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PREPARATION OF CHIRAL INDANONES AND DIHYDROCOUMARINS; APPLICATION TO SYNTHESIS OF (+)-3-(2,6-DIMETHOXYPHENYL) PENTANOIC ACID

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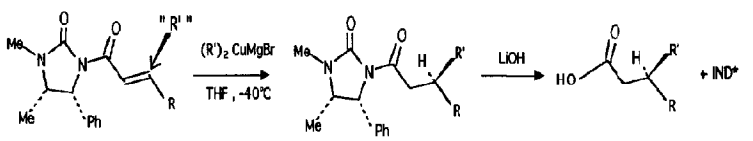
Abstract: Chiral β-aryl carboxylic acids, prepared by Michael addition of organocuprates to chiral unsaturated imides, are transformed into chiral 3-alkyl-4-benzoyloxyindan-1-ones via two intramolecular acylations, with intermediate formation of chiral 3-alkylindanones and corresponding dihydrocoumarins. The 3-(S)-ethyl-4-benzoyloxyindanone is transformed into(+)-3-(S)-(2,6-dimethoxyphenyl)pentanoic acid.

Enantioselective Michael addition of alkyl and arylcuprates to chiral unsaturated imides is a good way for synthesising chiral β-aryl carboxylic acids of high enantiomeric excess [1]. These acids can be cyclized via classical Friedel-Crafts reaction into indanones, the corresponding dihydrocoumarins being prepared by peracid oxidation of these indanones [2]. In order to obtain chiral β–o,o'- dimethoxyphenyl-carboxylic acids the dihydrocoumarins are hydrolyzed with benzoylation of the resulting phenol acids for successful new intramolecular acylation into 3-alkyl-4-O-benzoyl-indanones. As an example 3-(S)-ethyl-4-O-benzoyl-indan-1-one is re-oxidized into the corresponding dihydrocoumarin which is hydrolyzed with methylation to afford (+)-3-(2,6-dimethoxyphenyl)pentanoic acid.

Chiral β-aryl acids

Chiral imides **1** are obtained as previously described, starting from (-)-auxiliary imidazolidinone[1]. Cuprates are prepared with commercially available CuBr,Me_2S and Grignard reagents. Michael addition is performed in THF at -40°C, chiral acids **3** resulting from alkaline hydrolysis of intermediate saturated imides **2** [1](scheme 1 , Table 1). These imides **2** are obtained as homochiral compounds after one recrystallization. Hydrolysis and subsequent reactions are conducted with diastereoisomers of reported optical purity (table 1).

scheme 1



2 3

Comparing the specific rotation for acid **3c** in benzene with the litterature value (-31.8) [3] it appears that Michael addition of diphenylcuprate to imide **1c** is a better way for asymmetric synthesis in this case than Grignard addition to the chiral cinnamamide. Since the benzylic proton of the heterocyclic part of these compounds gives two well separated doublets, ^{1}H NMR spectroscopy is a convenient method for the d.e. determination of imides **2**. For acid **3c**, resulting from the recrystallized imide **2c**, a recent optical purity determination method[4] has been applied which indicates o.p. > 99% .

table 1 : chiral imides and acids

		imides 2		acids 3		
R	R'	Y% [a]	d.e.[b]	Y%[a]	$(\alpha)_D$ obs.[c]	config
a Me	Ph	78	87	80	+30(c=3 ; EtOH)[d]	S
b Et	Ph	60	90	70	+42(c=7;PhH) [e]	S
c iPr	Ph	60	94 [f]	90	+27(c=1.2;$CHCl_3$)[g]	R
d 3-Me 4-OMe Ph	iPr	60	80	88	-40(c=1;PhH)	S

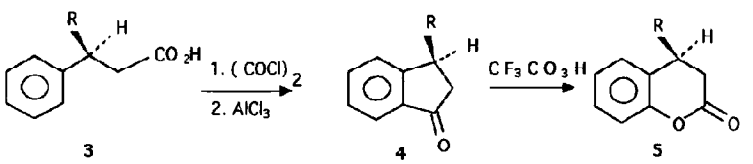
a after purification b. before purif. c. acids obtained from diastereoisomeric imides d.lit. $(\alpha)_D$ =+52(c=1 ; PhH)[5] e. lit. $(\alpha)_D$ =-49.6 (c=7 ;PhH)[6] f. for inverse Michael addition (R=Ph , R'=iPr) e.d.=90% g. $(\alpha)_D$ = -78 (c=1 ; PhH) for enantiomer (inverse addition) a somewhat greater value than lit. $(\alpha)_D$ = -41.05 in PhH [7] ; in $CHCl_3$ lit. $(\alpha)_D$ =-34.4 [8]

Chiral 3-alkylindan-1-ones and 4-alkyl-3,4-dihydrocoumarins

Acids **3** are cyclised as previously described[2]. Baeyer-Villiger oxidation of the resulting indanones **4**, performed with trifluoroperacetic acid, gives dihydrocoumarins **5** (scheme 2, table 2).

10 eq. of trifluoroacetic anhydride are added to a solution of 2 eq. H_2O_2 30% in dichloromethane at 10°C. After stirring for 1/2 h at RT the peracid is added to a solution of 1 eq. of indanone in CH_2Cl_2 (total concentration 0.5M). After stirring for 3 h the solution is washed with sodium sulfite 10%, sodium bicarbonate and water. After drying and concentration the residue is distilled to afford **5** .

scheme 2



Cyclization of acid **3d** gives 3-iPr-5-Me-6-OMe-indan-1-one with 75% yield, $(\alpha)_D$ = -13 (c=1 ; PhH). This indanone presents the inverse configuration to **4** (as a result of the Michael addition of a dialkylcuprate to the unsaturated imide **1d** in the first step) and does not give oxidation to the dihydrocoumarin **5**. The hydroxylation reaction on the aromatic nucleus seems to occur as described by Mc Lure [9] for aromatic ether oxidation with CF_3CO_3H.

