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An Efficient and Odorless Synthesis of Thioethers Using 2-[Bis(alkylthio)methylene]-3-oxo-*N*-*o*-tolylbutanamides as Thiol Equivalents

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Using 2-[bis(alkylthio)methylene]-3-oxo-*N*-*o*-tolylbutanamides **1** as odorless thiol equivalents, an efficient and odorless synthesis of thioethers has been developed. Promoted by NaOH in EtOH, the cleavage of **1** commences to generate thiolate anions, and the generated thiolate anions then react with halides to give various thioethers in good yield. It is noteworthy that only a very faint odor of thiols can be perceived during both the reaction and the workup.

Keywords α-oxo-ketene dithioacetals, odorless thiols equivalents, thioethers, halides

Introduction

The synthesis of thioethers has received more and more attention because of their useful applications as key reagents in organic synthesis,[1] bio-organic[2] and heterocyclic chemistry.[3] Various methods for their synthesis are available in the literature.[4] Among these methods, the most convenient and direct method involves the conversion of thiols to thioethers.[4] However, the thiols, in particular those with low molecular weight, used in the conversion are odorous, harmful, highly volatile and flammable, which can make serious environmental and safety problems. Thus, from the green chemistry point of view, an efficient and odorless procedure involving an environmentally friendly reagent for the synthesis of thioethers is of great importance and necessity. Recently, some efforts have been made to develop odorless synthesis of thioethers by several research groups. Node and co-workers[5] reported the reaction of alkyl halides and odorless 4-(trimethylsilyl)benzenethiol or [4-(trimethylsilyl)phenyl]methanethiol to give thioethers. Zhan *et al.*[6] described an odorless synthesis of allyl thioesters using odorless diaryl disulfides as thiol equivalents. Wang *et al*.[7] reported direct α-sulfenylation reaction of aldehydes/ketones and faint smelling *N*-(phenylthio)phthalimide catalyzed by pyrrolidine trifluoromethanesulfonamide. However, multi-step process of preparation, high cost of catalysts and toxicity of some precursors limit the practical application of those odorless thiol or sulfides as thiol equivalents.

As a part of our program to explore the application of α-oxo-ketene dithioacetals in organic synthesis, we recently initiated an investigation of α-oxo-ketene dithioacetals as odorless thiol equivalents to develop an environmental-responsible chemical method. We had found that various types of α-oxo-ketene dithioacetals could be used in thioacetalization,[8] thia-Michael additions[9] and synthesis of substituted dihydro-1,4-dithiins and dihydro-1,4-dithiepins[10] as non-thiolic and odorless thiol equivalents under acidic conditions. More recently, our work had revealed that thia-Michael reactions of α,β-unsaturated carbonyl compounds[11] and the thiolysis of 1,2-epoxides[12] could be achieved using 2-[bis(alkylthio)methylene]-3-oxo-*N*-*o*-tolyl-butanamides **1** as odorless thiol equivalents in the presence of NaOH in EtOH at room temperature (Scheme 1).

Compounds **1** were easily prepared from 3-oxo-*N*-*o*-tolylbutanamide (**2**), CS_2 and alkyl haildes in the presence of K_2CO_3 at room temperature in excellent yields[13] and easily cleaved to generate thiolate anions and compound **2** in the presence of NaOH in EtOH at room temperature, which is starting material for preparing compounds **1**, and can be simultaneously recovered from the reaction system in high yields (Scheme 1). It is worth noting that **1** are all odorless yellow solids and perfectly stable in open air. In extension of our research on the applications of compounds **1** as odorless thiol equivalents, we investigated the synthesis of thioethers using compounds **1** as odorless thiol equivalents under basic conditions.

Results and Discussion

According to our previous experiment,[11,12] we selected NaOH as catalysis and EtOH as reaction medium to investigate the synthesis of thioethers in our present work. The reaction of **1a** and 2-bromo-1-phenylethanone (**3a**) was chosen as a model reaction (Scheme

