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An efficient chemoselective etherification of phenols in polyfunctional aromatic compounds

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Abstract

A simple and efficient chemoselective alkylation of phenols in polyfunctional aromatic compounds with different alkyl halides in the presence of K_2CO_3/TBAB is reported. The method is successful with various hydroxy aromatic acids or oximes possessing other functional groups.

Keywords: Etherification; Phenol; Naphthoic acid; Tetrabutylammonium bromide; Chemoselective alkylation

1. Introduction

Naphthoic acid derivatives and phenolic ethers are constituents of some well-known pharmaceutical compounds.[1,2] Naphthoic acid derivatives play a crucial role in the development of new drugs against several human ailments and infectious diseases.[3–6] In our continuing effort to develop new antitubercular agents we were interested in preparing naphthoic acid derivatives, because several molecules with a naphthyl moiety are potent antitubercular agents (Fig. 1).[7,8] One such naphthyl derivative, a diaryl quinoline, is at an advanced stage in clinical trials.[9]

We required alkyl ethers of hydroxy naphthoic acids which could be later modified via carboxyl group manipulations. This led us to seek a chemoselective method for etherificaton of phenolic groups in hydroxy naphthoic acids. Earlier methods include Fischer ester formation then phenol alkylation, followed by saponification[10–12] or dialkylation of both the phenol and carboxylic acid groups followed by ester saponification.[13–16] Although the chemoselective preparation of hydroxy benzoic acid esters from hydroxy benzoic acids is known,[17–19] a method for chemoselective alkylation of phenols over carboxylic acids was only reported recently by Liu et al.[20] during the course of our studies and involves chemoselective alkylation of hydroxy benzoic acids with alkyl halides in the presence of tetrabutylphosphonium hydroxide as a phase transfer catalyst. Herein, we report an alternative, efficient, economical, high yielding, simple, and practical method for chemoselective alkylation of phenolic groups in hydroxy aromatic acids and hydroxy aromatic compounds possessing other potentially reactive functionalities.

Tetrabutylammonium bromide has been used as phase transfer catalyst in a variety of organic reactions and is known to enhance nucleophilicity.[21,22] A combination of tetrabutylammonium bromide and inorganic bases under microwave irradiation has also been used for alkylation of phenols.[23] The basis of a chemoselective alkylation of phenolic groups relies on substantial pK_a differences relative to other functionalities.

2. Results and discussion

1-Hydroxy-2-naphthoic acid on treatment with allyl bromide in the presence of anhydrous K_2CO_3 (10 mol %)

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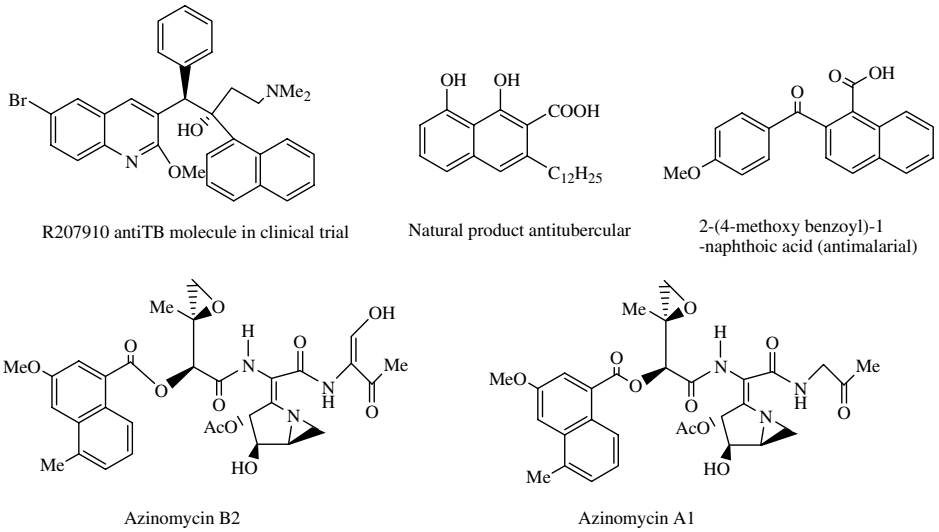
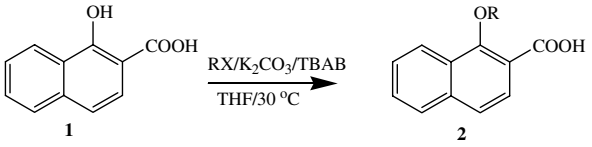


Fig. 1. Biologically important compounds with a naphthyl moiety.



