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OPTICALLY ACTIVE NAPROXEN BY KINETIC RESOLUTION

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Optically active naproxen is prepared from it's racemic precursor by kinetic resolution via the anhydride and it's reaction with optically active 1-(4-pyridyl)ethanol in high chemical and optical yield.

Several α-arylalkanoic acids are clinically used as nonsteroidal antiinflammatory agents (antiphlogistica).[1] Frequently one enantiomer exceeds the other in activity [1a] as it is the case for naproxen 3, one of the most potent and best tolerated pharmaceuticals of this family. The S(+) enantiomer exceeds the R(-) enantiomer by a factor 28 in activity.[1a,2] The present interest in this drug is particularly evident from a series of new procedures for naproxen syntheses in the recent literature, mainly in the patent literature [2,3] and from several patents dealing with ways for separating the antipodes.[2,4]

Our attempts to obtain optically active naproxen 3 by an asymmetric synthesis [5] via the reaction of 6-methoxy-2-naphtyl-methyl ketene with optically active α-phenylethanol in the presence of a tertiary amine base were only partly successful.[6] This was probably due to insufficient persistence of the ketene and to difficulties with ester hydrolysis without racemisation.

We are reporting now a successful stereospecific synthesis of optically active naproxen 3 from it's racemic precursor by a method recently developed for the synthesis of pyrethroid acids.[7]

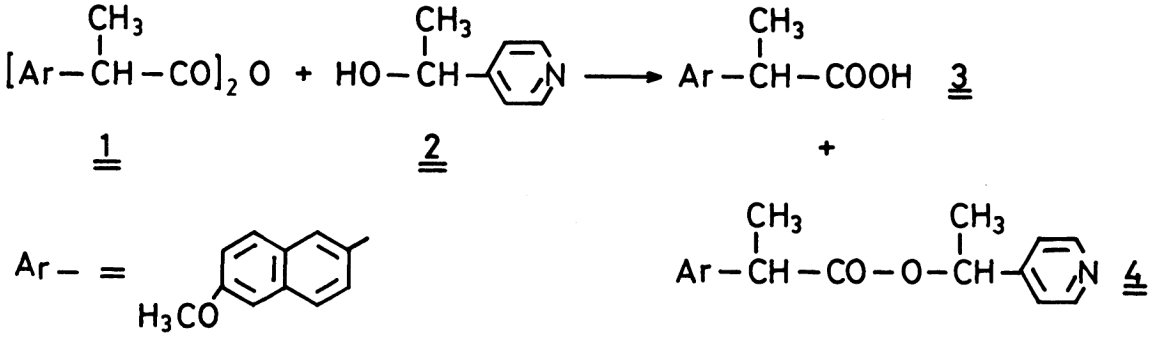

Table 1. Reaction of 2-(6-Methoxy-2-naphtyl)-propanoic Anhydride 1 and 1-(4-Pyridyl) ethanol 2 in a 1:1 molar ratio at 25°C

No.	1 (mmol)	Solvent (ml [a])	2	3 Yield/% [b]	3 e.e.[c] ± 2%	4 Yield/% [b]	4 d.e. [d] ± 2%
1	1.1	20T/26E	rac.	e)	-	48	64 [f]
2	1.1	40T/3E	rac.	e)	-	46	72 [f]
3	1.1	40T/3E	(-)S [g]	70	54 [h]	58	60 [i]
4	2.3	80T/5E	(+)R [k]	81	55 [l]	55	74 [m]

a) T = toluene, E = ether. b) Isolated yields.
c) Corrected for incomplete o.p. of 2. d) Analyzed by HPLC and in No. 1-2 by NMR; the d.e. values are not corrected for incomplete o.p. of 2 because racemic 2 induces even somewhat higher d.e.'s than optical active 2. [7,8]
e) Not analyzed. f) Excess R,R and S,S-diastereomer.
g) o.p. = 95%. h) Corrected for, [g] excess (-)R enantiomer.
i) Excess S,S over R,S. diastereomer. k) o.p. = 89%.
l) Corrected for, [k] excess (+)S enantiomer.
m) Excess R,R over S,R-diastereomer.

Racemic 2-(6-methoxy-2-naphtyl)propanoic acid [2,3] was transformed to the diastereomeric mixture of it's anhydride by treatment with acetic anhydride.[7] On reaction of 1 with an equimolar amount of optically active 1-(4-pyridyl)ethanol 2 naproxen 3 is obtained in 70-80% chemical yield and more than 50% optical yield. The second product, the ester 4 is isolated in more than 50% yield and 60-70% optical yield. As discussed previously this high asymmetric induction is due to kinetic resolution. [7] Correspondingly therefore one pair of diastereomers of 4 is obtained with high stereoselectivity from racemic 2.[8] The results recorded in Table 1 have not yet been optimized. 3 was obtained from 4 by acid hydrolysis in aqueous dioxane in 85% chemical yield without racemisation. [9] Because optically active 2 has been recovered from similar hydrolysis reactions [7] and because racemic 1 should be obtained, when R(-)-3 is treated with acetic anhydride and pyridine [7] this reaction sequence should be suited for the complete conversion of racemic -3 into S(+)-3, the pharmaceutically active naproxen.

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9) Merck ion-exchanger I, 13 h,90 °C; mp (3): 140-143 °C; $[\alpha]_D^{22}$ = -34.7° (c 1.0, $CHCl_3$) 60% overall o.y.

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