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Practical Synthesis and Highly Diastereoselective Diels−Alder Reactions of 1-Alkylthio-3-silyloxybutadienes

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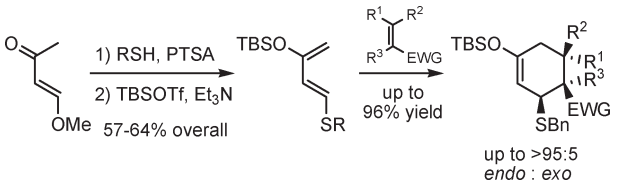

An efficient acid-catalyzed method for the synthesis of vinylogous thioesters was developed. 1-Alkylthio-3-silyloxybutadienes were then produced in high yields from the corresponding vinylogous thioesters. These dienes were highly reactive in Diels−Alder reactions, affording the cycloadducts in high *endo* selectivity under mild conditions.

The stereocontrolled production of a carbocycle has made the Diels−Alder cycloaddition a greatly valued reaction in organic synthesis.[1] Electron donating groups on the diene serve to enhance both the rate and regioselectivity of the reaction. Among the vast number of dienes developed for Diels−Alder and hetero-Diels−Alder reactions, Danishefsky's[2] and Rawal's[3] silyloxydienes stand out as being particularly reactive. As shown in Figure 1, the former diene bears an additional methoxy substituent, whereas the latter contains a dimethylamino group.

We were intrigued by the possibility of using an alkylthio substituent instead of the alkoxy or dialkylamino group. Specifically, we were interested in determining their stability, reactivity, and selectivity in Diels−Alder reactions. Although many sulfur-containing dienes have been reported,[4] the properties of 1-alkylthio-3-silyloxybutadienes analogous to Danishefsky's and Rawal's dienes have not yet been investigated.[5] In this paper, we describe the conditions required for the efficient preparation of 1-alkylthio-3-silyloxybutadienes in high yields and discuss their behavior in the Diels−Alder reaction.

To access 1-alkylthio-3-silyloxybutadienes, we needed an efficient method for vinylogous thioester synthesis. In contrast to the straightforward preparation of vinylogous amides,[3a] simple mixing of 4-methoxy-3-buten-2-one (**1**) with butanethiol in dichloromethane at room temperature did not result in any reaction. Thus, the synthesis of the desired vinylogous thioester through a direct addition−elimination reaction was attempted by using basic conditions (Scheme 1). We were encouraged by the isolation of the conjugate addition product (**2a**), although no vinylogous thioester (**3a**) was detected. Subjection of adduct **2a** to acidic conditions resulted in the elimination of the methoxy group, producing the desired vinylogous thioester **3a**.

The successful elimination of the methoxy group under acidic conditions prompted an attempt to directly convert **1** into **3a** by using acid catalysis. In the presence of catalytic *p*-toluenesulfonic acid, **3a** was obtained in a single step with a good *E*:*Z* ratio (Table 1, entry 1). Substitution of dichloromethane with toluene resulted in a small improvement in *E*:Z ratio and a significant improvement in yield (entry 2). Decreasing the temperature of the reaction resulted in an excellent *E*:*Z* ratio (entry 3).

The generality of this method for vinylogous thioester synthesis was then assessed for various thiols. The products **3a**−**c** derived from alkylthiols were produced with high *E* selectivity and isolated in good yields (entries 3−5). On the other hand, product **3d** derived from benzenethiol was obtained in a much reduced *E*:*Z* ratio (entry 6). In addition, the reaction leading to **3d** resulted in an incomplete conversion and the desired product could not be conveniently separated from the conjugate addition intermediate (**2d**) by distillation or chromatography. The minor *Z* isomer present in **3a**−**c** could be removed through column chromatography, affording geometrically pure (*E*)-**3** (>95:5 *E*:*Z*). Although we have found the vinylogous thioesters **3** to isomerize at ambient temperature, they could be stored for several weeks at −20 °C without any significant change in the *E*:*Z* ratio.

Formation of a silyl dienol ether from the vinylogous thioester with use of Ward's conditions produced the desired

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(2) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807–7808.

(3) (a) Kozmin, S. A.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 5252–5253. (b) Kozmin, S. A.; Green, M. T.; Rawal, V. H. *J. Org. Chem.* **1999**, *64*, 8045–8047.

