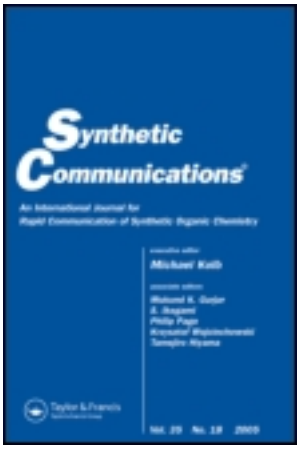

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Simple and Effective Method for Chemoselective Esterification of Phenolic Acids

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Version of record first published: 05 Aug 2006.

To cite this article: Wei Guo, Junfei Li, Ningjuan Fan, Weiwei Wu, Peiwen Zhou & Chizhong Xia (2005): A Simple and Effective Method for Chemoselective Esterification of Phenolic Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 35:1, 145-152

To link to this article: http://dx.doi.org/10.1081/SCC-200046532

Synthetic Communications®, 35: 145–152, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1081/SCC-200046532

A Simple and Effective Method for Chemoselective Esterification of Phenolic Acids

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Abstract: A new method for efficient and chemoselective esterification of phenolic acids in $KHCO_3$/alkyl halide/DMF reaction system is described, by which a series of phenoic acid esters were obtained in excellent yields.

Keywords: Phenolic acids, chemoselective esterification, alkyl halide

Phenolic acid esters motifs have been found in bioactive natural products, for example, the NF-κB inhibitors CAPE,[1] the honeybee propolis contact allergen prenyl caffeate,[2] and the EGCG mimic and HIV-1 reverse transcriptase inhibitor hydroxytyrosol gallate.[3] In many cases, phenolic acid esters are also used as important intermediates for the medicine synthesis.[4,5] Although these compounds are structurally unsophisticated, their reported synthesis typically suffer from a heavy burden of protecting groups for the purpose of improved chemoselectivity.[1–5] In the presence of strong protic acids (Fisher esterification), phenolic acids could be esterified with good

Received in Poland August 20, 2004
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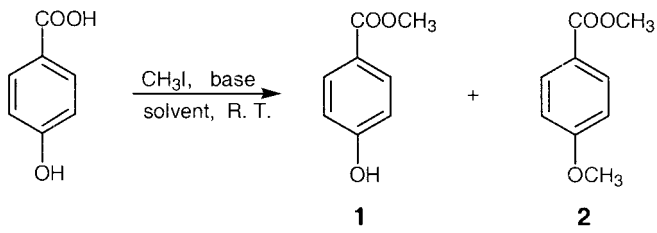
chemoselectivity,[6] but the harsh reaction conditions and the excess of alcohol made this strategy of limited applicability. The cesium salts of phenolic acids have been reported to react with alkyl halides in a highly chemoselective way,[2] but the yield is modest along with an excess of halides. Recently, Appentino et al. reported the preparation of phenolic acid esters with good chemoselectivity by Mitsunobu reaction,[7] but the modest yields and costly reagents limited it for practical applications. Herein, we hope to report a practical and effective reaction system, $KHCO_3$/alkyl halide/DMF, for chemoselective esterafication of phenolic acids.

Firstly, with 4-hydroxybenzoic acid (1.0 eq.) and CH_3I (1.5 eq.) as reaction substrates we screened a series of bases and solvents at room temperature to find optimal reaction conditions (Scheme 1 and Table 1). It is interesting to note that with $KHCO_3$ as base and DMF as solvent, the desired product was obtained in almost quantitative yield, and no side product **2** was observed (Table 1, entry 1). With DMSO as solvent, the yield was slightly decreased (Table 1, entry 2). However, acetone and THF failed to provide significant amounts of **1** even in lengthening time (Table 1, entries 3 and 4). With DMF as solvent, other bases were also investigated. When using K_2CO_3 (1.0 eq.), the reaction partly lost selectivity, and 9% of dialkylated product **2** was separated (Table 1, entry 5). However, $NaHCO_3$ and Na_2CO_3 gave good results comparable to $KHCO_3$ (Table 1, entries 6 and 7) in spite of the longer reaction time. When using stronger base NaOH (1 eq.), the reaction lost selectivity (Table 1, entry 8).

With DMF as optimal solvent and $KHCO_3$ as optimal base, we next studied the effect of reaction temperature and concentration of CH_3I to yield and selectivity of the reaction. Using 1.5 eq. of CH_3I, we found that when the temperature was 40°C, the reaction was completed after 1.5 hr without the loss of yield and selectivity. In addition, the reaction still worked well even if excessive CH_3I (4 eq.) was used at 40°C.