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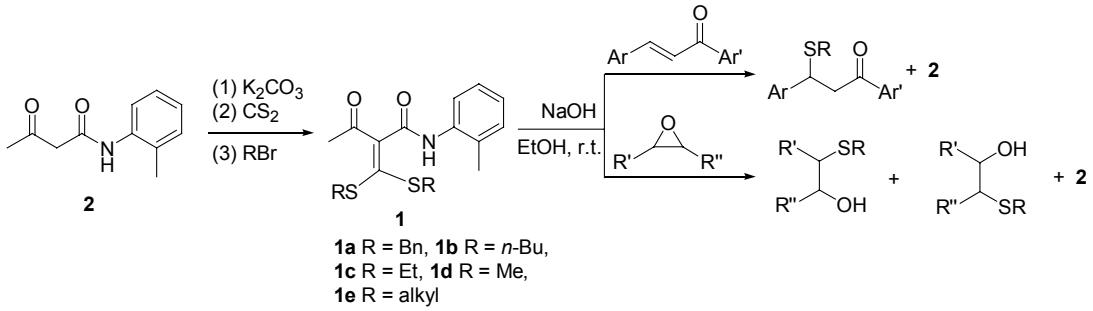
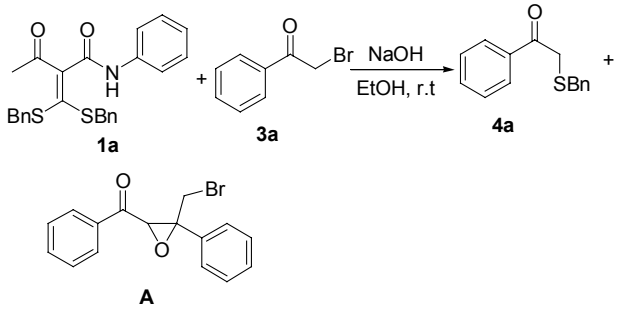
Scheme 1 Michael addition and thiolysis using **1** as odorless thiol equivalents



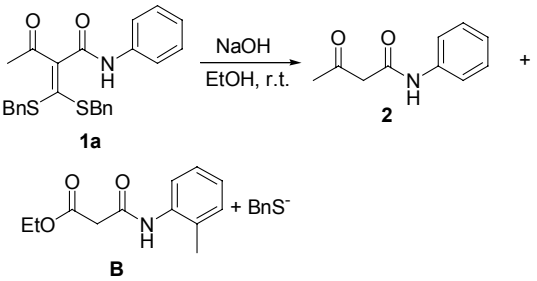
2). In a preliminary experiment, when the mixture of **1a** (1.0 mmol), **3a** (2 mmol) and NaOH (4.0 mmol) in EtOH (5 mL) was stirred at room temperature for 1 h, [3-(bromomethyl)-3-phenyloxiran-2-yl](phenyl)methanone (**A**), which is the product of the self-condensation of **3a**, was only obtained in nearly quantitative yield,[14] and desired product **4a** was not observed in the reaction. However, much to our delight, when **3a** (2 mmol) was added in one portion after **1a** (1.0 mmol) was treated with NaOH (4.0 mmol) in EtOH (5 mL) for 0.5 h, after which time cleavage of **1a** occurred to entirely generate benzyl sulfhydrate anion as monitored by TLC, desired product **4a** was efficiently obtained in 90% isolated yield and compound **2** was simultaneously recovered in 91% yield.

Scheme 2 Nucleophilic substitution reaction of **1a** and **3a**



To test the effect of amount of NaOH on the cleavage of **1a**, a range of reactions were performed under different conditions, and some results are summarized in Table 1. Apparently, the amount of NaOH has a dramatic influence on the cleavage of **1a** to give benzyl sulfhydrate anoin. It was found that increasing the molar ratio of NaOH/**1a** from 1∶1 to 3∶1 remarkably accelerated the cleavage of **1a** (Table 1, Entries 1—3), while further elevating the ratio slightly improved the cleavage velocity of **1a** (Table 1, Entries 4 and 5), which indicates that the perfect ratio can be obtained when the cleavage of **1a** is proceeded with a 3∶1 molar ratio of NaOH/**1a**. In addition, from the system, besides compound **2**, byproduct ethyl 3-(*o*-toluidino)-3-oxopropanoate (**B**) was obtained in low yield.

Table 1 The influence of the amount of NaOH on the cleavage of **1a**[a]



Entry	*n*(NaOH)∶*n*(**1a**)	Time/h	Yield of **2**[b]/%	Yield of **B**[b]/%
1	1∶1	10	85	11
2	2∶1	2	86	9
3	3∶1	0.75	90	7
4	4∶	0.5	91	7
5	5∶:1	0.4	87	10

[a] Conditions: **1a** (1.0 mmol), EtOH (5 mL), 25 ℃. [b] Isolated yields.