Scheme 1. Synthesis of alkyl ethers of 1-hydroxy-2-naphthoic acid.

and a catalytic amount of TBAB in anhydrous THF at ambient temperature for 10 min leads to 1-allyloxy-2-naphthoic acid (Scheme 1) as the only product in 90% yield. The use of tetrabutylammonium hydroxide on the other hand produced a mixture of the above desired compound along with allyl 1-allyloxy-2-naphthoate as a minor product. Similarly, benzyl bromide, ethyl bromoacetate, ethyl chloroacetate, 1-(2-chloroethyl)-piperidine, benzyl chloride, and *N*,*N*-di-isopropylaminoethyl chloride all reacted to form the respective 1-*O*-alkyl derivatives in good yields (Scheme 1, Table 1, entries 2–7).

Encouraged by these findings we carried out phenol alkylations on a variety of substrates with different alkyl halides and the results are depicted in Table 2. Chemoselective alkylation of the phenol in a hydroxy benzaldehyde oximes was also possible with benzyl bromide (Table 2, entries 12 and 13).

Table 1
Preparation of alkyl ethers of 1-hydroxy-2-naphthoic acid (Scheme 1)

Entry	RX	Time (min)	% Yield of **2** (isolated)
1	Allyl bromide	10	90
2	Benzyl bromide	10	91
3	Ethyl bromoacetate	10	90
4	Ethyl chloroacetate	90	60
5	1-(2-Chloroethyl)-piperidine	30	65
6	Benzyl chloride	20	85
7	*N*,*N*-Di-isopropylaminoethyl chloride	60	65

3. Conclusion

In summary, we have demonstrated that chemoselective alkylation of phenols in aromatic compounds having other reactive functionalities can be carried out successfully with a variety of alkyl halides using tetrabutylammonium bromide/K_2CO_3 in an organic solvent. The method is simple, economical, of high yield and useful in the preparation of alkoxy benzoic acid and alkoxy benzaldehyde oximes.

4. Typical experimental procedure and selected data

A mixture of the hydroxy aromatic compound (1 equiv), anhydrous K_2CO_3 (10 mol %), TBAB (10 mol %) and alkyl halide (1 equiv), in anhydrous THF was stirred at ambient temperature until TLC analysis showed the disappearance of the starting materials. The reaction mixture was filtered and the organic solvent was evaporated to give the desired ether. If needed, purification of the crude product was carried out over a short column of silica gel using a gradient of hexane: ethyl acetate as eluent.

4.1. 1-Allyloxy-2-naphthoic acid

White solid, mp 65–66 °C; FT-IR (KBr, cm^{-1}): 3745, 3116, 2641, 2231, 1744, 1699, 1516; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): δ 8.42 (d, $J = 8.05$ Hz, 1H, ArH), 7.79–7.22 (m, 4H, ArH), 7.24 (d, $J = 8.80$ Hz, 1H, ArH), 6.2–5.9 (m, 1H, CH_2=C*H*), 5.49–5.30 (m, 2H, CH_2=CH), 4.87 (dd, 2H, $J_1 = 2.63$ Hz, $J_2 = 2.64$ Hz, –OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): δ 171.0, 161.61, 137.64, 132.17, 129.75, 127.79, 126.07, 125.24, 124.61, 124.40, 119.24, 118.92, 105.91, 66.13; MS(ESI): 229 ($M+H^+$);

Table 2
Chemoselective alkylation of phenolic substrates with various alkyl halides

