Reactions of Vinyl Sulfoxides with Magnesium Amides. One-Pot Synthesis of Symmetrical and Unsymmetrical β-(Dialkylamino) Dithioacetals

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Vinyl sulfoxides ($PhSOCR^1{=}CHR^2$: R^1 = H, Me, or Ph; R^2 = H or Me) were treated with (dialkylamino)magnesium reagents, generated in situ from the reaction of EtMgBr with secondary amines (R^3R^4NH: R^3 = Et, *i*-Pr, or Bn; R^4 = Me, Et, or *i*-Pr) in refluxing Et_2O for 1 h, and stirring at room-temperature overnight gave the corresponding symmetrical β-(dialkylamino) dithioacetals [$(PhS)_2CR^1CHR^2NR^3R^4$] in 24−84% yields. When the (diethylamino)magnesium reagent was treated with appropriate thiols (RSH; R = *p*-ClC_6H_4 or Bn) prior to the interaction with phenyl vinyl sulfoxide, the corresponding unsymmetrical β-(diethylamino) dithioacetals [$(PhS)(RS)CHCH_2NEt_2$] were produced in 63−67% yields.

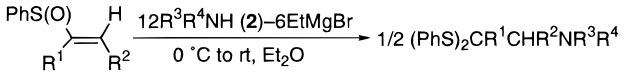
Introduction

Dithioacetals have been shown to be useful building blocks for specific C−C bond formation and functional group interconversion in organic synthesis.[1] Moreover, some of this class of compounds have attracted interest because of their biological activities.[2] Thus, β-amino dithioacetals are potentially useful not only in synthetic organic chemistry for further elaborations but also in medicinal chemistry. However, few synthetic methods are available for the formation of these derivatives, though there are several established methods for the preparation of simple dithioacetals.[1] As the only reported method, a two-step preparation of 2-amino-1,1-bis(alkylthio)ethanes, which begins with 1,1-bis(alkylthio)ethenes and has limited generality (three examples), has been recorded by Hamberger et al.[3] Therefore, any new efficient route to this class of molecules from readily accessible starting materials is of interest and value. In the course of our exploration on application of the magnesium amide-induced Pummerer-type reactions,[4] we examined the reaction of vinyl sulfoxides **1** with magnesium amides, generated by the treatment of ethylmagnesium bromide with secondary amines **2**, aimed at the development of a general method for the direct preparation of β-amino dithioacetal derivatives.[5] We have found that the reaction can afford symmetrical β-(dialkylamino) dithioacetals **3** (Scheme 1) and that the reaction in the presence of an appropriate thiol results in the formation of unsymmetrical β-(dialkylamino) dithioacetals **6** (Scheme 2).

Results and Discussion

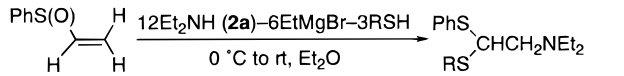
The transformation of vinyl sulfoxides **1**, commercially available or readily prepared by the reported procedures (see Experimental Section), into the amino dithioacetals **3** was performed as follows (Scheme 1). To a turbid solution of a (dialkylamino)magnesium reagent, generated by treating ethylmagnesium bromide (6 mmol) with one of the secondary amines **2** (12 mmol)[6] in refluxing Et_2O for 1 h, was added one of the sulfoxides **1** (1 mmol). The reaction mixture was stirred overnight at room temperature. After usual workup, the expected product **3** was isolated by purification using preparative TLC on silica gel. The results obtained by using four vinyl sulfoxides and three secondary amines are summarized in Table 1. It is very likely that the mechanism for the formation of the products involves the initial formation of the sulfonium ion intermediate **9** via the ylide **8** formed by the addition of the magnesium amide **7** to **1**[7a] and that the pathway from this intermediate to **3** is parallel to that for the formation of dithioacetals from simple sulfoxides and magnesium amides, which was proposed by us in a previous paper,[4a] as depicted in Scheme 3.[7b] With diethylamine (**2a**), diisopropylamine (**2b**), and *N*-

Scheme 1



1 **3**

Scheme 2



1a

6a R=4-ClC_6H_4 63%
6b R=Bn 67%

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(6) We observed that the yields of the products decreased with smaller molar amounts of either of ethylmagnesium bromide or secondary amines.

