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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

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To cite this article: Adelfo Reyes & Eusebio Juaristi (1995) USE of (S)-a-Methylbenzylamine in the Resolution of Racemic 2-Octanol and a-Methylbenzyl Alcohol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:7, 1053-1058, DOI: 10.1080/00397919508012667

To link to this article: http://dx.doi.org/10.1080/00397919508012667

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USE OF (S)-α-METHYLBENZYLAMINE IN THE RESOLUTION OF RACEMIC 2-OCTANOL AND α-METHYLBENZYL ALCOHOL

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Abstract: The title chiral amine can be a convenient substitute for brucine or strychnine in Ingersoll's classical method for the resolution of alcohols via fractional crystallization of their diastereoisomeric phthalate salts.

Introduction

Recent mechanistic studies in our group¹ required the use of enantiomerically pure (S)-(+)-2-octanol, which we prepared via the separation of the diastereoisomeric brucine salts of the hydrogen phthalate derivatives of racemic alcohol, according to the Ingersoll procedure.^{2,3} Nevertheless, consideration of the reduced toxicity, lower molecular weight, and more attractive price of (S)- α -methylbenzylamine [(S)- α -MBA] relative to brucine led to evaluation of the resolution procedure of (\pm)-2-octanol [(\pm)-1] depicted in Scheme 1.

Three reports in the literature suggested that the above proposal was reasonable. Indeed, Gough, et al.⁴ accomplished a partial resolution of racemic 2-methylcyclohexanol by a similar method. Furthermore, Fan and Wang⁵ and Pallavicini and coworkers⁶ have

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described the successful preparation of (S)-octyn-3-ol and (R)- and (S)-isopropylidene glycerol, respectively, following this approach.

In this paper we wish to report the efficient resolution of (\pm) -2-octanol [(\pm) -1] and (\pm) - α -methylbenzyl alcohol [(\pm) -2] by means of (S)- α -methylbenzylamine, according to the procedure described in Scheme 1.

Results and Discussion

A. Resolution of (±)-2-Octanol

Fractional crystallization from ethyl acetate of the diastereoisomeric salts formed by treatment of the hydrogen phthalates of racemic 2-octanol and (S)- α -methylbenzylamine afforded the (S,S) salts [(S,S)-4] in a remarkable 90.6 % of the theoretical yield. Removal of the chiral amine was carried out by simple treatment with 2 N HCl, followed by recrystallization from 90 % aqueous acetic acid to give the enantiomerically pure hydrogen phthalate of (S)-2-octanol [(S)-3]. Finally, saponification with KOH provided enantiomerically pure (S)-2-octanol [(S)-1].

On the other hand, concentration of the mother liquor containing an excess of diastereoisomeric salt (R,S)-4 afforded a viscous oil from which the present

(S)- α -methylbenzylamine was removed with 2 N HCl followed by recrystallization from 90 % aqueous acetic acid. Saponification of the resulting (*R*)-2-octyl hydrogen phthalate with KOH furnished the desired (*R*)-2-octanol in 85.0 % of the theoretical yield.

B. Resolution of (±)-α-Methylbenzyl Alcohol

Fractional crystallization from ethyl acetate of the diastereoisomeric salts prepared by treatment of the hydrogen phthalates of racemic α -methylbenzyl alcohol and (S)- α -methylbenzylamine afforded the (S,S) salt [(S,S)-6] in 69.0% of the theoretical yield. Removal of the chiral amine was carried out by treatment with 2 N HCl, followed by recrystallization from CS₂ to afford the enantiomerically pure hydrogen phthalate of (S)- α -methylbenzyl alcohol [(S)-5]. Finally, saponification with KOH provided enantiomerically pure (S)- α -methylbenzyl alcohol [(S)-2].

Concentration of the mother liquor enriched in the diastereoisomeric salt (R,S)-6 furnished a viscous oil, which was treated with 2 N HCl in order to remove the (S)- α -methylbenzylamine. Crystallization of the isolated mixture of hydrogen phthalates from CS₂ allowed for the separation of racemic compound, which is insoluble, and (R)- α -methylbenzyl hydrogen phthalate, which remains in solution. Saponification of this phthalate with KOH provided the desired (R)- α -methylbenzyl alcohol in 78.5 % of the theoretical yield.

