New One-Pot Preparation of α,β-Unsaturated Carboxylic Acid Esters from Carbonyl Compounds[1]

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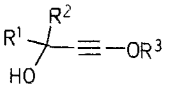
A series of α,β-unsaturated carboxylic acid esters have been prepared by the reaction of carbonyl compounds with alkoxy acetylide anions generated *in situ* from the readily available α-chloroacetaldehyde dialkyl acetals in the presence of lithium diisopropylamide, followed by aqueous acidic work-up.

Recently, a one-pot synthetic procedure for the preparation of 1-alkoxy-1-alkyn-3-ols, **1** by the reaction of alkoxy acetylide anion with carbonyl compounds has been reported.[2] The alkoxy acetylide anion was generated[3] *in situ* by treating α-chloroacetaldehyde dialkyl acetal with sodium amide in ammonia. Interested in the preparation of **1** as potential carbocationic precursors, we report our studies on the reaction of alkoxyacetylide anion with carbonyl compounds, which led to a new simple procedure for the preparation of α,β-unsaturated carboxylic esters.

When benzophenone was treated with methoxyacetylide anion as reported[3] followed by aqueous work-up, we isolated the corresponding methyl-3,3-diphenylacrylate (**3**) in 70 % yield and no expected 1-methyl-1-propyn-3,3-diphenyl-3-ol (**2**) was found. The formation of **3** from **2** can be easily rationalized by an acid catalyzed rearrangement (Meyer-Schuster rearrangement[4]). The reported[2] reaction appears to be general only for unactivated ketones such as 2-pentanone. Even products from unactivated ketones upon aqueous acidic work-up gave the corresponding α,β-unsaturated carboxylic esters in good to moderate yields.



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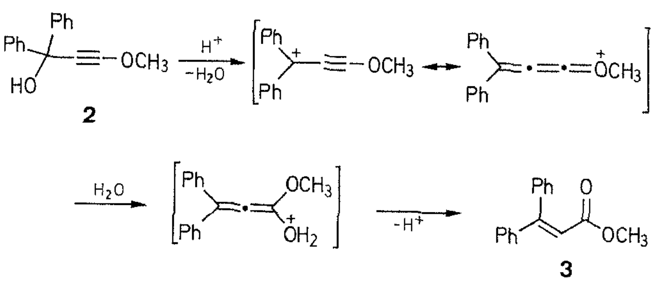

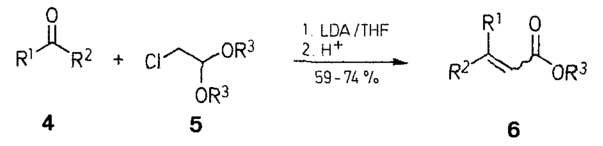

6	R¹	R²	R³	6	R¹	R²	R³
a	Ph	Ph	Me	e	–(CH₂)₅–		Me
b	Me	Ph	Et	f	2-norbornyl		Et
c	H	Ph	Et	g	2-adamantyl		Et
d	Me	Me	Et				

The usual procedure to prepare α,β-unsaturated carboxylic acid esters from carbonyl compounds (i.e., two carbon elongation) involves either the Reformatsky reaction[5] with the methyl bromoacetate with the carbonyl compound followed by dehydration or the well known Wittig procedure of direct olefination by the appropriate phosphonium ylide (Horner–Emmons reaction).[6] The boron trifluoride mediated synthesis of α-β unsaturated esters from alkoxyacetylenes and carbonyl compounds was also reported.[7] Our observation of the formation of α,β-unsaturated esters **6** from the reaction of alkoxyacetylide anions with carbonyl compounds **4** lead us to develop a general one pot procedure for their preparation. During our investigation we also found that alkoxyacetylide anion can be more easily prepared by treating the corresponding chloroacetaldehydedialkyl acetal **5** with lithium diisopropylamide (LDA) in tetrahydrofuran solution. Use of sodamide in low boiling toxic liquid ammonia is unnecessary. The reaction works well both in the case of aldehydes and ketones (activated and unactivated). The yields of the α,β-unsaturated esters are good to moderate (Table). Thus the presently developed one pot procedure to prepare α,β-unsaturated carboxylic esters from the readily available, inexpensive chloroacetaldehyde dialkylacetal should add a useful and convenient method to the existing synthetic arsenal.