On the basis of above experimental results along with our early studies,[11,12] the optimized reaction conditions were achieved, namely, reaction was carried out at room temperature, EtOH was used as the reaction medium, the feed molar ratio of NaOH/**1** was 3∶1, and the halides were added in one portion after the compounds **1** were thoroughly converted into compound **2** with the release of thiolate anions. Taking these optimized conditions, the scope of the procedure for the preparation of thioethers was then examined and the results were listed in Table 2. Compounds **1** could be used as diversified odorless thiol equivalents such as benzyl mercaptan, *n*-butyl mercaptan, ethanethiol, methane thiol and allyl mercaptain (Table 2, Entries 1—5) in the reaction. The reaction of **1** with *α*-brominated carbonyl compounds **3a**—**3d** rapidly offered the corresponding *α*-sulfenylated carbonyl compounds **4a**—**4k** in excellent yields (Table 2, Entries 1—11). However, when the reaction time was prolonged, the yields of **4a**—**4k** decreased due to generating complicated byproducts. In a similar fashion, with halohydrocarbons such as 1-(bromomethyl)-4-*tert*-butylbenzene (**3e**), 3-bromo-2-methylprop-1-ene (**3f**), 1-bromopropane (**3g**)

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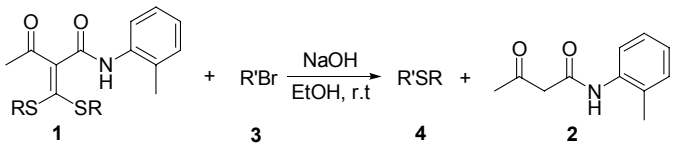
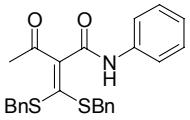
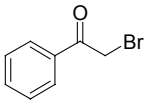
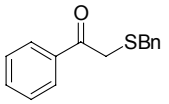
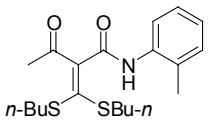
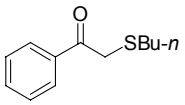
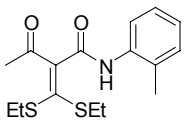
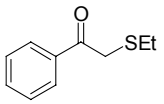
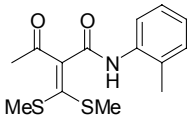
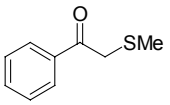
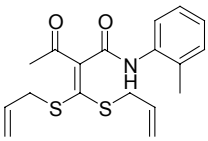
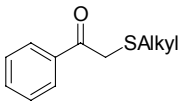
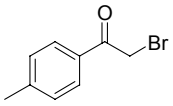
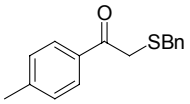
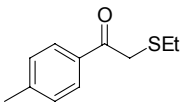
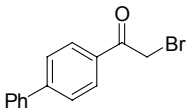
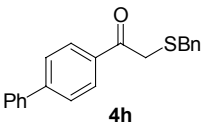
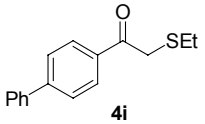
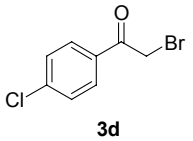
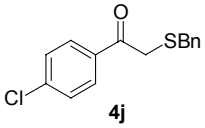
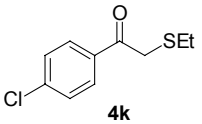
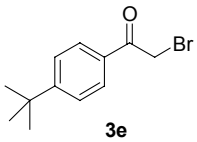
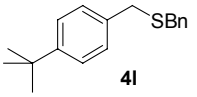
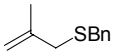
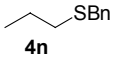
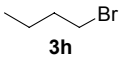
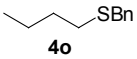
and 1-bromobutane (**3h**), thioether **4l**—**4o** were efficiently synthesized in good yields (Table 2, Entries 12—15). It is noteworthy that only a very faint odor of thiols can be perceived during both the reaction and the workup. Moreover, 3-oxo-*N*-*o*-tolylbutanamide **2** can be recovered in high yields in all cases.

