Notes

2-(Methoxymethyl)- and 2-(Bromomethyl)-3-aryl-2-propenoic Acids from Aromatic Aldehydes

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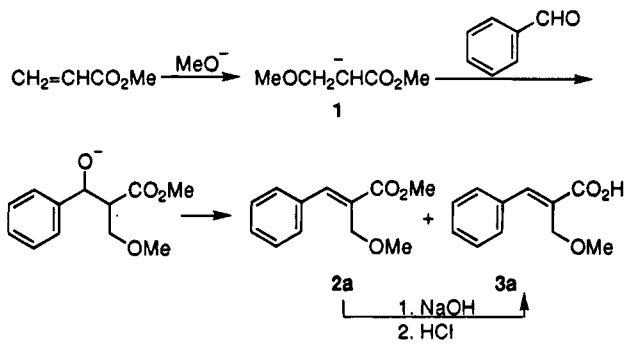
The sequence of Michael addition to activated olefins followed by reaction of the anions so formed with electrophiles, also termed "tandem vicinal difunctionalization,"[2] has received much attention in recent years because of its obvious value in synthesis. The Michael addends have been mostly carbanions, especially organocuprates; examples involving mercaptides are also fairly numerous. Alkoxides, on the other hand, have been used very rarely.[3] This Note describes the tandem vicinal difunctionalization of methyl acrylate with sodium methoxide and aromatic and heteroaromatic aldehydes.[4]

Results and Discussion

Addition of methyl acrylate and benzaldehyde to sodium methoxide in THF at room temperature gave a mixture of ester **2a**[6] and acid **3a** which on hydrolysis gave 2-(methoxymethyl)-3-phenyl-2-propenoic acid (**3a**) in 44% yield. The mechanism is believed to involve addition of the initially formed anion **1** to benzaldehyde followed by elimination of water:



The reaction seems to be fairly general for aromatic and heteroaromatic aldehydes (Table 1). The products are assumed to have the *trans* stereochemistry; small amounts of what appeared to be the *cis* isomers were sometimes detected in the crude products by ^{1}H NMR spectroscopy. The low yields of some of the acids reported in Table 1 are a consequence of their fairly high solubility in the crystallization solvents used for purification; the conversions determined by NMR spectroscopy of the crude products were usually in the range of 60%–70%. Some methyl 3-methoxypropanoate was usually formed. Aldehyde disproportionation (Cannizzaro reaction) did not occur to any appreciable extent except when sodium *tert*-butoxide was used with either methyl or *tert*-butyl acrylate. Thus the combination sodium *tert*-butoxide/*tert*-butyl acrylate/benzaldehyde gave a mixture of *tert*-butyl 2-(*tert*-butoxymethyl)-3-phenyl-2-propenoate and the corresponding acid in only low yield. To avoid the formation of mixed ethers, the acrylate and the alkoxide must be derived from the same alcohol; this surprisingly also applies to *tert*-butyl acrylate. Reaction of methyl crotonate with sodium methoxide and benzaldehyde gave only a trace of adducts of type **2** and **3**; cyclohexenone little or none. The reaction did not succeed with cyclohexanecarboxaldehyde, benzophenone, or the α-keto ester methyl phenylglyoxylate. Substitution of toluene for THF did not result in increased yields. Sodium methoxide prepared *in situ* from sodium hydride and methanol gave higher yields than commercial samples. Sodium hydride alone also led to products **2b/3b** in the case of *o*-tolualdehyde,[4,5] albeit in lower yields, presumably by initial ester cleavage by the hydride to produce some sodium methoxide. Surprisingly, the sodium salt of 2-hydroxybenzaldehyde did not react with methyl acrylate in THF either at room temperature or at reflux. The reaction probably requires higher temparatures since the potassium carbonate induced reaction of 2-hydroxybenzaldehyde with ethyl acrylate in refluxing DMF is reported[7] to give a mixture of 2*H*-1-benzopyran-3-carboxylic acid and its ethyl ester in 64% yield.

