

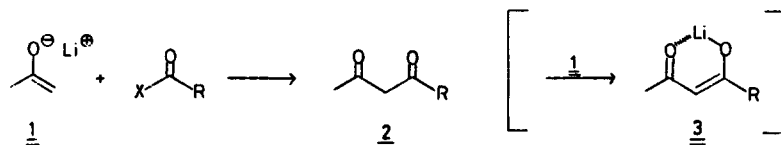
1.3-DIKETONES BY 1:1-REACTIONS OF Li-ENOLATES WITH ACID CHLORIDES
GENERATION OF KINETIC ENOLATES WITH MESITYL LITHIUM

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(Received in UK 10 February 1977; accepted for publication 21 February 1977)

It is generally quoted¹⁾ that the reaction of alkali enolates such as 1 with acylating reagents is not a practical method of preparing 1.3-dicarbonyl compounds 2 because of competing (e.g. O-acylation) and subsequent reactions (e.g. 2+1→3). Addition of one equiva-



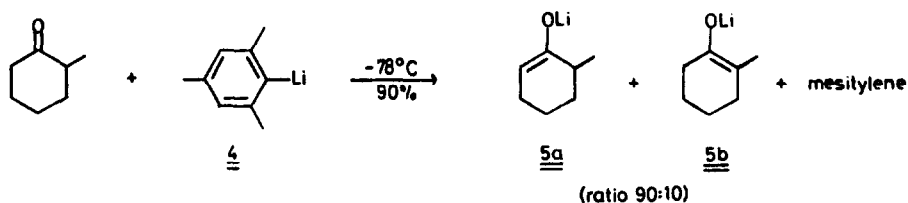
lent of an acid chloride to a twofold excess of the enolate gives reasonable to high yields calculated from the acylating reagent²⁾, but, since step 2→3 is deliberately included, a theoretical yield of only 50% with respect to the enolate 1³⁾; this is a serious disadvantage if 1 is to be considered the substrate and not the reagent. Furthermore, the diisopropylamine present besides the - otherwise extremely useful⁴⁾ - Li-enolates generated kinetically by LDA can cause problems in acylations with acid chlorides^{3, 5)}.

We would like to report here (i) a simple procedure which allows to obtain high yields of 1.3-dicarbonyl compounds from 1:1-reactions of amine free Li-enolates and acid chlorides and (ii) a convenient method of generating these enolates free of amines directly from ketones.

In reactions of enolates with sulfonylchlorides RSOCl, where problems similar to those mentioned above can be envisaged, we had found that addition of the enolate solution to the thiolating reagent stirred in THF at -100°C gave high yields even of sensitive α-RS-aldehydes⁶⁾. This same technique was now applied to the present reaction. A -78°C

cold solution of a Li-enolate, generated from the corresponding silyl enol ether and methyl lithium in THF (method A), is added slowly (within 15-40 min. for a 20 mmole-run)⁷⁾ to a THF solution of an acid chloride stirred at the same temperature. The 1,3-dicarbonyl compounds 2 shown in the accompanying table, are isolated in good yields after aqueous workup. As one can see, enolates of open chain and - more efficiently - cyclic ketones can be employed as reactand nucleophiles, and acid chlorides of aliphatic and aromatic carboxylic acids as well as dimethyl carbamoyl chloride as electrophiles. Even the 5-nitro-1,3-diketone from cycloheptanone and β -nitro-propionyl chloride can be prepared by this 1:1-stoichiometric reaction. Lowering the reaction temperature from -78° to -100°C improves the yields only by a few percent (see table).

To save the extra step of preparing silyl enol ethers from the starting ketones and to avoid the presence of amine formed when LDA or other amides are used for kinetic Li-enolate generation, we tested whether the hindered⁸⁾ hydrocarbon derivative mesitylene lithium (4) could be employed for this purpose. We added 2-methyl-cyclohexanone



to a solution of this readily available⁹⁾ Li-compound (-78°C) and determined by GC analysis of the $(\text{CH}_3)_3\text{Si}$ -derivatives that 5a (kinetic enolate) and 5b had been formed in high yield in a ratio of ca. 9:1. The results of acylations accomplished with enolates which were generated in this way (method B) are also listed in the table. The mesitylene (b.p. 165°C) can be separated from low boiling products by filtration through a short silicagel column. The IR, NMR, and MS spectral data obtained from the products described here were fully compatible with the structures given in the table.