(4) Selected examples of 1-alkylthio- and 1-arylthio-1,3-butadienes: (a) Cohen, T.; Mura, A. J.; Shull, D. W.; Fogel, E. R.; Ruffner, R. J.; Falck, J. R. *J. Org. Chem.* **1976**, *41*, 3218–3219. (b) Kozikowski, A. P.; Huie, E. *J. Am. Chem. Soc.* **1982**, *104*, 2923–2925. (c) Overman, L. E.; Petty, C. B.; Ban, T.; Huang, G. T. *J. Am. Chem. Soc.* **1983**, *105*, 6335–6337. (d) Grayson, J. I.; Warren, S.; Zaslona, A. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 967–976. (e) Pegram, J. J.; Anderson, C. B. *Tetrahedron Lett.* **1988**, *29*, 6719–6720. (f) Skowrońska, A.; Dybowski, P.; Koprowski, M.; Krawczyk, E. *Tetrahedron Lett.* **1995**, *36*, 8133–8136. (g) Maddaluno, J.; Gaonac'h, O.; Marcual, A.; Toupet, L.; Giessner-Prettre, C. *J. Org. Chem.* **1996**, *61*, 5290–5306. (h) Olsen, R. K.; Shao, R.-l. *J. Org. Chem.* **1996**, *61*, 5852–5856.

(5) Cyclic dienes derived from 2*H*-thiopyran-4-one were studied previously: (a) Ward, D. E.; Zoghaib, W. M.; Rhee, C. K. *Tetrahedron Lett.* **1990**, *31*, 845–848. (b) Ward, D. E.; Gai, Y. Z.; Zoghaib, W. M. *Can. J. Chem.* **1991**, *69*, 1487–1497. (c) Ward, D. E.; Gai, Y. *Tetrahedron Lett.* **1992**, *33*, 1851–1854. (d) Ward, D. E.; Gai, Y. *Can. J. Chem.* **1992**, *70*, 2627–2634. (e) Ward, D. E.; Nixey, T. E. *Tetrahedron Lett.* **1993**, *34*, 947–950. (f) Ward, D. E.; Nixey, T. E.; Gai, Y.; Hrapchak, M. J.; Abaee, M. S. *Can. J. Chem.* **1996**, *74*, 1418–1436. (g) Ward, D. E.; Gai, Y. *Can. J. Chem.* **1997**, *75*, 681–693.

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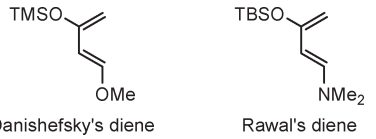


FIGURE 1. Reactive silyloxydienes.

SCHEME 1. Two-Step Synthesis of a Vinylogous Thioester

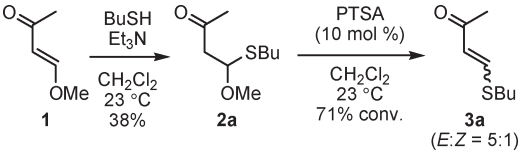
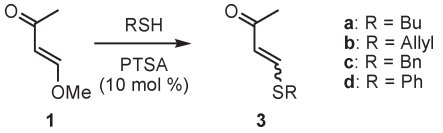


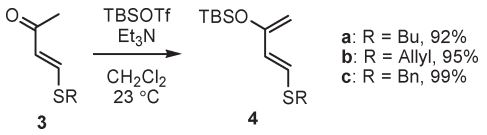
TABLE 1. Single-Step Synthesis of Vinylogous Thioesters



entry	product	T (°C)	solvent	E:Z[a]	yield (%)[b]
1	**3a**	23	CH_2Cl_2	7:1	32
2	**3a**	23	PhMe	8:1	79
3	**3a**	0	PhMe	20:1	70
4	**3b**	0	PhMe	10:1	60
5	**3c**	0	PhMe	25:1	64
6	**3d**	0	CH_2Cl_2	4:1	n.d.[c]

[a]Ratio determined by ^{1}H NMR on the crude reaction mixture. [b]Yield of purified E isomer. [c]The yield was not determined (see text).