Table 2 Preparation of thioethers using **1** as odorless thiol equivalents[a]



Entry	1	3	4	Yield of 4[b]/%	Yield of 2[b]/%
1	 **1a**	 **3a**	 **4a**	94	90
2	 **1b**	**3a**	 **4b**	92	89
3	 **1c**	**3a**	 **4c**	94	90
4	 **1d**	**3a**	 **4d**	91	92
5	 **1e**	**3a**	 **4e**	92	93
6	**1a**	 **3b**	 **4f**	95	90
7	**1c**	**3b**	 **4g**	91	89
8	**1a**	 **3c**	 **4h**	93	91
9	**1c**	**3c**	 **4i**	92	90

Continued

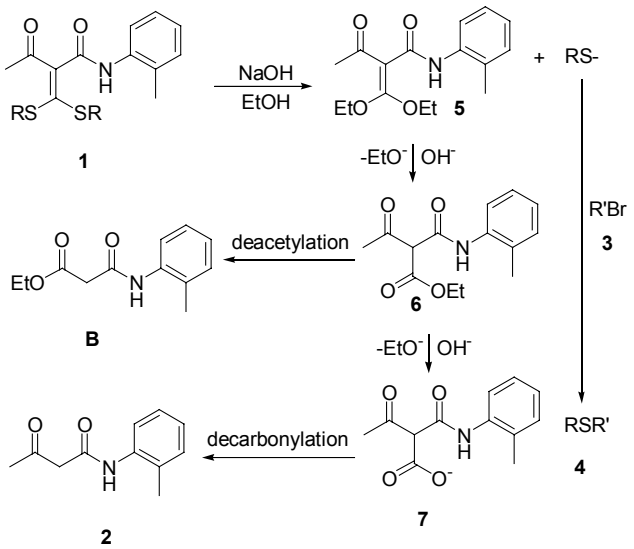
Entry	1	3	4	Yield of 4[b]/%	Yield of 2[b]/%
10	**1a**	 **3d**	 **4j**	94	93
11	**1c**	**3d**	 **4k**	95	90
12	**1a**	 **3e**	 **4l**	90	89
13	**1a**	 **3f**	 **4m**	87	91
14	**1a**	 **3g**	 **4n**	83	90
15	**1a**	 **3h**	 **4o**	88	90

[a] Conditions: **1** (1.0 mmol), **3** (2 mmol), NaOH (3.0 mmol), EtOH (5 mL), 25 ℃, 1 h. [b] Isolated yield.

On the basis of the above results along with our previous work,[11,12,15] a mechanism for the synthesis of thioethers **4** using **1** as odorless thiol equivalents is proposed. As discribed in Scheme 3, in the present of NaOH in EtOH, compound **1** is converted into 2-(diethoxymethylene)-3-oxo-*N*-*o*-tolylbutanamide (**5**) with the release of a thiolate anion via nucleophilic vinylic substitution processes. Further attack by OH^- on **5** results in the intermediate **6** and then **7**. **6** undergoes decarbonylation to afford **B**, while **7** occurs deacetylation to give **2**. The *in situ* thiolate anions perform necleophilic substitution reaction to halides **3** to afford corresponding thioethers **4a**—**4o**.

In conclusion, we have developed an efficient and odorless synthesis of thioethers using odorless and stable 2-[bis(alkylthio)methylene]-3-oxo-*N*-*o*-tolylbutanamides **1** as thiol equivalents. The procedure is characterized by odorlessness, simplicity and high yields.

Scheme 3 A proposed mechanism for the preparation of **4** using **1** as odorless thiol equivalents



Experimental

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 ℃ on a Varian NMR spectrometer at 500 MHz and 125 MHz, respectively, using TMS as internal standard. IR spectra were measured on a PE-2400 analyzer (Perkin-Elmer). Elemental analyes were measured on a PE-24 analyzer (PerkinElmer).

General procedure for the synthesis of thioethers using 2-[bis(alkylthio)menthyl-ene-3-oxo-*N*-*o*-tolylbutanamides 1 as odorless thiol equivalents

A mixture of **1** (1.0 mmol) and NaOH (3 mmol) in EtOH (99.5%, 5 mL) was stirred at room temperature for about 50 min, after which time the cleavage of **1** was completed to entirely generate thiolate anion. The halide (2.0 mmol) was then added in one portion. This reaction was completed as indicated by TLC. The resulting mix-

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ture was neutralized with aq. HCl (0.1 mol•L^{-1}, 10 mL), and extracted with Et_2O (15 mL×3). The combined organic extracts were washed with H_2O (15 mL×3), dried over $MgSO_4$, filtered and concentrated *in vacco*. Separation was carried out over silica gel chromatography (eluent: Et_2O-petroleum ether, V∶V=1∶30) to give a pure product **4**. **4a**—**4e**,[12] **4g** and **4k**,[16] **4m**,[17] **4n**, **4g**, **4o**, **4h** and **B**[18] are known compounds, and their spectroscopic data (NMR) and elemental analyses are in good agreement with those reported in literatures.