Table

1,3-Dicarbonyl derivatives from 1:1-reactions of Li-enolates with acid chlorides. Method A refers to enolate generation from silyl enol ethers and CH_3Li , method B to enolate formation from ketones and 1-lithio-2,4,6-trimethyl benzene

Li-enolate <u>1</u> of carbonyl compound (method of generation), acid chloride	reaction temp. [$^{\circ}\text{C}$]	1,3-dicarbonyl compound <u>2</u> ^{a)}		
		formula ^{b)}	m. p. [$^{\circ}\text{C}$] or b. p. [$^{\circ}\text{C}/\text{Torr}$]	yield of distilled, chromatographed, or recrystallized product [%]
3-pentanone (<u>B</u>), 2-methyl-propionyl chloride	- 78		108-113/20	55
3-methyl-2-pentanone (<u>B</u>), benzoyl chloride	- 78			57 ^{c)}
cyclohexanone (<u>B</u>), butyryl chloride	- 78		130-138/20	65
cyclohexanone, benzoyl chloride				
(<u>A</u>)	-100		87- 89	83
(<u>A</u>)	- 78		80- 84	81
(<u>B</u>)	- 78		80	71
cyclohexanone (<u>A</u>), pivaloyl chloride				
	-100		89- 92/55	80
	- 78		97-100/45	78
cycloheptanone, β -nitro-propionyl chloride				
(<u>A</u>)	-100		70- 73	65
(<u>A</u>)	- 78		70- 73	73
(<u>B</u>)	- 78		68- 69	67
cycloheptanone (<u>A</u>), 2-methyl-propionyl chloride				
	- 78		127-132/20	76
carbamoyl chloride	-100	R = $\text{CH}(\text{CH}_3)_2$ R = $\text{N}(\text{CH}_3)_2$	66- 69/10	84
cyclooctanone (<u>A</u>), 2-methyl-propionyl chloride				
	-100		120-128/10	74

a) The properties of known derivatives are identical with literature data.

b) The 1,3-dicarbonyl form is shown although most products are mixtures of carbonyl and enol form (by NMR analysis).

c) Adding 1/2 equivalent of benzoyl chloride to 1 equivalent of the enolate gave 49% (calcd. from acid chloride) or 25% (calcd. from enolate) of 1,3-diketone 2a.

References and Footnotes

- 1) Reviews: C.R.Hauser, F.W.Swamer, and J.T.Adams, *Org.Reactions* 8, 59 (1954); H.O.House, "Modern synthetic reactions", W.A.Benjamin, Inc. Menlo Park, California 1972, 2nd edition, chapt. 11; F.Korte (Edit.), "Methodicum Chemicum" Vol.5, Georg Thieme Verlag Stuttgart, Academic Press New York 1975, pg. 372. - For recent papers see for instance: H.O.House, R.A.Auerbach, M.Gall, and N.P.Peet, *J.Org.Chem.* 38, 514 (1973); R.G.Salomon and M.F.Salomon, *J.Org.Chem.* 40, 1488 (1975); T.Tanaka et al., *Tetrahedron Lett.* 1975, 1535; S.L.Hartzell and M.W.Rathke, *Tetrahedron Lett.* 1976, 2757. - 1:1-Acylation of ester enolates with ethyl chloroformate: T.J.Brocksom, N.Petragnani, and R.Rodrigues, *J.Org.Chem.* 39, 2114 (1974).
- 2) a) D.Seebach and V.Ehrig, *Angew.Chem.* 84, 107 (1972); *Angew.Chem.Intern.Edit.* 11, 127 (1972); D.Seebach, V.Ehrig, and M.Teschner, *Liebigs Ann.Chem.* 1976, 1357. - b) E.J.Corey and R.Ruden, *Tetrahedron Lett.* 1973, 1495.
- 3) Ester enolates have been acylated with 1:1-stoichiometry by using an equivalent excess of lithium cyclohexyl isopropyl amide: M.W.Rathke and J.Deitch, *Tetrahedron Lett.* 1971, 2953.
- 4) H.O.House, "Modern synthetic reactions", W.A.Benjamin, Inc. Menlo Park, California 1972, 2nd edition, pg. 568/569.
- 5) Acylation of Li-enolates generated with highly hindered alkoxides (I.Kuwajima, T.Sato, M.Arai, and N.Minami, *Tetrahedron Lett.* 1976, 1817; H.Quast and M.Heuschmann, *Synthesis* 1976, 117) have not been reported yet.
- 6) D.Seebach and M.Teschner, *Chem.Ber.* 109, 1601 (1976).
- 7) The -78°C solution of the enolate is either added with a syringe inserted into a cooling jacket or with a dropping funnel with jacket or - most conveniently - by pressing the solution from the flask in which the enolate had been generated into the reaction vessel through a short teflon tube (0.7 mm inner diameter) with inert gas pressure.
- 8) The use of 2.4.6-tri-sec.-butyl- and 2.4.6-tri-t-butyl-phenyllithium for this purpose is currently investigated in our laboratory.
- 9) From 1 equivalent of the commercial 1-bromo-2.4.6-tri-methyl-benzene and 2 equivalents of t-butyllithium, cf. D.Seebach and H.Neumann, *Chem.Ber.* 107, 847 (1974); *Tetrahedron Lett.* 1976, 4839.