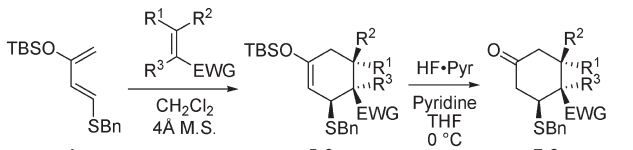
SCHEME 2. Synthesis of 1-Alkylthio-3-silyloxybutadienes

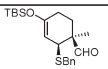
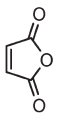
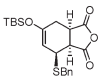
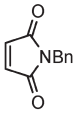
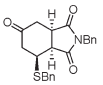
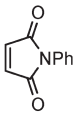
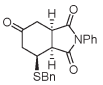
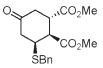


dienes **4** in high yield (Scheme 2).[5a] In the presence of acid or water, the dienes hydrolyze to their vinylogous thioester precursors. Use of a basic eluent (3% Et_3N/hexanes) in flash column chromatography allows for the isolation of all the dienes in near-quantitative yield. Although the dienes can be handled without any particular precautions, exposure to air results in slow oxidation to the corresponding sulfoxides.

Dienes **4a**−**c** displayed high *endo* selectivity in preliminary Diels−Alder experiments with methacrolein at ambient temperature (*endo*:*exo* > 10:1). Diene **4c** showed particular promise (*endo*:*exo* 14:1) and thus was selected for further investigation. Cycloadditions were performed in the presence of 4 Å molecular sieves to prevent the slow hydrolysis of the diene. The monoactivated dienophile methacrolein required heating and a concentrated reaction mixture for the reaction to proceed at a reasonable rate. Under these conditions, the cycloaddition was highly *endo* selective (entry 1). The excess methacrolein served to drive the reaction to completion prior to the formation of any byproduct,

TABLE 2. Diels−Alder Additions with 1-Benzylthio-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene 4c[a]



entry	dienophile	×	[diene] (M)	Product	*endo*: *exo*[b]	yield (%)[c]
1		3	neat	 **5**	7:1	96
2		0.95	0.1	 **6**	>95:5	99
3		1.5	0.1	 **7**	>95:5	53
4		1.5	0.1	 **8**	>95:5	83
5		1.5	5	 **9**	1:1	74

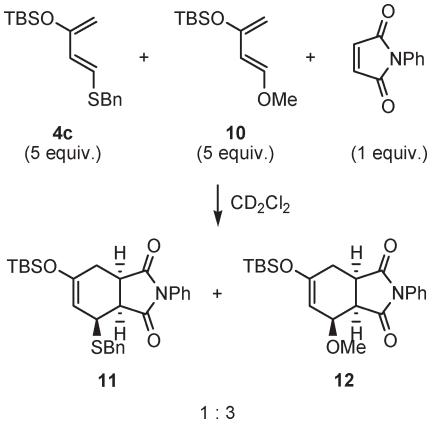
[a]Reactions in entries 1 and 5 were performed at 80 °C; reactions in entries 2−4 were performed at 23 °C. [b]Assignment of the *endo* and *exo* cycloadducts was based on comparison of ^{1}H NMR spectra with related compounds and through NOESY experiments (see the Supporting Information). [c]For entries 1−2: yield of pure isolated silyl enol ether cycloadduct. For entries 3−5: yield of pure isolated ketone (two-step process of cycloaddition and cleavage of the silyl enol ether on the crude cycloadduct).

allowing for the isolation of the cycloadduct in quantitative yield without the need for purification beyond removal of the excess methacrolein in vacuo. Doubly activated dienophiles formed cycloadducts with **4c** at ambient temperature with only one diastereomer detected by ^{1}H NMR analysis (entries 2−4, Table 2). The cycloaddition with maleic anhydride yields the cycloadduct in its essentially pure form (entry 2). As isolation of the remainder of the cycloadducts by chromatography was unsuccessful, cleavage of the silyl enol ether was performed on the crude cycloadduct with use of HF·pyridine complex,[6] resulting in good yields for the two-step process. (entries 3−5). Not surprisingly, the cycloaddition with dimethyl fumarate was not selective, with the *endo* and *exo* products being obtained in a 1:1 ratio (entry 5).[3a]

To determine the relative reactivity of 1-alkylthio-3-silyloxybutadienes, a competition reaction was performed between diene **4c** and a *tert*-butyl dimethylsilyl version of Danishefsky's diene (**10**). A limiting amount of *N*-phenylmaleimide was

(6) Lastdrager, B.; Timmer, M. S. M.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *J. Carbohydr. Chem.* **2007**, *26*, 41–59.

