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Efficient Preparation of Enol Carbonates by Selective *O*–Acylation of Ketone Sodium Enolates Generated in the Presence of TMEDA.

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Abstract: Generating sodium enolates in the presence of TMEDA followed by inverse addition to chloroformate esters leads cleanly to the *O*–acylated materials and provides a practical means of preparing such derivatives. In the absence of TMEDA mixtures of *O*– and *C*–acylated materials are obtained.

Enol carbonates have general utility as polymer precursors[1] and have also been shown to undergo aldol type condensation with aldehydes in the presence of Pd(II) and Sn(II).[2] Enol carbonates may be prepared readily by esterification of enol chloroformates with the requisite alcohol. However, attempts to generate the requisite enol chloroformate precursors by selective *O*–acylation of enolates (prepared using a wide range bases including sodium hydride, sodamide, lithium 2,2,6,6–tetramethylpiperidide,[3] and HMPA radical anion[4]) with phosgene have met with failure except when bis(keto)mercurials are employed.[5] These latter reagents efficiently provide enol chloroformates suitable for further elaboration, but the process presents toxicity and disposal problems.

The alternative pathway to enol carbonate esters involves selective *O*–acylation of enolates with the requisite chloroformate ester (**Figure 1**) but again the preferred course of reaction is *C*–acylation.[6]

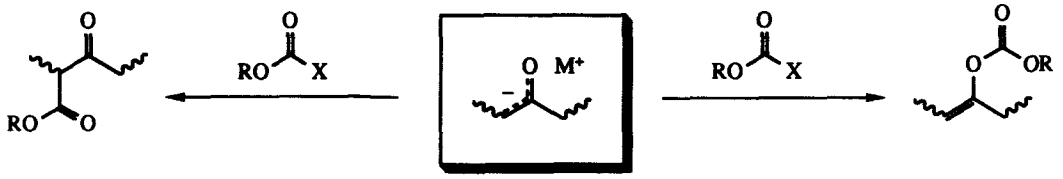
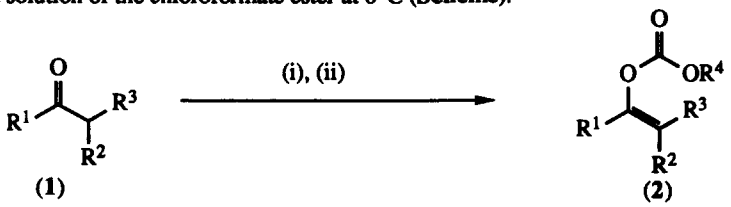


Figure 1

Improved ratios of *O*– *versus* *C*–nucleophilic attack of enolates may be obtained with increasing ionic nature of the enolate species. Thus the increased ionicity of potassium enolates favours *O*–attack;[7] whereas lithium and sodium enolates strongly favour *C*–attack. Industrial patents have described specific sets of conditions which permit selective *O*–acylation of the potassium enolate of acetone generated using potassium hydride.[8] Factors other than the nature of the electrophile and counterion which affect the ratio of *O*– to *C*– attack of enolates include temperature, stoichiometry of the reactants and polarity of the reaction medium.[6] Olofson has addressed the problem of generating enol carbonates and recommends the use of fluorocarbonates for *O*–acylating aldehydes[9] and ketones[10] and has also shown that α,β–unsaturated carbonyl compounds may be *O*–acylated

when the enolate is generated using potassium *t*–butoxide.[11] Enol carbonates have also been obtained by electrochemical generation of enolates from α–bromoketones in the presence of methyl chloroformate.[12] One means of circumventing the difficulties presented by achieving selective *O*–acylation of enolates is provided by the observation that enol esters may be prepared by the catalysed additions of carboxylic acids to alkynes.[13] Nevertheless, selective *O*–acylation of enolates with chloroformate esters remains an attractive proposition if a reliable and operationally simple procedure can be developed.[14]

This communication presents observations on the specific effect of TMEDA upon the ratio of *C*– *versus* *O*–acylation of sodium enolates of a range of ketones. Although intractable mixtures were obtained with a range of commonly used dipolar aprotic additives, generation of sodium enolates in ethereal solvents in the presence of TMEDA led solely to the observation of the desired enol carbonates when the enolate species were quenched by rapid inverse addition to a solution of the chloroformate ester at 0°C (**Scheme**).