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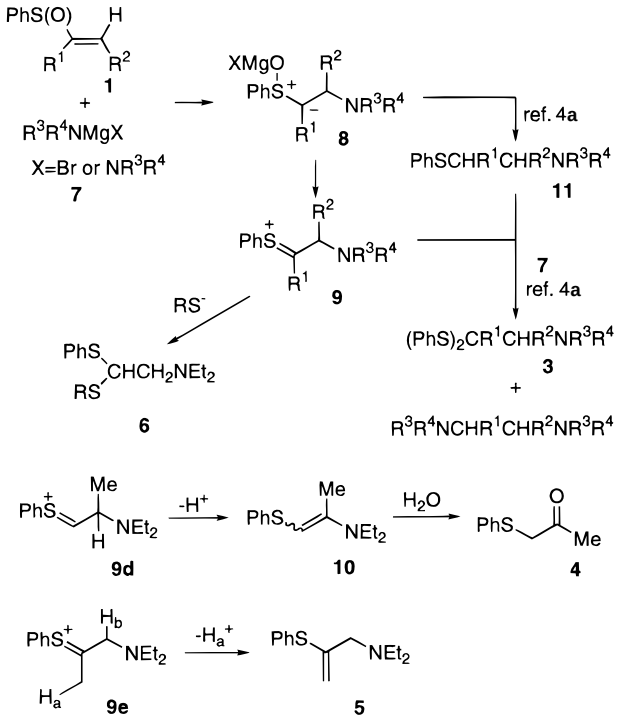
Table 1. Synthesis of Amino Dithioacetals 3 from Vinyl Sulfoxides 1 and Secondary Amines 2 According to Scheme 1

entry	1	2	product(s) (yield/%)[a]
1	$R^1 = R^2 = H$ (**1a**)	$R^3 = R^4 =$ Et (**2a**)	**3a** (79)
2	**1a**	$R^3 = R^4 =$ *i*-Pr (**2b**)	**3b** (74)
3	**1a**	$R^3 =$ Me, $R^4 =$ Bn (**2c**)	**3c** (71)
4	$R^1 =$ H, $R^2 =$ Me (**1b**)[b]	**2a**	**3d** (76), **4** (10)
5	$R^1 =$ Me, $R^2 = H$ (**1c**)	**2a**	**3e** (24), **5** (57)
6	$R^1 =$ Ph, $R^2 = H$ (**1d**)	**2a**	**3f** (84)

[a] Yields are based on **1** and isolated products after preparative TLC on SiO_2. [b] A mixture of stereoisomers was used.

Scheme 3



methylbenzylamine (**2c**), compound **1a** respectively afforded the corresponding products **3a, 3b,** and **3c** in good yields (entries 1−3). The reaction of phenyl 1-propenyl sulfoxide (**1b**) with the (diethylamino)magnesium reagent leads to the formation of the expected product **3d** along with a small amount of 1-(phenylthio)-2-propanone (**4**) (entry 4), which is thought to be derived from deprotonation of the sulfonium ion intermediate **9d** followed by hydrolysis of the resulting enamine **10** under the workup and/or isolation conditions (see Scheme 3). These two products were easily separated by preparative TLC on silica gel. While the corresponding amino dithioacetal **3e** could be obtained from the reaction of 1-methylethenyl phenyl sulfoxide (**1c**) and the (diethylamino)magnesium reagent, we found that the yield was rather lower and that 3-(diethylamino)-2-(phenylthio)propene (**5**) was produced as a major product (entry 5). These products were easily separated from each other by preparative TLC on silica gel as well and are potentially usable for an α-aminoacetone equivalent. Compound **5** is presumed to result from deprotonation of the hydrogen H_a from the intermediate **9e** (see Scheme 3). Interestingly, the deprotonation appears to be exclusive, because there was no indication for the presence of products arising from deprotonation of the hydrogen H_b in the reaction mixture as judged by its ^{1}H NMR spectrum. Entry 6 of Table 1 indicates that, of four vinyl sulfoxides tested, phenyl 1-phenylethenyl sulfoxide (**1d**) gave the best result.