Reaction of acid **3a** with hydrogen bromide in acetic acid at 60 °C gave 2-(bromomethyl)-3-phenyl-2-propenoic acid (**4a**) in 63% yield. This reaction also appears to be

Table 1. Preparation of Acids 3 by Reaction of RCHO with CH_2=$CHCO_2Me$/NaOMe Followed by Hydrolysis and Conversion of Acids 3 into Acids 4 with HBr

	R	3(%)	4(%)[a]
a	C_6H_5	44	63
b	2-MeC_6H_4	51	
c	2-$CF_3C_6H_4$	35	
d	3-BrC_6H_4	27	
e	4-$MeOC_6H_4$	66	
f	4-$O_2NC_6H_4$	*b*	
g	1-naphthyl	52	77
h	2-naphthyl	37	
i	9-anthryl	46	79
j	2-furyl	28	
k	3-furyl	22	
l	2-thienyl	60	
m	1-methyl-2-indolyl	32	
n	1,2-dimethyl-3-indolyl	0[c]	
o	2-benzofuryl	26	

[a] Yield from 2-(methoxymethyl)-3-aryl-2-propenoic acids. [b] Complex mixture, but some 2-(methoxymethyl)-3-(4-nitrophenyl)-2-propenoic acid was detected by ^{1}HNMR spectroscopy. [c] The product was methyl 1,2-dihydro-9-methyl-9*H*-carbazole-3-carboxylate.[5]

(1) Present address: 121 Spring House Way, Kennett Square, PA 19348.

(2) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225.

(3) A recent review[2] lists two examples involving alkoxides. Na salt of methyl hydroxyacetate: Gianturco, M. A.; Friedel, P.; Giammarino, A. S. *Tetrahedron* **1964**, *20*, 1763. Na salt of methyl diphenylhydroxyacetate: Flavin, M. T.; Lu. M. C. *Tetrahedron Lett.* **1983**, *24*, 2335.

(4) The reaction was discovered by chance during an attempt to generate the enolate of *o*-tolualdehyde with sodium hydride in THF and add it to methyl acrylate.[5]

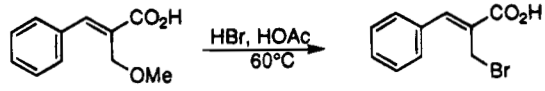
(5) Ciganek, E. *J. Org. Chem.* **1995**, *60*, in press.

(6) This ester has been prepared previously by a different method: Buggle, K.; Philbin, E. M.; Ryan, N. D. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2630.

(7) René, L.; Royer, R. *Eur. J. Med. Chem.* **1975**, *10*, 72.

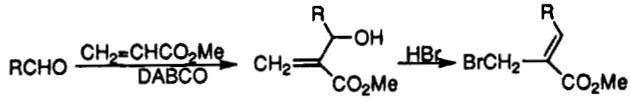
0022-3263/95/1960-4635$09.00/0

general (Table 1). Although it has not been established, acids **3** containing heteroaromatic groups are also expected to undergo this reaction as long as they are stable to hydrogen bromide. The much lower solubility of the 2-(bromomethyl)-3-aryl-2-propenoic acids in crystallization solvents permits use of the *crude* 2-(methoxymethyl)-3-aryl-2-propenoic acids in the ether cleavage; thus, 2-(bromomethyl)-3-phenyl-2-propenoic acid (**4a**) was obtained in 53% overall yield from benzaldehyde without purification of the intermediate **3a**.