(**1**) (**2**)

Reagents and conditions: (i), **Method A:** NaH, TMEDA, THF, reflux; **Method B:** $NaN(SiMe_3)_2$, TMEDA, THF, –78°C

(ii), Inverse addition of enolate solution to $R^4O(CO)Cl$, THF, 0°

Scheme

The enolates derived from saturated ketones were readily generated using sodium hydride (**Method A**), but enolates derived from aryl and α,β–unsaturated ketones were most efficiently generated using sodium hexamethyldisilazide at low temperature (**Method B**).[15] In no instance could the corresponding *C*–acylated materials be detected by GC.–MS. and NMR. analysis of the crude mixtures, making purification of the enol carbonates operationally simple. After standard quenching and work–up, the pure materials were readily obtained by rapid filtration through a plug of silica followed by reduced pressure distillation.[16,17] An impurity sometimes detected when phenyl chloroformate was used as the quench was diphenyl carbonate but this could be readily separated from the desired materials by reduced pressure distillation.

In the case of diethyl ketone, a single geometric isomer was obtained, as evidenced by G.C.–M.S. analysis and N.M.R. analysis of the crude mixture (**Table, entry a**) and n.O.e. difference experiments on the purified material indicated this to be the *E*–isomer (**2a**). Cyclohexanone (**Table, entry c**) and acetophenone (**Table, entry e**) likewise cleanly furnished the enol carbonates, as did cyclic and acyclic unsaturated ketones (**Table, entries f, g**). In the latter case, the enol carbonate (**2g**) obtained was the product of quenching the kinetic enolate of cyclohex–2–enone. The procedure is particularly well suited to the preparation of menthyl isopropenyl carbonate (**2d**), the subject of a series of patents and the initial impetus for this study.[8]

In conclusion, we have been able to demonstrate that the simple expedients of addition of TMEDA to the reaction medium during enolate generation and quenching by rapid inverse addition of this enolate to a solution of the chloroformate ester at 0°C permits selective *O*–acylation of sodium enolates of a range of representative ketones. The procedure is operationally simple and provides a general and ready access to enol carbonates.

2	R^1	R^2	R^3	R^4	Method[15]	Yield (%)[16]
a	Et–	Me–	H–	Ph–	A	43
b	Me_2CH–	Me–	Me–	Ph–	A	85
c	–$(CH_2)_5$–		H–	Ph–	A	48
d	Me–	H–	H–	(–)–menthyl	A	79
e	Ph–	H–	H–	Me–	B	80
f	CH_2=CH–	H–	H–	Ph–	B	30[17]
g	–CH=CH$(CH_2)_2$–		H–	Me–	B	34[17]

Table

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15 *General Procedures for enolate generation:* **Method A:** Sodium hydride (60% dispersion in oil, 1.1 equiv.) was washed under nitrogen with sodium dried hexane and residual hexane removed under vacuum. TMEDA (1 equiv) in THF (1 mLmmol^{-1}) was added to the sodium hydride and the mixture heated to 80°C. The ketone (1 equiv.) was added dropwise *via* a cannula over 15 min. The reaction was stirred for 1 h and cooled to 0°C to give a light grey heterogeneous mixture. **Method B:** The ketone (1 equiv.) was added dropwise over 10 min to a mixture of NaHMDS (1.0 M solution in THF, 1 equiv) and TMEDA (1 equiv.) at –78°C to give a dark green solution.This was stirred for a further 20 min and then allowed to warm to 0°C.
General procedure for quenching the enolate: The enolate solution generated as above was diluted with THF (5 mLmmol^{-1}) and was added rapidly *via* cannula to a solution of the chloroformate ester (1 equiv.) in THF (1 mLmmol^{-1}). After 1 min the reaction was quenched with sat. aq. NH_4Cl and extracted 3 times with Et_2O. The extracts were dried and concentrated *in vacuo*. Rapid filtration of the residue through a pad of silica, eluting with 30:1 hexane:Et_2O, gave material which was further purified by reduced pressure distillation.

