in an oil bath at 95–100 °C for 2 h. After cooling to room temperature, acetic acid was removed at room temperature and 1 mmHg. When essentially all acetic acid had been removed, the bath temperature was increased to 40–50 °C and the pressure was diminished to 0.1 mmHg to remove as much solvent as possible. The bath temperature was then increased to 140–150 °C, and a fraction of crude **5** (11.5 g), bp 82 °C (0.1 mmHg), was collected. This material was dissolved in 10 mL of ether, washed with saturated aqueous $NaHCO_3$ solution (3 × 10 mL), and extracted with ether (3 × 20 mL). The combined extracts were dried over $MgSO_4$, filtered, and distilled through a 20-cm Vigreux column to give 8.33 g (53%) of **5** as a clear liquid, bp 67 °C (0.1 mmHg): IR (neat film) 1720 (s) and 1650 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.51 (s, 18 H) and 6.25 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 27.90 (q), 81.75 (s), 130.60 (t), 138.35 (s), and 163.65 (s). A higher boiling fraction (1.15 g), bp >75 °C (0.1 mmHg), was identified by ^1H NMR spectroscopy as a mixture of **5** and **8**.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.81; H, 8.86.

Acknowledgment. We are pleased to acknowledge support of this work by the National Institutes of Health through Grant GM 25222.

Registry No. 1, 541-16-2; **5**, 86633-09-2; paraformaldehyde, 30525-89-4.

Supplementary Material Available: Experimental procedures for (a) preparation of sulfoxide **4** and diol diester **8** and conversion of each to **5**, (b) interconversion of **5** and sulfone **6**, and (c) conversion of **5** to sulfide **7** (5 pages). Ordering information is given on any current masthead page.

Practical Multigram Synthesis for 4(5)-Vinylimidazole

John M. Kokosa,* Richard A. Szafasz, and Eumar Tagupa

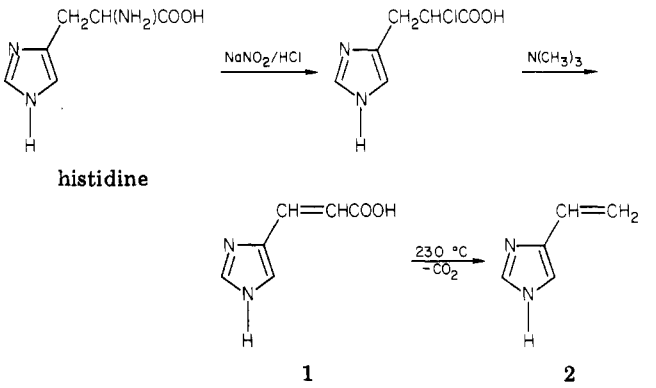
Department of Chemistry, Indiana University Northwest, Gary, Indiana 46408

Received December 24, 1982

We plan to use 4(5)-vinylimidazole (**2**) as a starting material for the synthesis of derivatives of histamine and histidine. This material has also shown considerable promise as a polymer formulant.[1] The published procedure (Scheme I) for the synthesis of **2** from histidine, however, results in yields of only 9.7%. In addition, the final step in the synthesis, involving a high-vacuum thermal decarboxylation of urocanic acid (**1**), is impractical for quantities greater than 5 g unless liquid nitrogen traps are used to capture evolved CO_2.[1a]

We now report an improved multigram synthesis for **2**. This procedure (Scheme II) utilizes a Wittig reaction with the known compound 1-(triphenylmethyl)imidazole-4-carboxaldehyde (**7**)[3] to synthesize the desired vinyl group. Thus, protection of the imidazole nitrogen of 4(5)-hydroxymethylimidazole hydrochloride (**3**), obtained from fructose,[2] with triphenylmethyl chloride yields **4**.[3] Oxidation of alcohol **4** with activated MnO_2 in dioxane yields aldehyde **7**,[3] and reaction of **7** with triphenylmethylphosphonium bromide and the dimsyl anion yields the vinylimidazole (**11**).[4] The triphenylmethyl group is easily removed with mild acid hydrolysis, and **2** is isolated essentially pure in an overall yield of 36% from fructose.

