search Council of the University of Cincinnati for a summer fellowship to W.C. Finally, we wish to thank Dr. Elwood Brooks for his help with the NMR spectra and Ms. Elaine Cudmore for the typing and drawings in this manuscript. The NMR spectrometer used in this study was purchased with the aid of an NSF instrumentation grant (CHE-8102974).

Registry No. **1a**, 24417-03-6; **1b**, 24432-51-7; **1c**, 56338-34-2; **1d**, 125972-91-0; **1e**, 119005-31-1; **2a**, 4391-83-7; **2b**, 62965-01-9; **2c**, 125972-92-1; **2d**, 78159-36-1; **2e**, 119005-32-2; **4**, 125641-47-6; **5a**, 56338-28-4; **5b**, 21384-41-8; **5c**, 54280-88-5; **5d**, 2952-05-8; **5e**, 125972-93-2; **6**, 25393-66-2; **7**, 23437-02-7; **8**, 942-94-9; **10a**, 13891-02-6; **10b**, 31121-09-2; **11**, 125972-94-3; 2-methylaziridine, 75-55-8; *threo*-2-azido-3-iodobutane, 4098-12-8; *cis*-2-butene, 590-18-1; *cis*-2,3-dimethylaziridine, 930-19-8; styrene oxide, 96-09-3; 1-propyl-4-phenyl-2-azetidinone, 103776-26-7; 1,2-epoxyhexane, 1436-34-6; 1-(phenylamino)-2-hexanol, 97206-75-2.

Notes

A Reinvestigation and Improvement in the Synthesis of *meso*-2,5-Dibromoadipates by Application of Le Chatelier's Principle

H. A. Watson, Jr., and B. T. O'Neill*

Pfizer Central Research, Groton, Connecticut 06340

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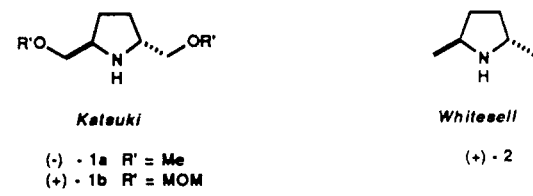
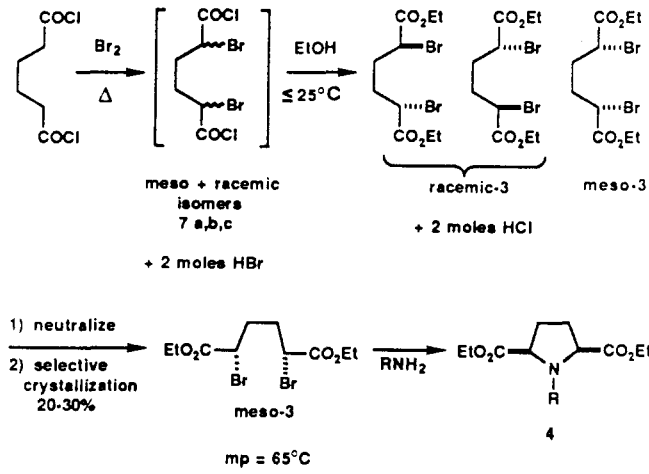
The preparation of 2,5-disubstituted pyrrolidines as intermediates for organic synthesis has continued to be an area of active study.[1] Recently, several C_2-symmetric chiral auxiliaries have been fashioned from 2,5-disubstituted pyrrolidines by Katsuki[2] and also by Whitesell.[3] After incorporation within a substrate, these ancillary reagents direct selective nucleophilic addition of enolates or enamines with electrophiles, often with high diastereoselectivity.[4]

In the case of compounds **1a** and **1b** (Chart I), pyrrolidine ring formation begins with ethyl 2,5-dibromoadipate commonly obtained as a mixture of three stereoisomers (as shown in Scheme I). The favored protocol uses only meso isomer **3** even though this results in formation of the incorrect *cis*-2,5-pyrrolidine dicarboxylate **4** which must be epimerized.[5] Fortunately, this epimerization is an efficient process.[6]

Chart I. C_2-Symmetric Secondary Amines



Scheme I



meso-2,5-Dibromoadipic esters have been generally more useful in heterocyclic synthesis than the *racemic* stereoisomers because they are nicely crystalline and efficiently separated from the lower melting racemic mixture.[7] The reaction of *meso*-**3** with primary amines affords only a single cis 2,5-disubstituted pyrrolidine isomer.[8] The racemic isomer is reported to form polymeric material and a mixture of cis and trans isomers upon direct nucleophilic addition of amines; however, the exact reasons for these differences in selectivity have not been determined.[8c] As a result of this precedent, we became interested in the application of *meso*-**3** to the synthesis of pyrrolidines and in elaborating the resulting product **4** into other bicyclic

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(6) Lowe, G.; Ridley, D. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2024. See also ref 1f.