3a **4a**

This simple and apparently novel sequence of reactions thus gives access to 2-(bromomethyl)-3-aryl-2-propenoic acids, molecules that have three functionalities amenable to further elaboration. It is related to the DABCO-catalyzed addition of acrylates to aldehydes (the Baylis–Hillman reaction[8]) to give 2-(hydroxyalkyl)-2-propenoic esters of type **5** which on treatment with hydrogen bromide or NBS/dimethyl sulfide[9] give 2-(bromomethyl)-2-propenoic esters. Esters of 2-(bromomethyl)-3-aryl-2-propenoic acids have also been made by NBS-bromination of the corresponding 2-methyl-3-aryl-2-propenoates.[10] Unlike the transformation described here, the Baylis-Hillman reaction succeeds with aliphatic aldehydes and



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α-keto esters. However, it can be rather slow or fail completely with certain aldehydes. Thus we find that the pseudo-first-order half lives for the DABCO-catalyzed reactions of benzaldehyde or 1-naphthaldehyde with excess methyl acrylate at room temperature are about 50 h and 12 days, respectively; 9-anthraldehyde did not react at all. The methoxide-induced addition of methyl acrylate to aromatic and heteroaromatic aldehydes may thus serve as an alternate method in cases where the Baylis–Hillman reaction is slow or fails altogether.

Experimental Section

General. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were determined in $CDCl_3$ unless otherwise specified. Melting points were measured in unsealed capillary tubes and are uncorrected.

Materials. Starting materials were obtained from Janssen Chimica or Aldrich Chemical Co. The THF used was EM Science anhydrous grade (stored over 4A sieves).

2-(Methoxymethyl)-3-phenyl-2-propenoic Acid (3a). General Procedure for the Synthesis of Acids 3. Methanol (3.93 g, 123 mmol) in 15 mL of anhydrous THF was added slowly with cooling to 5.90 g (130 mmol) of unwashed 50% NaH/oil and 30 mL of THF, the mixture was stirred at room temperature for 30 min and cooled with ice, and a mixture of 7.62 g (72 mmol) of acid-free benzaldehyde and 9.09 g (106 mmol) of methyl acrylate in 30 mL of anhydrous THF was added rapidly. The bath was removed, and the mixture was stirred for 90 min. Water (20 mL) was added, and the THF was removed under vacuum on a rotary evaporator. Aqueous sodium hydroxide solution (15%, 60 mL) was added to the residue, and the resulting solution was then heated under reflux for 30 min. The solution was cooled to about 50–60 °C[11] and washed with toluene. The toluene was extracted once with water, and the combined aqueous phases were washed once with toluene and acidified with concentrated HCl. Extraction with $CHCl_3$ gave 13.78 g of crude **3a** which was crystallized from *n*-BuCl to give 6.01 g (44%) of pure **3a**, mp 87–89 °C. ^{1}H NMR δ 11.7 (br, 1 H); 8.1 (s, 1 H); 7.6 (m, 2 H); 7.4 (m, 3 H); 4.3 (s, 2 H); 3.5 (s, 3 H). ^{13}C NMR δ 58.2, 66.1, 127.8, 128.5, 129.7, 130.0, 134.3, 146.9, 173.1. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.70; H, 6.27.

2-(Methoxymethyl)-3-(2-methylphenyl)-2-propenoic Acid (3b). Mp 103–104 °C (*n*-BuCl). ^{1}H NMR δ 8.2 (s, 1 H), 7.5 (d, J = 7 Hz, 1 H), 7.2–7.4 (m, 3 H), 4.2 (s, 2 H), 3.4 (s, 3 H), 2.3 (s, 3 H). ^{13}C NMR δ 20.4, 58.8, 66.9, 126.4, 128.9, 129.8, 123.0, 130.5, 134.1, 137.8, 145.8, 173.4. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 70.01; H, 6.80.

2-(Methoxymethyl)-3-[2-(trifluoromethyl)phenyl]-2-propenoic Acid (3c). Mp 123–124 °C (EtOAc). ^{1}H NMR δ 8.3 (q, J = 2 Hz, 1 H), 7.8 (d, J = 8 Hz, 1 H), 7.6 (m, 2 H), 7.5 (m, 1 H), 4.1 (s, 2 H), 3.4 (s, 3 H). Anal. Calcd for $C_{12}H_{11}F_3O_3$: C, 55.39; H, 4.26. Found: C, 55.22; H, 4.18.