It should be noted that attempts to prepare β-(alkylamino) dithioacetals by using primary amines, such as benzylamine and *n*-butylamine, instead of secondary amines did not meet with success. The reactions each resulted in formation of an intractable mixture of products, from which no trace of the expected product was isolated.

We next examined the reaction of vinyl sulfoxides **1** with the (dialkylamino)magnesium reagents in the presence of an appropriate thiol (Scheme 2), in expectation of the formation of unsymmetrical β-(diethylamino) dithioacetals through addition of a thiolate anion to the intermediate **9**. As expected, when the (diethylamino)-magnesium reagent was treated with a thiol, such as 4-chlorobenzenethiol or phenylmethanethiol, prior to the interaction with **1a**, the corresponding product **6a** or **6b** was produced in fair yields.[7c]

In summary, the results reported in the foregoing part indicate that the present reaction between vinyl sulfoxides and magnesium amides provides a simple and general approach to the preparation of β-(dialkylamino) dithioacetals. It has advantages not only in that the starting materials are readily available but also in that it can be applied to the preparation of the unsymmetrical β-(dialkylamino) dithioacetal derivatives. These advantages make this class of compounds potentially interesting in organic and medicinal chemistry.

Experimental Section

Starting Materials. Phenyl vinyl sulfoxide (**1a**) was commercially available. A mixture of phenyl (*E*)- and (*Z*)-1-propenyl sulfoxides **1b** was prepared according to the procedure reported by Craig et al.[8] 1-Methylethenyl phenyl sulfoxides (**1c**)[9] and phenyl 1-phenylethenyl sulfoxide (**1d**)[10] were prepared by the $NaIO_4$ oxidation of the corresponding sulfides, which were obtained according to the procedure reported by us.[4a] **1c**: R_f 0.44 (1:1 EtOAc−hexane); IR (neat) 1632, 1048 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 2.73 (3H, d, J = 1.6 Hz), 5.60 (1H, d, J = 1.6 Hz), 6.02 (1H, s), 7.3−7.8 (5H, m). **1d**: R_f 0.30 (1:3 EtOAc−hexane); IR (neat) 1614, 1575, 1051 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ 5.73 (1H, s), 6.10 (1H, s), 6.9−7.45 (10H, m).

2-(Diethylamino)-1,1-bis(phenylthio)ethane (3a). To a stirred solution of EtMgBr (6 mmol) in Et_2O (8 mL) at 0 °C under argon was added diethylamine (**2a**) (0.88 g, 12 mmol), and the mixture was heated at reflux temperature for 1 h. After cooling to 0 °C, phenyl vinyl sulfoxide (**1a**) (0.15 g, 1 mmol) was added. The mixture was warmed to room temperature and stirring was continued overnight. The resulting mixture was quenched with aqueous NH_4Cl and extracted with Et_2O three times. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the crude product was purified by preparative TLC on SiO_2 to give **3a** (0.13 g, 79%) as a yellow oil: R_f 0.47 (1:5 EtOAc−hexane); IR (neat) 1592, 1478, 1438, 1384, 1154, 1068, 1025, 748, 691 cm^{-1}; ^{1}H NMR (CCl_4, 60 MHz) δ 0.93 (6H, t, J

(7) (a) The clear addition of the amide **7** to the vinyl sulfoxide **1** may be explained by a six-membered ring intermediate. (b) The addition of **7** to the sulfonium ion **9** did not occur, most probably due to the steric hindrance of **7**. (c) Only a trace amount of the symmetrical dithioacetal **3a** was obtained in each reaction. This indicates that the rate of addition of the thiolate anion to **9** was much faster than that of formation of the β-aminoalkyl sulfide **11**, the interaction of which with **9** leads to **3a**.