Table. α,β-Unsaturated Esters **6** Prepared

Product		Yield (%)	bp (°C/mbar)	Molecular Formula[a] or Lit. bp (°C)/mbar
6a	Methyl 3,3-Diphenylacrylate	71	134/4	194/17[8]
6b	Ethyl 3-Phenylcrotonate (mixture of *E*- and *Z*-isomers, 83 : 17)[b]	64	102/4	146/21[9]
6c	(*E*)-Ethyl Cinnamate	67	103/4	144/20[10]
6d	Ethyl 3,3-Dimethylacrylate	61	51/40	135/10[11]
6e	Methyl Cyclohexylideneacetate	59	115/40	98/27[12]
6f	Ethyl 2′-Norbornylideneacetate (mixture of *E*- and *Z*-isomers, 82 : 18)[b]	72	74/1.3	$C_{11}H_{16}O_2$[c] (180.3)
6g	Ethyl 2′-Adamantylideneacetate	74	108/1.3	$C_{14}H_{20}O_2$[d] (220.3)

[a] Satisfactory microanalyses obtained: C ± 0.31, H ± 0.03.

[b] Determined by GC/MS and ^{1}H-NMR data.

[c] **6f:** IR (KBr): $\nu = 1700, 1650\ cm^{-1}$. MS: *m/z* (%) = 180 ($M^+$, 26); 152 (100). ^{13}C-NMR ($CDCl_3$/TMS): δ = 13.87, 27.28, 28.18, 35.79, 38.49, 39.32, 46.54, 58.73, 108.35, 166.42, 170.14.

[d] **6g:** IR (KBr): $\nu = 1700, 1655\ cm^{-1}$. MS: *m/z* (%) = 220 ($M^+$, 32), 174 (100). ^{13}C-NMR ($CDCl_3$/TMS): δ = 14.24, 27.83, 32.76, 36.75, 39.06, 40.02, 41.29, 59.24, 108.53, 166.89, 172.06.

The starting compounds, α-chlorodimethyl and α-chlorodiethyl acetals, the carbonyl compounds and LDA were commercially available materials and used as such. The THF used was rigorously dried over sodium metal. The authenticity of the products was confirmed by GC/MS, ^{1}H- and ^{13}C-NMR and IR spectroscopic analysis.

α,β-Unsaturated Esters 6; General Procedure:

To a well stirred solution of α-chloroacetaldehyde diethyl acetal (15 mmol) in dry THF (15 mL) maintained at 0 °C under dry N_2 atmosphere is added a 1.5 M solution of LDA in cyclohexane (30 mL, 45 mmol). After the addition the mixture is stirred at 0 °C for another 3 h. To this ice-cold brown mixture is added a solution of ketone (15 mmol) in dry THF (15 mL) dropwise over a period of 5 min. After the addition is complete, the mixture is brought to room temperature and the stirring continued for an additional 3 h. Then the mixture is quenched with 50 mL of 10% aq. H_2SO_4 (50 mL), and the stirring prolonged for 2 h more. The resulting mixture is extracted with diethyl ether (3 × 50 mL) and the organic layer is washed twice with water (100 mL), and dried ($MgSO_4$). The dry organic phase is evaporated under vacuum to an oily brown residue, which on column chromatography over silica gel (with 10% EtOAc in *n*-hexane as eluent) affords the corresponding esters. The isolated esters are characterized by their boiling points (comparison with the literature value) and by spectroscopic methods.

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