One-Pot Synthesis of 3-Hydroxymaleic Anhydrides by Cyclization of 1,1-Bis(trimethylsilyloxy)ketene Acetals with Oxalyl Chloride

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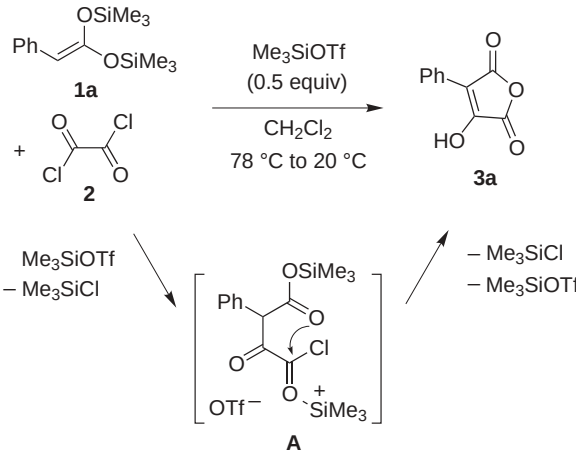
Abstract: Functionalized 3-hydroxymaleic anhydrides were prepared by cyclization of 1,1-bis(trimethylsilyloxy)ketene acetals with oxalyl chloride.

Key words: anhydrides, cyclizations, ketene acetals, oxalyl chloride, silyl enol ethers

Functionalized maleic anhydrides represent versatile building blocks for organic synthesis.[1] For example, pharmacologically relevant γ-alkylidenebutenolides have been prepared by Wittig reactions of maleic anhydrides.[2] Maleic anhydrides have been transformed into maleimides[3] which represent key-intermediates for the synthesis of 5-alkylidene-5*H*-pyrrol-2-ones.[3] The employment of maleic anhydrides as dienophiles in [4+2], [3+2] and [2+2] cycloaddition reactions allows the synthesis of a variety of carba- and heterocyclic frameworks.[4] Functionalized 3-alkanoylacrylic acids and naphthoquinones were prepared by Friedel–Crafts acylations using maleic anhydrides as reagents. The reaction of maleic anhydrides with enolates provides a convenient approach to 4-alkylidenebutane-1,3-diones.[5] A variety of functionalized α,β-unsaturated carbonyl compounds were prepared by reaction of maleic anhydrides with nucleophiles.[6]

Functionalized maleic anhydrides have been prepared by conjugate addition of nucleophiles onto parent maleic anhydride and subsequent halogenation and elimination.[7] 2-Methoxy-3-methylmaleic anhydride has been prepared by base-mediated condensation of ethyl propionate with diethyl oxalate[8] and subsequent methylation.[2a] 2-Methoxy-3-arylmaleic anhydrides are available by condensation of arylacetonitriles with diethyl oxalate to give open-chained pyruvates, subsequent methylation and treatment with acid.[9] 3-Hydroxymaleic anhydrides are of potential synthetic usefulness as precursors of enol triflates to be employed in palladium-catalyzed cross-coupling reactions. For example, the synthesis of (symmetrical) 2,3-dihydroxymaleic anhydride,[10a] 2,3-diacetoxymaleic anhydride[10b,c] and 2,3-dimethoxymaleic anhydride[10d] has been reported. In contrast, unsymmetrical 2,3-dihydroxymaleic anhydrides, containing one free and one protected hydroxy group, have not been prepared so far. Herein, we wish to report a new method for the synthesis of 3-hydroxymaleic anhydrides based on what are, to the best of our knowledge, the first cyclization reactions of 1,1-bis(trimethylsilyloxy)ketene acetals with oxalyl chloride.[11–14] This methodology allows a convenient one-pot synthesis of a variety of maleic anhydrides which are in many cases not directly available by other methods.



Scheme 1 Cyclization of 1,1-bis(trimethylsilyloxy)ketene acetal **1a** with oxalyl chloride.