SCHEME 3. Competition Reaction between Dienes 4c and 5



added to a solution containing equimolar amounts of the two dienes at room temperature (Scheme 3). After complete consumption of the dienophile (16 h), ^{1}H NMR analysis of the mixture revealed a product distribution of 3:1 with the alkoxy cycloadduct (**12**) being the major product. This result indicates that 1-alkylthio-3-silyloxybutadienes (**4**) are quite reactive dienes, being approximately three times less reactive than Danishefsky-type dienes (**10**). In comparison, Rawal's diene was found to be >3000 times more reactive than Danishefsky's diene **5** in its cycloaddition with methacrolein.[3b]

In summary, an efficient two-step method was developed for the synthesis of 1-alkylthio-3-silyloxybutadienes in high yield. These new dienes undergo efficient Diels–Alder reactions with high *endo* selectivity to produce highly functionalized cycloadducts. The sulfide moiety present in the cycloadducts provides a useful functional handle for further manipulations. For example, Pummerer, Stevens, and sigmatropic rearrangements on cycloadduct derivatives can be envisaged. Investigations along those lines are under way and will be reported in due course.

Experimental Section

Representative Procedure for the Synthesis of Vinylogous Thioesters: *trans*-4-Benzylthio-3-buten-2-one (3c). A 250-mL round-bottomed flask equipped with a stir bar and septum was purged with nitrogen and placed in an ice bath. The addition of *trans*-4-methoxy-3-buten-2-one (2.04 mL, 20.0 mmol) was followed by the sequential addition of toluene (67 mL), benzyl mercaptan (2.47 mL, 21.0 mmol), and *p*-toluenesulfonic acid monohydrate (0.380 g, 2.00 mmol). After 165 min, the reaction was quenched with saturated aqueous sodium bicarbonate. The organic layer was decanted and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic layers were dried over sodium sulfate and concentrated in vacuo. The crude yellow oil was purified by flash column chromatography on silica gel with 5% EtOAc/toluene as eluent. The title product was obtained as a yellow oil (2.47 g, 64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J = 15.4 Hz, 1H), 7.37–7.34 (m, 4H), 7.32–7.27 (m, 1H), 6.17 (d, J = 15.5 Hz, 1H), 4.04 (s, 2H), 2.19 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 146.0, 135.4, 129.0, 128.8, 127.9, 124.2, 36.7, 27.4. FTIR (thin film) ν_{max} 3029, 1661, 1548, 1495, 1454, 1356, 1255 cm^{-1}. HRMS (EI$^+$) m/z calcd for $C_{11}H_{12}OS$ [M]$^+$ 192.0609, found 192.0610.

Representative Procedure for the Synthesis of Dienes: 1-Benzylthio-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene (4c). A 25-mL round-bottomed flask containing a stir bar and *trans*-4-benzylthio-3-buten-2-one (**3a**) (0.214 g, 1.11 mmol) was sealed with a septum. The flask was purged with nitrogen, then CH_2Cl_2 (10 mL), Et_3N (0.466 mL, 3.00 mmol), and *tert*-butyldimethylsilyltrifluoromethane sulfonate (0.267 mL, 1.16 mmol) were added sequentially. After 3 h of stirring at room temperature, the reaction mixture was concentrated in vacuo. The resulting red mixture was chromatographed rapidly through a 9×2.5 cm column of silica gel with 3% Et_3N/hexanes as eluent. The title product was obtained as a yellow oil (0.337 g, 99% yield), and was immediately placed under an inert atmosphere and stored at −20 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.30 (m, 4H), 7.27–7.25 (m, 1H), 6.51 (d, J = 14.9 Hz, 1H), 6.00 (d, J = 14.9 Hz, 1H), 4.17 (s, 1H), 4.15 (s, 1H), 3.99 (s, 2H), 0.97 (s, 9H), 0.14 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 137.3, 129.0, 128.8, 127.5, 125.8, 125.0, 93.6, 37.2, 26.0, 18.4, −4.5. FTIR (thin film) ν_{max} 3030, 2956, 2929, 2857, 1681, 1611, 1566, 1494, 1471, 1453, 1361, 1310, 1253 cm^{-1}. HRMS (EI$^+$) m/z calcd for $C_{17}H_{26}OSiS$ [M]$^+$ 306.1471, found 306.1476.

