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KOH-PROMOTED REACTION OF C,O,O-TRIS(TRIMETHYLSILYL) KETENE ACETAL WITH ALDEHYDES: PRACTICAL AND EASY ACCESS TO (E)-α,β-ETHYLENIC CARBOXYLIC ACIDS

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KOH-PROMOTED REACTION OF C,O,O-TRIS(TRIMETHYLSILYL) KETENE ACETAL WITH ALDEHYDES: PRACTICAL AND EASY ACCESS TO (*E*)-α,β-ETHYLENIC CARBOXYLIC ACIDS

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ABSTRACT

The use of a catalytic amount of KOH has been found to be very efficient in promoting reaction of silylketene acetal **1** with aldehydes **2** to afford the corresponding (*E*)-α,β-ethylenic carboxylic acids **3** under very mild conditions.

Conjugated (*E*)-ethylenic carboxylic acids have great importance in synthetic chemistry, and new methods are constantly sought with the aim of obtaining more simple and efficient routes to prepare them with high *E* stereoselectivity. We have recently reported the use of Lewis acids and fluorides as catalysts in the reaction of C,O,O-tris(trimethylsilyl)ketene acetal **1** with aldehydes **2**, leading to the corresponding alkenoic acids **3**.[1]

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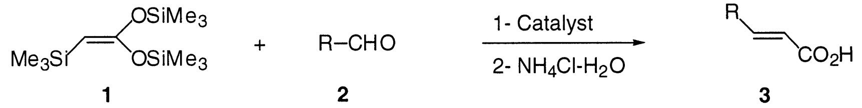


Scheme.

We have found that solid KOH can induce cleavage of the O-Si bond of trimethylsilylenols at room temperature. The enolate generated in situ can efficiently be used in aldolization reactions.[2] The simplicity with which solid KOH can be handled, therefore, encouraged us to explore its potential as a catalyst for the direct synthesis of unsaturated carboxylic acids **3** by means of the silyl ketene acetal **1** (Scheme). We report herein our findings of this investigation.

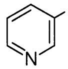
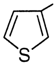
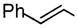
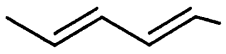
We first examined the reaction of **1** with benzaldehyde to determine the best conditions for this aldolization-olefination process. Potassium hydroxide (1%) is indeed an excellent promoter for this reaction. Too much catalyst is harmful, probably because of the retrograde aldol reaction. The use of *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO) as solvent seems to be essential, since most of the benzaldehyde was recovered when the reaction was performed in tetrahydrofuran (THF). It is noteworthy that the reaction is very clean and, in all cases, no side-products were observed.

Finally, in order to check the generality of this new procedure, a large array of aldehydes was used. The results are summarized in the Table.

The reaction was exceptionally effective with aromatic as well as aliphatic aldehydes. Non-enolizable aromatic aldehydes with electron-withdrawing or electron-donating groups give in all cases the desired α,β-ethylenic carboxylic acids **3** in good yields and with a total *E* stereoselectivity. Unsaturated aldehydes undergo 1,2-addition exclusively, leading to the corresponding conjugated alkenoic acids. It is of interest to notice that, from a synthetic viewpoint, the reaction was also quite efficient with enolizable aldehydes. Moreover, the use of KOH is also quite effective in the reaction of **1** with phenylacetaldehyde, leading to (*E*)-4-phenyl-2-butenoic acid[17] **3j**, which is difficult to obtain by other methods.

In conclusion, the results reported here show that solid KOH (1%) is an extremely useful alternative promoter to Lewis acids and fluorides, which are usually used in the aldol-type reactions of silyl enol ethers. The use of KOH constitutes a significant improvement because of its low cost, reduced health hazard, and ease in handling.

