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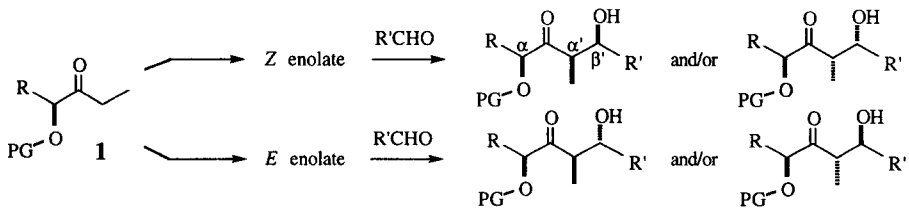
A Simple Procedure for the Preparation of Enantiopure Ethyl α-Hydroxyalkyl Ketones

Ricardo Martín, Oscar Pascual, Pedro Romea,* Roser Rovira, Fèlix Urpí,* and Jaume Vilarrasa*

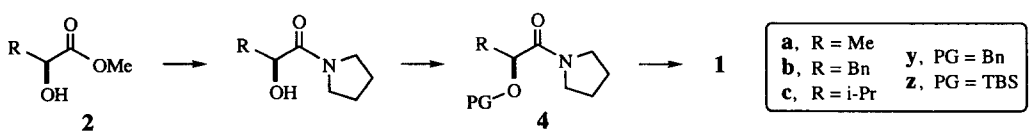
Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, 08028 Barcelona, Catalonia (Spain)

Abstract: Amides derived from pyrrolidine and methyl (*S*)-lactate, methyl (*S*)-2-hydroxy-3-phenylpropanoate, or methyl (*S*)-2-hydroxy-3-methylbutanoate, after *O*-benzylation and *O*-silylation have been treated with EtLi or EtMgCl under suitable conditions, to give excellent overall yields of enantiopure ethyl ketones. The chelating ability of α-OBn amides (and even of α-O-TBS amides, which has been demonstrated by NMR to be better than that of *N*-OMe amides) accounts for the performance of the approach.

Since the pioneering work of Masamune et al. with mandelic acid derivatives,[1] several groups have taken advantage of ethyl hydroxyalkyl ketones **1** to control the stereochemical outcome of aldol-like reactions.[2] Paterson et al., eg, have elegantly shown how *syn*(α,α')-*syn*(α',β') and *syn-anti* ketodiols arising from lactate-derived ethyl ketones (**1**, R = Me, PG = Bn or Bz, respectively) can be manipulated in different ways to afford enantiopure α'-methyl β'-hydroxy carbonyl compounds,[2d] useful building blocks in the total synthesis of polypropionate metabolites.[3] Appropriate choice of the hydroxyl protecting group of **1** and enolisation conditions may also permit to obtain either the *anti-syn* or *anti-anti* ketodiols as the major compounds.[2b]



The great availability of enantiopure α-hydroxy acids (including those readily obtained from natural L-amino acids), as well as the fact that there are a few possibilities for the conversion of carboxylic acids and derivatives into alkyl ketones,[1,2,4] make the above-mentioned approach to aldol-like products really competitive. As known, currently the most common method involves treatment of esters with MeNHOMe·HCl and $AlMe_3$ excess,[4a] followed by reaction with EtMgX to yield the desired ethyl ketone. To overcome two shortcomings of this protocol —rather expensive reagents for a multi-gram scale preparation of a starting material and unstability of silyl-based protecting groups under the reaction conditions—, we have developed a practical route to chiral ethyl ketones that can be summarised as follows:



