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SYNTHESIS AND REACTIONS OF NOVEL SUBSTITUTED β-HYDROXY-γ-IMINO ESTERS

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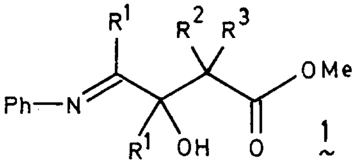
Summary : α-Iminoketones react with simple lithium ester enolates to give substituted β-hydroxy-γ-imino esters. Some reactions of these esters are reported.

The reactions of simple carbonyl compounds and imines with α-lithiated esters have been the subject of several studies. Thus, addition of lithium ester enolates to aldehydes and ketones provides a simple alternative to the Reformatsky reaction.[1] The reaction of various types of imines with lithiated esters has been exploited as a potential method for the synthesis of the β-lactam ring.[2]

In this paper we report the synthesis of some novel substituted β-hydroxy-γ-imino esters, **1**, by reaction of two α-iminoketones, **2** and **3**, with various lithium ester enolates, **4**, generated *in situ* from the related carboxylic esters and LDA in THF. The potential interest of compounds **1** relies on the fact that they are both β-hydroxy esters and α-hydroxy imines. These structures have aroused interest both from the synthetic and the theoretical standpoint.[4]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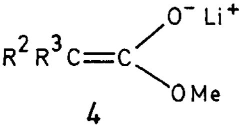
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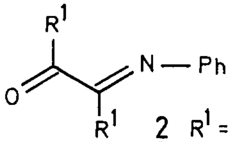
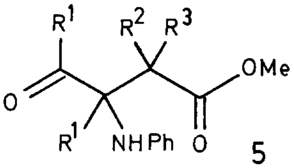

2 R^1 = Me
3 R^1 = Ph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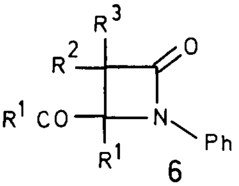
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Data on the synthesis and properties of **1** are gathered in the Table. Lithium derivatives of these esters carrying aromatic groups on the α-positions (**4**, R^2 = Ph, R^3 = H, Me, Ph) failed to react probably on account of their greater stabilization.

Table.- Synthesis of β-hydroxy-γ-imino esters $PhN=NC(R^1)C(OH)(R^1)C(R^2R^3)CO_2Me$, 1

Comp.[a]	R^1	R^2	R^3	Molar ratio 4:2(3)	t[b] (min)	mp(°C) or bp(°C/Torr)	Yield(%)[c]	i.r.(cm^{-1})[d]		
								ν(OH)	ν(C=O)	ν(C=N)
1a	Me	H	H	1.2	10	158-160/0.03[e]	75(95)	3350	1735	1665
1b	Me	Me	H	1.2	10	[f]	(100)	3360	1740	1665
1c	Me	Me	Me	2.1	30	128-130/0.1[e]	80(100)[g]	3330	1730	1660
1d	Ph	H	H	2.0	15	-	65(90)[g]	3300 3480	1730	1650
1e	Ph	Me	H	2.0	30	75-76 (ethanol)	75(100)	3425	1700	1650
1f	Ph	Me	Me	2.0	120	122-123 (ethanol)	75(85)	3330	1675	1645

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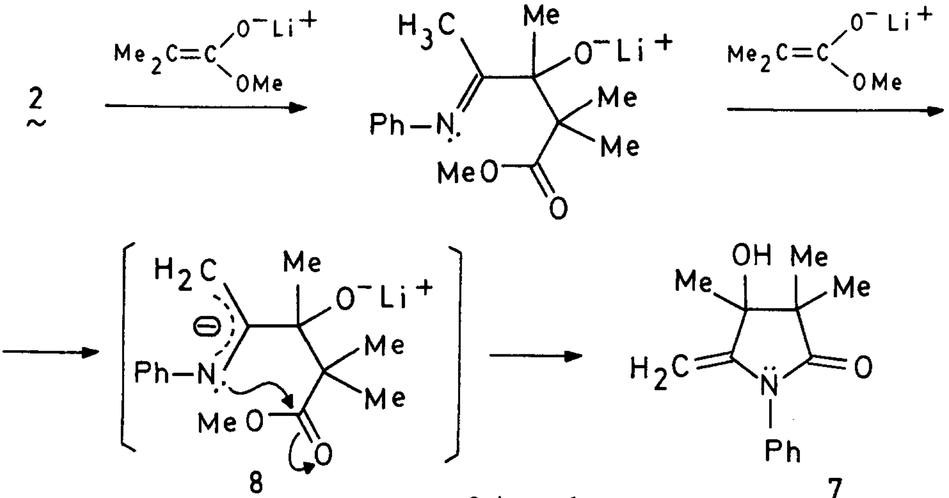
a) Compounds 1a-c become coloured on standing at room temperature. 1e and 1f give satisfactory analyses. b) All reactions were run at -78° except for 1f which was carried out at -78° for 60 min. and at room temperature for the remaining 60 min. c) Yields without parentheses refer to isolated products. Those within parentheses are estimated from ^1H n.m.r. spectra of the reaction mixture residue. d) In KBr for 1e and 1f. Liquid film for the remainder. e) Some decomposition is observed in distillation, particularly in 1c. f) Equimolecular mixture of diastereoisomers that can be separated by chromatography over SiO_2 with hexane-AcOEt (9:1). g) Yields in isolated product refer to these obtained by chromatography on SiO_2 using benzene-ethyl ether (9:1) as eluent.