(7) The racemic compound melts below room temperature (mp 9–10 °C) while *meso*-**3** melts at 65 °C.

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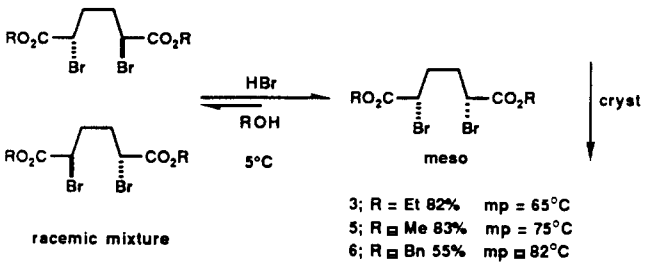
0022-3263/90/1955-2950$02.50/0

ring systems.[8d] Nevertheless, for this approach to be of practical value, an efficient synthesis of *meso*-3 was required.

The reported synthesis of *meso*-3 indicated that bromination of adipoyl chloride proceeded unselectively but quantitatively under the classic Hell–Volhard–Zelinskii conditions[9] and led to a equimixture of *racemic* and *meso*-2,5-dibrominated isomers.[10] Furthermore, after esterification with ethanol and neutralization, only 30% of the desired meso isomer was obtained by direct crystallization.[11]

To enhance the production of this isomer without resorting to separation and waste of the racemic material, we have developed a modification of the existing synthesis which effects equilibration of the isomers.[12] The modification takes advantage of the widely different crystalline properties of the racemic and *meso*-dibromoadipic esters and the fact that the three stereoisomers were found to be in equilibrium under certain circumstances in alcohol solution. Crystallization of the higher melting meso isomer and its removal from the equilibrium mixture causes a shift toward the formation of further quantities of desired product. This is an example of Le Chatelier's principle[13] which states: "If a system in equilibrium is altered in any way, the system will shift so as to minimize the effect of the change". This method works reproducibly well and has been shown to afford good yields at preparatively useful scale.

To effect equilibration of the isomers, one makes a simple change in the workup of the esterification reaction. Previous conditions had called for neutralization of the acidic reaction mixture before isolation of *meso*-3. However, if this neutralization step is omitted and the acidic alcoholic mixture is allowed to stand, crystallization of the meso isomer occurs spontaneously and subsequently continues from the filtrate after isolation of the first crop. Initial examination of the first and ensuing filtrates by ^{13}C NMR spectroscopy indicated that both the meso and racemic isomers are present in approximately equivalent amounts, but once crystallization begins, the corresponding shift in the equilibrium affords a preponderance of the meso isomer. The mixture must be filtered and the filtrate allowed to equilibrate several times due to the thickness of the precipitate that forms, but we have obtained an 82% yield of *meso*-3 from just three crops by using the concentrations indicated in the Experimental Section. The methyl and benzyl dibromoadipic esters have also been prepared. The benzyl ester yield was low because only two crops were taken in the single experiment attempted. *In the case of meso-3, this process has been successful on a variety of preparative scales.*



The actual mechanism of the epimerization is unclear; however, we favor a reversible S_N2 displacement of the α,α'-dibromo ester with bromide ion, present in the reaction mixture as HBr. This appeared more likely than an alternative acid-catalyzed enolization and equilibration of the α,α'-dibromo ester because of the expected poor formation of the required ester enol. Prior inefficient conversions of adipoyl chloride to *meso*-3 may now be rationalized by observing that neutralization of the reaction mixture causes removal of bromide ion from the organic phase, thus preventing equilibration. In the latter instance, only the amount of *meso*-3 present at the point of quenching can then be isolated. We believe this procedure should enhance the availability of a variety of heterocyclic compounds made from dibromoadipate.