2-(Methoxymethyl)-3-(3-bromophenyl)-2-propenoic Acid (3d). Mp 124–126 °C (EtOAc). ^{1}H NMR δ 8.0 (s, 1 H), 7.7 (d, J = 0.5 Hz, 1 H), 7.5 (d/d, J = 8/2 Hz, 1 H), 7.4 (d, J = 8 Hz, 1 H), 7.3 (m, 1 H), 4.2 (s, 2 H), 3.5 (s, 3 H). Anal. Calcd for $C_{11}H_{11}BrO$: C, 48.73; H, 4.09; Br, 29.41. Found: C, 48.45; H, 4.13; Br, 29.51.

2-(Methoxymethyl)-3-(4-methoxyphenyl)-2-propenoic Acid (3e). Mp 133–134 °C (MeCN). ^{1}H NMR δ 8.0 (s, 1 H), 7.5 (d, J = 9 Hz, 2 H), 6.9 (d, J = 9 Hz, 2 H), 4.3 (s, 2 H), 3.8 (s, 3 H), 3.5 (s, 3 H). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 65.05; H, 6.13.

2-(Methoxymethyl)-3-(1-naphthyl)-2-propenoic Acid (3g). Mp 163–164 °C (*n*-PrOH). ^{1}H NMR δ 8.7 (s, 1 H), 8.0 (m, 1 H), 7.9 (m, 2 H), 7.7 (m, 1 H), 7.5–7.6 (m, 3 H), 4.2 (s, 2 H), 3.4 (s, 3 H). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.13; H, 5.73.

2-(Methoxymethyl)-3-(2-naphthyl)-2-propenoic Acid (3h). Mp 143–144 °C (EtOAc). ^{1}H NMR δ 8.2 (s, 1 H), 8.1 (s, 1 H), 7.5–7.9 (m, 6 H), 4.4 (s, 2 H), 3.6 (s, 3 H). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.14; H, 5.77.

2-(Methoxymethyl)-3-(9-anthryl)-2-propenoic Acid (3i). Mp 170–171 °C (*n*-PrOH). ^{1}H NMR δ 8.6 (s, 1 H), 8.5 (s, 1 H), 8.0–8.1 (m, 4 H), 7.5–7.6 (m, 4 H), 4.0 (s, 2 H), 3.0 (s, 3 H). Anal. Calcd for $C_{19}H_{16}O_3$: C, 78.06; H, 5.52. Found: C, 77.78; H, 5.57.

2-(Methoxymethyl)-3-(2-furyl)-2-propenoic Acid (3j). Mp 133–134 °C (MeCN). ^{1}H NMR δ 7.7 (s, 1 H), 7.6 (d, J = 1.5 Hz, 1 H), 6.8 (d, J = 3.5 Hz, 1 H), 6.6 (d/d, J = 3.5/1.5 Hz, 1 H), 4.6 (s, 2 H), 3.4 (s, 3 H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.30; H, 5.43.

2-(Methoxymethyl)-3-(3-furyl)-2-propenoic Acid (3k). Mp 83–84 °C (EtOAc). ^{1}H NMR δ 7.9 (s, 1 H), 7.8 (d, J = 1.5 Hz, 1 H); 7.5 (t, J = 1.5 Hz, 1 H); 6.7 (d, J = 1.5 Hz, 1 H), 4.4 (s, 2 H), 3.4 (s, 3 H). Anal. Calcd for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.24; H, 5.56.

2-(Methoxymethyl)-3-(2-thienyl)-2-propenoic Acid (3l). Mp 125–126 °C (EtOAc). ^{1}H NMR δ 8.2 (s, 1 H), 7.6 (d, J = 5Hz, 1 H), 7.4 (d, J = 3.5 Hz, 1 H), 7.1 (d/d, J = 5/3.5 Hz, 1 H), 4.5 (s, 2 H), 3.5 (s, 3 H). Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08; S, 16.17. Found: C, 54.41; H, 5.19; S, 15.85.