Table 2 : chiral indanones and dihydrocoumarins

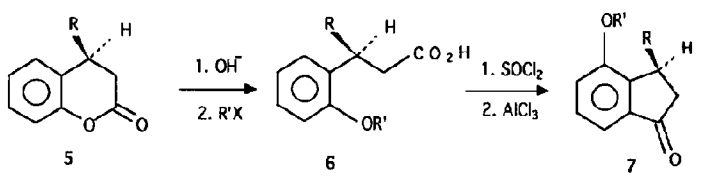
	indanones 4		dihydrocoumarins 5	
R	Y % [a]	$(\alpha)_D$ obs.	Y% [a]	$(\alpha)_D$ obs. in PhH[d]
a Me	70	+14(c=2 ; acetone)[b]	72	-34 (c=1)[c]
b Et	74	+24(c=2.8 ; $CHCl_3$)	75	-71.7 (c=5.9)[d]
c iPr	90	+4 (c=2.7 ; PhH)	80	-65 (c=2.2)

a. after purif. b. lit. $(\alpha)_D$ =16 (c=2 ; acetone)[5] c. lit. $(\alpha)_D$=-30(c=1 ; PhH)[5]
d. lit. $(\alpha)_{578}$ =+69.8 (c=5.9 ; PhH) for 95% e.e. [6] the table's value is given for 578 nm

Chiral 3-alkyl-4-benzoyloxyindan-1-ones

Starting from dihydrocoumarins **5**, the following reactions are envisaged: conversion into phenolic acids which may be recyclized into 4-hydroxyindanones **7**, re-oxidation of **7** into corresponding dihydrocoumarins which are converted into β-(2,6-dihydroxyphenyl)carboxylic acids by another opening reaction. The first part of this synthesis (scheme 3) brings up the question of which protecting group has to be used for phenol function .

scheme 3



House [10] has claimed that 3-(o-methoxyphenyl)propanoyl chloride does not give intramolecular Friedel-Crafts acylation, even under particular conditions, because of tetramer formation due to competitive intermolecular reaction. Such a reaction route seems to be due to the great electrodonating effect of the methoxy group (σ^+_p = -0.78). The use of an O-Bz protecting group, with a minor donating effect (σ_p = -0.13) appears to be more attractive. In fact 3-(o-benzoyloxyphenyl)propanoyl chloride's intramolecular acylation is observed as a convenient route to prepare 4-methoxyindan-1-one[11]. In relation to this synthesis the yields are optimized by changing experimental conditions .

*Acids **6** : 1.05 eq. KOH (pellets) is stirred in dioxane (1.5 mL/mmole of **5**) and water added just to dissolve the base. 1 eq. of **5** is added, the medium being stired for 1 h. Benzoyl chloride is added, stirring is carried on for 1h. After acidification (HCl 1M) the acid is extracted with dichloromethane and purified by column chromatography (silica gel-eluant CH_2Cl_2).*
For dihydrocoumarin **5c**, the preceeding reaction failed. Phenolic acid formation is observed (IR) but the nucleophilic attack of intermediate phenate on benzoyl chloride does not occur, probably due to steric hindrance.

***Intramolecular acylation** : 3 eq. $AlCl_3$ are stirred in dichloromethane, acid chloride of **6** added at once (concentration 0.5M) at room temperature. The medium is stirred for 24h at RT. After hydrolysis, extraction,drying,concentration the indanones **7** are Kugelrohr distilled (Table 3).*

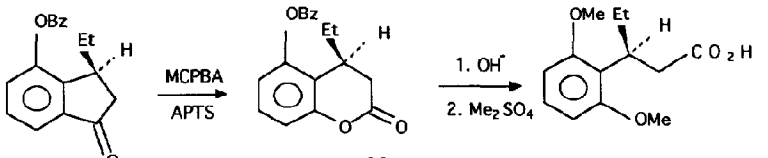
Table 3 : indanones 7 , R'= Bz

R	acids 6 Y%	indanones 7 Y%	indanones 7 $(\alpha)_D$ in $CHCl_3$
a Me	90	51	+27 (c=1.1)
b Et	92	87	+53 (c=2.3)

Synthesis of (+)-3-(2,6-dimethoxyphenyl)pentanoic acid 9

The synthesis of acid **9** has been achieved from indanone **7b** (scheme 4).

scheme 4



Baeyer-Villiger oxidation of this indanone is performed in refluxing dichloroethane, with a catalytic amount of paratoluenesulfonic acid. Two eq. of peracid are first added followed 4h later by another 2 eq. portion. After a total of 6h reaction 's time and usual treatment followed by chromatography(SiO_2 , CH_2Cl_2) 50% yield of **8** *are obtained.This dihydrocoumarin is dissolved in dioxane and aqueous NaOH 30% added (6eq.). A precipitate appears which is dissolved by adding minimum water. The medium is stirred for 3h, at that time 4 eq. dimethylsulfate are added with stirring for 3h at RT. The medium is then heated for 1/2h at 50°C acidified and extracted with diethylether. Acid* **9** *is purified by distillation : b.p. = 180 °C(0.1 mm) , 71% yield from* **8** .

The preceeding schemes present a relatively simple pathway from α, β unsaturated carboxylic acids to chiral β–(2,6-dimethoxyphenyl) acids, the two enantiomers being attainable [1].

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