Experimental Section[14]

Step 1: *dl*- and *meso*-2,5-Dibromoadipoyl Dichloride (7a–c). A 2-L four-neck round-bottom flask equipped with a constant-addition dropping funnel,[15] mechanical stirrer, thermometer, and efficient reflux condenser was placed on a steam bath. Effluent from the reflux condenser was vented to a scrubber system capable of trapping bromine and hydrogen bromide gas.[16] A 200-W GE sun lamp was positioned 2–3 in. from the side of the flask.[17] The above-described equipment was charged with 98% adipoyl chloride (200 g, 1.093 mol). The sun lamp was turned on, and the dihalide was heated to 75–85 °C and stirred. Neat bromine (146 mL, 2.83 mol) was added dropwise very slowly over a 6-h period (ca. 24 mL/h) using the constant-addition funnel. The dark mixture was maintained at 75–85 °C for 2 additional hours. The reaction was conveniently monitored by removal and quenching of an aliquot into ethanol followed by thin-layer analysis (elution with chloroform; if the reaction was not complete, increments of 0.25 equiv of bromine were introduced to drive the reaction of completion). Once the reaction was judged to be complete, the heating was stopped and the dropping funnel was replaced with a nitrogen inlet tube. Excess bromine was then purged from the reaction flask with a gentle stream of nitrogen gas. The crude reaction mixture was used directly in the next step.

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(12) A report by Blackman[8c] also describes the synthesis of the crystalline *meso*-3 in 30% yield. They were able to improve the overall yield to 60% by careful fractional distillation of the mother liquors. We believe that equilibration of the mixture of isomers may occur upon heating and is driven towards formation of the meso isomer as it is distilled. A related investigation (Buchman, E. R.; Reims, A. O.; Skei, T.; Schlatter, M. J. *J. Am. Chem. Soc.* **1942**, *64*, 2696) described the preparation of *meso*-7 in 70% yield. This procedure is reported to fail for the corresponding diethyl ester and like the report by Blackman requires fractional distillation to obtain the stated yield. These latter two reports have received little attention in the literature.

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(14) ^1H and ^{13}C NMR spectra were determined with a Varian XL 300 (300-MHz proton and 75.429-MHz carbon-13). Chemical shifts are expressed in ppm relative to tetramethylsilane in the case of proton spectra and relative to the center resonance of $CDCl_3$ (77 ppm) in the case of carbon-13 spectra. Elemental analyses, infrared spectroscopy, and low-resolution mass spectrometry were performed by the Pfizer Analytical Chemistry Department. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover apparatus. Thin-layer chromatography (TLC) was performed on 0.25 mm, 5 × 20 cm Kieselgel-60 F254 silica gel plates (EM Science) using a chamber containing finely ground iodine–silica gel mixture for development. Solvents were commercially available and were used as received. Adipoyl chloride was obtained from the Aldrich Chemical Co.

(15) Available from the Kontes Glass Co. Catalog no. K-634620. This apparatus was more effective than a standard addition funnel or syringe drive equipment.

(16) Our scrubber system was set up with 10% solutions of sodium thiosulfate and sodium hydroxide.

(17) The lamp accelerated reactions on laboratory scale but was omitted on preparative runs.

Step 2: *meso*-Diethyl 2,5-Dibromoadipate (3). A 2-L three-neck round-bottom flask was equipped with paddle stirrer and thermometer and was cooled in an ice bath. The flask was charged with ethanol (650 mL), and the crude product from the previous step (ca. 1.1 mol) was added to the flask over 45 min with the temperature maintained below 25 °C. The resulting suspension was stirred for 16 h at room temperature and was then cooled to 5 °C for 30 min. the suspension was filtered, the moist cake was reslurried briefly in fresh ethanol (250 mL at 10–15 °C), and the suspension was pulled dry once again. The white solid was dried in a vacuum oven at 30 °C. There was obtained 205 g (52%) of *meso*-3, mp 64–66 °C (lit.[10] mp 65–66 °C). The clear yellow ethanol mother liquors from above were combined and concentrated to a volume of 600 mL. The solution was seeded and was stirred overnight. After being cooled to 10 °C and stirred for 30 min, the slurry that resulted was filtered, and the moist cake was restirred in cold ethanol (150 mL). The product *meso*-3 was obtained by filtration and vacuum drying. Crop 2; 92 g (23%), mp 64–66 °C. Continued concentration of the mother liquors lead to the isolation of an additional 28 g (7%) of *meso*-3 (total yield three crops 325 g, 82%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.19 (4 H, q, J = 6 Hz), 4.19 (2 H, obscured), 2.23 (2 H, m), 2.0 (2 H, m), 1.26 (6 H, t, J = 6 Hz); ^{13}C NMR ($CDCl_3$, 75.429 MHz) δ 169.1, 62.2, 44.7, 32.4, 13.9; IR (KBr) γ 2978, 1729, 1376, 1267, 1158 cm^{-1}; MS m/e 360 (M^+). Anal. Calcd for $C_{10}H_{16}Br_2O_4$: C, 33.36; H, 4.48; Br, 44.39. Found: C, 33.51; H, 4.45; Br, 44.39.

