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STEREOSELECTIVE SYNTHESIS OF OPTICALLY ACTIVE α-METHYL ESTERS

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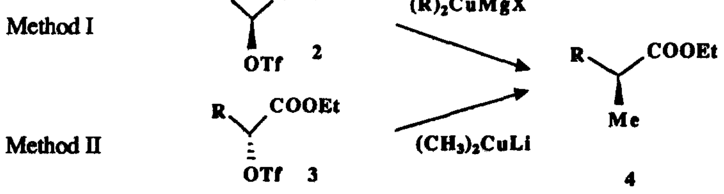
Abstract: *Trifluoromethanesulfonic esters of α–hydroxyesters which are easily available from the corresponding esters and triflic anhydride react with lithium dimethylcuprate in ether or magnesiocuprates in THF to provide α-methyl esters in high enantiomerical purity.*

Optically active α-alkyl esters are useful intermediates in the synthesis of various natural products. They are essentially obtained by α-alkylation of chiral enolates[1] or congeners.[2] However in spite of the high enantiomeric excesses observed in some cases, the chiral inductors which are used are generally very sophisticated molecules making these reactions difficult to apply on a large scale.

Enantiomerically pure α-hydroxyesters are now commun substrates easily available from the "chiral pool", by enantioselective ketone reduction,[3] hydroxylation of chiral enolates[4] or opening of glycidic esters.[5] Substitution reactions on such substrates containing leaving groups bonded to carbon would provide the most direct access to α-alkyl esters. Among the vast array of organometallic compounds, organocopper based reagents have provided one of the most popular tools for carbon-carbon bond construction. However, these reactions present limitations and it is well known that the displacement processes at secondary centers bearing tosylates are of limited interest due to the highly competitive reduction and elimination pathways;[6] although it was recently reported that such substitutions are greatly facilitated when assisted by heteroatom,[7] the reaction of lithium homocuprates with α-tosyloxyesters was shown to give a complex reaction from which, beside the formation of a β-ketoester, the desired α-methyl esters could only be isolated in a 20% yield.[8]

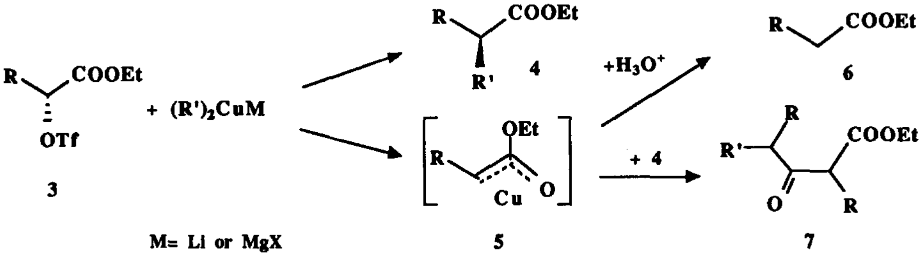


We thought that by using a better leaving group it would perhaps be possible to control this reaction, and we want to report here that triflic esters derived from α-hydroxyesters react with lithio or magnesiocuprates to give α-substituted esters in high optical purity.

Preliminary experiments were achieved with nosylates and brosylates. Due to a concurrent reaction with the aromatic moiety, results were rather disappointing. In contrast, triflates which are easily prepared from the reaction of the α-hydroxyesters **1** [9] with triflic anhydride[10] react very quickly with the cuprates at low temperature to give mainly the substituted esters **4** (Table I).

The reaction is highly dependent on the nature of the cuprate, on the solvent and even on the nature of the copper salt; it may be achieved in two ways: by reacting a dialkylcuprate with a lactate derivative **2**, or by reacting a dimethylcuprate with an alkyl substituted α-trifluorosulfoxyester **3**.

In both cases, the major side reaction was the reduction which was due to the formation of an intermediate copper enolate **5**. Depending on the temperature reaction, this intermediate may be stable or react with the alkylated ester to give a Reformatsky type condensation and thus lead to a β-ketoester **7** and/or to the alcohols resulting from further addition to the ester and carbonyl groups. We never observed the concurrent elimination which was reported during the substitution of simple tosylates[6].



scheme 2

From Table I, it appears that the best results were obtained with homocuprates by using a very weakly basic solvent (ether-pentane or THF-ether-pentane with magnesiocuprates) and that the reduction is largely favoured in THF (compare 4 to 5 and 10 to 11). It must be noticed that the use of higher order cuprates activated by Lewis acids which were claimed to prevent reduction during the reaction of γ-mesyloxy enoates, was rather inefficient (entry 3)[11]. In the absence of Lewis acid, these cuprates effect mainly the cleavage of the S-O bond.