Experimental

Melting points were determined on a Electrothermal Melting Point Apparatus and are uncorrected.

Optical rotations of compounds were determined on a Perkin-Elmer 241 polarimeter.

A. Resolution of (±)-2-Octanol

According to the procedure described by Ingersoll,² 13.0 g (0.1 mol) of (\pm)-2-octanol and 14.8 g (0.1 mol) of phthalic anhydride were heated to 110-115°C for 12 h. The mixture was allowed to cool, treated with 15.0 g (0.14 mol) of Na₂CO₃ in 800 mL of water, and washed with three 75-mL portions of benzene. Crystallization of the hydrogen phthalates was induced by treatment with a slight excess of conc. HCl, and Downloaded by [Moskow State Univ Bibliote] at 05:44 04 November 2013

recrystallization from 90 % aqueous acetic acid afforded 25.6 g (92.2 % yield) of product [(±)-3], mp 54-55°C. Twenty five grams (89.5 mmol) of the (±)-2-octyl hydrogen phthalates $[(\pm)-3]$ were dissolved in 100 mL of ethyl acetate and treated with 10.9 g (11.5 mL, 90.0 mmol) of (S)-a-methylbenzylamine at ambient temperature. The reaction mixture was cooled to 0°C for 4 h in order to allow the crystallization of 16.25 g (45.3 % of original mixture of phthalates, 90.6 % of theoretical yield) of the (S,S) diastereoisomeric salt [(S,S)-4], mp 124-125°C, $[\alpha]_D = +20.2$ (c = 5.0, CH₃OH). The above salt [(S,S)-4, 16.25 g, 40.7 mmol] was dissolved in 25 mL of 2 N HCl and the resulting solution was extracted with two 25-mL portions of EtOAc. The combined organic extracts were washed with water, dried over anh. Na2SO4, and concentrated to give 11.2 g (98.9 %) of the crude product, which was recrystallized from aqueous 90.0% acetic acid to afford 8.7 g (77.3 % yield) of pure (S)-2-octyl hydrogen phthalate [(S)-3], mp 74-75°C, $[\alpha]_D$ = + 48.4 (c = 5.0, EtOH). (S)-2-Octyl hydrogen phthalate (8.7 g, 31.3 mmol) was suspended in 16.0 mL of water containing 4.5 g of KOH and heated to reflux with simultaneous azeotropic removal of the alcohol. Extraction with ethyl acetate and concentration gave 3.4 g of the crude product which was distilled at reduced pressure, bp 75°C / 5.7 mm, to give the pure product [(S)-1], $[\alpha]_D$ = + 10.0 (c = 5.18, EtOH) [lit.¹ [α]_D= + 10.0 (c = 5.0, EtOH)].

Concentration of the mother liquor containing the diastereoisomeric salts (*R*,*S*)- and (*S*,*S*)-4 afforded 19.3 g (54.2 % of the starting mixture) of a viscous oil, which was treated with 30 mL of 2 N HCl and then extracted with two 25-mL portions of EtOAc, dried over anh. Na₂SO₄ and concentrated to give 13.4 g (97.3 %) of the crude product. Recrystallization from aqueous 90 % acetic acid gave 13.3 g (60.0 % yield) of (*R*)-2-octyl hydrogen phthalate [(*R*)-**3**], mp 72-74°C, $[\alpha]_D = -47.0$ (c = 5.2, EtOH). (*R*)-2-Octyl hydrogen phthalate (13.0 g, 46.8 mmol) was treated with 25 mL of water containing 6.5 g of KOH and heated to reflux with azeotropic removal of the desired alcohol. Extraction with EtOAc and concentration afforded 5.15 g (85.0 % of theoretical yield) of (*R*)-2-octanol [(*R*)-1], bp 166-168°C, $[\alpha]_D = -9.3$ (c = 4.4, EtOH).

