$); Compound **3b**: IR (KBr): 3251, 2364, 1627, 1580, 1356, 1227, 850, 785 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3 + DMSO/d_6$): δ 10.04 (s, 1H, ArOH), 8.01–7.94 (m, 2H, ArH), 7.90 (s, 1H, =CH), 7.63–7.52 (m, 2H, ArH), 7.30 (d, 1H, ArH, $J = 7.9$ Hz), 6.88–6.81 (m, 2H, ArH); ESMS m/z (%): 284 (100, $[M+H]^+$); Compound **3c**: IR (KBr): 3232, 2365, 1626, 1588, 1351, 1258, 1096, 783 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3 + DMSO/d_6$): δ 10.39 (s, 1H, Ar–OH), 8.03 (d, 1H, ArH, $J = 8.7$ Hz), 7.87 (s, 1H, =CH), 7.50 (s, 1H, ArH), 7.35–7.29 (m, 3H, ArH), 6.91–6.81 (m, 2H, ArH); ESMS m/z (%): 273 (100, $[M+H]^+$), 275 (33, $[M+2+H]^+$), 237 (15, $[M\text{-}Cl]^+$); Compound **3d**: IR (KBr): 3136, 2369, 1602, 1512, 1453, 1249, 1178, 1024, 886, 811, 777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3 + DMSO/d_6$): 10.10 (s, 1H, Ar–OH), 8.11 (d, 1H, ArH, $J = 8.6$ Hz), 7.89 (s, 1H, =CH), 7.48 (d, 2H, ArH, $J = 8.6$ Hz), 6.98–6.86 (m, 4H, ArH), 3.84 (s, 3H, $-OCH_3$); ESMS m/z (%): 269 (100, $[M+H]^+$), 238 (30, $[M-OCH_3]^+$); Compound **3e**: IR (KBr): 3444, 2930, 2367, 1730, 1640, 1398, 1261, 1138, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3 + DMSO/d_6$): δ 7.97 (d, 2H, ArH, $J = 7.9$ Hz), 7.86 (d, 2H, ArH, $J = 7.2$ Hz), 7.77 (d, 2H, ArH, $J = 8.1$ Hz), 7.55–7.30 (m, 4H, ArH), 7.25 (s, 1H, =CH); FABMS m/z (%): 288 (30, $[M]^+$).