Tetrahedron Letters,Vol.27,No.41,pp 4941-4944,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

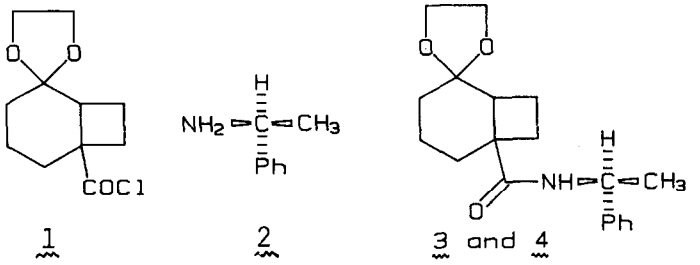
CLEAVAGE OF HINDERED α-METHYLBENZYLAMIDES, INTERMEDIATES IN THE RESOLUTION OF CARBOXYLIC ACIDS

Francis X. Webster, Jocelyn G. Millar, and Robert M. Silverstein*

State University of New York
College of Environmental Science and Forestry
Syracuse, NY 13210

ABSTRACT: α-Methylbenzylamides, useful intermediates in the resolution of carboxylic acids, are cleaved with a two step procedure; enolizable amides are not racemized.

The usefulness of diastereomeric α-methylbenzylamides in the resolution of racemic carboxylic acids has been amply demonstrated.[1] We have found, for example, that diastereomers 3 and 4 [2] prepared from racemic acid chloride 1 and the commercially available (S)-(-)-α-methylbenzylamine 2 are readily separated by preparative flash liquid chromatography on a multigram scale. Unfortunately, these amides proved remarkably difficult to cleave. Since racemization at the carbon atom next to the carboxyl group in 3 or 4 is impossible, standard hydrolytic methods were tried. Potassium hydroxide in refluxing ethanol or refluxing ethylene glycol yielded starting material. Potassium hydroxide in ethylene glycol at 200°C in a sealed stainless steel bomb for 24 hours completely cleaved the amide, but, under these extreme conditions the ketal moiety underwent partial conversion to a hydroxyl group. Furthermore, nucleophilic attack did not occur at the hindered carbonyl center; rather, the compound apparently underwent nucleophilic displacement at the benzylic carbon atom, resulting in the isolation of 1-phenylethanol instead of the expected 1-phenylethylamine (Scheme 1). Other basic hydrolytic methods that were ineffective included

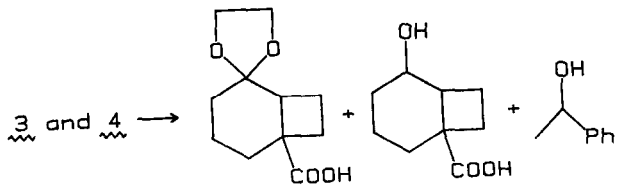


1 2 3 and 4

potassium hydroxide in glycerol at 180°C and in water in a sealed bomb at 200°C. Acidic hydrolysis was also tried on the free ketone; hydrochloric acid (6 N) at reflux completely consumed the starting material, but the product, after esterification with diazomethane, consisted of 30% of the desired keto-ester and a large amount of non-volatile residue.

These failures prompted an investigation of methods of cleaving the model compound N-(1-phenylethyl)-2,2-dimethylpropanamide 5.[3] Treatment of 5 with dinitrogen tetroxide[4] at 0°C in various solvents yielded only starting material. Sonnet's method of N-alkylation with ethylene oxide, followed by acid catalyzed transacylation,[5] also failed. At this point, we considered a two-step sequence: cleavage of the hindered secondary amide to a primary amide, which can then be converted to a carboxylic acid. [6,7] Hydrogenolysis of the benzylic-nitrogen bond of 5 (10% Pd on C, 1 atm, room temp.[8]) was unsuccessful. However, treatment of 5 with a slight excess of lithium metal in liquid ammonia containing excess water gave pivalamide in essentially quantitative yield.[9] Under identical conditions, amides 3 and 4 were cleaved quantitatively to the primary amides 6 and 7, which were then hydrolyzed by potassium hydroxide in ethylene glycol.[6]