The known 1,1-bis(trimethylsilyloxy)ketene acetal **1a** was prepared by deprotonation of phenylacetic acid with lithio-1,1,1,3,3,3-hexamethyldisilazane and subsequent addition of trimethylchlorosilane to the dianion thus formed.[15] The reaction of **1a** with oxalyl chloride (**2**) in the presence of trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf) afforded the 3-hydroxymaleic anhydride **3a** in up to 70% yield (Scheme 1).[16] The direct reaction of the dianion of phenylacetic acid[17] with oxalyl chloride or diethyl oxalate resulted in the formation of complex mixtures. In fact, the employment of 1,1-bis(trimethylsilyloxy)ketene acetal **1a**, which can be regarded as a masked dianion, proved mandatory to induce a clean cyclization. During the optimization, the following parameters proved to be important: a) the employment of 0.5 equivalents of Me_3SiOTf (the use of stoichiometric amounts of $TiCl_4$ resulted in the formation of complex mixtures), b) the solvent (CH_2Cl_2), c) the reaction time and d) the temperature. The formation of **3a** can be explained by Me_3SiOTf-mediated attack of the carbon atom of **1a** onto **2** to give intermediate **A** and subsequent cyclization via the oxygen atom.

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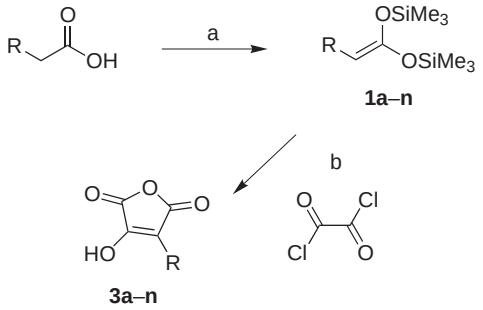

Scheme 2 Synthesis of **3a**–**n**: *a*, (1) Li[N(SiMe$_3$)$_2$] (2.0 equiv), THF, –78 °C, (2) Me$_3$SiCl (2.2 equiv), –78 °C → 20 °C; *b*, Me$_3$SiOTf (0.5 equiv), CH_2Cl_2, –78 °C → 20 °C, 12 h, then 20 °C, 3 h.

Table 1 Products and Yields

3	R	Yield (%)[a]
a	Ph	70
b	4-MeC_6H_4	73
c	4-ClC_6H_4	65
d	4-(MeO)C_6H_4	53
e	3,4-(MeO)$_2C_6H_3$	70
f	Me	20
g	Et	36
h	*n*-Pr	42
i	*n*-Pent	50
j	*n*-Oct	56
k	Allyl	20
l	MeO	53
m	PhO	50
n	BnO	40

[a] Yields of isolated products.

To study the preparative scope, the substituents of the 1,1-bis(trimethylsilyloxy)ketene acetal were systematically varied (Scheme 2, Table 1). The cyclization of 1,1-bis(trimethylsilyloxy)ketene acetals **1a**–**e** with oxalyl chloride afforded the aryl-substituted 3-hydroxymaleic anhydrides **3a**–**e**. The ketene acetals **1f**–**j** were prepared from propionic-, butanoic-, pentanoic-, heptanoic- and decanoic acid, respectively. The cyclization of **1f**–**j** with oxalyl chloride afforded the alkyl-substituted 3-hydroxymaleic anhydrides **3f**–**j**. The cyclization of oxalyl chloride with **1k**, prepared from pent-4-enoic acid, gave the allyl-substituted maleic anhydride **3k**. The methoxy-, phenyloxy- and benzyloxy-substituted 3-hydroxymaleic anhydrides **3l**–**n** were prepared from the corresponding 1,1-bis(trimethylsilyloxy)ketene acetals **1l**–**n**. All cyclizations proceeded in good to moderate yields and with very good regioselectivity.

We currently study the functionalization of the 3-hydroxymaleic anhydrides by palladium-catalyzed cross-coupling reactions of the corresponding enol triflates.

