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Asymmetric synthesis of ketoprofen : a surprising base catalyst effect during asymmetric addition of pantolactone to methyl (3-benzoylphenyl) ketene

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Abstract : The best diastereoselectivity of addition of a chiral alcohol to the ketene derived from ketoprofen was obtained with R or S pantolactone (ed=99%). Depending on the tertiary amine used both for ketene formation and as catalyst during addition, the diastereoisomeric ratio of esters could be strongly modified and even inverted. Mild saponification afforded R or S ketoprofen in enantiomeric excess of up to 99%.

2-(3-Benzoylphenyl) propionic acid **1** (ketoprofen) is a non-steroïdal anti-inflammatory drug commercially available as the racemic mixture[1,2]. Since for this class of 2-aryl propionic acids, often only one enantiomer is biologically active[3], many asymmetric syntheses have been developed. However most of them are not applicable with ketoprofen. Only four such asymmetric syntheses have been described, all of them recently.

- The stereoselective alkylation with methyl iodide of the corresponding aryl acetic acid derivatized as the chiral amide[4]. Racemizing amide cleavage conditions did not afford S-(+)-ketoprofen of sufficient enantiomeric purity and a later separation by recrystallisation of diastereoisomers resulting from reaction with R-(+)-methylbenzylamine was necessary in order to obtain S-(+)-ketoprofen in 96% excess.

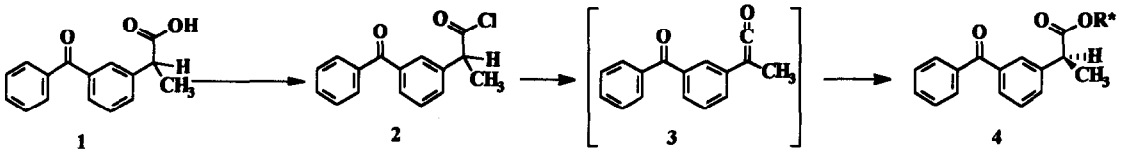
- The enantioselective hydrogenation of 2-(3-benzoylphenyl)propionic acid in the presence of chiral phosphines[5,6]. Only 71% enantiomeric excess was obtained in the more favourable cases.

- From (E) 3-m-trimethylsilylphenyl-3-methyl allyl alcohol[7a]. This recent approach made use of a combination of Sharpless epoxidation followed by stereoselective hydrogenolysis of a benzylic carbon-oxygen bond to establish the stereochemistry. S-(+)-Ketoprofen was obtained in 98% ee. Following the same method[7b], the 3-m-iodo-3-methyl allyl alcohol gave (S) ketoprofen in 97% ee by successive coupling of benzylzinc and oxidation with potassium permanganate.

- Very recently[8], asymmetric addition of chiral lactate to the ketene derived from ketoprofen in the presence of ethyl dimethyl amine was reported to give 71% enantiomeric excess after saponification of the intermediate ester by LiOH.

Asymmetric addition of a chiral alcohol to ketenes derived from 2-aryl propionic acids is a very convenient method widely discussed in the literature[9-23], ketene formation and alcohol addition normally occurring in a one pot procedure. It has been shown that if after ketene formation, resulting from the action of triethylamine or dimethyl propyl amine on the corresponding acid chloride, an organic base such as pyridine or 1,4-diazabicyclo[2,2,2]octane (DABCO) is added to the solution, the stereoselectivity of the chiral alcohol addition can be greatly enhanced[11-13]. Therefore, with the aim of synthesizing optically pure ketoprofen, we investigated the reaction of the ketene derived

from ketoprofen (Scheme 1) in order to select both chiral alcohol and basic catalyst. Moreover, since the synthesis occurs in a one pot procedure from the acid chloride, unlike other workers we set out to use the same tertiary base for both steps.



Scheme 1

For convenience, all the reactions were first performed in THF. The acid chloride **2**, resulting from reaction at room temperature of racemic ketoprofen and oxalyl chloride, is easily isolated pure after distillation.

