Efficient Condensation between Glyoxal Hydrates and Sulfonium Salts Leading to Highly Functionalized 1,4-Diketones

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Received 4 May 2008

Abstract: α-Alkylthio-substituted α,β-unsaturated 1,4-dicarbonyl compounds with three different functionalities are easily available through condensation of sulfonium salts and various aromatic or aliphatic glyoxal hydrates catalyzed by Na_2SeO_3 or a combination of selenium dioxide and Na_2CO_3.

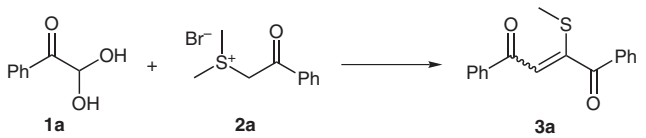
Key words: alkenes, catalysis, condensation, sulfur, selenium

α-Alkylthio-substituted α,β-unsaturated 1,4-dicarbonyl compounds are useful building blocks in the field of chemical synthesis.[1] Attractively, this trifunctional-substituted alkenes allow access to a range of potential building blocks through further selective transformations.[2] For example, such compounds have been used to synthesize substituted furans[1a,c] and 1,4-dicarbonyl compounds.[1b] Two other procedures are known to prepare this type of compounds. One method based on the oxidation of acetophenones using DMSO, CuO, and I_2 can only lead to symmetric diaryl 1,4-diketones.[3] The other method is photoaddition of 1,2-diketones and phenylglyoxal to alkylthioacetylenes, which are difficult to prepare.[1c] Herein, we report a new and efficient reaction to synthesize α-alkylthio-substituted α,β-unsaturated 1,4-dicarbonyl compounds from sulfonium salts and various glyoxal hydrates catalyzed by SeO_2 and Na_2CO_3. It is noteworthy that Na_2SeO_3 or a combination of SeO_2 and Na_2CO_3 serve as a condensation catalyst for the first time.

Several bases (10 mol%) were tested in the reaction of phenyl glyoxal hydrate (**1a**) with dimethyl phenacyl sulfonium bromide (**2a**) in the presence of selenium dioxide (5 mol%) in dry acetonitrile at room temperature. Strong inorganic bases such as Na_2CO_3, K_2CO_3, Cs_2CO_3, and NaOH are more reactive than weak bases such as NaOAc, $NaHCO_3$ (entries 1–6, Table 1). Using Na_2SeO_3 alone can also catalyze the condensation reaction to produce **3a** in 71% yield (entry 7, Table 1). Considering the milder conditions of Na_2CO_3 and SeO_2, we chose them as catalysts for the condensation, although NaOH and SeO_2 gave similar yield (entry 4, Table 1).

Next, the effect of the molar ratio of SeO_2 to Na_2CO_3 on the yield was investigated and is presented in Figure 1. The highest yield was achieved for 4 mol% of SeO_2 and 10 mol% of Na_2CO_3 (entry 9, Table 1). The use of a higher or lower amount of SeO_2 gave lower chemical yields (entry 10, 11, Table 1). In contrast, without SeO_2 the reaction was far from complete (<1% yield) even after 72 hours in the presence of 10 mol% Na_2CO_3 (entry 8, Table 1). A decrease in the amount of base (Na_2CO_3, 5 mol%) reduced the efficiency of the reaction (entry 12, Table 1). When phenyl glyoxal hydrate (**1a**) was replaced by phenyl glyoxal, the reaction was completed within two hours, with a decreased yield (entry 13, Table 1). When water (1.0 equiv) was added, fair yield was obtained with a prolonged reaction time (entries 14, Table 1). This suggests that small amount of water is needed in the conden-

Table 1 Optimization Studies for the Reaction of Phenyl Glyoxal Hydrate (**1a**) with Dimethyl Phenacyl Sulfonium Bromide (**2a**) Catalyzed by Bases and SeO_2[9]



Entry	Base (mol%)	SeO_2 (mol%)	Time (h)	Yield (%)[a]	*Z*/*E*[a]
1	Na_2CO_3 (10)	5	7	77	2.3:1
2	Cs_2CO_3 (10)	5	6	64	1.5:1
3	K_2CO_3 (10)	5	7	71	2.0:1
4	NaOH (20)	4	6	79	1.6:1
5	NaOAc (10)	5	24	71	1.5:1
6[b]	$NaHCO_3$ (20)	5	45	74	2.0:1
7	Na_2SeO_3 (10)	0	4	71	2.6:1
8	Na_2CO_3 (10)	0	72	0	
9[b]	Na_2CO_3 (10)	4	4	81	1.3:1
10	Na_2CO_3 (10)	1	12	58	2.7:1
11	Na_2CO_3 (10)	20	24	35	2.3:1
12	Na_2CO_3 (5)	5	24	73	1.5:1
13[b,c]	Na_2CO_3 (10)	4	2.5	51	1.3:1
14[b,d]	Na_2CO_3 (10)	5	30	53	1.9:1

[a] Yields and isomer ratios determined by HPLC.
[b] Isolated yields, and isomer ratios determined from isolated products.
[c] Using phenyl glyoxal instead of phenyl glyoxal hydrate (**1a**).
[d] Water (1 equiv) was added.

