This article was downloaded by: [Florida Atlantic University] On: 14 October 2014, At: 13:56 Publisher: Taylor & Francis Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry Publication details, including instructions for

authors and subscription information: http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF OPTICAL ACTIVE 2-ARYLPROPIONIC ACIDS

B. Wang ^a & H.-Zh. Ma ^a

^a Department of Chemistry , Northwest University , Xi'An, 710068, P.R. China Published online: 09 Nov 2006.

To cite this article: B. Wang & H.-Zh. Ma (2001) SYNTHESIS OF OPTICAL ACTIVE 2-ARYLPROPIONIC ACIDS, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 31:7, 1047-1051, DOI: 10.1081/SCC-100103535

To link to this article: http://dx.doi.org/10.1081/SCC-100103535

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at <u>http://www.tandfonline.com/page/terms-and-conditions</u>

SYNTHESIS OF OPTICAL ACTIVE 2-ARYLPROPIONIC ACIDS

B. Wang* and H.-Zh. Ma

Department of Chemistry, Northwest University, 710068, Xi'An, P.R. China

ABSTRACT

(S)-2-(6'-methoxyl- α -naphthyl)propionic acid ((S)-Naprofen, ee% = 99) has been prepared by starting from (6-methoxyl- α -naphthyl)propan-1-one and D-sorbitol under ZnCl₂ catalysis.

2-Arylpropionic acid and its derivatives are pharmaceutically and agriculturally useful products,^{1,2} specifically the optical isomer possesses an extra biological or pharmaceutical activity. A well-known example is 2-(6'-methoxyl- α -naphthyl) propionic acid, whose S isomer (Naproxen) is 28 times as active as the R isomer as an antiflammatory agent.^{3,4} For the preparation of optically active 2-arylalkanoic acids, many different synthetic strategies have been reported: the use of racemates resolving by optically active bases; asymmetric hydrogenation of prochiral unsaturated 2-aryl carboxylic acids; asymmetric carboalkoxylation of aryl alkotones; asymmetric carbonylation of benzyl halides; and asymmetric cross-coupling reactions of organometallic reagents either with aryl and vinyl halides or with allylic derivatives.³⁻⁵ Among these routes is the Castaldi et al.⁶

^{*} Corresponding author.

procedure, as shown in Scheme 1, where the stereospecific rearrangement of optically active acetals to esters is the key step, and depending on the nature of X group, basic or acidic catalysts are used to catalyze this step. This procedure has been applied to prepare (S)-(+)-Naproxen commercially by the Zambon Company of Italy, but the yield is relatively low (80%), the procedure is long, the chiral auxilliary is expensive and can be reused, which make production costly.



Scheme 1.

Another industrial method is the Monsanto procedure,⁷ as shown in Scheme 2, which applies an electrochemical process that can get high-yield product (95%) with ee% = 98.5, but the catalyst turnover is only 215 and the reaction must be performed under 13.5 Mpa, which leads to difficult production.

Here we report a very practical one-step method of (S)-(+)-Naproxen preparation involving the cheap chiral auxiliary, D-sorbitol, and $ZnCl_2$ catalyst, synthesis of optically active acetals, and stereospecific rearrangement. The route can be summarized as Scheme 3 shows. Compared with Scheme 1, the procedure has been simplified, the yield increased upto 87%, ee%=99, and it is easily industrialized.

In theory, D-sorbitol reaction with (6-methoxyl- α -naphthyl)propan-1-one under ZnCl₂ catalyst, two types of 1,2-(S)-O-(6-methyhoxyl- α naphthyl)propylidene-D-sorbitol and 1,2,5,6-O-diketal (Scheme 3) formed in polar solvent (DMF), existing kinetically and thermal controlled



Scheme 2.

intermediate. But in polar solvent, the rearrangement of acetal is difficult, so the mixture solvent of DMF and trimethoxyl orthoformate was used. The periodate oxidation results indicate that 1 mol intermediate acetal produces 2.2 mmol formaldehyde (calc. 2 mmol) and 3.8 mmol (calc., 4 mmol) of formic acid. 1,2-(S)-O-(6-Methoxyl- α -naphthyl)propylidene-D-sorbitol is the main intermediate.