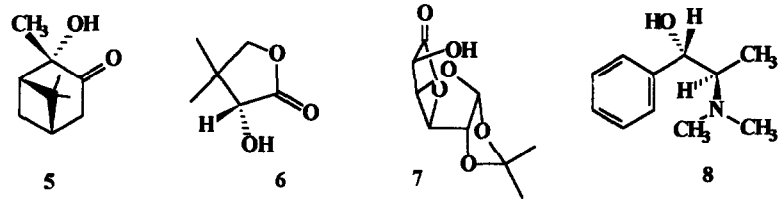
The following four readily available chiral alcohols were first selected (Scheme 2). Following Larsen's observations[19], these alcohols, which are sterically hindered near the hydroxy group and also offer the possibility of formation of a favorable hydrogen bond, should give rise to an excellent diastereoselectivity in the addition :

- 2-hydroxy pinan-3-one **5**, a tertiary alcohol successfully used as chiral auxiliary in the asymmetric synthesis of α-amino esters by protonation or alkylation of the corresponding enolates[24].

- R-(-) pantolactone **6**, a naturally occurring product, chiral addition of which to the ketenes derived from 2-(p-isobutyl phenyl) or 2-(6-methoxy naphthyl) propionic acid (ibuprofen and naproxen respectively) give the respective 2-aryl propionate esters in up to 99% de[19,20].

- 1,2-O-isopropylidene-α-D-glucurono-6,3-lactone **7** which is easily prepared[25] from commercially available glucurono-6,3-lactone. Its rigid and bicyclic structure is very close to that of pantolactone.

- (+) N-methylephedrine **8**, which is both a chiral alcohol and a tertiary amine. In this case no additional base is necessary.



Scheme 2

In each case, a THF solution of the acid chloride of ketoprofen was cooled to -10°C and triethylamine (1.1 equiv) was added followed by the chiral alcohol 3h later. The results are shown in Table 1. It can be seen that, firstly, pantolactone is the only alcohol affording an excellent diastereoselectivity and secondly there is a surprising difference in diastereoselectivity between the pantolactone and sugar derivative although their structures are very close. 2-Hydroxy pinan-3-one, even though it is a hindered tertiary cyclic alcohol, gave approximately the same selectivity as N-methyl ephedrine. It seems that, as in the case of pantolactone, a tetrasubstituted carbon α to the alcohol group is necessary for good selectivity.

Pantolactone **6** were therefore used as the chiral alcohol in all subsequent experiments. In order to determine the influence of temperature, we performd the reaction at various temperatures. As seen in Table 2, both in THF and in

toluene the selectivity depends only slightly on temperature provided it is lower than -10°C. However, at room temperature the selectivity is greatly reduced.

Table 1 : ratios were determined from the ^1H NMR spectrum of the crude reaction mixture

Alcohol	RR/SR ratio of esters
(-)2-hydroxy pinan-3-one	63:37
R-(-) pantolactone	96.5:3.5
1,2-O-isopropylidene-α-D-glucurono-6,3-lactone	58:42
(+) N-methylephedrine	65:35

Table 2 : Temperature and solvent dependence of the diastereoisomeric RR/SR ratio

Temperature	THF	Toluene
-78°C	98.5:1.5	99.5:0.5
-40°C	98:2	99:1
-10°C	96.5:3.5	98.5:1.5
+20°C	83:17	85:15

Diastereoselectivity is also slightly improved when THF is replaced by a less polar solvent such as toluene; in this case even at -10°C about 97% de was obtained.

Finally, we compared the influence of the basic catalyst on the stereoselectivity. With this aim, triethylamine was successively replaced by six bases of various bulkiness : pyridine, trimethylamine, N-methyl morpholine (NMM), 1,8-diazabicyclo[5,4,0]undec-7-ene(1,5-5) (DBU) and 1,2,2,6,6-pentamethyl piperidine (PMP) (Table 3). For each base two standard experiments were carried out using pantolactone as chiral alcohol.