In order to obtain good results, it was necessary to adjust the reactivity of the triflate to the reactivity of the cuprate in order that the latter react quickly enough to prevent the side reactions. For instance, the formation of α-bromoesters was observed during the reaction of hindered triflates (R = *n*-octyl) with magnesiocuprates. In contrast, lithium homocuprates were too reactive and gave instantaneously the reduction even at temperatures lower than -90°C (entry 1). If the reaction rate was decreased by changing the metal (1 ver-

Table I. Triflate substitution by dialkylcuprates

Entry	2 or 3	cuprate	Solvent	Temp.(°C) /Time(h)	Procedure	Yield of 4 (G.L.C)
1	Me	$(nBu)_2CuLi$ (b)	Et_2O / nC_6H_{14}	-80° / 1	A	10%
2	Me	$(nBu)_2CuMgBr$ (b)	THF / Et_2O; 3/1	-40° / 1	B	48%
3	Me	$(nBu)_2CuCNLi_2$	THF; BF_3-Et_2O	-80° / 1	A (c)	35%
4	Me	$(nOct)_2CuMgBr$ (a)	THF	-80° / 1	B	35%
5	Me	$(nOct)_2CuMgBr$ (a)	THF / Et_2O; 3/1	-80° / 1	B	65%
6	*n*Bu	$(CH_3)_2CuLi$ (a, d)	Et_2O	-70° / 1	C	60%
7	*n*Bu	$(CH_3)_2CuLi$ (a)	Et_2O	-60° / 0.2	C	55%
8	*n*Bu	$(CH_3)_2CuCNLi_2$	THF / Et_2O; 1/1	-50° / 1	C	34% (e)
9	*n*Bu	$(CH_3)_3CuCNLi_3$	THF / Et_2O; 1/1	-50° / 3	C	0% (e)
10	*n*Bu	$(CH_3)_2CuLi$	THF	-80° / 1	B	20%
11	*n*Bu	$(CH_3)_2CuLi$ (a)	Et_2O/nC_5H_{12}; 1/2	-70° / 0.5	C	73%
12	*n*Pent	$(CH_3)_2CuLi$ (b)	Et_2O/nC_5H_{12}; 1/2	-80° / 1	C	80%

a) copper reagent prepared with CuI b) copper reagent prepared with CuBr-Me_2S c) BF_3-Et_2O is added to the cuprate before the addition of triflate d) methyllithium with or without lithium bromide gives the same results e) α-hydroxy- ester **1** is the major product.

Procedure A: triflate diluted in Et_2O is added to organocuprate at the indicated temperature ;

Procedure B: triflate diluted in Et_2O and cooled to the indicated temperature, is added to organocuprate at the same temperature;

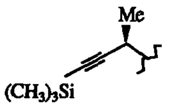
Procedure C: organocuprate (0.2M) cooled to the indicated temperature is added to triflate (diluted in pentane-0.1M) and cooled to the same temperature.

sus 2), the cuprate (6 versus 1) or the salt (12 versus 11), it was possible to minimize the reduction reaction and to obtain the desired substituted esters in satisfactory yields (Table II).

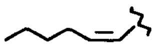
Table II. α-methylesters 4

R	Meth.	Yield of 4	Abs.conf.	$[\alpha]_D^{20}$ 4
*n*Bu	II	53% (a)	S	20.8 (c= 7.4; pentane)
*n*Pen	II	62% (b)	S	15.6 (c= 12.8; pentane)
*n*Oct	I	51% (c)	S	15.7 (c= 2.3; pentane)
*n*Non	II	65% (c)	S	12.7 (c= 28; pentane)
R_1	II	40% (c)	2S,3S	1.8 (c= 10.1; pentane)
R_2	I	35% (c)	S	126.4 (c= 2.2; CH_2Cl_2)
R_3	I	52% (c)	S	29.2 (c= 2.3; CH_2Cl_2)
R_4	I	37% (c)	S	11.6 (c= 3.4; CH_2Cl_2)

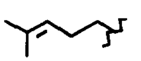
Method I: reaction of triflate **2** on cuprate R_2CuMgX.
Method II: reaction of dimethylcuprate on triflate **3**.



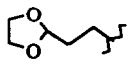
R_1



R_2



R_3



R_4

(a) Bp= 65°C/15 mbar; (b) Bp= 93-95°C/25 mbar; (c) purified by column chromatography on silica gel, eluent: 5% of Et_2O in pentane.

As anticipated, the stereochemical outcome in all cases studied was that resulting from inversion of configuration. The stereochemistry was established by comparison with known esters and the enantiomeric excesses were measured by capillary VPC after saponification (NaOH/EtOH), formation of the acid chloride and reaction with (R) α-methylbenzylamine. These excesses ranged from 95 to 99%, and, as some racemization was expected during the treatment, we may assume that these esters are virtually optically pure.

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9- $[\alpha]_D^{20}$ of α-hydroxyesters **1** prepared according to[5]: R= *n*Bu: 6.5° (neat); R= *n*Pent: 6.6° (c= 7.1; MeOH); R= *n*Non: 1.0° (c= 3.1; MeOH); R= R_1: 2.05° (c=7.5; MeOH).

10- α-Trifluorosulfoxyesters were prepared according to a slight modification of the reported procedure (Feenstra R.W., Stokkingreef E.H.M., Nivard R.J.F., Ottenheijen H.C.J., *Tetrahedron Lett.*, 1987, **28**, 1215) by slow addition of the hydroxyester (diluted in CH_2Cl_2) to a mixture of 2,6-lutidine (1.2 eq.) and triflic anhydride (1.2 eq.) at -5°C; $[\alpha]_D^{20}$ of α-trifluorosulfoxyesters **3**: R= *n*Bu: 40.3° (c= 4.5; pentane); R= *n*Pent: 36.0° (c= 23; pentane); R= *n*Non: 33.3° (neat); R= R_1: - 26.5° (c=9.1; pentane).

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