Conversion of methyl (*S*)-lactate (**2a**), methyl (*S*)-2-hydroxy-3-phenylpropanoate (**2b**), and methyl (*S*)-2-hydroxy-3-methylbutanoate (**2c**) into the corresponding pyrrolidine amides (**3a–c**) was achieved **in high yields** by treatment with 1.1-4.0 equiv of pyrrolidine without solvent (see Table 1).[5] No racemisation took place under these conditions,[6] as shown by HPLC analysis of their Mosher esters (>99% ee). All these reactions have been scaled up to 40 mmol affording pure products without requirement of chromatographic separation. Protection of the hydroxyl groups of **3a–c** as benzyl ethers, by treatment with $PhCH_2Cl$ (BnCl) under phase-transfer conditions ($Oct_3NMe^+Cl^-$, NaOH, toluene, rt), and as t-$BuMe_2Si$ ethers (TBS-Cl, imidazole, DMAP, DMF, rt) was always accomplished in high yields.[7]

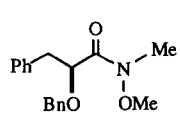
Table 1 also shows the yields of ethyl ketones **1** obtained by treatment of **4** with EtLi or EtMgCl.[8] Most reactions appeared to be **very fast**. Sometimes, small amounts of tertiary alcohols were detected but they were removed by column chromatography; only in one case, in the reaction of **4ay** with EtMgCl, the ketone (**1ay**) was contaminated with 10% of the corresponding tertiary alcohol that posed separation difficulties. In general, use of THF rather than Et_2O in the 3rd step gave better yields. From a practical point of view (for large-scale operations) EtMgCl is recommended, as the corresponding reactions can be performed using an ice bath.

Table 1. Preparation of **1** from Hydroxy Esters **2**

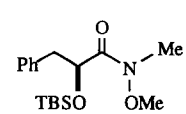
entry	ester	*1st step, react. cond.*[a]	amide, yield	*2nd step*	protect. amide, yield	*3rd step, react. cond.*[f]	ketone, yield
1	**2a**	1.1 equiv, rt, 3 d	**3a**, 82%[b]	BnCl	**4ay**, 86%	EtLi (1.1), –78 °C, 5 min	**1ay**, 81%
2						EtMgCl (2.0), –20 °C, 30 min	**1ay**, 90%[g]
3				TBSCl	**4az**, 94%	EtLi (1.2), –78 °C, 10 min	**1az**, 84%
4						EtMgCl (4.0), 0 °C, 2 h	**1az**, 85%[h]
5	**2b**	4.0 equiv, rt, 5 d	**3b**, 93%[c]	BnCl	**4by**, 75%[e]	EtLi (1.25), –78 °C, 15 min	**1by**, 85%
6						EtMgCl (2.0), 0 °C, 15 min	**1by**, 92%
7				TBSCl	**4bz**, 91%	EtLi (1.5), –78 °C, 15 min	**1bz**, 86%
8	**2c**	4.0 equiv, 45 °C, 5 d	**3c**, 100%[d]	BnCl	**4cy**, 85%	EtLi (1.25), –78 °C, 15 min	**1cy**, 88%
9						EtMgCl (2.0), 0 °C, 15 min	**1cy**, 84%
10				TBSCl	**4cz**, 85%	EtLi (2.0), –40 °C, 1 h	**1cz**, 65%

[a]Pyrrolidine amount, temperature, time. [b]After distillation (crude yield was quantitative). [c]After recrystallisation (crude yield was quantitative). [d]Not purified; chromatographically pure. [e]In CH_2Cl_2 (**3b** was quite insoluble in toluene). [f]RM (no. equiv), temperature, time. Solvent: THF. Concentration of **4ay–4cz**: 0.1 M. Workup: addition of aq NH_4Cl; extraction with CH_2Cl_2; separation by "flash" chromatography. [g]Ketone–tertiary alcohol ratio equal to 10:1. [h]A 5% of tertiary alcohol was also isolated.