SYNLETT 2008, No. 15, pp 2317–2320
Advanced online publication: 21.08.2008
DOI: 10.1055/s-2008-1078267; Art ID: W07308ST

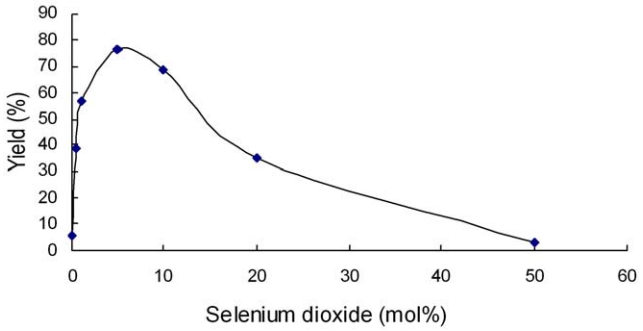


Figure 1 Yields of the reactions between **1a** and **2a** in the presence of SeO_2 (0–50 mol%) and Na_2CO_3 (10 mol%) in MeCN for 12 h

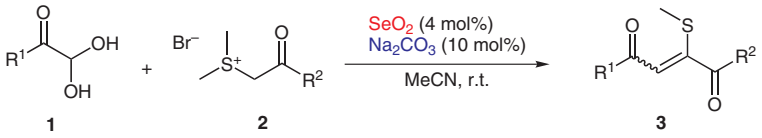
sation to generate hydroxide from Na_2SeO_3, and beneficial to the catalytic reaction.

In order to expand the scope of the catalytic reaction, the condensation between substituted sulfonium salts (**2a–g**, Table 2) and substituted glyoxals (**1a–f**, Table 2) were also examined using the optimized conditions. As shown in Table 2, a variety of aromatic and heteroaromatic substituted carbonyl sulfonium salts reacted readily with **1a** in dry acetonitrile catalyzed by SeO_2 and Na_2CO_3 to afford the corresponding compound **3** in good to high yields (entries 1–5, Table 2). Aliphatic substituted sulfonium salts did not react with **1a** to give the desired products (entry 6, Table 2), which is probably due to the slightly weaker acidity of the aliphatic substituted sulfonium salts. Both aromatic and aliphatic glyoxal hydrates readily reacted with the sulfonium salts to give the corresponding products in good yields. However, the aliphatic glyoxal hydrate (**1e**) was less reactive than the aromatic ones and longer reaction time was needed (entry 11, Table 2), probably due to the electron-donating nature of the alkyl group attached to the carbonyl group of the glyoxal. Double bond and ester groups are tolerated under these conditions (entries 3, 7, 8, 12, Table 2).

Counterions of the sulfoniums were found to have a profound effect on the yields and the configurations of the products as shown in Table 3. Sulfonium salt **2h** (X = Cl) condensed with **1a** gave **3a** in only 34% yield with the worst *Z*/*E* selectivity (entry 1, Table 3). For **2i** (X = I), the yield of **3a** was slightly lower (66%) than for **2a** (X = Br) and it had better *Z*/*E* selectivity (entry 3, Table 3). When dipropyl phenacyl sulfonium bromide (**2j**) was treated with **1a**, (*Z*,*E*)-1,4-diphenyl-2-propylsulfanyl-but-2-ene-1,4-dione (**3m**) was obtained in 81% yield (entry 4, Table 3). For methyl propyl phenacyl sulfonium bromide (**2k**), a mixture of **3a** and **3m** was obtained in 68% yield (**3m/3a** ca. 3:1, entry 5, Table 3).