Scheme I



The preceding steps are carried out with ease, and all intermediates are solids, easily purified and obtained in high yield. Protection of the ring nitrogen with the triphenylmethyl group yields only the 4-substituted product **4**,[3] presumably because of the steric bulk of the triphenylmethyl group. Only the products of the Wittig reaction need to be separated by chromatography. However, it proved necessary to use a large excess (2 equiv) of NaH and Ph_3PCH_3Br in the Wittig reaction in order to avoid significant reduction of the aldehyde **7** to alcohol **4**. Thus, reaction of the aldehyde **7** in dry Me_2SO with 1 equiv of Ph_3PCH_3Br and 1.3 equiv of NaH resulted in a 23% yield of the vinyl product **11**, 4.2% of unreacted aldehyde **7**, and 37% alcohol **4**. Use of 2 equiv of NaH/Ph_3PCH_3Br, however, resulted in an 82% yield of the vinyl product **11** with no discernible unreacted aldehyde **7** or alcohol **4**. The vinyl compound **11** prepared by this method is identical with that prepared by reacting 4(5)-vinylimidazole with triphenylmethyl chloride.[5] Attempts to similarly prepare 4(5)-vinylimidazole (**2**) from the unprotected 4(5)-imidazolecarboxaldehyde (**10**)[6] were unsuccessful, presumably due to the relatively acidic N–H on the imidazole ring.

A second synthetic route, utilizing the benzyl group to protect the ring nitrogen, was also explored. The alcohol **3**, when reacted with benzyl chloride, yielded an approximately 2:1 ratio of the *N*-benzyl protected 4- and 5-alcohols **5** (28.4%) and **6** (13.5%), respectively. Assignment of the structures for **5** and **6** is based upon comparison of the melting points of **6** and the known compound.[7]

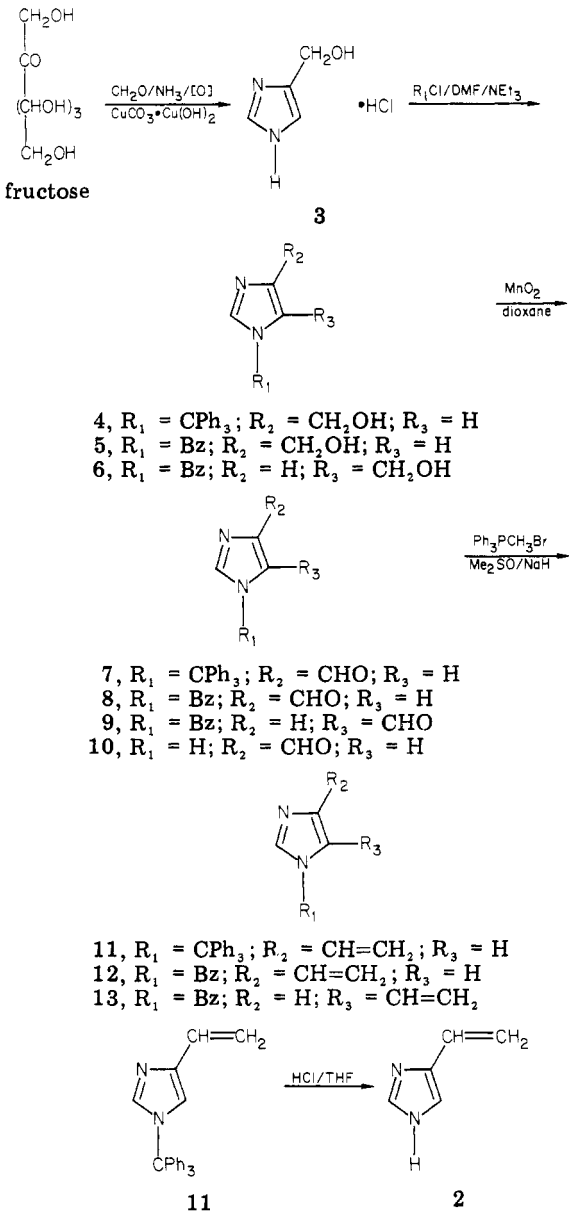
Oxidation of **5** and **6** with activated MnO_2 in dioxane yielded the corresponding aldehydes **8** (73%) and **9** (94%). The aldehydes, under Wittig conditions, yielded the vinyl compounds **12** (70%) and **13** (59%), respectively. Again it proved necessary to use a large excess (2 equiv) of NaH and Ph_3PCH_3Br, since equivalent amounts resulted in the formation of alcohols **5** and **6** as primary products. This route, however, is less desirable since the benzyl-protected compounds were obtained in relatively low yields (8.2% and 4.2%, respectively, from fructose).