With DMF as optimal solvent and $KHCO_3$ as optimal base, we further investigated the chemoselective esterafication of various phenolic acids at 40°C (Table 2). For methylation, almost all reactions showed excellent



Scheme 1.

Table 1. Base and solvent effect at room temperature in the chemoselective esterification of 4-hydroxybenzoic acid[a]

Entry	Base (eq.)	Solvent	Time (h)	Yield (**1**)%[b]	Yield (**2**)%
1	$KHCO_3$ (1.2)	DMF	3	98	n. d.
2	$KHCO_3$ (1.2)	DMSO	5	85	n. d.
3	$KHCO_3$ (1.2)	Acetone	24	20	n. d.
4	$KHCO_3$ (1.2)	THF	24	8	n. d.
5	K_2CO_3 (1.0)	DMF	3	85[c]	9%[c]
6	$NaHCO_3$ (1.2)	DMF	5	88	n. d.
7	Na_2CO_3 (1.0)	DMF	5	91	n. d.
8	NaOH (1.0)	DMF	5	58[c]	35[c]

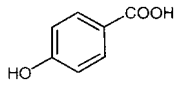
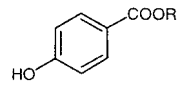
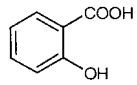
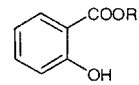
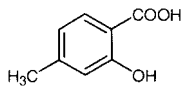
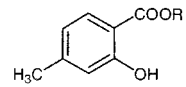
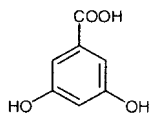
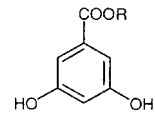
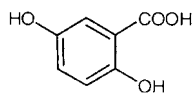
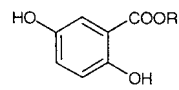
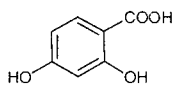
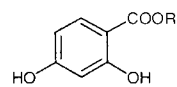
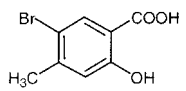
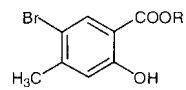
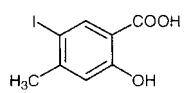
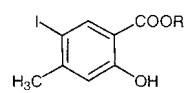
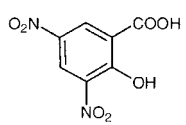
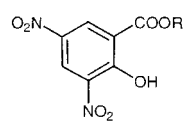
[a]Mole ratio of 4-hydroxybenzoic acid : $CH_3I = 1 : 1.5$.
[b]Isolated yields by simple work up described in Experimental section.
[c]Purified by column chromatography.

yield and chemoselectivity in 1–3 h. One noteworthy point is that the numbers and position of phenolic hydroxyls or carboxyls involved in the aromatic ring did not affect the good yield and selectivity. For phenolic acids bearing electron-withdrawing groups, such as Br and I, the reaction was also good (Table 2, entries 7 and 8). However, when 3, 5-dinitrosalicyclic acid was used, no any product was detected either in lengthening time or at elevated temperature (Table 2, entry 9). Obviously, it is due to the weak nucleophilic activation of the carboxylate anion, resulting from strong electron-withdrawing nitro groups.

In addition to methyl ester of phenolic acid, we also applied this method to prepare benzyl ester of phenolic acids considering its clean and convenient deprotection by Pd/C hydrogenation. Initially, we tested the reaction of 4-hydroxybenzoic acid with benzyl chloride in the above condition. However, the reaction was very slow, and after 56 h, 20% desired product was only separated. Once temperature was evaluated to 60°C, after 24 h the desired product was obtained in 34% yield along with 23% dialkylated product. When more active benzyl bromide was used, most of the reactions were finished after 3 h at 40°C with excellent selectivity and yields (Table 2). Furthermore, we also checked up 4-hydroxycinnamic acid and its derivative in view of their versatility in medicine synthesis and relation to the NF-$_k$B inhibitors CAPE.[1] The results obtained also showed excellent selectivity and yields (Table 2, entries 12 and 13).

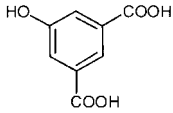
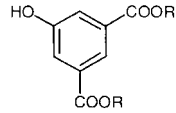
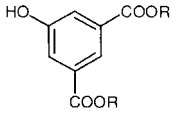
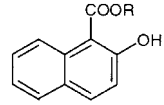
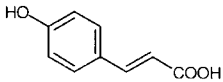
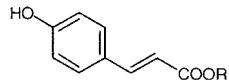
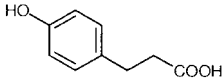
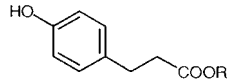
In summary, $KHCO_3$/alkyl halide/DMF reaction system provides a clean, practical method for chemoselective esterification of phenolic acids in high yields. We hope this method could provide some application in medicine synthesis.