- in the first experiment (procedure a) a THF solution of acyl chloride was treated with a base (1.1 equiv) at -10°C. The mixture was allowed to stand at room temperature for 3h and was then cooled to -10°C and the alcohol solution was added.
- in the second experiment (procedure b) the addition of reactants was reversed. A solution of chiral alcohol and base (1.1 equiv) was treated with an acyl chloride solution at -10°C and was then allowed to stand at room temperature for 3h.

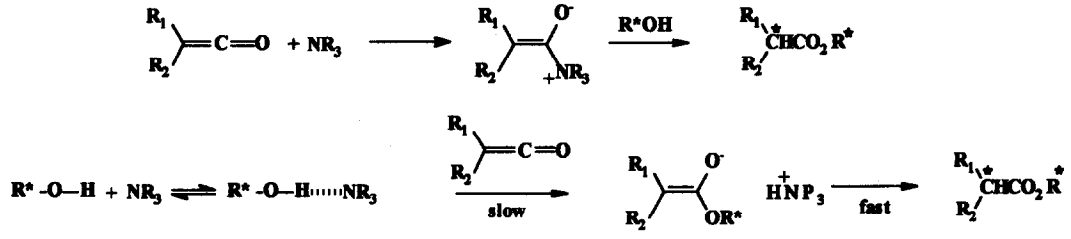
It can be seen that procedure b, used in the literature in the case of unstabie ketenes[21,22], did not significantly affect the diastereoisomeric ratio as compared to that for procedure a. With less hindered nucleophilic bases (trimethylamine, triethylamine or NMM) the RR isomer was formed with excellent diastereoselectivity. On the other hand, pyridine or hindered bases (DBU or PMP) afforded mainly the SR isomer, but with low diastereoselectivity.

Thus, starting from the same chiral alcohol it is possible to obtain predominantly one or the other enantiomer of ketoprofen merely by changing the base, as long as the same base is used both for ketene formation and as catalyst. If triethylamine is used in stoichiometric amount for ketene formation and pyridine is the basic catalyst (0.1 equiv) during the alcohol addition, then the RR isomer is obtained in poor diastereoisomeric excess (40%).

table 3 : Dependence of the RR/SR diastereoisomeric ratio on the base catalyst (solvent : THF)

base	procedure a	procedure b
NMM	99:1	97:3
triethylamine	98.5:1.5	96:4
trimethylamine	94:6	90:10
pyridine	44:56	46:54
PMP	41:59	43:57
DBU	46:54	38:62

Several possible mechanisms have been proposed[10-19] and discussed in two reports[9,23]. They involve either initial addition of amine on ketene followed by asymmetric protonation by a chiral alcohol, or initial formation of an amine-alcohol complex which then reacts with the ketene affording an ion pair. Collapse of the latter gives rise to the observed stereoselectivity. However, until now, it has not been possible to distinguish between the two mechanisms (Scheme 3).



Scheme 3

We think that both mechanisms can be involved, the predominance of one or the other depending on the nature of the base. In the case of a nucleophilic unhindered base, this readily reacts with the ketene affording the least hindered enolate. Protonation with pantolactone is then very stereoselective. It can be noted that when the amount of base reaches 2 equiv with respect to the acyl chloride, a slight decrease of ester ed was observed. On the other hand with a very hindered base such as nucleophilic DBU[26] or non-nucleophilic PMP, addition to the ketene is disfavored and an amine-alcohol complex, which becomes the new chiral auxiliary, can be formed. Since amine complexation should take place on the least hindered face of pantolactone, the stereoselectivity of addition can be strongly affected and even reversed.

The last point concerned saponification of the ester 4 which should take place without racemization. We preferred to use treatment with a water-ethanol-carbonate solution at room temperature for two hours instead of the literature conditions[8] (LiOH solution). Thus, R-ketoprofen was isolated in 98% enantiomeric excess and 85% yield from racemic ketoprofen. However, it has been shown that generally only the S enantiomer of 2-aryl propionic acids is biologically active[3]. To obtain S-ketoprofen by this method it is necessary to first reverse the configuration of the R-pantolactone which is the only isomer commercially available. This can be readily done using various procedures[27]. Starting from S-pantolactone, S-ketoprofen is obtained in 98% enantiomeric excess from its racemic mixture when the reaction is carried out at -10°C in toluene, and in ee>99% if the reaction is carried out at -78°C.