B. Resolution of (±)-α-Methylbenzyl Alcohol

According to the procedure of Housa and Kenyon,⁷ a mixture of 8.7 g (71.0 mmol) of (\pm) - α -methylbenzyl alcohol, 11.0 g (74.0 mmol) of phthalic anhydride, and 5.82 g

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(73.0 mmol) of dry pyridine was heated to 105°C for 2 h. The reaction mixture was allowed to cool, and crystallization of the hydrogen phthalates was induced by addition of benzene to furnish 16.4 g (85.0 % yield) of the racemic product [(±)-5], mp 107-108°C. Racemic α -methylbenzyl hydrogen phthalate [(±)-5] (12.4 g, 45.9 mmol) was dissolved in 120 mL of Et₂O and treated with 5.5 g (45.4 mmol) of (S)-α-methylbenzylamine at ambient temperature. The reaction was cooled to 0°C for 2 h in order to facilitate the crystallization of 17.2 g (95.8 % yield) of the mixture of diastereoisomeric salts, which were recrystallized twice from hot ethyl acetate to give 6.2 g (69.0 % of theoretical yield) of the (S,S) salt [(S,S)-6], mp 156-157 °C, $[\alpha]_D = +15.8$ (c = 5.4, CH₃OH). The above salt [(S,S)-6, 6.0 g], 15.3 mmol] was dissolved in 20 mL of 2 N HCl and the resulting solution was extracted with two 20-mL portions of EtOAc. The combined organic extracts were washed with water, dried over anh. Na₂SO₄, concentrated and redissolved in CS₂, filtered and evaporated to give 3.99 g (96.4 % yield) of pure (S)- α -methylbenzyl hydrogen phthalate [(S)-5] as a viscous oil, $[\alpha]_D = +22.7$ (c = 4.0, CH₃OH). (S)- α -Methylbenzyl hydrogen phthalate (2.7 g, 10 mmol) was suspended in 5 mL of water containing 1.4 g of KOH and heated to reflux with concomitant azeotropic removal of the alcohol. Extraction with two 10-mL portions of EtOAc and concentration afforded 1.06 g (95.4 % yield) of crude product [(S)-2], which was purified by distillation at atmospheric pressure, bp 190°C, $[\alpha]_D = -41.9$ (c = 5.9, EtOH) [lit.⁸ $[\alpha]_D = -41.3$ (neat)].

Concentration of the mother liquor containing the diastereoisomeric salts (*R*,*S*)- and (*S*,*S*)-6 afforded 11.0 g (64.0 % of the starting mixture) of a viscous oil, which was treated with 50 mL of 2 N HCl, and then extracted with two 50-mL portions of EtOAc. The usual work-up procedure afforded 6.0 g (80.0 % yield) of an oil enriched in the (*R*) enantiomer, $[\alpha]_D = -12.7$ (c = 14.8, CH₃OH). Crystallization from 50 mL of CS₂ gave 2.7 g of crystals, mp 112-114°C, corresponding to essentially racemic 5, $[\alpha]_D = -0.7$ (c = 5.0, CH₃OH), and 3.3 g (55.6 % yield) of (*R*)- α -methylbenzyl hydrogen phthalate [(*R*)-5, oil], $[\alpha]_D = -23.8$ (c = 4.0, CH₃OH). (*R*)- α -Methylbenzyl hydrogen phthalate (3.3 g, 12.2 mmol) was treated with 6.2 mL of water containing 1.7 g of KOH and heated to reflux with concomitant azeotropic removal of the desired alcohol. Extraction with EtOAc and concentration afforded 1.04 g (69.8 % yield) of (*R*)- α -methylbenzyl alcohol [(**R**)-**2**], $[\alpha]_D = +40.9$ (c = 8.7, EtOH) [lit.⁸ $[\alpha]_D = +42.0$ (neat)].

Acknowledgements

We are grateful to Prof. I. Regla, FES-Zaragoza, UNAM, for a generous gift of (S)- α -methylbenzylamine.

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(Received in the USA 19 September 1994)