Table. Conversion of Aldehydes **2** into Acids **3** by Means of Silylketene Acetal **1**

Acids **3**	R	Time (h)	Yield (%)	Lit. Yield (%)	M.p. (°C)	Lit. m.p. (°C)
3a	Ph–	0.5	96	92[3]	132–133	132[3]
3b	p-NCPh–	4.0	70	50[4]	256	255–256[12]
3c	p-O$_2$NPh–	3.5	80	95[3]	286	286[3]
3d	p-(Me)$_2$NPh–	5.0	75	69[5]	230–232	233–235[13]
3e	m-PhOPh–	5.0	94	80[6]	111–112	111–113[6]
3f		4.0	93	45[7]	233	232–235[14]
3g		4.0	88	78[8]	146–148	146–147[15]
3h		5.0	86	79[3]	164–166	163[3]
3i		4.0	81	56[9]	186–187	187[9]
3j	PhCH$_2$–	1 min	55	3[10]	62–63	64–65[16]
3k	nC$_7$H$_{15}$–	5.0	76	65[11]	oil	oil[11]

EXPERIMENTAL

All experiments were carried out under a nitrogen atmosphere. Unless otherwise noted, starting materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone prior to use. Chlorotrimethylsilane was distilled from magnesium. Diisopropylamine was distilled from CaH$_2$ and stored over molecular sieves. Lithium diisopropylamide (LDA) was prepared in situ according to the method of Gaudemar.[18] Chemical shifts are given in ppm (*J* in Hz) relative to TMS. TLC monitoring was performed using a mixture of cyclohexane–ethyl acetate as eluent (70/30).

Preparation of C,O,O-Tris(trimethylsilyl)ketene Acetal 1

To a cooled (−80°C) solution of LDA prepared from phenanthrene (2.3 g, 12.5 mmol), diisopropylamine (11.1 g, 0.11 mol), hammered lithium (0.7 g, 0.1 mol) in ether (20 mL)-THF (20 mL) was added a solution of trimethylsilyl α-trimethylsilylated acetate[19] (14.28 g, 0.07 mol) in THF (10 mL) during 30 min. The resulting mixture was stirred at the same temperature for 1 h, then quenched with chlorotrimethylsilane (13 mL, 0.1 mol) at −80°C. After being stirred at the same temperature for 30 min, the solution was gradually warmed to room temperature and filtered through a pad of Celite. The solvent was removed under reduced pressure and the residue distilled; b.p. 86°C (10 mmHg); yield 91%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H, $Si(CH_3)_3$), 0.17 (s, 9H, $OSi(CH_3)_3$), 0.23 (s, 9H, $OSi(CH_3)_3$), 2.95 (s, 1H, CH=); MS: $M^+ = 276$. Anal. calcd for $C_{11}H_{28}O_2Si_3$: C, 47.76; H, 10.20. Found: C, 47.70; H, 10.15.

Synthesis of Unsaturated Carboxylic Acids 3: Typical Procedure

To a stirred solution of the corresponding aldehyde **2** (1.7 mmol) and reagent **1** (0.552 g, 2 mmol) in 5 mL of DMF, was added solid KOH ($1.1\ 10^{-3}$ g, 0.02 mmol) at room temperature. After being stirred at room temperature until the total disappearance of the starting material, the reaction mixture was then hydrolyzed with a saturated solution of NH_4Cl (20 mL). Acid-basic work-up, to remove any remaining non-acidic material, gave acids **3**, which were purified by recrystallization. The acids were fully characterized by melting points and spectra comparison with authentic samples.

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17. (*E*)-4-Phenyl-2-butenoic acid ($PhCH_2CH=CHCO_2H$) (recrystallized from petroleum ether), m.p. 62°–63°C; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.50 (dd, 2H, $J=6.81$ Hz, $J=1.50$ Hz), 5.77 (dt, 1 H, $J=15.53$ Hz, $J=1.50$ Hz), 7.39 (m, 6H), 11.61 (s, 1H); ^{13}C NMR δ 38.5, 121.6, 126.7, 128.7, 128.8, 137.2, 150.1, 171.8.
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