* Present Address: Department of Science and Mathematics, GMI Engineering & Management Institute, Flint, MI 48502.

(1) (a) Overberger, C. G.; Glowaky, R. C.; Pacansky, T. J.; Sannes, K. N. *Macromol. Synth.* **1974**, *5*, 43. (b) Overberger, C. G.; Mitra, S. *Pure Appl. Chem.* **1979**, 51, 1391 and references therein.
(2) Totter, J. R.; Darby, W. J. In "Organic Syntheses"; Horning, E. C., Ed.; Wiley: New York, 1955; Collect. Vol. III, p 460.
(3) Kelly, J. L.; Miller, C. A.; McLean, E. W. *J. Med. Chem.* **1977**, *20*, 721.
(4) Freenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128.
(5) Overberger, C. G.; Schiavone, R. J., The University of Michigan, personal communication, 1983.
(6) Popadopoulos, E. P.; Jarrar, A.; Issidorides, C. H. *J. Org. Chem.* **1966**, *31*, 615.
(7) Jones, R. G.; McLaughlin, K. C. *J. Am. Chem. Soc.* **1949**, *71*, 2444.

0022-3263/83/1948-3605$01.50/0

Scheme II



In conclusion, the present procedure for the synthesis of **2** is a distinct improvement over the previous synthesis.[1a] Not only is the starting material (fructose) inexpensive and readily available, but the overall yield of **2** from fructose is 36% as compared to a 9.7% yield from histidine using the previous route. In addition, the 4(5)-vinylimidazole obtained from this route is a pure monomer containing no discernible polymer, whereas the previous route affords material which must be purified to rid it of polymer material.[1a] Also, this route should prove practical and convenient for the synthesis of **2** in multigram quantities, utilizing standard laboratory techniques and apparatus.

Experimental Section

Melting points are uncorrected. IR spectra were determined with a Beckman IR-8. NMR spectra were determined on a Varian EM-360 with Me_4Si as an internal standard in $CDCl_3$ solvent. Dry column silica gel chromatography was performed with Fluka AG silica gel 60 F254 in 2.5-cm diameter nylon columns, and the fractions were located by UV and the sample puncture technique.[8] TLC was performed on Eastman chromagram silica gel sheets (No. 13181 with fluorescent indicator) by using acetone for **5**, **6**, **8**, and **9**, $CHCl_3$ for **4**, **7**, **11**, and **12**, 5% methanol in $CHCl_3$ for **13**, and 10% ethanol in $CHCl_3$ for **2** as eluents. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

4(5)-(Hydroxymethyl)imidazole Hydrochloride (3). This compound is prepared in 57% yield from fructose by Darby and Totter's procedure.[2]

1-(Triphenylmethyl)-4-(hydroxymethyl)imidazole (4). This compound was prepared in 92% yield according to the literature procedure: mp 222–223 °C (lit.[3] mp 219–221 °C); IR (KBr) 3200 cm^{-1} (br, OH); NMR δ 7.20 (m, 16 H, Ar H), 6.70 (s, 1 H, Ar H), 4.50 (s, 2 H, CH_2OH), 2.92 (br s, 1 H, CH_2OH).

