Polystyryl–Mercury Trifluoroacetate. A Convenient and Mild Reagent for Thioacetal and Thioketal Hydrolysis[1]

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We describe herein a simple, mild, and effective technique for hydrolyzing thioacetals and thioketals, based on the use of a polystyryl–mercury trifluoroacetate reagent. Principal advantages of this new method over existing mercury(II) procedures are as follows:[3] (1) products are isolated by simple filtration and solvent evaporation, (2) spent and unused mercury is rendered innocuous by polymer attachment, (3) an inert atmosphere is not required for effective hydrolysis,[4] (4) acetal and ketal formation is avoided, and (5) the polymeric reagent is unreactive toward alkenes.

Scheme I illustrates the key features of this new desulfurization. A dithiane is dissolved in dichloromethane and then mixed with reagent 1 (ca. 2.1 mmol of Hg/mmol of dithiane) and water. Resinous trifluoroacetic acid is released into the water phase, aldehyde (or ketone) is expelled into the organic layer, and mercaptan is retained on the polymer in the form of a mercury salt.

The efficacy and convenience of this approach is demonstrated by the conversion of 2-phenyl-1,3-dithiacyclohexane to benzaldehyde. Thus, stirring a dichloromethane solution of the dithiane with 1 and water for 2 h at room temperature afforded a 92% yield of benzaldehyde (isolated from the dichloromethane layer by simple solvent evaporation). Titration of the aqueous phase also revealed quantitative formation of trifluoroacetic acid. Further examples of the use of 1 are presented in Table I.

Two difficulties commonly associated with mercury(II) dithiane desulfurization procedures are (1) formation of acetals and ketals as side products and (2) reaction of double bonds within the substrate molecule.[3] Triphase hydrolysis avoids the former problem by virtue of the absence of alcoholic cosolvents. It is also interesting and significant to note that 1 shows no apparent reactivity toward alkenes under triphase conditions.[5] Like many mercury(II)-based reagents, however, 1 is unable to hydrolyze 1,2-dicarbonyl derivatives; e.g., 2-benzoyl-2-methyl-1,3-dithiacyclohexane is recovered quantitatively after attempted hydrolysis.

Polystyryl–mercury trifluoroacetate is very easy to prepare and provides the basis for an extremely simple

method for hydrolyzing thioketals and thioacetals. It should find broad use.

Scheme I. Triphase Hydrolysis of Dithianes
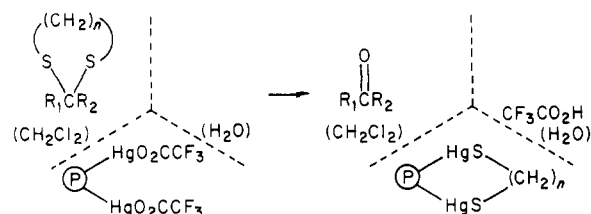
1, 50% ring substitution

Table I. Triphase Thioacetal and Thioketal Hydrolysis

R_1	R_2	n	solvent	temp, °C	time, h	yield,[a] %
n-C_5H_{11}	H	2	CH_2Cl_2	23	96	42
n-C_5H_{11}	H	2	$CHCl_3$	50	48	77
n-C_5H_{11}	H	3	$CHCl_3$	50	48	93
C_6H_5	H	2	CH_2Cl_2	23	2	95
C_6H_5	H	3	CH_2Cl_2	23	2 (3.5)	82 (92)
n-C_5H_{11}	CH_3	3	CH_2Cl_2	23	4.5 (7)	86 (79)
n-C_6H_{13}	$(CH_2)_2CH_3$	3	CH_2Cl_2	23	4.5 (5)	96 (87)
C_6H_5	CH_3	3	CH_2Cl_2	23	5 (5)	90 (65)
-$(CH_2)_5$-		2	$CHCl_3$	50	3.5	79
-$(CH_2)_5$-		3	CH_2Cl_2	23	5 (5)	90 (72)
3-cholestanone		3	$CHCl_3$	23	(3.5)	(88)
CH_3	C_6H_5CO	3	$CHCl_3$	50	48	0[b]

[a] Glc yield; numbers in parentheses refer to 4-mmol-scale reactions and isolated yields. [b] 96% recovery of starting dithiane.

