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A simple catalytic route to naproxen

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Abstract—We report herein the asymmetric synthesis of naproxen involving catalytic enantioselective methylation for the first time. The reaction is conducted in a solid–liquid biphasic system using chiral quaternary ammonium salts.

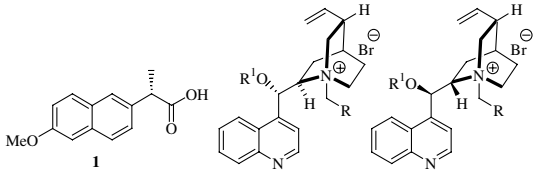
1. Introduction

Naproxen [(*S*)-2-(6-methoxy-2-naphthyl)propanoic acid] **1** is one of the most popular non-steriodal anti-inflammatory drugs.[1] It is an arylpropionic acid with a stereogenic centre. It has been shown that the activity of (*S*)-enantiomer of this class of drugs is greater than the (*R*)-isomer, because it is able to form a larger number of interactions at the active site of the cyclooxygenase enzyme.[2] For example, the pharmacological activity of the (*S*)-enantiomer of 2-(6-methoxy-2-naphthyl)propanoic acid is 28 times greater than its (*R*)-enantiomer.[2]

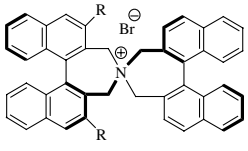
Methods reported for obtaining naproxen are either by resolution[3] or by asymmetric synthesis[4] usually with the use of chiral auxiliaries.[5] The main disadvantages of the above methods is the need to recycle the undesired isomer or to recover the chiral auxiliary, respectively. A more practical approach would be the use of a chiral catalyst.

In asymmetric synthesis, alkylation of a prochiral substrate is an attractive approach. Although the enantioselective alkylation of arylpropionic acids has been reported using chiral auxiliaries,[6] there is none using a catalytic method. We report herein the results of enantioselective methylation using chiral quaternary ammonium salts as catalysts under solid–liquid phase-transfer conditions.

Chiral quaternary ammonium salts have been used in asymmetric alkylations.[7] In fact, the first successful example was reported by the Merck group in the asymmetric alkylation of a cyclic ketone intermediate leading to the synthesis of indacrinone using *N*-(4-trifluoromethylbenzyl)cinchoninium bromide as chiral phase-transfer catalysts (PTC) in aqueous NaOH.[8]



a) R = 9-Anthracene, R^1 = Allyl.
b) R = 2-Fluorophenyl, R^1 = Allyl.



4 (R = 3,4,5-F_3-Ph)

2. Results and discussion

Prochiral substrates **5a–c** were prepared by esterifying 6-methoxy-2-naphthyl acetic acid[9] with different alcohols. Our initial efforts in methylating **5a** using various inorganic bases like powdered NaOH, KOH and CsOH along with tetrabutylammonium bromide in toluene at room temperature were unsuccessful; in all the cases the methylated product was obtained in poor yields. Use of sodium methoxide did not improve the yield,

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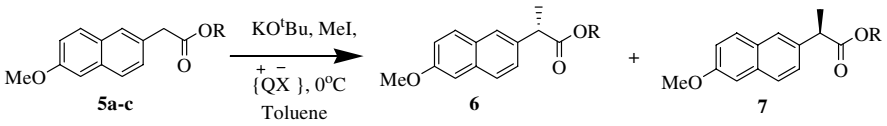

Scheme 1. Phase-transfer catalysed methylation of **5a–c**.

however, the use of stronger bases like potassium *tert*-butoxide under similar conditions gave the methylated product in good yields.

Switching to chiral quaternary ammonium salt, *O*-(9)-allyl-*N*-9-anthracenylmethylcinchoninium bromide **2a** as the catalyst, substrate **5a** was methylated in toluene[10] at 0 °C using potassium *tert*-butoxide as the base. Products **6a** and **7a** were obtained in 88% yield but with very poor enantioselectivity (15%) (Scheme 1). Cyclohexyl ester **5b** and *tert*-butyl ester **5c** were also tried as synthons (Table 1).

Table 1. Methylation of esters **5a–c** catalysed by **2a**

Entry	Substrate (R)	Time (h)	% Ee[a]	Yield[b] (%)
1	**5a** (isopropyl)	11	15	84
2	**5b** (cyclohexyl)	8	8	88
3	**5c** (*tert*-butyl)	19	18	86

[a] Determined using chiral HPLC.
[b] Yields of isolated product.