1-Benzyl-4-(hydroxymethyl)imidazole (5) and 1-Benzyl-5-(hydroxymethyl)imidazole (6). To a slurry of dry **3** hydrochloride (13.45 g, 0.100 mol) in dry DMF (50 mL) and triethylamine (55 mL, 0.40 mol) was added distilled benzyl chloride (17.7 mL, 0.150 mol) via a dropping funnel over a 5-min period. The mixture was refluxed for 3 h. An additional 5.9 mL (0.050 mol) of BzCl and 10 mL of Et_3N (0.07 mol) were added, and reflux was continued for an additional 1 h. The solvents were evaporated in vacuo, water (100 mL) was added to the oil, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ was dried (K_2CO_3) and evaporated to yield 9.74 g of crude benzylated product. The oily material was crystallized twice with acetone to yield pure **6**: 1.86 g; mp 137–138 °C (lit.[7] mp 139–140 °C; IR (KBr) 3100 (OH, br), 1630, 1560, 1490 cm^{-1} (Ar); NMR δ 3.00 (br s, 1 H, OH), 4.53 (s, 2 H, CH_2OH) 5.30 (s, 2 H, $CH_2C_6H_5$), 7.01 and 7.54 (2 s, 2 H, Im H), 7.37 (m, 5 H, C_6H_5).

The acetone soluble material (7.80 g), substantially **5**, as determined by NMR, was further purified by dry column silica gel chromatography with acetone as the eluent to yield pure **5**: 5.34 g (28.4%); mp 79.5–80 °C; IR (KBr) 3150 cm^{-1} (OH); NMR δ 4.63 (s, 2 H, CH_2OH), 5.13 (s, 2 H, $CH_2C_6H_5$), 6.95 and 7.50 (2 s, 2 H, Im H), 7.30 (m, 5 H, C_6H_5). Anal. [as the picrate, mp 157.5–158 °C (ethanol)]. Calcd for $C_{17}H_{15}N_5O_3$: C, 48.93; H, 3.62; N, 16.78. Found: C, 48.96; H, 3.63; N, 16.77.

An additional 0.67 g of pure **6** was also recovered from the column for a total of 2.53 g (13.5%).

1-(Triphenylmethyl)-4-imidazolecarboxaldehyde (7). This compound was prepared according to the literature procedure: 90% yield; mp 165–181 °C (lit.[3] mp 189–192 °C); IR (KBr) 1680 cm^{-1} (C=O); NMR δ 7.30 (m, 17 H, Ar H), 9.90 (s, 1 H, CHO).

1-Benzyl-4-imidazolecarboxaldehyde (8) and 1-Benzyl-5-imidazolecarboxaldehyde (9). Alcohol **5** (0.140 g, 0.778 mmol) was stirred with dioxane (15 mL) and activated MnO_2 (1.40 g) at 80 °C for 6 h. The mixture was filtered and the solvent removed. There was obtained pure **8**: 0.101 g (73%); an oil; IR (film) 3130 (Ar H), 2850, 2760 (aldehyde CH), 1675 cm^{-1} (C=O); NMR δ 5.16 (s, 2 H, $CH_2C_6H_5$), 7.34 and 7.61 (2 s, 2 H, Im H), 7.27 (m, 5 H, C_6H_5) 9.86 (s, 1 H, CHO). Anal. [as the oxime, mp 163–165 °C (aqueous ethanol)] Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.52; H, 5.55; H, 20.80.