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= 7.2 Hz), 2.56 (4H, q, J = 7.2 Hz), 2.80 (2H, d, J = 6.8 Hz), 4.33 (1H, t, J = 6.8 Hz), 7.05−7.65 (10H, m); MS (rel intensity) m/z 317 (M^+, 1.4), 208 (8.0), 86 (100). Anal. Calcd for $C_{18}H_{23}NS_2$: C, 68.09; H, 7.30; N, 4.41; S, 20.20. Found: C, 67.86; H, 7.35; N, 4.39; S, 19.97.

Compounds **3b**−**f**, **4**, and **5** were prepared following the above-mentioned procedure. Spectral and analytical data of these products are as follows.

2-(Diisopropylamino)-1,1-bis(phenylthio)ethane (3b): R_f 0.43 (1:10 EtOAc−hexane); IR (neat) 1583, 1474, 1438, 1384, 1363, 1209, 1166, 1066, 1025, 742, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.95 (12H, d, J = 6.9 Hz), 2.94 (2H, d, J = 6.9 Hz), 2.95−3.1 (2H, m), 4.43 (1H, t, J = 6.9 Hz), 7.2−7.3 (6H, m), 7.4−7.5 (4H, m); MS (rel intensity) m/z 236 [(M − SPh)$^+$, 6.3], 235 (6.3), 114 (100). Anal. Calcd for $C_{20}H_{27}NS_2$: C, 69.51; H, 7.88; N, 4.05; S, 18.56. Found: C, 69.28; H, 8.02; N, 4.25; S, 18.30.

2-(*N*-Benzyl-*N*-methylamino)-1,1-bis(phenylthio)ethane (3c): R_f 0.33 (1:30 EtOAc−hexane); IR (neat) 1582, 1493, 1479, 1453, 1438, 1025, 737, 692 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 2.22 (3H, s), 2.80 (2H, d, J = 6.8 Hz), 3.53 (2H, s), 4.43 (1H, t, J = 6.8 Hz), 7.05−7.55 (15H, m); MS (rel intensity) m/z 365 (M, 0.67), 218 (40), 134 (100). Anal. Calcd for $C_{22}H_{23}NS_2$: C, 72.29; H, 6.34; N, 3.83; S, 17.54. Found: C, 72.15; H, 6.36; N, 3.61; S, 17.30.

2-(Diethylamino)-1,1-bis(phenylthio)propane (3d): R_f 0.31 (1:10 EtOAc−hexane); IR (neat) 1582, 1478, 1438, 1383, 1068, 1024, 743, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.93 (6H, t, J = 7.3 Hz), 1.26 (3H, d, J = 6.5 Hz), 2.4−2.7 (4H, m), 3.16 (1H, dq, J = 6.8, 6.5 Hz), 4.53 (1H, d, J = 6.8 Hz), 7.15−7.3 (6H, m), 7.35−7.45 (4H, m); MS (rel intensity) m/z 221 [(M − PhSH)$^+$, 8.0], 100 (100). Anal. Calcd for $C_{19}H_{25}NS_2$: C, 68.83; H, 7.60; N, 4.23; S, 19.34. Found: C, 68.67; H, 7.47; N, 4.22; S, 19.45.

1-(Phenylthio)-2-propanone (4).[11] Spectroscopic data of this product were identical with the literature values reported by Bordwell et al.[11b]

1-(Diethylamino)-2,2-bis(phenylthio)propane (3e): R_f 0.38 (1:10 EtOAc−hexane); IR (neat) 1582, 1473, 1438, 1059, 1024, 749, 703, 692 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.95 (6H, t, J = 7.2 Hz), 1.27 (3H, s), 2.69 (4H, q, J = 7.2 Hz), 2.79 (2H, s), 7.1−7.3 (6H, m), 7.4−7.6 (4H, m); MS (rel intensity) m/z (%) 331 (M^+, 8.0), 222 (59), 86 (100). Anal. Calcd for $C_{19}H_{25}NS_2$: C, 68.83; H, 7.60; N, 4.23; S, 19.34. Found: C, 68.69; H, 7.55; N, 4.17; S, 19.05.

