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Note

A simple synthesis of α-methyl-γ-keto acids

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The reaction of the anion derived from α-marpholinonitriles with methyl acrylate in excess of NaH in DMF gives γ-keto acids in high yield. This process is highly convenient for the synthesis of various α-substituted-γ-keto acids, which can be easily converted to naturally occurring α-substituted -γ-lactones.

Keywords: Morpholinoacetonitrile, γ-keto acids, conjugate addition, enolate alkylation, lactone

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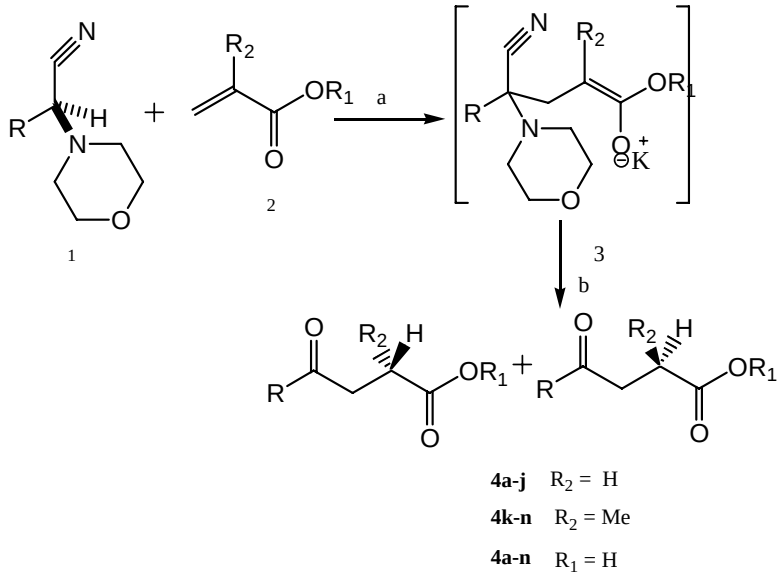
γ-Keto acids are highly useful compounds in organic synthesis. It can be used for synthesis of 5-membered heterocyclic compound like β-lactum antibiotics[1-2], lactonic sexphermones[3] pyridoxines, piperidines, pyrrolidines[4] lactones[5], dihydronaphthalenes[6], lignans[7] etc. Due to its biological importance, large amount of work devoted to develop synthetic routes for synthesis of γ-keto acids. There are several methods for synthesis of γ-keto acids[8-11], such as photo oxygenation of 5-hydroxymethyl-2-furfural followed by reduction[12], conversion of γ-lactones to γ-keto acids by using base and alkylating agent[13-17]. The stereoselective 2-alkyl and 2,2-dialkyl-γ-keto acids were prepared from γ-keto acids in multisteps sequence as given by Meyer *et al.*[18]. But these methods have some restrictions such as multistep sequences, high temperature requirement etc. Due to its importance in organic synthesis new method has been developed for synthesis of α-methyl-γ-keto acids from α-morpholinoacetonitrile. α-Morpholinoacetonitrile can be easily prepared in gram scale from corresponding aldehyde.

In this method α-substituted-γ-keto acids are conveniently prepared by conjugate addition of α-morpholinoacetonitrile to methyl methacrylate or methyl acrylate in dry NaH/DMF solution (**Scheme I**). The reaction mixture acidified with dil. HCl (*2N*) followed by extraction in ether, which gave α-methyl-γ-keto acids in high yield.

α-Morpholinoacetonitriles are prepared from corresponding aldehydes by using reported procedure[19]. Our results represent simple and convenient synthesis of γ-keto acids from the corresponding aldehydes. γ-Keto acids are prepared from α-morpholinonitriles in one pot synthesis. The required α-marpholinonitriles in dry DMF, NaH in excess was added; reaction mixture was stirred for half an hr to ensure complete formation of carbanion. A solution of acrylate in dry DMF was added slowly in reaction mixture at 0^{o}C and stirred for 2-3 hr at room temperature. Reaction mixture was acidified with dil. HCl and product formed was extracted with ether. Ether layer was washed with sodium bicarbonate solution and water layer was acidified with conc. HCl. White precipitate of γ-keto acids was filtered and purified by column chromatography. The determination of purity was made by HPLC analysis using column RP C18 Lichrocart 12.5 cm in buffer solution (*p*H = 3) with 20% acetonitrile for evolution at 25°C and UV detection at 254 nm (retention time at flow rate 0.5 mL/min). Results are summarized in **Table I**.

It was reported that using hydrochloric acid could deprotect the morpholine group. Sodium hydride in DMF is sufficient stronger base to bring about safonification under reaction condition. This simultaneous process resulted into simple synthesis of γ-keto acids. This one pot synthesis of γ-keto acid from α-morpholinoacetonitrile is much more economical. The use of methylacrylate was proved feasible for sequential alkylation's to give regio and stereoselectivity. Chelation of alkali metal with neighbouring morpholine group might be responsible for the geometrical presence. Now we would like to examine this reaction with variety of carbon electrophile and their stereochemistry. In this reaction the minor product isolated as amides in 5-15% yield. The formation of amide indicates that atmospheric oxygen has been used in reaction.