Entry	Substrate	RX	Time (min)	Product	% Yield[a]
1	2-Hydroxy naphthoic acid	Allyl bromide	10	2-Allyloxynaphthoic acid	95
2	2-Hydroxy naphthoic acid	Benzyl bromide	10	2-Benzyloxynaphthoic acid	90
3	2-Hydroxy naphthoic acid	Ethyl bromoacetate	15	2-*O*-(Ethoxycarbonyl methyl)naphthoic acid	90
4	Salicylic acid	Allyl bromide	10	2-Allyloxybenzoic acid	95
5	Salicylic acid	Benzyl bromide	10	2-Benzyloxybenzoic acid	90
6	Salicylic acid	Ethyl bromoacetate	20	2-*O*-(Ethoxycarbonylmethyl)benzoic acid	80
7	Salicylic acid	1-(2-Chloroethyl)piperidine	60	2-*O*-(2-Piperidin-1-yl-ethyl)benzoic acid	65
8	2-Hydroxynaphthoic acid	1-(2-Chloroethyl)piperidine	240	2-*O*-(2-Piperidin-1-yl-ethyl)naphthoic acid	90
9	4-Hydroxyphenylacetic acid	Benzyl bromide	30	4-Benzyloxyphenylacetic acid	93
10	4-Nitrophenol	Benzyl bromide	450	4-Benzyloxynitrobenzene	95
11	4-Hydroxyacetophenone	Benzyl bromide	450	4-Benzyloxyacetophenone	90
12	4-Hydroxy-3-methoxybenzaldehyde oxime	Benzyl bromide	400	4-Benzyloxy-3-methoxybenzaldehyde oxime	85
13	4-Hydroxybenzaldehyde oxime	Benzyl bromide	400	4-Benzyloxybenzaldehyde oxime	65
14	4-Cyanophenol	Benzyl bromide	10	4-Benzyloxybenzonitrile	90

[a] Yields refer to isolated yield.

Anal. Calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.65; H, 5.33.

4.2. 2-Benzyloxy-1-naphthoic acid

White solid, mp 77–80 °C; FT-IR (KBr, cm^{-1}): 3745, 3395, 2714, 2092, 1647, 1518; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): δ 8.76 (d, $J = 8.7$ Hz,1H, ArH), 7.89–7.32 (m, 9H, ArH), 7.14 (d, $J = 9.0$ Hz, 1H, ArH), 5.55 (s, 2H, –OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): δ 172.5, 165.09, 137.31, 135.69, 132.31, 129.46, 129.17, 129.06, 128.96, 128.88, 128.82, 125.77, 123.97, 119.75, 104.99, 67.85; MS(ESI): 279 ($M+H^+$); Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.65; H, 5.09.

4.3. 4-Benzyloxyphenylacetic acid

White solid, mp 110 °C; FT-IR (KBr, cm^{-1}): 3376, 3042, 2373, 1712, 1615, 1519; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): δ 7.31–6.08 (m, 9H, ArH), 5.11 (s, 2H, –OCH_2), 3.56 (s, 2H, –$COCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): $\delta = 172.84$, 155.50, 136.07, 130.84, 128.97, 128.69, 128.58, 125.81, 116.01, 67.22, 40.89; MS(ESI): 243 ($M+H^+$); Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.34; H, 5.85.

4.4. 4-Benzyloxy-3-methoxybenzaldehyde oxime

White solid, mp 97–102 °C; FT-IR (KBr, cm^{-1}): 3763, 3296, 2931, 1810, 1590, 1515; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): δ 8.03 (s, 1H, –CH), 8.43–6.84 (m, 8H, ArH), 5.15 (s, 2H, –OCH_2), 3.92 (s, 3H, –OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): $\delta = 150.36$, 137.08, 128.99, 128.36, 127.61, 125.71, 121.89, 113.72, 109.03, 71.24, 56.2; MS(ESI): 258 ($M+H^+$); Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.01; H, 5.86; N, 5.41.

4.5. 1-Benzyloxy-4-nitrobenzene

White solid, mp 90–93 °C; FT-IR (KBr, cm^{-1}): 3429, 3082, 1764, 1592, 1511, ^1H NMR (200 MHz, $CDCl_3$–CCl_4): δ 8.21–6.96 (m, 9H, ArH), 5.14 (s, 2H, –OCH_2); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): δ 164.00, 142.15, 135.90, 129.19, 128.89, 127.83, 126.28, 115.21, 71.04; MS(ESI): 230 ($M+H^+$); Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.10; H, 4.86; N, 6.09.