Table 2. Chemoselective Esterification of Phenolic acids Using $KHCO_3$/alkyl halide/DMF reaction system[a]

Entry	Substrate	Product	Type of esters	Yield (%)[b]
1			R = CH_3 **1**	99
			R = CH_2Ph **3**	94
2			R = CH_3 **4**	98
			R = CH_2Ph **5**	95
3			R = CH_3 **6**	96
			R = CH_2Ph **7**	96
4			R = CH_3 **8**	98
			R = CH_2Ph **9**	95
5			R = CH_3 **10**	99
			R = CH_2Ph **11**	91
6			R = CH_3 **12**	94
			R = CH_2Ph **13**	92
7			R = CH_3 **14**	92
			R = CH_2Ph **15**	90
8			R = CH_3 **16**	93
			R = CH_2Ph **17**	94
9			R = CH_3 **18**	n.d
			R = CH_2Ph **19**	n.d

(*continued*)

Table 2. Continued

Entry	Substrate	Product	Type of esters	Yield (%)[b]
10			R = CH_3 **20**	95
			R = CH_2Ph **21**	92
11			R = CH_3 **22**	96
			R = CH_2Ph **23**	95
12			R = CH_3 **24**	98
			R = CH_2Ph **25**	95
13			R = CH_3 **26**	96
			R = CH_2Ph **27**	91

[a]All reactions were performed at 40°C. Mole ratio of phenolic acid : alkyl halides = 1 : 1.5.

[b]Isolated yields by simple workup described in the Experimental section.

EXPERIMENTAL SECTION

General. The carboxylic acids, $KHCO_3$, CH_3I and benzyl bromide are available commercially without further purification. Solvents were dried according to standard procedures. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Huanghai GF_{254} silica gel-coated plates.

General Procedures for the Preparation of Phenolic acid ester: 2 mmol phenolic acid was dissolved in 3.0 mL dry DMF, 2.4 mmol $KHCO_3$ was added and stirred for several minutes at room temperature. Then, 3 mmol CH_3I were added. The reaction mixture was allowed to 40°C with a water bath and monitored by TLC. Upon completion, the reaction mixture was added to 10 ml water and extracted with ethyl acetate. The organic layer was subsequently washed with 5% $NaHCO_3$ and 5% NaCl, and dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the desired products. Benzyl esters of phenolic acid may be prepared according to the similar method, and the excess benzyl bromide can be easily removed by column chromatography (EtOAc/hexane).

The NMR and IR spectra of the following esters were in complete agreement with those of the authentic samples: methyl 4-hydroxybenzoate, methyl 4-methoxybenzoate, benzyl 4-hydroxybenzoate, methyl salicylate, methyl 2,6-dihydroxybenzoate, methyl 2,5-dihydroxybenzoate, methyl 2,4-dihydroxybenzoate, dimethyl 5-hydroxyisophthalate, Methyl 3-(4-hydroxyphenyl)propionate (Aldrich), benzyl salicylate (Acros), methyl 4-methylsalicylate,[8] benzyl 2,5-dihydroxybenzoate,[9] methyl 2-hydroxy-1-naphthoate,[10] methyl 4-hydroxycinnamate.[11] For others, spectral data are given below, which are consistent with the assigned structures.

Benzyl 4-methylsalicylate (7): Oil; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 2.36 (s, 3H), 5.39 (s, 2H), 6.71 (d, $J = 7.5$, 1H), 6.82 (s, 1H), 7.42 (m, 6H), 7.77 (d, $J = 7.8$, 1H); IR (KBr) cm^{-1}: 3180, 3035, 2360, 1670, 1624, 1502, 1388; MS m/z: 242 (M); *Anal.* Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found C, 74.33; H, 5.80.

Benzyl 2,6-dihydroxybenzoate (9): M.p. 66–68°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 5.50 (s, 2H), 6.47 (d, $J = 8.4$, 2H), 7.30 (m, 1H), 7.44 (s, 5H), 9.71 (b, 2H); IR (KBr) cm^{-1}: 3388, 1668, 1637, 1575, 1319, 1228, 1195, 1161, 1103; MS m/z: 244 (M); *Anal.* Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found C, 68.81; H, 4.94.

Benzyl 2,4-dihydroxybenzoate (13): M.p. 94–96°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 5.35 (s, 3H), 5.52 (s, 1H), 6.35 (d, $J = 9$, 1H), 6.40 (s, 1H), 7.40 (m, 5H), 7.78 (d, $J = 8.7$, 1H), 10.99 (s, 1H); IR (KBr) cm^{-1}: 3375, 1662, 1624, 1377, 1261; MS m/z: 244 (M); *Anal.* Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found C, 68.83; H, 4.93.