This method can be used for synthesis of α-substituted-γ-keto acids. This method has been developed for the synthesis of regio and stereoselective synthesis of α-substituted-γ-keto acids. α-Substituted-γ-keto acids can be easily converted to naturally occurring α-substituted-γ-lactones.



4a-j R_2 = H

4k-n R_2 = Me

4a-n R_1 = H

a. NaH in DMF at rt, 2-3 hr; b. HCl (6*N*).

Scheme I

Table I — Characterization of γ-Keto acids

Compd	R-group	R_2	m.p./b.p.°C	Yield (%)	Retention time (min)	Purity (%)
4a	4,OMe-C_6H_4-	H	130-32	90	2.14	91.4
4b	3,4, (-OMe)$_{2-}$ C_6H_3-	H	146-48	92	2.30	89.7
4c	4,Cl-C_6H_4-	H	193-95	85	2.56	96.7
4d	2,4, (-OMe)$_{2-}$ C_6H_3-	H	126-28	88	2.29	90.5
4e	C_6H_5-	H	107-09	89	2.33	94.3
4f	CH_3	H	Oil	78	-	-
4g	CH_3-CH_2-	H	Oil	82	-	-
4h	CH_3-CH_2-CH_2-	H	Oil	83	-	-
4i	CH_3-CH-CH_3	H	Oil	75	-	-
4j	3,NO_2-C_6H_4-	H	58	65	2.95	75.6
4k	4, OMe-C_6H_4-	Me	125-27	80	2.23	98.5
4l	3,4, (-OMe)$_{2-}$ C_6H_3-	Me	72-74	84	2.36	97.8
4m	4,Cl-C_6H_4-	Me	184-86	79	2.75	77.8
4n	C_6H_5-	Me	110-12	78	2.45	84.0

Experimental Section

All melting points or boiling points were determined that indicate oil-bath temperature and are uncorrected. IR spectra were determined on a Perkin-Elimer spectrometer model 1615. ^{1}H NMR spectra were determined for all compounds reported in Varian spectrometer (300 MHz) in $CDCl_3$. The determination of purity was made by HPLC analysis using column RP C^{18} Lichrocart 12.5 cm in buffer solution (*p*H = 3) with 20% acetonitrile for evolution at 25°C and UV detection at 254 nm (retention time at flow rate 0.5 mL/min, retention time of compounds are given in **Table I**). Mass spectra (GCMS) were recorded on a Shimadzu Q 5050 instrument. Progress of reaction was checked by TLC analysis. Analytical value of C, H, and N for all compounds was observed as calculated.

General procedure: Preparation of γ-keto acids 4a-4n. A solution of α-aryl-4-morpholineacetonitrile (10 mmole) in DMF was added dropwise to NaH (10 mmole) solution in DMF at 0°C with constant stirring for 30 min. Methyl acrylate/methyl methacrylate (12 mmole) in DMF was added to solution at 0°C and stirring continued for 2-3 hr at room temp. After

complete disappearances of starting material, reaction mixture was acidified with (6*N*) HCl and water was added to reaction mixture. Product was extracted in ether and washed with sodium bicarbonate solution. Aqueous layer acidified with conc. HCl gives white precipitate of acids or oil of acids in excellent yield.

4-Oxo-4-(4-methoxyphenyl)-4-butyric acid 4a: IR (nujol): 3350, 1695, 1664, 1600-1512 cm^{-1}, ^1H NMR: 2.8 (t, *J* = 6Hz, 2H), 3.28 (t, *J* = 6Hz, 2H), 3.9 (s, 3H), 6.95 (d, *J* = 8 Hz, 2H), 7.98 (d, *J* = 8 Hz, 2H). MS (m/z): 51, 77, 107, 135, 208 (M^+).

4-Oxo-4- (3,4-dimethoxyphenyl)-4-butyric acid 4b: IR (nujol): 3350, 1693, 1663, 1600-1512 cm^{-1}, ^1H NMR: 2.8 (t, *J* = 6Hz, 2H), 3.28 (t, *J* = 6Hz, 2H), 3.93 (s, s, 6H), 6.88 (d, *J* = 8.1 Hz, 1H), 7.5 (s, 1H), 7.61 (d, *J* = 8.3Hz, 1H). MS (m/z): 51, 77, 137, 165, 238 (M^+).

4-Oxo-4-(4-chlorophenyl)-4-butyric acid 4c: IR (nujol): 3340, 1690, 1667, 1600-1520 cm^{-1}, ^1H NMR: 2.83 (t, *J* = 6Hz, 2H), 3.3 (t, *J* = 6Hz, 2H), 7.3-7.38 (d, *J* = 6.51Hz, 2H), 7.88-7.92 (d, *J* = 6.5Hz, 2H), MS (m/z): 51, 111, 140, 213 (M^+).