In a similar fashion, when **6** (0.300 g, 1.67 mmol) in dioxane (30 mL) was stirred with activated MnO_2 (3.0 g) for 6 h at 80 °C, the mixture filtered and the solvent evaporated, there was obtained pure **9**: 0.280 g (94%); mp 51–52 °C (pentane); IR (KBr) 3090 (Ar H), 2820, 2750 (aldehyde CH), 1675 cm^{-1} (C=O); NMR δ 5.43 (s, 2 H, $CH_2C_6H_5$), 7.25 (m, 5 H, C_6H_5), 7.73 and 7.85 (2 s, 2 H, Im H), 9.80 (s, 1 H, CHO). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.82; H, 5.53; N, 14.97.

1-(Triphenylmethyl)-4-vinylimidazole (11). A 55% dispersion of NaH in mineral oil (3.42 g, 80.5 mmol NaH) was added to an oven-dried, 250-mL, three-necked, round-bottomed flask containing a stir bar and was washed with three portions of dry hexane to remove the mineral oil. A rubber septum, stopper, and three-way stopcock connected to a dry nitrogen source and aspirator vacuum were fitted to the flask, and the system was alternately evacuated and filled with nitrogen three times. Me_2SO (75 mL) was added via syringe and the mixture heated at 75–80 °C for 1.5 h. After the mixture cooled to 50 °C, Ph_3PCH_3Br (28.6 g, 80.1 mmol; dried at 100 °C/24 h/0.4 torr) was added directly through the stopper and the green mixture stirred at 50 °C for 0.5 h. Aldehyde **7** (13.6 g, 40.2 mmol) was added through the stopper and the yellowish brown mixture stirred at 70 °C for 4.5 h. The mixture was cooled to 45–50 °C and poured into water (500 mL) with stirring. The precipitate was suction filtered,

(8) Hadd, H. E.; Caspi, E. *J. Chromatogr.* **1972**, *71*, 353.

washed, and dried in vacuo to yield 19.8 g of the crude mixture consisting of **11** and Ph_3PO. The mixture was dissolved in warm $CHCl_3$ (25 mL) and chromatographed on a 2.5 cm × 1.5 m nylon column containing dry column silica gel and using $CHCl_3$ for elution. The column was allowed to overrun by 200 mL to afford maximum separation, and the product was isolated to yield pure **11** (11.1 g, 82%). An analytical sample was recrystallized from $CHCl_3$ petroleum ether (bp 30–60 °C); mp 205–207 °C (lit.[5] mp 205–207 °C); IR (KBr) 3070 (Ar H), 1640 cm^{-1} (C=C); NMR (H_g refers to the vinyl proton geminal to the Im ring at C-1, H_c refers to the vinyl proton cis to the Im ring at C-2, H_t refers to the vinyl proton trans to the Im ring at C-2) δ 5.05 (dd, 1 H, H_g, J_{cg} = 10.0 Hz, J_{gt} = 2.0 Hz), 5.73 (dd, 1 H, H_t, J_{ct} = 18.0 Hz), 6.50 (dd, 1 H, H_c), 6.70 (s, 1 H, Im H-5), 7.20 (m, 16 H, Ar H, Im H-4). Anal. Calcd for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.50; H, 6.14; N, 8.22.

A Wittig reaction was also performed in a similar manner using only 1 equiv of Ph_3PCH_3Br. Thus, reaction of 55% sodium hydride dispersion (0.570 g, 13.4 mmol), Ph_3PCH_3Br (3.62 g, 10.1 mmol), and **7** (3.41 g, 10.1 mmol) in Me_2SO (15 mL), after reaction and a workup as above, yielded **11** (0.774 g, 22.8%), **7** (0.143 g, 4.2%), and **4** (1.26 g, 36.7%), all with melting points and spectra identical with those above.

