α-Alkoxyacrylic Acids from α-Keto Acids

Robert B. Bates* and Sriyani Caldera

Department of Chemistry, University of Arizona, Tucson, Arizona 85721

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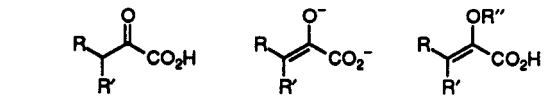
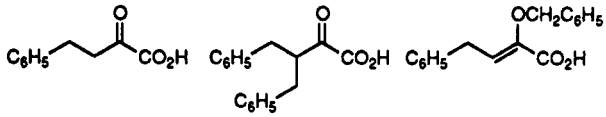
Success in making and alkylating the dianion from 2,3-dimethyl-1,3-butadiene[1] prompted us to try analogous chemistry with dianions **2**. We wish to report that dianions **2** can be prepared in high concentration from the corresponding α-keto acids **1** and that their methylation and primary alkylation on oxygen provide good routes to α-alkoxyacrylic acids **3**.



1 **2** **3**

	R	R′
a	H	H
b	Me	H
c	Me	Me



4 **5** **6**

Some α-alkoxyacrylic acids (**3**) have been prepared previously by multistep routes,[2-7] which include a method for making higher members of the series **3a**, R″ ≠ Me, from **3a**, R″ = Me, and alcohols with palladium(II) catalysis.[8]

The best base–solvent system for generating dianions **2** was found to be Lochmann's base (*n*-butyllithium/potassium *tert*-butoxide) in THF–hexane. HMPA was added to all reactions after it was found to double the yield in reaction 1 (Table I).

As can be seen in Table I, dialkyl sulfates gave the best yields, but halides, tosylates, and triflates can also be used. The only *secondary* alkyl reagent we tried was isopropyl bromide, which gave only 5% yield; fortunately, α-isopropoxyacrylic acid (**3a**, R″ = *i*-Pr) can be made from α-methoxyacrylic acid (**3a**, R″ = Me) by exchange.[8]

As alkyl groups were added to the β-carbon of pyruvic acid (**1a**), the reactions went in progressively lower yields. Thus, 2-oxobutanoic acid (**1b**) gave (*Z*)-2-alkoxy-2-butenoic acids **3b** in 65% yield with >99% stereoselectivity (NMR) and 3-methyl-2-oxobutanoic acid (**1c**) gave 3-methyl-2-alkoxy-2-butenoic acids **3c** in 12–30% yield.

A 2:1 mixture of (*Z*)-2-ethoxy-2-butenoic acid (**3b**, R″ = Et) and its stereoisomer had been inadvertently prepared by a nonstereoselective method;[7] the reported NMR assignments for the stereoisomers (made on unstated grounds) are reversed and the reported chemical shifts are all too small by about 0.10 ppm. We base our NMR assignments on the expectations that (1) R and R′ will absorb farther downfield in the ^{1}H NMR spectra when they are *Z* to the carbonyl group[9] and (2) The *Z* geometry should be greatly preferred for dianion **2b** due to steric hindrance between the methyl and carboxylate groups in the *E* isomer.[10]

Table I. Reactions of Dianions from α-Keto Acids 1 with Alkylating Agents RY

reactn no.	starting acid	RY	time, days	product	% yield[a]
1	**1a**	Me_2SO_4	0.5	**3a**, R″ = Me	96 (80)
2	**1a**	MeOTf	0.5	**3a**, R″ = Me	20
3	**1a**	Et_2SO_4	1	**3a**, R″ = Et	60 (50)
4	**1a**	EtOTs	1	**3a**, R″ = Et	50
5	**1a**	EtOTf	1	**3a**, R″ = Et	50
6	**1a**	EtBr	6	**3a**, R″ = Et	35
7	**1a**	EtI	6	**3a**, R″ = Et	15
8	**1a**	BnBr	1.5	**3a**, R″ = Bn	20
9	**1b**	Me_2SO_4	1	**3b**, R″ = Me	65
10	**1b**	MeOTf	0.5	**3b**, R″ = Me	35
11	**1b**	Et_2SO_4	4	**3b**, R″ = Et	65
12	**1b**	EtOTf	1	**3b**, R″ = Et	60 (50)
13	**1c**	Me_2SO_4	0.5	**3c**, R″ = Me	30
14	**1c**	MeOTf	0.5	**3c**, R″ = Me	0
15	**1c**	Et_2SO_4	1	**3c**, R″ = Et	12

[a] Yield by NMR (isolated yield in parentheses).

We observed only small amounts of C-alkylation accompanying most of the desired O-alkylations. The largest amount of C-alkylation was observed in reaction 7 with benzyl bromide, which gave the simple C-alkylation product **4** in 8% yield and its further C- and O-alkylation products **5** and **6** in ca. 2% yield each. C-Alkylation of pyruvic acid has been accomplished indirectly via the dianion of pyruvic acid dimethylhydrazone in 70% yield with an *n*-butyl halide and in 48% yield with an isopropyl halide.[11]

α-Alkoxyacrylic acids **3** are useful intermediates in several kinds of reactions.[7,10-12] Esters of the less sterically hindered acids **3** have been used as monomers, especially subject to *radical* polymerization due to captodative stabilization of the radicals which they give upon addition of a radical at the 3-position.[13] Two α-alkoxyacrylic acids (5-enolpyruvylshikimic acid 3-phosphate and chorismic acid) are key intermediates in the shikimic acid biosynthetic pathway.[14]

Experimental Section

α-Keto acids **1a** and **1b**, the sodium salt of **1c**, and potassium *tert*-butoxide were used as purchased from Aldrich Co. TLC was carried out on silica gel using petroleum ether/methanol/

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acetic acid (8/1/0.5) and double elution. NMR spectra were obtained on a Bruker WM-250 instrument in $CDCl_3$ with TMS as an internal standard. Reactions were carried out under argon.