2-(Methoxymethyl)-3-(1-methyl-2-indolyl)-2-propenoic Acid (3m). Mp 158–159 °C (dec, EtOAc). ^{1}H NMR δ 8.1 (s, 1 H), 7.7 (d, J = 8 Hz, 1 H), 7.3–7.5 (m, 2 H), 7.1–7.2 (m+s, 2 H), 4.4 (s, 2 H), 3.8 (s, 3 H), 3.5 (s, 3 H). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.29; H, 6.12; N, 5.64.

(8) Baylis, A. B.; Hillman, M. E. D. Ger. Offen. DE 2,155,113 (1972). Hillman, M. E. D.; Baylis, A. B. U.S. Patent 3,743,669 (1973). Review: Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.

(9) Hubschwerlen, C.; Charnas, R.; Angehrn, P.; Furlenmeier, A.; Graser, T.; Montavon, M. *J. Antibiot.* **1992**, *45*, 1358 and references cited therein.

(10) Beech, W. F.; Legg, N. *J. Chem. Soc.* **1950**, 2806. Eagan, M. C.; Cromwell, N. H. *J. Org. Chem.* **1974**, *39*, 3863.

(11) With some of the higher molecular weight aldehydes the sodium salt of the acid precipitated at this point. The mixture was cooled with ice, and the salt was collected by filtration and converted into the acid as described.

2-(Methoxymethyl)-3-(2-benzofuryl)-2-propenoic Acid (3o). Mp 150–152 °C (EtOAc). ^{1}H NMR δ 7.8 (s, 1 H), 7.6 (d, J = 8 Hz, 1 H), 7.5 (d, J = 8 Hz, 1 H), 7.4 (m, 1 H), 7.3 (m, 1 H), 7.2 (s, 1 H), 4.7 (s, 2 H), 3.5 (s, 3 H). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.95; H, 5.17.

2-(Bromomethyl)-3-phenyl-2-propenoic Acid (4a). General Procedure for the Synthesis of Acids 4. Crude acid **3a**, prepared as described above from 7.62 g of benzaldehyde, was warmed until it melted, 70 mL of 30% HBr in acetic acid was added, and the mixture was stirred in a 60 °C bath for 30 min. The product started to precipitate within a few minutes. The mixture was poured onto ice and extracted with $CHCl_3$. Crystallization from EtOAc gave 11.28 g (53% from benzaldehyde) of **4a** in two crops, mp 162–163 °C (lit.[12] 160–162 °C).^{1}H NMR δ 8.0 (s, 1 H); 7.6 (m, 2 H); 7.4–7.5 (m, 3 H) , 4.4 (s, 2 H). ^{13}C NMR [$(CD_3)_2CO$] δ 26.9; 128.8, 129.1, 129.5, 129.6, 134.3, 142.3, 166.4. Anal. Calcd for $C_{10}H_9BrO_2$: C, 49.82; H, 3.76; Br, 33.15. Found: C, 49.71; H, 3.66; Br, 33.23.

2-(Bromomethyl)-3-(1-naphthyl)-2-propenoic Acid (4g). Mp 218–219 °C (anisole). ^{1}H NMR [$(CD_3)_2CO$] δ 8.5 (s, 1 H), 8.0–8.1 (m, 3 H), 7.9 (d/d, J = 6/1 Hz, 1 H), 7.6–7.8 (m, 3 H), 4.6 (s, 2 H). Anal. Calcd for $C_{14}H_{11}BrO_2$: C, 57.76; H, 3.81; Br, 27.45. Found: C, 57.97; H, 3.89; Br, 27.70.

2-(Bromomethyl)-3-(9-anthryl)-2-propenoic Acid (4i). Mp 221 °C (dec, anisole). ^{1}H NMR δ 8.7 (s, 1 H), 8.5 (s, 1 H), 8.1 (m, 2 H), 8.0 (m, 2 H), 7.5–7.6 (m, 4 H), 4.0 (s, 2 H). Anal. Calcd for $C_{18}H_{13}BrO_2$: C, 63.36; H, 3.84; Br, 23.43. Found: C, 63.20; H, 3.83; Br, 23.34.

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