1-Benzyl-4-vinylimidazole (12) and 1-Benzyl-5-vinylimidazole (13). In an analogous manner, a solution of hexane washed 55% NaH oil dispersion (0.870 g, 20.0 mmol NaH), and Ph_3PCH_3Br (7.14 g, 20.0 mmol) in Me_2SO (15 mL) was heated for 30 min at 50 °C. To the greenish amber solution was added **8** (1.86 g 10.0 mmol) in Me_2SO (3 mL) via syringe. The red solution was stirred at 65 °C for 3 h and poured into water (200 mL). Extraction of the oil into $CHCl_3$, extraction on the $CHCl_3$ with 10% HCl, neutralization of the acid, and back-extraction of the water with $CHCl_3$ yielded pure **12**: an oil; IR (film) 3100, 3040, 2940, 1635 (vinyl), 1490, 1440, 1350, 1230, 1245, 970, 900, 820, 720 cm^{-1}; NMR δ 5.00 (s, 2 H, $CH_2C_6H_5$), 5.05 (dd, 1 H, Hg, J_{gt} = 10.0 Hz, J_{gc} = 2.0 Hz), 5.77 (dd, 1 H, H_t, J_{ct} = 18.0 Hz), 6.57 (dd, 1 H, H_c), 6.80 (s, 1 H, Im H-5), 7.43 (s, 1 H, Im H-2), 7.25 (m, 5 H, C_6H_5). Anal. [as the picrate, mp 183–185 °C] Calcd for $C_{18}H_{15}N_5O_6$: C, 52.05; H, 4.12; N, 16.86. Found: C, 52.12; H, 3.95; N, 16.98.

Similarly, **13** was prepared by using 55% NaH oil dispersion (0.544 g, 13.0 mmol), Me_2SO (10 mL), Ph_3PCH_3Br (4.64 g, 13.0 mmol), and **9** (1.21 g, 6.50 mmol) in Me_2SO (3 mL). The solution was heated at 65 °C for 4 h and worked up as above. The crude solid was dissolved in $CHCl_3$ and precipitated with petroleum ether (bp 30–60 °C) to yield **13** (0.707 g, 59%) with the following physical properties: mp becomes a glass above 140 °C, completely melts at 210 °C; IR (KBr) 3120, 3040, 2940, 1635 (vinyl), 1490, 1440, 1350, 1230, 1110, 900, 810, 720 cm^{-1}; NMR δ 5.10 (dd, 1 H, H_g, J_{gt} = 12.0 Hz, J_{gc} = 2.0 Hz), 5.13 (s, 2 H, $CH_2C_6H_5$), 5.50 (dd, 1 H, H_t, J_{ct} = 18.0 Hz), 6.40 (dd, 1 H, H_c), 7.25 (m, 6 H, C_6H_5, Im H-5), 7.43 (s, 1 H, Im H-2). Anal. Calcd for $C_{12}H_{12}N_2 \cdot 1/2H_2O$: C, 74.46; H, 6.80; N, 14.26. Found: C, 74.58; H, 6.78; N, 14.50.

4(5)-Vinylimidazole (2). To a stirred mixture of **11** (6.72 g, 20.0 mmol) in THF (25 mL) was added 6 N hydrochloric acid (6.7 mL, 40.0 mmol). The resulting solution was refluxed for 2 h, the THF evaporated in vacuo (45 °C bath), and the resulting solid added to water (25 mL). The solid triphenylmethanol was suction filtered and washed, and the filtrate neutralized with $NaHCO_3$. The water was evaporated in vacuo (bath 45–50 °C), and the oil was treated with absolute alcohol (100 mL) and evaporated to dryness in vacuo. The solid was extracted with $CHCl_3$, and the solvent was dried (K_2CO_3) and evaporated to yield pure **2**: 1.62 g (86%); mp 80–82 °C (lit.[1a] mp 83.2–84.5 °C); NMR δ 4.85 (dd, 1 H, H_g, J_{cg} = 10.0 Hz, J_{gt} = 1.0 Hz), 5.47 (dd, 1 H, H_t, J_{ct} = 18.0 Hz), 6.47 (dd, 1 H, H_c), 6.83 (s, 1 H, Im H-5), 7.40 (s, 1 H, Im H-2).