α-Alkoxyacrylic Acids 3. To a stirred three-necked round-bottom flask containing potassium *tert*-butoxide (1.0 g, 9 mmol) in THF (20 mL) at −70 °C was added the pyruvic acid (**1a** or **1b**, 3.6 mmol) in 5 mL of THF over 5 min. For **1c**, the sodium salt (3.6 mmol) was added directly to the flask. HMPA (5 mL) and THF (20 mL) were added through an addition funnel. After 20 min, BuLi in hexane (1.6 M, 7 mL, 11.2 mmol) was added over 5 min. After 1 h at -70 °C, electrophile (10.5 mmol) was added over 5 min to the suspension (yellow for **2a** and **2b**, orange for **2c**) and the mixture was allowed to warm to 25 °C and then stirred for the indicated time. Yields were measured by NMR as a function of time, with the maximum yield at the time given in the table.

The volume was reduced to 10 mL by rotary evaporation. (For yield estimates, evaporation was continued to remove THF, and the NMR of the residue was measured in D_2O using a weighed amount of sodium 3-(trimethylsilyl)-1-propanesulfonate as an internal shift and quantitative standard.) To isolate the product, 5 mL of water was added to dissolve the suspension. One or two pellets of KOH were added if the solution was not strongly basic. The layers were separated and the organic layer was washed with 5 mL of water. The water layers were washed 10 × 5 mL of chloroform to remove HMPA and the organic layers were discarded. The aqueous layer was acidified to pH 2–3 in an ice bath with 10% HCl and extracted 5 × 10 mL of ether. The combined organic layers were dried ($MgSO_4$). The solvent was removed by rotary evaporation and the residue was analyzed by NMR. Acids **3–6** all crystallized. Acids **3** were purified by recrystallization (from petroleum ether, except where noted) and/or preparative TLC (silica gel extracted with ethyl acetate). Minor byproducts **4–6** detected by NMR were not purified. Satisfactory elemental analyses were obtained on the new acids **3** (**3a**, R″ = Bn; **3b**, R″ = Me; **3c**, R″ = Me and Et). Melting points and NMR parameters of acids **3–6** are as follows.

α-Methoxyacrylic acid (3a, R″ = Me): mp 51–52 °C (lit.[4] mp 52 °C); ^1H NMR δ 3.66 (s), 4.70 (d, J = 2.9 Hz), 5.40 (d, J = 2.9 Hz); ^{13}C NMR δ 55.5, 94.7, 151.2, 166.1.

α-Ethoxyacrylic acid (3a, R″ = Et): mp 56–58 °C (lit.[2] mp 62 °C); ^1H NMR δ 1.38 (t, J = 7.0 Hz), 3.85 (q, J = 7.0 Hz), 4.65 (d, J = 2.5 Hz), 5.40 (d, J = 2.5 Hz); ^{13}C NMR δ 14.0, 64.3, 95.7, 150.1, 167.5.

α-(Benzyloxy)acrylic acid (3a, R″ = Bn): mp 96–96.5 °C after recrystallization from ethyl acetate–petroleum ether; ^1H NMR δ 4.81 (d, J = 2.9 Hz), 4.90 (s), 5.57 (d, J = 2.9 Hz), 7.38 (m); ^{13}C NMR δ 70.8, 97.0, 127.5, 128.3, 128.7, 135.3, 149.7, 166.4.

(*Z*)-2-Methoxy-2-butenoic acid (3b, R″ = Me): mp 54–55 °C; ^1H NMR δ 1.83 (d, J = 7.2 Hz), 3.69 (s), 6.52 (q, J = 7.2 Hz); ^{13}C NMR δ 11.4, 60.1, 127.0, 146.2, 169.0.

(*Z*)-2-Ethoxy-2-butenoic acid (3b, R″ = Et): mp 50–51 °C; ^1H NMR δ 1.31 (t, J = 7.2 Hz), 1.83 (d, J = 7.0 Hz), 3.90 (q, J = 7.2 Hz), 6.56 (q, J = 7.0 Hz); ^{13}C NMR δ 11.6, 15.3, 68.1, 127.2, 145.1, 169.4.

3-Methyl-2-methoxy-2-butenoic acid (3c, R″ = Me): mp 70–71 °C; ^1H NMR δ 1.93 (s), 2.13 (s), 3.60 (s); ^{13}C NMR δ 20.2, 20.3, 59.7, 140.8, 147.5, 168.9.

3-Methyl-2-ethoxy-2-butenoic acid (3c, R″ = Et): mp 53–54 °C; ^1H NMR δ 1.31 (t, J = 7.0 Hz), 1.92 (s), 2.13 (s), 3.77 (q, J = 7.0 Hz); ^{13}C NMR δ 15.2, 20.1, 20.6, 68.0, 139.2, 140.5, 168.7.

4-Phenyl-2-oxobutanoic acid (4): ^1H NMR δ 2.98 (t, J = 7.3 Hz), 3.26 (t, J = 7.3 Hz), 7.25 (m).

4-Phenyl-3-benzyl-2-oxobutanoic acid (5): ^1H NMR δ 2.73 (dd, J = 14.0, 6.8 Hz), 3.04 (dd, J = 14.0, 8.1 Hz), 4.00 (p, J = 7.5 Hz).

(Z)-2-(Benzyloxy)-4-phenyl-2-butenoic acid (6): ^1H NMR δ 3.47 (d, J = 7.8 Hz), 4.94 (s), 6.57 (t, J = 7.8 Hz).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra of acids **3-6** (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.