The specific rotations of ethyl ketones **1az** (α_D = –10.8, *c* 2.0, $CHCl_3$), **1by** (α_D = –74.5, *c* 2.0, $CHCl_3$), and **1cy** (α_D = –94.5, *c* 2.0, $CHCl_3$), obtained by using either EtLi or EtMgCl, were identical. The specific rotations of **1by** and **1bz**, when prepared from methyl hydroxamates (*N*-methoxy amides, or "Weinreb amides") **5by** and **5bz**, were also identical to those of the samples prepared from **4by** and **4bz**, respectively. The e.e. of **1az**, **1cy**, and **1cz** were checked to be >98% as follows: conversion of a sample of the pure ketone to its tertiary alcohol, deprotection, and GC analysis on a chiral column. In short, no racemisation at all could be noted along the process (**2** → **3** → **4** → **1**) in the cases examined.



5by

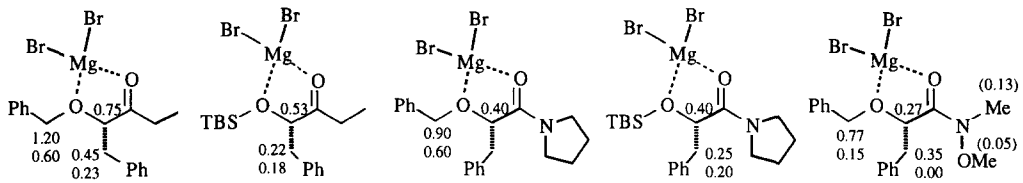


5bz

Thus, for the preparation of α-hydroxy ketones from α-hydroxy esters or acids, use of **pyrrolidine-derived amides** is as efficient as and less expensive than that of **Weinreb amides**. An α-alkoxy substituent likely plays in the former the same role that the *N*-OMe group in the latter (stabilisation of tetrahedral reactive intermediates by chelation).[9] The corollary is that in these cases the use of Weinreb amides is not required.

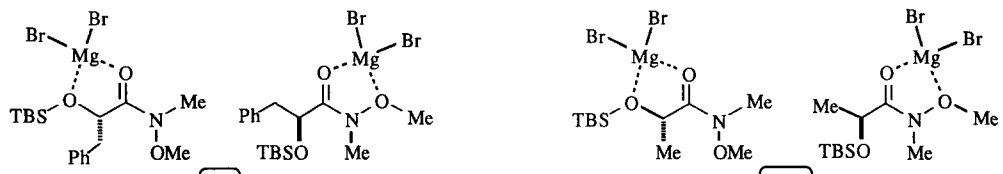
To gain more insight into the subject, we have compared the coordinating abilities of ethyl ketones, pyrrolidine-derived amides, and Weinreb amides with regard to $MgBr_2$, in $CDCl_3$ at rt. Indeed, a parallelism should be expected between the coordination abilities of these substrates and the relative stabilities of the tetrahedral intermediates arising from nucleophilic additions.

When equimolar amounts of Et_2O–$MgBr_2$ are added to samples of $PhCH_2CH_2COCH_2CH_3$, $PhCH_2CH_2$-$CON(CH_2)_4$, and $PhCH_2CH_2CON(OMe)Me$, changes are detected by ^1H NMR at both sides of the CO group in the first two cases.[10] In the third case, two species are formed in a 3:1 ratio:[11] the major one shows the same pattern as the preceding, monocoordinated complexes (ie, it is believed to be the CO-coordinated $PhCH_2CH_2CON(OMe)Me$–$MgBr_2$–Et_2O species), while the minor species can be attributed to the expected chelate (ie, to the bidentate species) as the protons of the N(OMe)Me moiety undergo significant downfield shifts.[11,12] Moreover, **1by**, **1bz**, **4by**, **4bz**, and **5by** plus equimolar amounts of Et_2O–$MgBr_2$ give one set of signals in every case, with remarkable shifts at lower field of all or most CH protons, several benzyl protons, and even the Si-Me protons of **1bz** and **4bz**. The most relevant ^1H-NMR changes are indicated as $\Delta\delta$ values in the following formulas (although only bidentate species are depicted, it is obvious that each one may be in a dynamic equilibrium with distinct percentages of monodentate species, as the differences among the observed $\Delta\delta$ values suggest):