Experimental Section

General Methods. Unless stated otherwise, all reagents and chemicals were obtained commercially and were used without purification. One percent cross-linked polystyrene (gel type, 200–400 mesh) was purchased from Bio-Rad Laboratories, Richmond, CA. All ^{1}H NMR and IR spectra were recorded on Varian A-60 and Beckman Acculab 7 spectrometers, respectively. Product mixtures were analyzed by GLC on a Hewlett-Packard Model 5830 A flame-ionization instrument (2 ft × 0.125 in. UCW-982 on Chromosorb W column). Thioacetals and thioketals were prepared from the corresponding aldehydes and ketones, using procedures similar to those previously described.[6] 2-Benzoyl-2-methyl-1,3-dithiacyclohexane was synthesized from 2-methyl-1,3-dithiacyclohexane and benzonitrile.[7]

Polystyryl–Mercury Trifluoroacetate (1). To a solution of 6.40 g (15 mmol) of mercury trifluoroacetate dissolved in 220 mL of dichloromethane was added 3.12 g of 1% cross-linked polystyrene (30 mmol of C_6H_5), and the mixture was stirred for 48 h at room temperature. The polymer was filtered, washed with 6 × 50 mL of dichloromethane, and dried (23 °C, 24 h (0.1 mm)) to yield 7.69 g (98%) of 1: IR (Nujol) 1690, 1200, 860, 820 cm⁻¹. The absence of mercury in the filtrate confirmed that mercuration of the polymer was quantitative.

Benzaldehyde. To a mixture of 4.4 g (8.45 mmol of Hg) of 1 suspended in 10 mL of dichloromethane was added a solution of 0.784 g (4.0 mmol) of 2-phenyl-1,3-dithiacyclohexane dissolved in 10 mL of dichloromethane. After the mixture was stirred for 10 min, 10 mL of water was added and the three-phase mixture then stirred at room temperature for 3.5 h. The resin was removed by filtration and washed with 3 × 30 mL of dichloromethane, and the combined filtrate was dried (Na_2SO_4). Evaporation of solvent

(1) Supported by the Division of Basic Energy Sciences of the Department of Energy (Contract EG-77-S-02-4446).

(2) On leave from the Institute of Macromolecular Chemistry of the Czechoslovak Academy of Sciences.

(3) For recent dithiane hydrolysis procedures, see: Grobel, B.-T.; Seebach, D. *Synthesis* **1977**, 357. Bates, G. S.; O'Doherty, J. *J. Org. Chem.* **1981**, 46, 1745. Degani, I.; Fochi, R.; Regondi, V. *Synthesis* **1981**, 51.

(4) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, 36, 366.

(5) Heating a mixture of 0.22 g (0.42 mmol of Hg) of 1, 0.42 mmol of 1-octene in 1 mL of CHCl₃, and 1 mL of water for 2 weeks at 50 °C did not result in any loss of alkene.

(6) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, 40, 231.

(7) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, 36, 3553.

afforded 0.389 g (92%) of benzaldehyde having and IR and ^{1}H NMR spectrum identical with those of an authentic sample.

Efficient Synthesis of 3,4,5-Trimethoxybenzaldehyde via Reissert Aldehyde Synthesis

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3,4,5-Trimethoxybenzaldehyde (**1c**, TMBA) is an important intermediate in the synthesis of both drugs and alkaloids. Until recently, the only satisfactory method for large-scale preparation has been the Rosenmund reduction of 3,4,5-trimethoxybenzoyl chloride.[1] While this method has been improved,[2] it still suffers from being inconvenient to run in the laboratory. Catalyst poisoning can also be a problem.
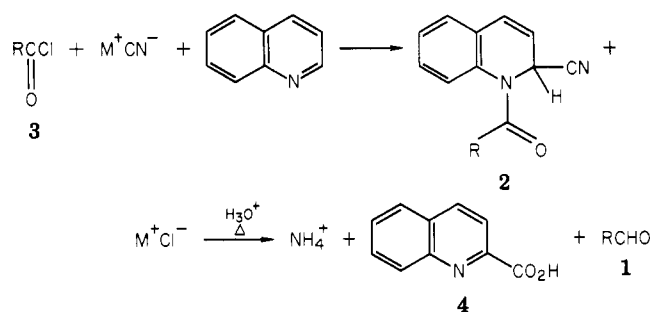
The Reissert aldehyde synthesis (Scheme I)[3] is ideally suited to run in the laboratory as it requires no special apparatus or catalyst and utilizes inexpensive reagents such as sodium cyanide (or hydrogen cyanide), quinoline (or isoquinoline), and sulfuric acid in addition to the appropriate acid chloride. Many investigators have used this method for the preparation of many aldehydes,[4] but in the case of TMBA, only low yields have been reported for the synthesis of the Reissert intermediate, as well as its subsequent hydrolysis.[5-7]

Our own investigations into an efficient and convenient, as well as inexpensive, method of TMBA preparation prompted us to report our success with this method.

Results and Discussion

The preparation of 3,4,5-trimethoxybenzoyl chloride (**3c**) was straightforward from the corresponding acid and thionyl chloride. The preparation of the Reissert intermediate, **2**, was accomplished in 95% yield using the following biphasic conditions: nearly 1 equiv of aqueous sodium cyanide[8] was rapidly stirred with quinoline while a dichloromethane solution of the acid chloride was added dropwise. Failure of this method occurs when excess sodium cyanide is added and may possibly be the reason for poor yields reported by past workers. The hydrolysis of **2** was effected in nearly quantitative yield with refluxing 30% sulfuric acid.