Also prepared by procedures related to that described above were the corresponding *meso*-dimethyl and -dibenzyl adipates:

***meso*-Dimethyl 2,5-dibromoadipate (5)**: 83.3% in three crops; mp 75–76 °C (lit.[12] mp 74 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.2 (2 H, dd, J = 8 Hz, J = 6 Hz), 3.73 (6 H, s), 2.22 (2 H, m), 2.0 (2 H, m); ^{13}C NMR ($CDCl_3$, 75.429 MHz) δ 169.6, 53.1, 44.3, 32.4.

***meso*-Dibenzyl 2,5-dibromoadipate (6)**: 55.2% in two crops; mp 81–83 °C (lit.[11d] mp 83 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (10 H, s), 5.2 (4 H, s), 4.26 (2 H, dd, J = 6 Hz, J = 4 Hz), 2.28 (2 H, m), 2.05 (2 H, m); ^{13}C NMR ($CDCl_3$, 75.429 MHz) δ 168.9, 135, 128.7, 128.6, 128.3, 67.8, 44.5, 32.4.

Registry No. (±)-3, 124819-16-5; *meso*-3, 54221-37-3; (±)-5, 124819-17-6; *meso*-5, 53490-47-4; (±)-6, 124756-17-8; *meso*-6, 124985-73-5; $ClCO(CH_2)_4COCl$, 111-50-2.

Silica Impregnated with Tetramethylammonium Salts as Solid–Solid–Liquid Triphase Catalysts

Onn Arrad* and Yoel Sasson

The Casali Institute of Applied Chemistry, School of Applied Science and Technology, The Hebrew University of Jerusalem, 91904 Jerusalem, Israel

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Since its introduction, phase-transfer catalysis (PTC) has become a very common synthetic tool. However, the separation of soluble phase-transfer catalysts from the reaction products is usually a laborious step, where many losses occur. In the recent decade much effort has therefore been put in the research of polymer-bound catalysts (triphase catalysis), which were usually based on polystyrene resins.[1-3] Although at first quite promising, this approach has encountered some difficulties,[4,5] and it is rarely used in synthetic chemistry.[4,6] Some of the catalysts are commercially available, but they are quite expensive.[7] Also, separation by filtration and recycling seems to be far from trivial. Their low physical stability makes them prone to pulverization when reaction mixtures are vigorously agitated,[3,4] and they have a tendency to swell and form gels.[3,4] To improve this physical instability of the catalysts, polystyrene has been substituted by inorganic supports such as silica or alumina.[3,8] But these catalysts can be loaded only to a relatively low degree,[9] their preparation requires some synthetic effort, and the supports may catalyze some side reactions by themselves.[10,11] In a different approach, the need of a phase-transfer catalyst is circumvented by impregnation of the inorganic reagent itself on a support, but then, the latter is required in large amounts.[12,13]

It has been shown in this laboratory that tetramethylammonium halides are very active phase-transfer catalysts when polar solvents such as ethanol are employed.[14] These salts are very stable to relatively high temperatures and to strongly basic conditions. The chloride and bromide salts are commercially available in bulk, and because of their low molecular weight they are very cost effective catalysts.[14] Unfortunately most PTC reactions require an apolar reaction medium,[15] and it has been generally accepted that tetramethylammonium halides are not active in such systems, since they are completely insoluble in the respective solvents.[16,17]

We have taken advantage of this fact and impregnated these salts on a commercial silica support. As will be shown below for some model reactions, this combination makes very efficient "triphase catalysts," even with apolar solvents, provided the inorganic reagent is applied as a solid rather than in an aqueous solution, thus preventing the excess hydration of these hydrophylic catalysts. According to the same principle, we have shown recently the potential of some commercial ion exchange resins (of the strongly basic type) as triphase catalysts.[18]

Results and Discussion

Synthetic Features. Alkyl chlorides and bromides in aromatic hydrocarbon have been reacted with alkali salts of iodide, acetate, and formate ions in the presence of (5–7.5 mol %) tetramethylammonium halides (TMAX) impregnated on silica (Silica D 22 of Degussa Co., is a non surface treated precipitated silica;[19] its surface area is due to primary colloidal size[20]). After filtration of the two solid

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