4-Oxo-4-(2,4-dimethoxyphenyl)-4-butyric acid 4d: IR (nujol): 3350, 1692, 1663, 1600-1514 cm^{-1}, ^1H NMR: 2.82 (t, *J* = 6Hz, 2H), 3.28 (t, *J* = 6Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 6.84 (d, *J* = 7.6 Hz, 1H), 7.4 (d, *J* = 7.6 Hz, 1H), 7.51 (s, 1H), MS (m/z): 51, 77, 137, 165, 238 (M^+).

4-Oxo-4-phenyl-4-butyric acid 4e: IR (nujol): 3346, 1695, 1661, 1600-1500 cm^{-1}, ^1H NMR: 2.86 (t, *J* = 6Hz, 2H), 3.28 (t, *J* = 6Hz, 2H), 7.44-7.502 (t, *J* = 5.3Hz, 2H), 7.56 (d, *J* = 3.3Hz, 1H), 7.95 (d, *J* = 8.2Hz, 2H), MS (m/z): 51, 77, 105, 178 (M^+).

4-Oxo-pentanoic acid 4f: ^1H NMR: 2.12 (s, 3H), 2.64 (t, 2H), 2.79 (t, 2H), 5.65 (bs, 1H).

4-Oxo-hexanoic acid 4g: ^1H NMR: 1.13 (t, 3H, *J* = 6.4 Hz), 2.53 (q, 2H, *J* = 6.4 Hz), 2.62 (t, 2H), 2.76 (t, 2H), 5.55 (bs, 1H).

4-Oxo-heptanoic acid 4h: ^1H NMR: 1.09 (t, 3H, *J* = 6.4 Hz), 1.22 (m, 3H), 2.60 (t, 2H, *J* = 6.7 Hz), 3.24-3.38 (m, 4H), 5-5.5 (bs, 1H).

5-Methyl-4-oxo-hexanoic acid 4i: ^1H NMR: 1.23 (dd, 6H), 2.62 (t, 2H, *J* = 6.2 Hz), 2.97 (m, 1H), 3.24-3.38 (m, 2H), 5-5.5 (bs, 1H).

2-Methyl-4-oxo-4-(4-methoxyphenyl)-4-butyric acid 4k: IR (nujol): 2670 broad, 1706, 1680, 1599, 1508 cm^{-1}, ^1H NMR: 1.31 (d, *J* = 6.9 Hz, 3H), 2.98-3.064 (dd, *J* = 7.5, 2 Hz, 1H), 3.095-3.18 (m, 1H), 3.37-3.46 (dd, *J* = 7.8, 2 Hz, 1H), 3.87 (s, 3H), 6.93 (d, *J* = 8 Hz, 2H), 7.95 (d, *J* = 8 Hz, 2H). MS (m/z): 51, 56, 77, 92, 107, 122, 135, 220 (M^+).

2-Methyl-4-oxo-4-(3,4-dimethoxyphenyl)-4-butyric acid 4l: IR [nujol]: 3368, 1706, 1607, 1599, 1509 cm^{-1}, ^1H NMR: 1.32 (d, *J* = 7.23 Hz, 3H), 2.9-3.078 (dd, *J* = 7.5, 2.1Hz, 1H), 3.08-3.16 (m, 1H), 3.4–3.49 (dd, *J* = 7.6, 2.1 Hz, 1H), 3.93 (s, 3H), 3.95 (s, 3H), 6.89 (d, *J* = 8.1 Hz, 1H), 7.52 (s, 1H), 7.61 (d, *J* = 8.3Hz, 1H), MS (m/z): 51, 56, 77, 92, 107, 122, 137, 165, 251 (M^+).

2-Methyl-4-oxo-4-(4-chlorophenyl)-4-butyric acid 4m: IR [nujol]: 3340, 1708, 1687, 1592, 1457 cm^{-1}, ^1H NMR: 1.3 (d, *J* = 7.3Hz, 3H), 2.9-3.061 (dd, *J* = 6.3, 1.9Hz, 1H), 3.074-3.168 (m, 1H), 3.4-3.49 (m, 1H), 7.3-7.4 (d, *J* = 6.51Hz, 2H), 7.9-7.99 (d, *J* = 6.5Hz, 2H).

2-Methyl-4-oxo-4-phenyl-4-butyric acid 4n: IR [nujol]: 1705, 1677, 1595, 1530, 1408, 1313, 947 cm^{-1}, ^1H NMR: 1.31 (d, *J* = 7.5Hz, 3H), 2.9-3.051 (dd, *J* = 7.2, 2.1Hz, 1H), 3.07-3.201 (m, 1H), 3.4-3.49 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.44-7.502 (t, *J* = 5.3Hz, 2H), 7.56 (d, *J* = 3.3Hz, 1H), 7.99 (d, *J* = 8.2Hz, 2H). MS (m/z): 51, 56, 77, 05, 191 (M^+).

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