Facile Conversion of Succinic- to Maleic-Type Anhydrides, Thioanhydrides, and Imides[1]

Michael J. Kates and J. Herman Schauble*

Department of Chemistry, Villanova University, Villanova, Pennsylvania 19085

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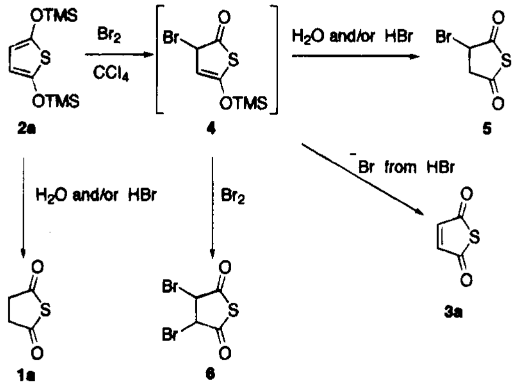
Maleic-type anhydrides and imides are of considerable importance, principally due to their utility in organic synthesis. Furthermore, in recent years, a number of naturally occurring substituted maleic anhydrides have been reported, some of which exhibit unusual biochemical activity.[2] In contrast, only a few maleic-type thioanhydrides have been reported.[3]

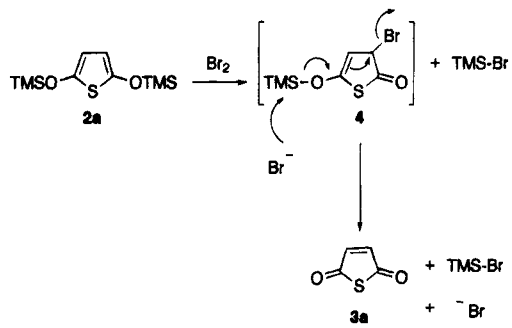
Although methods for the synthesis of specific maleic anhydrides, thioanhydrides, and imides are known, no efficient or general method for preparation of these compounds from the readily available succinic-type congeners has been developed. Thus, while procedures for introduction of the carbon−carbon double bond by dehydrohalogenation,[3b,4,6] dehydration,[5] or phenylsulfoxide[6] elimination of appropriately substituted succinic anhydride or imide precursors are known, such reactions are limited by low efficiency and chemoselectivity in processes (typically free-radical) used for introducing appropriate leaving groups.

Herein, we report a facile two-step *in situ* process for the conversion of succinic-type anhydrides, thioanhydrides, and imides to the corresponding maleic-type systems. The discovery of this process stemmed from an attempt to synthesize 3,4-dibromosuccinic thioanhydride (**6**) by reaction of 2,5-bis((trimethylsilyl)oxy)thiophene (**2a**) with reagent grade bromine (1:2 molar ratio respectively). While the desired dibromide was obtained, it was accompanied by succinic (**1a**) 3-bromosuccinic (**5**), and maleic (**3a**) thioanhydrides (Scheme 1). Formation of thioanhydride **1a** is due to hydrolysis[7] of the starting thiophene **2a** by water and/or hydrogen bromide from nonanhydrous bromine.[8] Thioanhydrides **5** and **3a** both apparently occur via the intermediate 3-bromo-5-((trimethylsilyl)oxy)-2,3-dihydrothiophene-2-one (**4**). Hydrolysis of the latter would afford thioanhydride **5**, while competitive (catalytic) nucleophilic attack by bromide ion (from hydrogen bromide) on the (trimethylsilyl)oxy group would result in a novel 1,4-elimination, affording thioanhydride **3a** (Scheme 2).

Scheme 1



Scheme 2



When thiophene **2a** was added to *pure* bromine (1:2 molar ratio), under anhydrous conditions, *only* dibromide **6** was obtained in 91% isolated yield. Use of an equimolar ratio of reactants, resulted in approximately equimolar amounts of starting thiophene **2a** and dibromide **6**, suggesting the second bromination step is faster than the first. However, when the reaction was carried out using *pure* bromine in only slight molar excess (1:1.05 molar ratio) in the presence of a catalytic amount of tetra-*n*-butylammonium bromide (1.0 mol%), at 0 °C in dichloromethane for 15 min, *only* maleic thioanhydride (**3a**) was formed. This result is consistent with the pathway proposed for the formation of **3a** in Scheme 2 and suggests that, under the conditions employed, the rate of elimination of trimethylsilyl bromide is considerably faster than the second bromination. Use of *n*-bromosuccinimide or iodine monochloride as electrophiles afforded results similar to those obtained with bromine; however, under similar conditions, iodine gave no reaction.

Analogous to the behavior of 2,5-bis((trimethylsilyl)oxy)thiophene) (**2a**), reaction of the corresponding 2,5-bis((trimethylsilyl)oxy)furan (**2e**) with 2 molar equiv of *pure* bromine afforded *only* the 3,4-dibromosuccinic anhydride (**7**) in 89% isolated yield, while equimolar amounts of reactants gave approximately equimolar amounts of starting furan **2e** and dibromide **7**. However, reaction of **2e** with reagent grade ("wet") bromine (1:2 molar ratio) gave a mixture of succinic and maleic anhydrides. Thus, reaction of equimolar amounts of furan **2e** with *pure* bromine in the presence of tetra-*n*-butylammonium bromide gave *only* maleic anhydride (**3e**). Reaction of iodine with furan **2e** afforded polymeric material along with some anhydride **3e**. Oxidation of 3-methyl-2,5-bis((trimethylsilyl)oxy)furan to 3-methyl-

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[1] (a) Presented at the 29th Middle Atlantic Regional Meeting of the American Chemical Society, American University, Washington, DC, and, in part, at the 34th National Organic Symposium, The College of William and Mary, Williamsburg, VA 1995.