4.6. Benzyloxyacetophenone

Colorless oil, FT-IR (neat) cm^{-1}: 3745, 3034, 1742, 1684, 1517; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): δ 7.55–7.17 (m, 9H, ArH), 5.09 (s, 2H, –OCH_2), 2.57 (s, 3H, –$COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): δ 197.76, 159.39, 138.95, 136.91, 129.96, 129.02, 128.50, 127.91, 121.68, 120.68, 113.8, 70.54, 27.01; MS(ESI): 227 ($M+H^+$); Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.60; H, 6.27.

4.7. 2-O-(2-Piperidin-1-yl-ethyl)-benzoic acid

Yellow oil, IR (neat) cm^{-1}: 2936, 1676, 1300; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): 7.79 (dd, 1H, $J = 7.9$ Hz, 1.5Hz, 1H, ArH), 7.47–6.82 (m, 3H, ArH), 4.46 (t, 2H, $J = 6.0$ Hz, 2H, OCH_2), 2.74 (t, 2H, $J = 6.0$ Hz, NCH_2), 2.52–2.47 (m, 4H, $2 \times CH_2$), 1.65–1.55 (m, 4H, $2 \times CH_2$), 1.49–1.45 (m, 2H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): 170.1, 162.0, 135.9, 130.3, 119.4, 118.0, 63.2, 57.5, 55.1, 26.3, 24.5; MS (ESI): 250 ($M+H^+$); Anal. Calcd for $C_{18}H_{21}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.25; H, 7.72; N, 5.65.

4.8. 2-O-(2-Piperidin-1-yl-ethyl)-naphthoic acid

Yellow oil, IR (neat) cm^{-1}: 2934, 1660, 1257; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): 8.39 (d, 1H, $J = 7.8$ Hz, 1.5 Hz, ArH), 7.76–7.72 (m, 2H, ArH), 7.62–7.47 (m, 2H, ArH), 7.24 (d, $J = 7.8$ Hz, 1H, ArH), 4.51 (t, $J = 6.0$ Hz, 2H, OCH_2), 2.78 (t, $J =$ 6.0 Hz, 2H, NCH_2), 2.56–2.51 (m, 4H, $2 \times CH_2$), 1.67–1.46 (m, 6H, $3 \times CH_2$), ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): 171.1, 161.3, 137.58, 129.71, 126.07, 125.25, 124.71, 124.37, 118.92, 106.51, 63.30, 57.58, 55.21, 26.31, 24.55; MS (ESI): 300 ($M+H^+$); Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.00; H, 7.12; N, 4.65.

4.9. 1-Pentyloxynaphthalene-2-carboxylic acid

Solid, mp 50–52 °C; IR (KBr) cm^{-1}: 2935, 1659, 1339; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): 8.41 (d, 1H, $J = 8.0$ Hz, ArH), 7.76–7.71 (m, 2H, ArH), 7.60–7.44 (m, 2H, ArH), 4.36 (t, 2H, $J = 6.6$ Hz, OCH_2), 1.87–1.74 (m, 2H, CH_2), 1.45–1.30 (m, 4H, $2 \times CH_2$), 0.94 (t, $J =$ 6.9 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3 + CCl_4$): 171.4, 161.4, 137.5, 129.6, 127.7, 126.0, 125.2, 124.6, 124.3, 118.8, 106.1, 65.7, 28.7, 28.5, 22.7, 14.4; MS (ESI): 258 ($M+H^+$); Anal. Calcd for $C_{16}H_{17}O_3$: C, 74.39; H, 7.02. Found: C, 74.37; H, 7.09.

4.10. 1-Ethoxycarbonylmethoxynaphthalene-2-carboxylic acid

Solid, mp 69–70 °C; IR (KBr) cm^{-1}: 3449, 1736; ^1H NMR (200 MHz, $CDCl_3$–CCl_4): 8.40 (d, 1H, $J = 8.0$ Hz, ArH), 7.84–7.72 (m, 2H, ArH), 7.63–7.50 (m, 2H, ArH), 7.26 (d, 1H, $J = 10.6$ Hz), 4.88 (s, 2H, OCH_2CO), 4.29 (q, 2H, $J = 7.2$ Hz, OCH_2), 1.31 (t, $J = 7.2$ Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$–CCl_4): 170.5, 167.5,161.8, 137.8, 129.9, 127.8, 127.8, 126.1, 125.1, 124.6, 124.4, 119.1, 105.3, 61.9, 61.5, 14.5. MS (ESI): 259 ($M+H^+$); Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.67; H, 5.19.

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