1by–$MgBr_2$ **1bz**–$MgBr_2$ **4by**–$MgBr_2$ **4bz**–$MgBr_2$ **5by**–$MgBr_2$

On the other hand, **5bz** and **5az** plus Et_2O–$MgBr_2$ show two different sets of signals in 1:1 and 3.5:1 ratios, respectively; in the light of the corresponding δ values these two species can be attributed in each case to the two possible chelates shown below:



5bz–$MgBr_2$ 1:1 iso-**5bz**–$MgBr_2$ **5az**–$MgBr_2$ 3.5:1 iso-**5az**–$MgBr_2$

It is seen that: (i) ethers at the α position of ketones and carboxamides give rise to more stable chelates than the methoxy group on the nitrogen (the first four structures should be compared to the above-mentioned case of $PhCH_2CH_2CON(OMe)Me$, in which the bidentate species is not predominant; moreover, the fact that only the fifth structure, **5by**–$MgBr_2$, is observed by NMR points out that chelation through the CON(OMe) moiety has hardly chance); (ii) the TBS-O (t-$BuMe_2SiO$) groups of **1bz** and **4bz** contribute significantly, although not so much as BnO ($PhCH_2O$), to the chelation of $MgBr_2$, an argument in favour of the possible involvement of silyl ethers in complexation phenomena concerning enolate chemistry, a matter of discussion;[12] (iii) while in **5by** BnO clearly "overcomes" *N*-OMe, in the case of **5bz** a 1:1 equilibrium mixture of the two bidentate complexes is obtained, the steric interactions probably leveling the complexation ability of *C*α-OTBS and *N*-OMe; and (iv) however, when steric hindrance at both sides is similar (see **5az**) *C*α-OTBS "overcomes" *N*-OMe. In summary, the contribution to the chelation appears to follow this order: *C*α-OBn >> *C*α-OTBS > *N*-OMe.

It is well-established that a *C**-OR near a CO group can afford blocked, common-ring complexes with Lewis acids, which usually makes easier and more stereoselective certain nucleophilic attacks to (and enolisation reactions of) carbonyl and carboxyl derivatives.[12] What we have shown for the first time, to our knowledge, after comparing the relative complexation abilities of ethyl ketones, amides, and Weinreb amides (unsubstituted and α-O-substituted), is that these bidentate complexes may be much stronger than those arising from the CON(OMe) groups.

Acknowledgments

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5. For an example of formation of *N*-acylpyrrolidines in this way, see: Ito, Y.; Kobayashi, Y.; Kawabata, T.; Takase, M.; Terashima, S. *Tetrahedron* **1989**, *45*, 5767. One carboxamide (**4ay**) was then reduced to the corresponding aldehyde with Red-Al.
6. On heating, partial racemisation takes place, as expected. For instance, heating of **3b** and pyrrolidine excess at 70 °C overnight gave a 15% of racemisation.
7. For reviews, see: Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley: New York, 1991. Kocienski, P. J. *Protecting Groups;* Thieme: Stuttgart, 1994.
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10. In the ketone, the methylene protons (of both sides) are shifted 0.30 ppm at lower field on complexation; the remaining protons are shifted 0.1 ppm or less. In the pyrrolidine derivative, $\Delta\delta = 0.20$ for the α-CH_2 protons and $\Delta\delta = 0.23$ for one of the *N*-CH_2 methylenes; the remaining signals are shifted less than 0.1 ppm. There seems that the formation constant of the ketone–$MgBr_2$–Et_2O complex is somewhat higher than that of the amide–$MgBr_2$–Et_2O complex.
11. This ratio did not change along the time nor after ultrasound irradiation of the NMR sample (the equilibrium between the two species is immediately reached). The methylene protons of the major species underwent a downfield shift of 0.20 ppm; the *N*-Me protons also moved, $\Delta\delta = 0.22$, but the OMe protons not at all. The methylene protons of the minor species did not change, while the *N*-Me protons were shifted 0.18 ppm and the *N*-OMe protons 0.36 ppm (!) at lower field as well.
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