Scheme 3.

EXPERIMENTAL

All ¹H NMR spectra were recorded at 400 MHz, all ¹³C NMR spectra at 100 MHz in D₄-methanol. MS, IR (KBr pellets) and m.p. tested.

Synthesis of 1

A mixture of 1 mmol D-sorbitol (1.82 g), 1 mmol (6-methoxyl- α -naphthyl)propan-1-one (2.2 g), and 0.01 mol, ZnCl₂ (1.3 g) in 10 cm³ DMF and 30 cm³ trimethoxyl orthoformate was heated 3 h to 130°–140°C in air. Then the solvent was evaporated by reduced pressure. The residue was crystallized in methanol (20 cm³×3) and chromatographed on silica column (CH₂Cl₂: MeOH = 70:30). A pale yellow product was obtained and analyzed. M.p. 84°–86°C. [α]_D²⁰=+126° (cl.8, CHCl₃), yield 90%, ee% = 92.

Elemental analysis: Found: C 60.4%, H 7.4%; Calculated: C 60.4%, H 7.4%.



MS(m/e): 397(M-1⁺, 20), 398(M⁺, 14), 105(105).

IR (KBr): 3450br, 2900, 1726, 1604, 1540, 1445, 1320, 1225, 1110, 1030, 985, 780, 685 cm^{-1} .

¹H NMR (δ , ppm, DMF-d₇) 7.4(m, naphthyl, H₁₋₈), 4.0(s, OMe), 1.2(d, CH₃), 3.5(q, CH), 4.7(d, H₁₃), 4.5(dd, H₁₄), 3.9(dd, 3.7(dd, H₁₆), 4.1(dd, H₁₇), 4.3(dd, H₁₈), 5.1(-OH), ¹³C NMR(δ , ppm, DMF-d₇), 170(CO), 129(C₁), 127(C₂), 124(C₃), 128(C₄), 129(C₅), 126(C₆), 125(C₇), 130(C₈), 131(C₉), 132(C₁₀), 39.5(C₁₁), 21(C₁₂), 81(C₁₃), 78(C₁₄), 76(C₁₅), 74(C₁₆), 76(C₁₇), 78(C₁₈), 55(s, OMe).

Hydrolysis of 1

The solid was dissolved in 40 cm³ methanol and 10 cm³ hydroxyl chlorite was added and refluxed 2 h, then the solvent was evaporated by reduced pressure. The residue was dissolved in 1 M NaOH solution (50 cm³), extracted by CHCl₃, and chromatographed on silica column (CH₂Cl₂: MeOH=70:30). A white product was obtained (2 g, yield 87%) and analyzed. M.p. 154°-156°C. $[\alpha]_D^{20} = +63.2^\circ$ (cl.8. CHCl₃), ee% = 99, ref^{3,4} m.p. 154°-156°C. $[\alpha]_D^{20} = +63.5^\circ$ (cl.8. CHCl₃).

REFERENCES

- 1. Shen, T.Y. Angew Chem. Int. Ed. Engl. 1972, 11, 460.
- Artl, D.; Jautelat, M.; Lantzsch, R. Angew Chem. Int. Ed. Engl. 1981, 20, 703.
- 3. Oreste, P.; Franca, S.; Giuseppina, V. J. Org. Chem. 1987, 52, 10.
- 4. Alper, H.; Hamel, H. J. Am. Chem. Soc. 1990, 112, 2803.
- 5. Harikisan, R.S.; Nanjundiah, S.B.; Jaimala, R.; Dilip, G.K. Tetrahedron: Asymmetry **1992**, *3*(2), 163.
- Castaldi, G.; Cavicchioli, S.; Giordano, C.; Uggeri, F. J. Org. Chem. 1987, 60, 1027.
- 7. Noyori, R.J. CHEMTECH 1992, 360.

Accepted May 8, 2000

Downloaded by [Florida Atlantic University] at 13:56 14 October 2014