Methyl 5-bromo-4-methylsalicylate (14): M.p. 46–47°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 2.37 (s, 3H), 3.93 (s, 3H), 6.87 (s, 1H), 7.96 (s, 1H), 10.57 (s, 1H); IR (KBr) cm^{-1}: 1678, 1616, 1442, 1334, 1253, 1207; MS m/z: 244 (M), 246 (M + 2); *Anal.* Calcd for $C_9H_9BrO_3$: C, 44.11; H, 3.70. Found C, 44.23; H, 3.73.

Benzyl 5-bromo-4-methylsalicylate (15): M.p. 61–62°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 2.37 (s, 3H), 5.37 (s, 2H), 6.88 (s, 1H), 7.42 (s, 5H), 7.98 (s, 1H), 10.60 (s, 1H); IR (KBr) cm^{-1}: 1666, 1616, 1477, 1396, 1245; MS m/z: 320 (M), 322 (M + 2); *Anal.* Calcd for $C_{15}H_{13}BrO_3$: C, 56.10; H, 4.08. Found C, 56.09; H, 4.07.

Methyl 5-iodo-4-methylsalicylate (16): M.p. 62–64°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 2.42 (s, 3H), 3.95 (s, 3H), 6.92 (s, 1H), 8.23 (s, 1H), 10.61 (s, 1H); IR (KBr) cm^{-1}: 3155, 2952, 1674, 1610, 1469, 1440, 1338, 1255; MS m/z: 292 (M); *Anal.* Calcd for $C_9H_9IO_3$: C, 37.01; H, 3.11. Found C, 37.08; H, 3.09.

Benzyl 5-iodo-4-methylsalicylate (17): M.p. 64–65°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 2.42 (s, 3H), 5.39 (s, 2H), 6.93 (s, 1H), 7.44 (m, 5H), 8.25 (s, 1H), 10.64 (s, 1H); IR (KBr) cm^{-1}: 1672, 1610, 1463, 1392, 1255, 1213; MS m/z: 368 (M); *Anal.* Calcd for $C_{15}H_{13}IO_3$: C, 48.94; H, 3.56. Found C, 48.90; H, 3.51.

Dibenzyl 5-hydroxyisophthalate (21): M.p. 116–118°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 5.36 (s, 4H), 6.48 (b, 1H), 7.41 (m, 10H), 7.79 (s, 2H), 8.30 (s, 1H); IR (KBr) cm^{-1}: 3436, 1720, 1697, 1388, 1334; MS m/z: 362 (M); *Anal.* Calcd for $C_{22}H_{18}O_5$: C, 72.92; H, 5.01. Found C, 74.91; H, 4.97.

Benzyl 2-hydroxy-1-naphthoate (23): M.p. 81–82°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 5.59 (s, 2H), 7.18 (d, $J = 8.7$, 1H), 7.35–7.54 (m, 8H), 7.76 (d, $J = 7.5$, 1H), 7.91 (d, $J = 8.7$, 1H), 8.82 (d, $J = 8.4$, 1H); IR (KBr) cm^{-1}: 1691, 1633, 1598, 1518, 1170; MS m/z: 278 (M); *Anal.* Calcd for $C_{18}H_{14}O_3$: C,77.68; H, 5.07. Found C, 77.72; H, 5.04.

Benzyl 4-hydroxycinnamate (25): M.p. 90–92°C; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 5.25 (s, 2H), 6.01 (b, 1H), 6.34 (d, $J = 15.9$, 1H), 6.85 (d, $J = 8.1$, 2H), 7.34–7.42 (m, 7H), 7.67 (d, $J = 15.9$, 1H); IR (KBr) cm^{-1}: 1641, 1465, 1377, 1244, 1203; MS m/z: 254 (M); *Anal.* Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found C, 75.36; H, 5.59.

Benzyl 3-(4-hydroxyphenyl)propionate (27): Oil; ^{1}H-NMR (300 MHz, δppm, $CDCl_3$): 2.64 (t, 2H), 2.89 (t, 2H), 4.95 (b, 1H), 5.10 (s, 2H), 6.72 (d, $J = 7.8$, 2H), 7.04 (d, $J = 7.8$, 2H), 7.32 (m, 5H); IR (KBr) cm^{-1}: 3396, 3031, 2927, 2358, 1699, 1614,1456; MS m/z: 256 (M); *Anal.* Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found C, 74.92; H, 6.24.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (No. 20272034), and the Natural Science Foundation of Shanxi Province, China (No. 20041006).

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