2-(Benzylthio)-1-*p*-tolylethanone (**4f**): White solid, m.p. 61—63 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.42 (s, 3H), 3.66 (s, 2H), 3.76 (s, 2H), 7.25—7.26 (m, 3H), 7.30—7.35 (m, 4H), 7.83—7.84 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 23.5, 37.5, 40.2, 126.8, 128.3 (2C), 128.6 (2C), 129.1 (2C), 129.6 (2C), 133.1, 137.2, 140.3, 193.0; IR (KBr) v: 3051, 2926, 1665, 1603, 1558, 1279 cm^{-1}. Anal. calcd for $C_{16}H_{16}OS$: C 74.96, H 6.29; found C 74.83, H 6.37.

2-(Benzylthio)-1-(4-phenylphenyl)ethanone (**4h**): White solid, m.p. 108—110 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.70 (s, 2H), 3.78 (s, 2H), 7.27 (m, 1H), 7.33 (t, J=7.5 Hz, 2H), 7.37—7.41 (m, 3H), 7.47—7.50 (t, J=7.5 Hz, 2H), 7.63 (d, J=8 Hz, 2H), 7.68 (d, J=8 Hz, 2H), 8.01 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 35.58, 35.85, 127.00, 127.03 (2C), 127.06 (2C), 128.05, 128.30 (2C), 128.72 (2C), 129.05 (2C), 129.07 (2C), 133.78, 137.03, 139.54, 145.78, 198.76; IR (KBr) v: 3065, 2921, 1672, 1604,1559, 1450, 1194 cm^{-1}. Anal. calcd for $C_{21}H_{18}OS$: C 79.21, H 5.70; found C 79.35, H 5.61.

1-(4-Phenylphenyl)-2-(ethylthio)ethanone (**4i**): White solid, m.p. 75—77 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.29 (t, J=14.5 Hz, 3H), 2.62 (q, J=14.5 Hz, 2H), 3.83 (s, 2H), 7.39—7.42 (m, 1H), 7.46—7.49 (m, 2H), 7.63 (dd, J=8.5, 3.5 Hz, 2H), 7.70 (d, J=8 Hz, 2H), 8.06 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 13.9, 26.1, 36.5, 127.0 (4C), 128.0, 128.7 (2C), 129.2 (2C), 133.6, 139.6, 145.8, 193.9; IR (KBr) v: 3055, 2926, 1665, 1604, 1420, 1283 cm^{-1}. Anal. calcd for $C_{16}H_{16}OS$: C 74.96, H 6.29; found C 74.85, H 6.31.

2-(Benzylthio)-1-(4-chlorophenyl)ethanone (**4j**): White solid, m.p. 85—87 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.60 (s, 2H), 3.74 (s, 2H), 7.26—7.27 (m, 1H), 7.32—7.34 (m, 4H), 7.43 (d, J=8 Hz, 2H), 7.86 (d, J=8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 35.5, 35.8, 127.1, 128.3 (2C), 128.7 (2C), 129.0 (2C), 129.9 (2C), 133.4, 136.8, 139.5, 192.9; IR (KBr) v: 3067, 2923, 1672, 1584, 1453, 1271 cm^{-1}. Anal. calcd for $C_{15}H_{13}ClOS$: C 65.09, H 4.73; found C 65.21, H 4.64.

(4-*tert*-Butylbenzyl)(benzyl)sulfane (**4l**): Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.36 (s, 9H), 3.61 (s, 2H), 3.65 (s, 2H), 7.25—7.27 (m, 1H), 7.34—7.39 (m, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 31.7 (3C), 34.8, 35.5, 35.9, 125.7 (2C), 127.3, 128.8 (2C), 129.0 (2C), 129.4 (2C), 135.4, 138.6, 150.1; IR (KBr) v: 3060, 2962, 1683, 1540, 1419, 1235 cm^{-1}. Anal. calcd for $C_{18}H_{22}S$: C 79.94, H 8.20; found C 79.81, H 8.27.

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