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References

(1) *Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons Ltd: Chichester, **1995**, 3207.
(2) (a) Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 62. (b) Ingham, C. F.; Massy-Westropp, R. A.; Reynolds, G. D.; Thorpe, W. D. *Aust. J. Chem.* **1975**, *28*, 2499. (c) Massy-Westropp, R. A.; Price, M. F. *Aust. J. Chem.* **1980**, *33*, 333.
(3) James, G. D.; Mills, S. D.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2581.
(4) For reviews, see for example: (a) Danishefsky, S. J.; Kitahara, T.; Schuda, P. F.; Golob, D.; Dynak, J.; Stevens, R. V. *Org. Synth.* **1983**, *61*, 147. (b) Kloetzel, M. C. *Org. React.* **1948**, *4*, 1. (c) Alder, K. In *Neuere Methoden der Präparativen Organischen Chemie*, Part 2; Foerst, W., Ed.; Verlag Chemie: Berlin, **1953**. (d) See also: Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Org. Chem.* **1985**, *50*, 2576. (e) Kozikowski, A. P.; Huie, E.; Springer, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 2059.
(5) Murray, W. V.; Wachter, M. P. *J. Org. Chem.* **1990**, *55*, 3424.
(6) Jacobi, P.; Blum, C. A.; DeShimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384.
(7) Kaydos, J. A.; Smith, D. L. *J. Org. Chem.* **1983**, *48*, 1096.
(8) Schreiber, J. *Annalen* **1947**, *2*, 84.
(9) Edwards, R. L.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1538.
(10) (a) Nef, J. U. *Justus Liebigs Ann. Chem.* **1910**, *376*, 115. (b) Yalpani, M.; Wilke, G. *Chem. Ber.* **1985**, *118*, 661. (c) Goodwin, S.; Witkop, B. *J. Am. Chem. Soc.* **1954**, *76*, 5599. (d) Stachel, H.-D.; Schachtner, J.; Seidel, J. *Z. Naturforsch. B* **1996**, *51*, 409.
(11) (a) For a review of silyl enol ethers, see: Brownbridge, P. *Synthesis* **1983**, 85. (b) For a review of 1,3-bis(trimethylsilyloxy)-1,3-butadienes, see: Langer, P. *Synthesis* **2002**, 441.
(12) (a) For the synthesis of α-hydroxy-γ-alkylidenebutenolides from 1,3-bis(trimethylsilyloxy)-1,3-butadienes, see: Langer, P.; Schneider, T.; Stoll, M. *Chem.–Eur. J.* **2000**, *6*, 3204. (b) For palladium-catalyzed functionalizations, see: Langer, P.; Eckardt, T.; Schneider, T.; Göbel, C.; Herbst-Irmer, R. *J. Org. Chem.* **2001**, *66*, 2222. (c) See also: Ahmed, Z.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3753.
(13) For the synthesis of 2,3-dihydro-2,3-diones from silyl enol ethers, see: (a) Murai, S.; Hasegawa, K.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 636; *Angew. Chem.* **1975**, *87*, 668. (b) Kappe, C. O.; Kollenz, G.; Wentrup, C. *Heterocycles* **1994**, *38*, 779.
(14) For the synthesis of 4-hydroxy-2*H*-pyran-2-ones from silyl enol ethers, see: Effenberger, F.; Ziegler, T.; Schonwalder, K.-H.; Kesmarszky, T.; Bauer, B. *Chem. Ber.* **1986**, *119*, 3394.

(15) For the synthesis of 1,1-bis(trimethylsilyloxy)ketene acetals, see: (a) Ainsworth, C.; Kuo, Y.-N. *J. Organomet. Chem.* **1972**, *46*, 73. (b) Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617. (c) Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247.

(16) To a CH_2Cl_2 solution (17.8 mL) of oxalyl chloride (0.20 mL, 2.3 mmol) and **1a** (0.50 g, 1.8 mmol) was added a CH_2Cl_2 solution (5 mL) of TMSOTf (0.16 mL, 0.9 mmol) at 78 °C. The temperature of the solution was allowed to rise to 20 °C during 12 h. After stirring for 3 h at 20 °C, an aq solution of HCl (10%) was added. The organic and the aqueous layer were separated and the latter was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane–EtOAc) to give **3a** as a yellow solid (240 mg, 70%), mp 164 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.50 (m, 3 H, Ar), 8.05–8.08 (m, 2 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 112.0 (C), 126.9 (C), 128.8 (CH), 129.1 (CH), 130.3 (CH), 149.4 (C), 163.4 (C), 163.5 (C). IR (neat): 3244 (s), 3123 (w), 1840 (s), 1760 (s), 1673 (s), 1393 (s), 1262 (s), 939 (s), 762 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 190 (43) [M$^+$], 162 (100), 145 (22), 118 (27), 105 (15), 89 (81), 77 (8). Anal. Calcd for $C_{10}H_6O_4$: C, 63.16; H, 3.18. Found: C, 62.87; H, 3.63.

(17) For a review of dianions of carboxylic acids, see: Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 521.