16 All novel materials isolated possessed microanalytical and / or spectroscopic data in accord with those expected. Selected data: (**2a**) b.p. 100°C / 0.5 mm Hg; Found C, 69.74, H, 6.38; $C_{12}H_{14}O_3$ requires C, 69.88, H, 6.84 %; ν_{max} (film) 1769, 1703, 1593, 1494, 1459 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.11 (3H, t, *J* 7.5 Hz), 1.66 (3H, d, *J* 7.0 Hz), 2.34 (2H, q, *J* 7.5 Hz); 5.16 (1H, q, *J* 6.9 Hz), 7.24–7.36 (3H, m), 7.38–7.46 (2H, m); $^m/_z$ (CI) 224 (100%, MNH_4^+), 207, 86. (**2b**) b.p. 120°C / 0.7 mm Hg; Found C, 71.97, H, 7.78; $C_{14}H_{18}O_3$ requires C, 71.77, H, 7.74%; ν_{max} (film) 1773, 1594, 1495, 1459 cm^{-1}; δ_H (200 MHz, $CDCl_3$), 1.12 (6H, d, *J* 7.0 Hz), 1.59 (3H, s,), 1.78 (3H), 2.98 (1H, sept, *J* 6.9 Hz), 7.20–7.28 (3H, m), 7.29–7.45 (2H, m); $^m/_z$ (CI) 253 (20 %, MNH_4^+), 236, 235, 96. (**2c**) b.p. 140°C / 0.5 mm Hg; Found C, 71.81, H, 6.12; $C_{13}H_{14}O_3$ requires C, 71.54, H, 6.47%; ν_{max} (film) 1768, 1593, 1495 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 1.63–1.69 (2H, m), 1.70–1.85 (2H, m), 2.11–2.20 (2H, m), 2.21–2.29 (2H, m), 7.20–7.33 (3H, m),7.34–7.45 (2H, m); $^m/_z$ (CI) 236 (100%, MNH_4^+), 219, 98. (**2e**) b.p. 115°C / 0.5 mm Hg; Found C, 67.24, H, 5.57; $C_{10}H_{10}O_3$ requires C, 67.40, H, 5.66%; ν_{max} (film) 1773, 1646, 1441 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.87 (3H, s), 5.16 (1H, d, *J* 2.4 Hz), 5.47 (1H, d, *J* 2.4 Hz), 7.35–7.41 (3H, m), 7.50–7.55 (2H, m); $^m/_z$ (CI) 179 (100%, MH^+), 120. (**2f**) b.p. 90°C / 1.0 mm Hg; Found C, 69.46, H, 5.53; $C_{11}H_{10}O_3$ requires C, 69.46, H, 5.30%; ν_{max} (film) 1777, 1648, 1230 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.10 (1H, m), 5.19 (1H, m), 5.32 (1H, d, *J* 11.1 Hz), 5.59 (1H, d, *J* 17.4 Hz), 6.35 (1H, dd, *J* 17.4, 11.1Hz), 7.23–7.32 (3H, m), 7.38–7.47 (2H, m). (**2g**) b.p. 105°C / 1.0 mm Hg; ν_{max} (film) 1761, 1661, 1567, 1442 cm^{-1}; δ_H (200 MHz, $CDCl_3$), 2.22-2.38 (4H, m), 3.84 (3H, s), 5.45–5.48 (1H, m), 5.74–5.79 (1H, m), 5.80–5.99 (1H, m) ; $^m/_z$ (CI), 172 (MNH_4^+), 155, 96.

17 The low purified yields noted in the case of carbonates (**2f, g**) appear to be due to appreciable polymerisation during distillation.

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