EXPERIMENTAL

^1H NMR spectra were recorded on a Brucker AC-250 spectrometer and mass spectra with a JEOL JMS DX 300 instrument

2-(3-benzoylphenyl)propionic acid chloride **2**

A solution of ketoprofen (10g, 40 mmoles) in oxalyl chloride (35ml, 10 equiv.) was stirred at room temperature for 1h. After removing excess oxalyl chloride, the ketoprofen acid chloride was distilled under vacuum.

$b.p._{0.8mbar}$ = 186-188°C, yield=90%

Preparation of esters **4**

Procedure a : To a solution of acid chloride **2** (2.7g, 10mmoles) in THF or toluene (10ml) was added at -10°C under N_2 a solution of tertiary amine (11mmoles) in the same solvent (5ml). The yellow slurry formed was stirred for 3h at room temperature and then cooled to the required temperature before addition of a solution of the chiral alcohol (12mmoles) in the same solvent (5ml). The white slurry obtained was stirred for an additional 2h. The amine hydrochloride was removed by filtration and the solution concentrated under vacuum. The residual viscous oil was dissolved in ether and the solution washed successively with a 1N HCl solution (10ml), water (10ml), a saturated aqueous $NaHCO_3$ solution (3x10ml) and finally water (10ml). The ether solution was dried over $MgSO_4$ and was then evaporated. The diastereoisomeric ratios were determined from the NMR spectra of the crude products. The residual oil was purified by chromatography on silica gel with ether-hexane as eluent. Yield 90%.

Properties of the esters : from **5** : oil, R_f=0.52 (ether/hexane, 50:50), FAB-MS (GT) : 405 $(M+H)^+$

Anal. Calcd. for $C_{26}H_{28}O_4$: C, 77.20; H, 6.98. Found : C, 77.39; H, 6.81.

from **6** : oil, R_f=0.35 (ether/hexane, 50:50), FAB-MS (GT) : 367 $(M+H)^+$

Anal. Calcd. for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05. Found : C, 72.28; H, 6.17.

from **7** : oil, R_f=0.43 (ether/hexane, 50:50), FAB-MS (GT) : 453 $(M+H)^+$

Anal. Calcd. for $C_{25}H_{24}O_8$: C, 66.36; H, 5.35. Found : C, 66.27; H, 5.31.

from **8** : oil, R_f=0.47 (ether/hexane, 66:34), FAB-MS (GT) : 416 $(M+H)^+$

Anal. Calcd. for $C_{27}H_{29}NO_3$: C, 78.04; H 7.04. Found : C, 78.19; H, 6.91.

Procedure b : To a solution of the chiral alcohol (12mmoles) and the tertiary amine (11mmoles) in THF or toluene (10ml) was slowly added at the required temperature a solution of the acid chloride (10mmoles) in the same solvent (10ml). The slurry was stirred for 2h, cooled to -10°C, filtered and the solution evaporated under vacuum. The residual viscous oil was treated as above.

Saponification of the pantolactone ketoprofen ester

To a solution of pantolactone ketoprofen ester (10mmoles) in methanol (50ml) was added at room temperature a solution of Na_2CO_3 (20mmoles) in water (50ml). The solution was stirred until disappearance of the starting material (about 2 h). Methanol was evaporated and the residual aqueous solution was washed with ethyl acetate. The pH was adjusted to 1 with a 2N HCl solution and the solution was extracted with ether (2x50ml). The ether solution was dried over MgSO4 and evaporated. The crude product was crystallized from benzene-petroleum ether (6/20). (S)

ketoprofen : m.p.= 118°C, yield = 95%, $[\alpha]_D$ + 56.7° (c=1, CH_2Cl_2), ee > 99 % from (S)(+) pantolactone, Litt.[28] $[\alpha]_D$ +57.1° (c=0.76, CH_2Cl_2)

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