[2] (a) Singh, S. B.; Zink, D. L.; Liesch, J. M. et al. *Tetrahedron* **1993**, *49*, 5917. (b) Itoh, S.; Esaki, N.; Masaki, K.; Blank, W.; Soda, K. *J. Ferment. Bioeng.* **1994**, *77*, 513. (c) Buttery, R. G.; Seifert, R. M.; Ling, I. C.; Soderstorm, E. I.; Yerington, A. P. *ACS Symp. Ser. 170 (Qual. Sel. Fruits Veg. North Am.)* **1981**, 29. (d) Stinson, S. *Chem. Eng. News* **1995**, May 22. (e) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.

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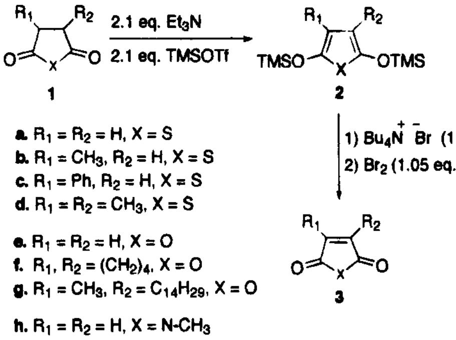
Scheme 3



maleic anhydride with both bromine and iodine was previously noted in 1980 by Brownbridge and Chan;[9] however, no yields or experimental details were given.

Reaction 2,5-bis((trimethylsilyl)oxy)-*N*-methylpyrrole **(2h)** with pure bromine or iodine monobromide in the presence of tetra-*n*-butylammonium bromide afforded *N*-methylmaleimide **(3h)** in excellent yield.

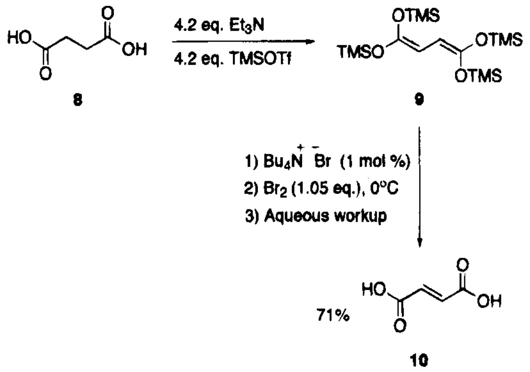
The 2,5-bis((trimethylsilyl)oxy)thiophenes, furans, and pyrole (Scheme 3) were readily obtained by reaction of the respective succinic-type thioanhydrides, anhydrides, and imide with trimethylsilyl triflate (TMSOTf) and triethylamine in anhydrous ether[10] and isolated by short path vacuum distillation in 85−90% yields, prior to oxidation to the maleate-type systems. However, *in situ* preparation and subsequent oxidation was more convenient. In a typical procedure, succinic thioanhydride, anhydride, or *N*-methylimide (10.0 mmol) in 50 mL of anhydrous ether is reacted under argon with TMSOTf and triethylamine (21.0 mmol each) at 0 °C to rt over 1−2 h (reaction monitored by ^{1}H NMR), followed by addition of *pure* tetra-*n*-butylammonium bromide (1 mol %) in 50 mL of dichloromethane and subsequent addition of pure bromine (10.5 mmol) at 0 °C for 15 min, affording maleic thioanhydrides **3a−d**, anhydrides **3e−g**, and imide **3h** in excellent overall yields (Scheme 3, Table 1).

Extension of the above succinate to maleate-type transformation to acyclic systems appears quite promising. Thus, reaction of succinic acid **(8)** (1.0 molar equiv) with TMSOTf and triethylamine (4.2 molar equiv each) gave the novel 1,1,4,4-tetra((trimethylsilyl)oxy)-1,3-butadiene **(9)**, which underwent reaction with tetra-*n*-butylammonium bromide (1 mol %) and 1.05 molar equiv of pure bromine, to afford fumaric acid **(10)** in 71% isolated yield (Scheme 4).

Table 1

products	yields (%)	products	yields (%)
3a	96	**3e**	94
3b	92	**3f**	84
3c	97	**3g**	91
3d	89	**3h**	94

Scheme 4



Application of this two-step oxidative sequence for conversion of succinate to maleate-type systems has been applied as a key step in the total synthesis of chaetomellic anhydride A **(3g)**, the corresponding acid of which exhibits potent and highly specific farnesyl protein transferase inhibitory activity.[11,12] Thus, reaction of 3-tetradecyl-4-methyl-2,5-bis((trimethylsilyl)oxy)furan with tetra-*n*-butylammonium bromide and bromine as described above gave **3g** in 91% isolated yield.

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Supporting Information Available: Experimental procedures and characterization data for compound **9** (4 pages).

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(12) The total synthesis of chaetomellic anhydrides A and B (**3**, $R_1 = CH_3$, $R_2 = (Z)\text{-}CH_2(CH_2)_5CH{=}CH(CH_2)_8$ will be communicated separately.

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