Acknowledgment. This work was supported in part by an Indiana University Northwest Grant-in-Aid of Research (Grant No. 22-601-44).

Registry No. **2**, 3718-04-5; **3**, 32673-41-9; **4**, 33769-07-2; **5**, 85102-84-7; **5** picrate, 86803-32-9; **6**, 80304-50-3; **7**, 33016-47-6; **8**, 85102-93-8; **9**, 85102-99-4; **11**, 86803-29-4; **12**, 86803-30-7; Ph_3PCH_3Br, 1779-49-3; benzyl chloride, 100-44-7.

Anhydrous *tert*-Butyl Hydroperoxide in Toluene: The Preferred Reagent for Applications Requiring Dry TBHP

J. Gordon Hill, Bryant E. Rossiter, and K. Barry Sharpless*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received August 12, 1983

In 1979 we reported an azeotropic procedure for preparing anhydrous solutions of *tert*-butyl hydroperoxide in a variety of solvents.[1] We noted that azeotropically dried solutions of TBHP in benzene and toluene were very stable to storage, whereas solutions prepared by using halogenated solvents (e.g., CH_2Cl_2 and $ClCH_2CH_2Cl$) were less stable, releasing oxygen even at freezer temperatures. Benzene, in every other way the ideal solvent for this process, was rejected due to its supposed toxicity. Thus, during the past 4 years, we and others have generally used dichloroethane and methylene chloride for preparing dry TBHP solutions, in spite of the aforementioned stability problem. Drs. Lendon Pridgen and Lee Webb of Smith Kline and French (SKF) alerted us to a potential thermal hazard in using dichloroethane for azeotropic drying of TBHP (especially on a large scale).[2] The SKF scientists then kindly offered to subject dry TBHP solutions in other solvents to safety tests using their adiabatic calorimeter. Details of their tests will appear elsewhere,[3] but solutions of TBHP in toluene proved to be by far the most stable. The solutions of TBHP in halogenated solvents, especially dichloroethane, were the least stable. In fact, although we have often used dichloroethane as the azeotropic solvent for drying up to 10 mol of TBHP, we now recommend that the scale be no larger than 3 mol of TBHP if the intended solvent be any other than toluene or benzene. If the lower volatility of toluene presents a problem at the workup stage for a specific application, then the use of TBHP in benzene or methylene chloride is recommended.

We have found that TBHP in toluene is excellent for *all*[1,4,5] applications requiring anhydrous TBHP and, therefore, now use only these toluene solutions in our laboratory. For those accustomed to following the earlier azeotropic drying procedure, please note that the new one calls for a Dean–Stark apparatus. The higher boiling point of toluene leads to large loses of TBHP if the previous nonequilibrium distillation technique is used. However, with the Dean–Stark unit in place only the few percent of TBHP soluble in the separated water is lost.

The most common use for anhydrous TBHP solutions is in the titanium-catalyzed asymmetric epoxidation,[4] and these toluene solutions are perfect for that application. While the asymmetric epoxidation can be performed in other solvents, including toluene, we still prefer to use methylene chloride as the bulk solvent to which the TBHP/toluene solution is added. In one case where an asymmetric epoxidation was run in pure toluene, the rate was noticeably slower than that for the same epoxidation with methylene chloride as the bulk solvent.[6]

(1) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63.
(2) Private communication to K.B.S.
(3) Lendon N. Pridgen and Lee Webb, unpublished results.
(4) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl Chem.* **1983**, *55*, 589. This is currently the best source of information about the titanium-catalyzed asymmetric epoxidation.
(5) Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.*, communication in this issue.
(6) J. Gordon Hill, unpublished result.

0022-3263/83/1948-3607$01.50/0