Diels–Alder Reaction: 2-(Benzylthio)-4-(*tert*-butyldimethylsilyloxy)-1-methylcyclohex-3-enecarbaldehyde (5). A pressure vessel containing 1-benzylthio-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**4c**) (0.640 g, 2.09 mmol) and 4 Å molecular sieves (0.1 g) was equipped with a stir bar and septum. The vessel was purged with nitrogen prior to the addition of methacrolein (0.516 mL, 6.26 mmol). The septum was replaced with a pressure cap prior to heating the reaction mixture to 85 °C. After 12 h, the reaction mixture was transferred to a round-bottomed flask and the excess methacrolein was removed in vacuo. The resulting mixture was filtered through a pad of Celite with use of CH_2Cl_2, then concentrated in vacuo to yield a yellow oil (0.757 g, 96% yield) as a mixture of *endo*/*exo* isomers (7:1). ^{1}H NMR (500 MHz, $CDCl_3$, *endo* isomer) δ 9.59 (s, 1H), 7.33–7.29 (m, 4H), 7.26–7.22 (m, 1H), 4.82 (d, J = 4.9 Hz, 1H), 3.74 (s, 2H), 3.21 (d, J = 3.6 Hz, 1H), 2.12–2.00 (m, 3H), 1.66–1.60 (m, 1H), 1.08 (s, 3H), 0.96 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.1, 151.9, 138.3, 129.1, 128.7, 127.25, 104.4, 48.3, 46.9, 37.3, 26.3, 26.3, 25.8, 19.6, 18.1, −4.3, −4.3. FTIR (thin film) ν_{max} 3062, 3029, 2929, 2858, 2712, 1725, 1658, 1602, 1495, 1472, 1454, 1390, 1365, 1342, 1253, 1206, 1071, 1006 cm^{-1}. HRMS (CI$^+$) m/z calcd for $C_{21}H_{33}O_2SiS$ [M + H]$^+$ 377.1971, found 377.1981.

Silyl Enol Ether Cleavage: 7-(Benzylthio)-2-phenyltetrahydro-2*H*-isoindole-1,3,6-(6,*H*)-trione (8). A vial containing the crude cycloadduct **7** (156 mg, 0.326 mmol) and stir bar was sealed with a septum and placed under an atmosphere of nitrogen at 0 °C. THF (1.30 mL), pyridine (0.326 mL), and pyridine hydrofluoride (0.161 mL, 1.79 mmol) were added sequentially. After 3.5 h, the reaction had ceased to progress by TLC. A 1:1 mixture of water and Et_2O (2 mL) was added to the reaction mixture. The organic layer was decanted, and the aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL). The organic layers were combined and dried over sodium sulfate. The orange solution was concentrated under reduced pressure. Flash column chromatography on silica gel (55% EtOAc/hexanes) afforded the title compound as a white solid (0.100 g, 84% yield). Mp 171–174 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (t, J = 7.9 Hz, 2H), 7.44 (t, J = 7.9 Hz, 1H), 7.35–7.30 (m, 6H), 7.29–7.25 (m, 1H), 3.87 (d, J = 13.3 Hz, 1H), 3.82 (d, J = 13.6 Hz, 1H), 3.68 (dd, J = 8.8, 4.4 Hz, 1H), 3.48 (dd, J = 9.8, 5.4 Hz, 1H), 3.41 (dd, J = 18.9, 9.5 Hz, 1H), 2.94 (dd, J = 9.1, 1.6 Hz, 2H), 2.56 (dd, J = 18.6, 3.8 Hz, 1H), 2.50 (dd, J = 18.3, 4.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.3, 177.0, 175.1, 136.6, 131.8, 129.5, 129.2, 129.2, 128.9, 127.8, 126.8, 45.1, 44.3, 39.3, 38.2, 37.1, 36.6. FTIR (thin film) ν_{max} 2930, 2858,

1782, 1657, 1472, 1362, 1255, 1204, 913, 841, 782, 702. HRMS (EI^+) *m*/*z* calcd for $C_{21}H_{19}NO_3S$ $[M]^+$ 365.1086, found 365.1096.

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Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.