^{13}C N.m.r. spectra of 1 are consistent with the hydroxy-imino ester structure. Thus signals at 177.2-181.6 and 172.5-175.5 ppm are, respectively, assigned to the methoxycarbonyl and imino carbon atoms. The absence of signals above 190 ppm, which would be present in compounds related to 5 and 6[5], allows us to discard these possibilities. The fact that neither 5 nor 6 could be isolated, not even detected in the reaction mixture, points to a totally regioselective addition to the carbonyl group. Double addition to both carbonyl and imino groups has not been observed in the presence of excess of enolate.

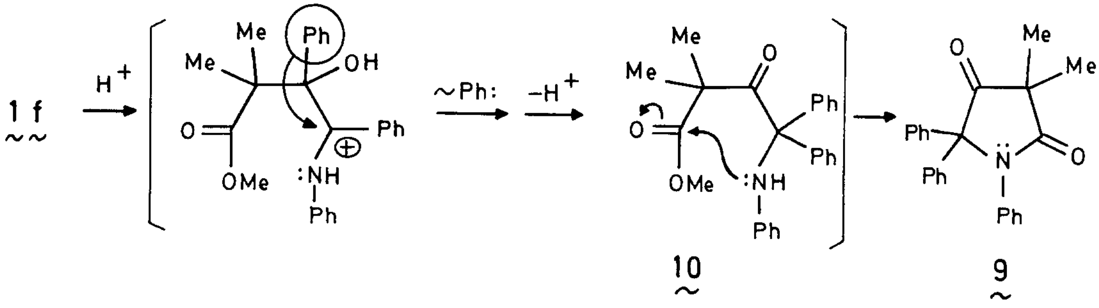
The reaction of methyl lithio*iso*butyrate with 2 (molar ratio 2.1) at -78° yields 1c quantitatively. After standing the mixture was allowed to reach room temperature whereupon progressive formation of γ-methylene-γ-lactam, 7,[6] was observed. A final yield of 35% was reached after three days reaction. This reaction may be interpreted as an initial addition of the enolate to 2 followed by attack of a second enolate ion to the intermediate formed to yield 8 which in turn cyclizes to 7 by an intramolecular aminolysis process (Scheme 1). Apparently, when the reaction is carried out at -78°, 8, if formed at all, does not cyclize. In fact a 10 min. reaction of equimolar amounts of reagents yields 85% of 1c and 15% of unreacted 2. Furthermore, 1c gives an excellent yield of 7 by treatment with two equivalents of LDA in THF. Compound 7 is structurally related to some enamides used as intermediates in corrin synthesis.[7]



Scheme 1

With the compounds 1a and 1b enolization of the α-hydrogenated ester group prevents cyclization to the related γ-lactam when an excess of enolate is used.

In the reaction of 2 with methyl lithiopropionate an equimolar mixture of diastereoisomers is obtained, but with 3 only one diastereoisomer results. A totally site-selective and stereoselective reaction is thus observed.



Scheme 2

When **1f** is refluxed with concentrated hydrochloric acid in methanol a 2,4-pyrrolidinedione, **9**, results. Its formation may be accounted for by a process related to the α-ketol rearrangement in the hydroxy-imine moiety yielding **10** which in turn gives an intramolecular aminolysis (Scheme 2). Aminolyses in acid medium, although infrequent, are not unknown.[8]

The synthetic uses of β-hydroxy-γ-imino esters **1** and of enamide **7** and the extension of the above reactions to various α-iminoketones and enolates are now under study.

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6. Structure of **7** has been confirmed by X-ray analysis. We thank Profs. S. Garcia Blanco and S. Martinez Carrera for this study which shall be published elsewhere.
7. See for example: I. Felner, A. Fischli, A. Wick, M. Pesaro, D. Bormann, E. L. Winnaker and A. Eschenmoser, *Angew. Chem.*, **79**, 863 (1967)
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