3-(Diethylamino)-2-(phenylthio)propene (5): R_f 0.24 (1:10 EtOAc−hexane); IR (neat) 1608, 1583, 1475, 1439, 1384, 1067, 748, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.02 (6H, t, J = 7.4 Hz), 2.56 (4H, q, J = 7.4 Hz), 3.21 (2H, s), 4.81 (1H, s), 5.33 (1H, s), 7.25−7.4 (3H, m), 7.45−7.5 (2H, m); MS (rel intensity) m/z 253 (M^+, 54), 150 (100). Anal. Calcd for $C_{13}H_{19}NS$: C, 70.54; H, 8.65; N, 6.33; S, 14.48. Found: C, 70.31; H, 8.70; N, 6.39; S, 14.19.

2-(Diethylamino)-1-phenyl-1,1-bis(phenylthio)ethane (3f): R_f 0.31 (1:10 EtOAc−hexane); IR (neat) 1581, 1479, 1439, 1205, 899, 747, 689 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.78 (6H, t, J = 7.2 Hz), 2.30 (4H, q, J = 7.2 Hz), 3.16 (2H, s), 6.85−7.7 (15H, m); MS (rel intensity) m/z 284 [(M − SPh)$^+$, 4.8], 256 (13), 110 (33), 77 (100). Anal. Calcd for $C_{24}H_{27}NS_2$: C, 73.24; H, 6.91; N, 3.56; S, 16.29. Found: C, 73.11; H, 6.70; N, 3.57; S, 16.36.

1-[(4-Chlorophenyl)thio]-2-(diethylamino)-1-(phenylthio)ethane (6a). A solution of 4-chlorobenzenethiol (0.43 g, 3 mmol) in Et_2O (5 mL) was added slowly to a stirred solution of the (diethylamino)magnesium reagent, prepared in situ from EtMgBr (6 mmol) and diethylamine (12 mmol) in Et_2O (8 mL) under the same conditions as described above, at 0 °C under argon. After stirring for 30 min, phenyl vinyl sulfoxide (**1a**) (0.15 g, 1 mmol) was added at the same temperature. The resulting reaction mixture was then allowed to warm to room temperature and stirred overnight. Workup and subsequent purification of the crude product were carried out in a similar fashion as above to give **6a** (0.22 g, 63%) as a yellow oil: R_f 0.31 (1:10 EtOAc−hexane); IR (neat) 1582, 1573, 1475, 1438, 1387, 1094, 1025, 1013, 824, 746, 691 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.93 (6H, t, J = 7.2 Hz), 2.54 (4H, q, J = 7.2 Hz), 2.78 (2H, d, J = 6.4 Hz), 4.29 (1H, t, J = 6.4 Hz), 7.0−7.5 (9H, m); MS (rel intensity) m/z 242 [(M − SPh)$^+$, 0.24], 208 (0.6), 144 (2.7), 86 (100). Anal. Calcd for $C_{18}H_{22}ClNS_2$: C, 61.43; H, 6.30; Cl, 10.07; N, 3.98; S, 18.22. Found: C, 61.43; H, 6.19; Cl, 9.90; N, 3.90; S, 18.39.

1-(Benzylthio)-2-(diethylamino)-1-(phenylthio)ethane (6b) was prepared following a procedure similar to that described above for the preparation of **6a**: R_f 0.42 (1:5 EtOAc−hexane); IR (neat) 1601, 1583, 1494, 1478, 1453, 1438, 1069, 750, 693 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ 0.87 (6H, t, J = 7.2 Hz), 2.42 (4H, q, J = 7.2 Hz), 2.70 (2H, d, J = 6.2 Hz), 3.87 (1H, t, J = 6.2 Hz), 3.90 (2H, s), 7.0−7.5 (10H, m); MS (rel intensity) m/z 331 (M^+, 0.27), 274 (0.93), 220 (0.59), 209 (1.2), 110 (1.4), 91 (14), 86 (100). Anal. Calcd for $C_{19}H_{25}NS_2$: C, 68.83; H, 7.60; N, 4.23; S, 19.34. Found: C, 68.57; H, 7.68; N, 4.35; S, 19.11.

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