Based on the results, *tert*-butyl ester **5c** was chosen as substrate for optimisation of reaction conditions. Reactions were done in different solvents and various temperatures (Table 2, entries 1–8). Catalyst **2a** gave the highest selectivity for the desired (*S*)-isomer (78:22) (Table 2, entry 5), when the methylation was done in a mixture of toluene:dichloromethane (7:3) at −50 °C. Spiro quaternary ammonium salt (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide **4** gave the product with 74% selectivity in 72% yield.[11]

We next tried two other chiral quaternary ammonium salts, which are known to give good enantioselectivities in alkylation reactions. The use of *O*-(9)-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide **3a** gave the (*R*)-enantiomer with 80% selectivity. While the use of *O*-(9)-allyl-*N*-(2-fluorobenzyl)cinchonidinium bromide **3b** also gave the (*R*)-enantiomer but with decreased selectivity. Recrystallisation of the crude product (56% ee) was tried from different solvents like hexane, 2-propanol, *n*-butanol and *tert*-butanol. Single recrystallisation from *tert*-butanol yielded the product with 93% ee. Finally the *tert*-butyl ester was hydrolysed with 6 M HCl to give naproxen in 94% yield.

The reaction discussed is a classical example of a solid–liquid phase-transfer catalysed reaction, where the C–H acidic compound is being deprotonated by the chosen strong base generating a reactive anion in the presence of the chiral quaternary ammonium salt.[12] The ion-pair formed by the anion thus formed with the positively charged nitrogen of the chiral PTC results in asymmetric induction. Though such solid–liquid phase-transfer reactions using strong base like KO^{t}Bu have been reported using chiral crown ethers or cinchona alkaloids in Michael additions, along with its mechanism,[13] to the best of our knowledge this is the first report of it being used in direct asymmetric alkylation.

3. Conclusions

We have designed a new catalytic route to naproxen involving asymmetric methylation. Prochiral ester precursors **5a–c**, which can be easily prepared, are enantioselectively methylated using chiral quaternary ammonium salts under solid–liquid biphasic system. *O*-(9)-Allyl-*N*-(9-anthracenylmethyl)cinchoninium bromide gave the best result.

4. Experimental

General procedure for asymmetric methylation: To a stirred solution of prochiral ester **5a–c** (3.67 mmol) and catalyst (0.36 mmol or 0.036 mmol),[14] in an appropriate

Table 2. Reaction conditions for the methylation of *tert*-butyl (6-methoxy-2-naphthyl) acetate **5c**

Entry	Solvent	Temp (°C)	Catalyst	Time (h)	Yield[a] (%)	% Selectivity[b] (*S*:*R*)
1	CH_2Cl_2	−20	**2a**	6	70	62:38
2	CH_2Cl_2/toluene (7:3)	−20	**2a**	10	75	75:25
3	Chlorobenzene	−20	**2a**	18	68	72:28
4	Anisole	−20	**2a**	16	69	70:30
5	CH_2Cl_2/toluene (7:3)	−50	**2a**	14	74	78:22
6	CH_2Cl_2/toluene (7:3)	−50	**3a**	14	78	20:80
7	CH_2Cl_2/toluene (7:3)	−30	**3b**	12	72	36:64
8	CH_2Cl_2/toluene (7:3)	−40	**4**	8	72	74:26

[a] Isolated yields.
[b] Selectivity was determined using chiral HPLC; the absolute configuration was determined by comparison of the specific rotation and retention time of the hydrolysed ester with (*R*)- and (*S*)-2-(6-methoxy-2-naphthyl)propanoic acid.

solvent (15 mL) was added KO^{t}Bu (0.399 g, 3.55 mmol) at −50 °C, followed by addition of methyl iodide (2.08 g, 14.68 mmol) via syringe pump under an argon atmosphere. The contents were stirred for 6–18 h and the reaction then quenched by diluting with water (5 mL). The aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane/ethyl acetate, 98:2), to give the product in 68–78% yield. In case of *tert*-butyl ester (**5c**) the methylated product (**6c** and **7c**) was recrystallised with *tert*-butanol to afford the product **6c** with 93% ee. (Chiralcel OD-H, hexane/isopropanol 95.5:0.5, t_R = 14.0 min, t_S = 15.7 min, 0.5 mL/min, 254 nm). Mp 92–93 °C (lit. mp 94–96 °C).[15] $[\alpha]_D^{25} = +24.8$ (*c* 1, CH_2Cl_2) {lit. $[\alpha]_D^{25} = +26.9$ (*c* 1, CH_2Cl_2)}.[15] IR (KBr) *v* 2977, 2938, 1724, 1610, 1458, 1393, 1370, 1327, 1265, 1203, 1163, 1025, 858 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.38 (s, 9H), 1.52 (d, *J* = 7.18, 3H), 3.73 (q, *J* = 7.14, 1H), 3.90 (s, 3H), 7.11–7.25 (m, 3H), 7.40 (dd, *J* = 2.8, 5.49, 1H), 7.64 (s, 1H), 7.69 (dd, *J* = 2.9, 5.66, 1H). MS (APCI): *m/z* (%) 286 (M^+, 5), 230 (40), 185 (100).

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