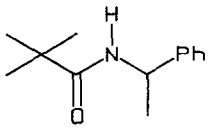
SCHEME 1



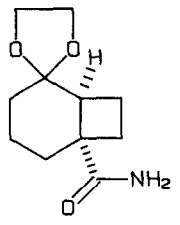
The latter alkaline hydrolysis, however, though suitable for the non-enolizable amides 3, 4, and 5, would result in racemization of enolizable amides. Therefore, we evaluated Olah's reagent, nitrosonium tetrafluoroborate in acetonitrile,[7] for the conversion of enolizable amides to carboxylic acids. We synthesized the enolizable amide N-(1-phenylethyl)-2-ethylhexamide 8,[10] and recrystallized the diastereomeric mixture twice from hexane, thus obtaining a 90:10 mixture with the less polar diastereomer predominating (HPLC); the mixture was converted to 2-ethylhexanamide by our reductive cleavage with $Li/NH_3/H_2O$. The primary amide was cleaved with nitrosonium tetrafluoroborate,[7] which gave 2-ethylhexanoic acid in a 90:10 enantiomeric ratio (80% ee: ^{13}C NMR of the quinine salts[11]). Thus, within the experimental error involved in the use of two different techniques for determining enantiomeric composition, there was no

detectable racemization.

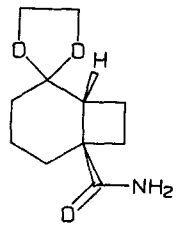
In summary, highly hindered secondary amides can be reductively cleaved with $Li/NH_3/H_2O$ to primary amides, which can be conveniently cleaved with $KOH/HOCH_2CH_2OH$ if the amides are non-enolizable or if racemization is not a concern. Enolizable primary amides can be converted to carboxylic acids without racemization by Olah's method.



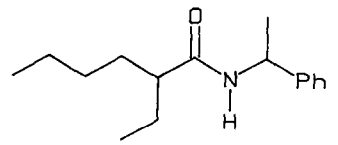
5



6



7



8

EXPERIMENTAL: General procedure illustrated by the reductive cleavage of N-(1-phenylethyl)-2,2-dimethylpropanamide (5). In a 500 mL, three-neck, round-bottom flask was dissolved 3.00 g (14.6 mmoles) of N-(1-phenylethyl)-2,2-dimethylpropanamide in 45 mL of THF containing 7.5 mL water. The flask was equipped with a mechanical stirrer, an ammonia inlet, and a cold finger containing Dry ice/acetone. About 280 mL of ammonia was added giving a clear, homogeneous solution. Small pieces of lithium wire (409 mg, 58.4 mmoles) were added in one portion to the stirred solution, and vigorous stirring was continued until all of the blue color had disappeared, giving a viscous white gel. The ammonia was evaporated with the aid of a hot-water bath (60°C). The residue (white solids, THF, and water) was washed well with 2 x 125 mL TFH. The combined washing was evaporated, and the residue was dissolved in 200 mL of chloroform. The chloroform solution was dried (Na_2SO_4), filtered, and evaporated, and the white residue was dried in vacuo to yield 1.42 g (96%) pivalamide, m.p. 153-154°C (Lit. 154°C). Spectral properties were identical to those of an authentic sample.

ACKNOWLEDGEMENT: This study was supported by a grant from the National Science Foundation. We thank Patrick Pennock for technical assistance.

REFERENCES:

1. a. Jacques, J.; Colet, A.; Wilson, S.H. in "Enantiomers, Racemates, and Resolution", John Wiley and Sons: New York, 1981; pp. 329-330. b. Sonnet, P.E. J. Org. Chem. 1982, 47, 3793.

2. Separation of 3 and 4 led to optically pure enantiomers of grandisol. Webster, F.X.; Silverstein, R.M. Manuscript submitted.

3. Watanabe, Y.; Mukaiyama, T.; Chem. Lett. 1981, 285.

4. White, E.H. J. Amer. Chem. Soc. 1955, 77, 6088.

5. Sonnet, P.E.; Heath, R.R. J. Chem. Ecol. 1982, 8, 41.

6. Kewman, M.S.; Wise, R.M. J. Amer. Chem. Soc., 1956, 42, 450.

7. Olah, G.A.; Olah, J.A. J. Org. Chem. 1965, 30, 2386.

8. Freifelder, M. in "Practical Catalytic Hydrogenation", John Wiley and Sons: New York, 1971, pp. 198-205.

9. For an example of a benzylic oxygen cleavage see: Minnella, A.E.; Hale, S.S. J. Org. Chem. 1975, 40, 3151.

10. Hiraki, Y.; Tai, A. Bull. Chem. Soc. 1984, 57, 1570.

11. Webster, F.X.; Zeng, X.-n.; Silverstein, R.M. J. Org. Chem. 1982, 47, 5225.

(Received in USA 23 June 1986)