

## OPTICALLY ACTIVE NAPROXEN BY KINETIC RESOLUTION

Amelie FRANCK and Christoph RÜCHARDT\*  
 Chemisches Laboratorium der Universität Freiburg,  
 Albertstr. 21, D-7800 Freiburg, BRD

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

Several  $\alpha$ -arylalkanoic acids are clinically used as nonsteroidal antiinflammatory agents (antiphlogistica).<sup>1)</sup> Frequently one enantiomer exceeds the other in activity<sup>1a)</sup> 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.<sup>1a,2)</sup> 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<sup>2,3)</sup> and from several patents dealing with ways for separating the antipodes.<sup>2,4)</sup>

Our attempts to obtain optically active naproxen 3 by an asymmetric synthesis<sup>5)</sup> via the reaction of 6-methoxy-2-naphthyl-methyl ketene with optically active  $\alpha$ -phenylethanol in the presence of a tertiary amine base were only partly successful.<sup>6)</sup> 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 its racemic precursor by a method recently developed for the synthesis of pyrethroid acids.<sup>7)</sup>

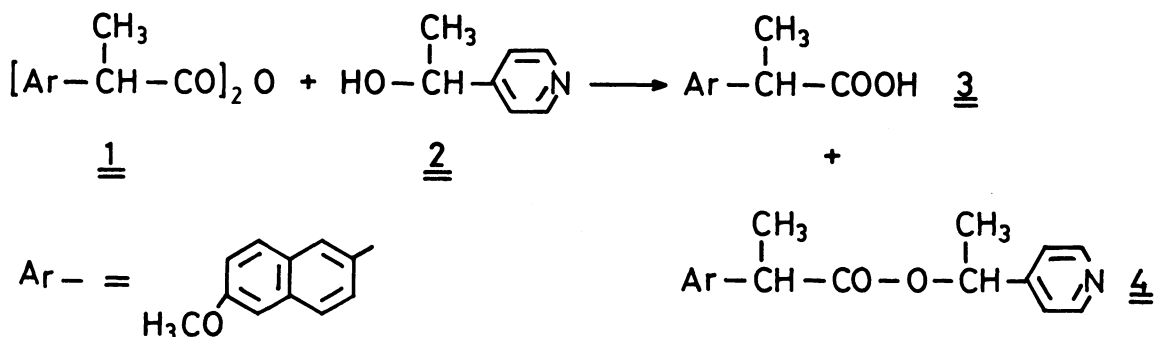


Table 1. Reaction of 2-(6-Methoxy-2-naphtyl)-propanoic Anhydride 1 and 1-(4-Pyridyl) ethanol 2 in a 1:1 molar ratio at 25°C

No.	<u>1</u> (mmol)	Solvent (ml <sup>a)</sup> )	<u>2</u>	<u>3</u> Yield/% <sup>b)</sup>	e.e. <sup>c)</sup> ± 2%	<u>4</u> Yield/% <sup>b)</sup>	d.e. <sup>d)</sup> ± 2%
1	1.1	2OT/26E	rac.	e)	-	48	64 <sup>f)</sup>
2	1.1	4OT/3E	rac.	e)	-	46	72 <sup>f)</sup>
3	1.1	4OT/3E	(-)S <sup>g)</sup>	70	54 <sup>h)</sup>	58	60 <sup>i)</sup>
4	2.3	8OT/5E	(+)R <sup>k)</sup>	81	55 <sup>l)</sup>	55	74 <sup>m)</sup>

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. <sup>7),8)</sup>

e) Not analyzed. f) Excess R,R and S,S-diastereomer.

g) o.p. = 95%. h) Corrected for, <sup>g)</sup> excess (-)R enantiomer.

i) Excess S,S over R,S diastereomer. k) o.p. = 89%.

l) Corrected for, <sup>k)</sup> excess (+)S enantiomer.

m) Excess R,R over S,R-diastereomer.

Racemic 2-(6-methoxy-2-naphtyl)propanoic acid <sup>2,3)</sup> was transformed to the diastereomeric mixture of its anhydride by treatment with acetic anhydride. <sup>7)</sup> 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. <sup>7)</sup> Correspondingly therefore one pair of diastereomers of 4 is obtained with high stereoselectivity from racemic 2. <sup>8)</sup> 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. <sup>9)</sup> Because optically active 2 has been recovered from similar hydrolysis reactions <sup>7)</sup> and because racemic 1 should be obtained, when R(-)-3 is treated with acetic anhydride and pyridine <sup>7)</sup> 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;  $[\alpha]_D^{22} = -34.7^\circ$  (c 1.0, CHCl<sub>3</sub>) 60% overall o.y.

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