This efficient synthesis of TMBA requires only small quantities of solvents and involves only simple workup procedures. The quinaldic acid, **4**, can even be decarboxylated for the recycle of quinoline,[9,10] constituting a synthesis consuming only cyanide. This route to TMBA should be a convenient alternative to the Rosenmund reduction.

Scheme I. Reissert Aldehyde Synthesis^{a,b}

^{a} a, R = alkyl; b, R = aryl; c = 3,4,5-trimethoxybenzoyl.
^{b} M = H, Na, K.

Experimental Section

Preparation of 1,2-Dihydro-1-(3,4,5-trimethoxybenzoyl)-2-quinolinecarbonitrile. NaCN was obtained from Fisher Scientific and used without further purification. Quinoline was obtained from Eastman, redistilled, and stored over KOH. 3,4,5-Trimethoxybenzoyl chloride was vacuum distilled prior to use [180 °C (15 mmHg)].

A three-neck, 250-mL, round-bottom flask, equipped with mechanical stirrer, baffle, addition funnel, and nitrogen inlet (vented through a safety bubbler), was charged with 160 mmol (8.3 g) of NaCN and 25 mL of H_2O, and the suspension was stirred to dissolve the salt. Then 170 mmol (22.0 g) of quinoline in 50 mL of CH_2Cl_2 was added. As the mixture was briskly stirred, 167 mmol (38.6 g) of 3,4,5-trimethoxybenzoyl chloride in 75 mL of CH_2Cl_2 was added via the addition funnel over 2.5 h. Initially the mixture became orange and then turned yellow. TLC showed that only trace amounts of the acid chloride remained (Et_2O–hexane). After stirring for an additional 2 h, the mixture was poured into a separatory funnel, and the CH_2Cl_2 layer was withdrawn. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and discarded. The combined CH_2Cl_2 layers were extracted first with saturated Na_2CO_3 solution (2 × 100 mL), then with 10% HCl (2 × 100 mL), and finally with H_2O (2 × 100 mL). The CH_2Cl_2 solution was dried over K_2CO_3 and placed in a 500-mL distillation flask with 250 mL of EtOH. The solvent was distilled through a Vigreux column to a temperature of 80 °C. Crystallization began, and after cooling to 0 °C, the crystals were collected, washed with 50 mL of EtOH, and vacuum dried at 80 °C to give 35.0 g of white crystals, mp 184–187 °C; ^{1}H NMR (CDCl$_3$, 60 MHz) δ 3.65 (s, 6 H), 3.85 (s, 3 H), 6.05 (dd, J = 4.5 Hz, 2 H), 6.5 (s, 2 H), 6.55–7.25 (m, 5 H). Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.81; H, 5.18; N, 8.06. A second crop of crystals, 17.8 g, was obtained from the mother liquors, mp 159–161 °C.[11] The combined weight, 52.8 g, represents a 95% yield of **2**.

Preparation of 3,4,5-Trimethoxybenzaldehyde by Hydrolysis of 2. SG Extra charcoal was obtained from R. W. Greefe and Co. A three-neck, 500-mL, round-bottom flask, equipped

(1) K. W. Rosenmund, *Ber. Dtsch. Chem. Ges.*, **51**, 585 (1918). For a review of this method, see E. Mossetig and R. Mozingo, *Org. React.*, **4**, 362 (1948).

(2) J. A. Peters and H. van Bekkum, *Recl. Trav. Chim. Pays-Bas*, **100**, 21 (1981), and references therein.

(3) A. Reissert, *Ber. Dtsch. Chem. Ges.*, **38**, 1603, 1610, 3415, 3427 (1905).

(4) For a review of this method, see E. Mosettig, *Org. React.*, **8**, 218 (1954); W. E. McEwen and R. L. Cobb, *Chem. Rev.* **55**, 51 (1955); F. D. Popp, *Adv. Heterocycl. Chem.*, **9**, 1 (1968).

(5) N. Sugasawa and I. Tsuda, *J. Pharm. Sci.*, **56**, 557 (1936); *Chem. Abstr.*, **32**, 5836 (1936).

(6) H. Buchanan et al., *J. Chem. Soc.*, 325 (1944).

(7) There is a recent patent concerning the use of the Reissert method to produce TMBA. However, the yields are not given for any steps in the process [see *Chem. Abstr.*, **90**, 104001a (1979); J. M. Cuixart Grande (Tresquim, S.A.) Spanish Patent 465 841 (1978)].

(8) When excess sodium cyanide is used, considerable polymer is formed. The yield of desired product drops considerably.

(9) D. L. Hamick et al., *J. Chem. Soc.*, 1724 (1938); 1809 (1939); 173, 659 (1949).

(10) M. Zelinski, *J. Chem. Phys.*, **47**, 3686 (1967).

(11) This material is spectroscopically identical upon comparison of a 60-MHz NMR spectrum and appears to be either a polymorph or geometrical isomer of the higher melting form.