With cyclosulfonium salts, a similar pattern of condensation and dealkylation was followed. Dealkylation resulted in the fission of the rings, leading to the more functionalized α-alkylthio-substituted α,β-unsaturated 1,4-dicarbonyl compounds. Sulfonium salt **2l** (X = Cl) gave **3n** in 73% yield, (entry 6, Table 3). In the case of **2n** (X = I), **3p** was formed in only 6% yield (entry 9, Table 3), probably due to the ring closure of product **3p** to form the polar vi-

Table 2 Scope of the Reaction of the Glyoxal Hydrate (**1**) with the Sulfonium Salt **2** Catalyzed by SeO_2 and Na_2CO_3[9]

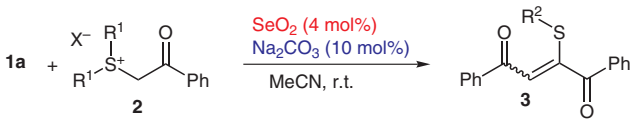


1 2 3

Entry	R^1	1	R^2	2	Time (h)	3	Yield (%)[a]	*Z*/*E*[b]
1	Ph	**1a**	Ph	**2a**	4.5	**3a**	81	1.3:1
2	Ph	**1a**	4-FC_6H_4	**2b**	2.5	**3b**	79	1.8:1
3	Ph	**1a**	4-$AcOC_6H_4$	**2c**	2	**3c**	79	1.6:1
4	Ph	**1a**	2-MeO-C_6H_4	**2d**	15	**3d**	77	1.0:1
5	Ph	**1a**	2-furyl	**2e**	4	**3e**	72	1.8:1
6	Ph	**1a**	*t*-Bu	**2f**	40	**3f**	0	
7	Ph	**1a**	Styryl	**2g**	2	**3g**	66	3.3:1
8	4-$AcOC_6H_4$	**1b**	Ph	**2a**	10	**3h**	72	1.4:1
9	4-FC_6H_4	**1c**	4-FC_6H_4	**2b**	3	**3i**	85	1.9:1
10	2-furyl	**1d**	Ph	**2a**	9	**3j**	58	1.6:1
11	*t*-Bu	**1e**	Ph	**2a**	30	**3k**	80	2.8:1
12	Styryl	**1f**	Ph	**2a**	2	**3l**	34	1.5:1

[a] Isolated yields.
[b] Isomeric ratios determined from isolated products.

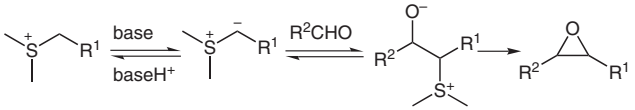
Table 3 Reactions of Phenyl Glyoxal Hydrate (**1a**) with (Cyclo)sulfonium salts **2** Catalyzed by SeO_2 and Na_2CO_3[9]



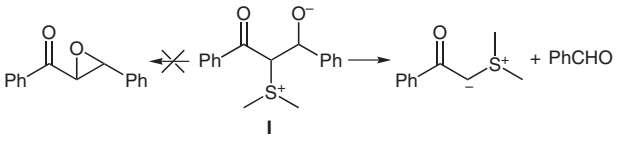
Entry	X	R^1	**2**	Time (h)	R^2	**3**	Yield (%)[a]	*Z*/*E*[b]
1	Cl	Me	**2h**	11	Me	**3a**	34	1.8:1
2	Br	Me	**2a**	4	Me	**3a**	81	2.3:1
3	I	Me	**2i**	1.1	Me	**3a**	66	3.2:1
4	Br	Pr	**2j**	7	Pr	**3m**	81	1.7:1
5[c]	Br	Pr (Me)	**2k**	6	Pr (Me)	–[c]	68	1.5:1
6	Cl	$(CH_2)_4$	**2l**	17	$(CH_2)_4Cl$	**3n**	73	1.0:1
7	Br	$(CH_2)_4$	**2m**	12	$(CH_2)_4Br$	**3o**	50	2.2:1
8[d]	Br	$(CH_2)_4$	**2m**	30	$(CH_2)_4Br$	**3o**	43	2.0:1
9	I	$(CH_2)_4$	**2n**	2	$(CH_2)_4I$	**3p**	6	4.6:1
10	Br	$(CH_2)_5$	**2o**	13	$(CH_2)_5Br$	**3q**	50	1.4:1
11	Br	$(CH_2)_6$	**2p**	20	$(CH_2)_6Br$	**3r**	56	1.9:1

[a] Isolated yields.
[b] Isomeric ratios determined from isolated products.
[c] For methyl propyl phenacyl sulfonium bromide (**2k**), a mixture of **3a** and **3m** was obtained.
[d] Catalyzed by Na_2SeO_3 (10 mol%) alone.

nyl sulfonium salt during purification. When sulfoniums **2m**, **2o**, and **2p** (X = Br) were, respectively, condensed with **1a**, the corresponding products were obtained in fair yields (entries 7, 8, 10, 11, Table 3). These types of compounds are more functionalized than those accessible from current procedures,[1c,3] and are potentially useful for building multifunctionalized medium-sized thioether rings via an intramolecular reaction.



Scheme 1 General mechanism for the sulfur ylide epoxidation reaction via a betaine intermediate



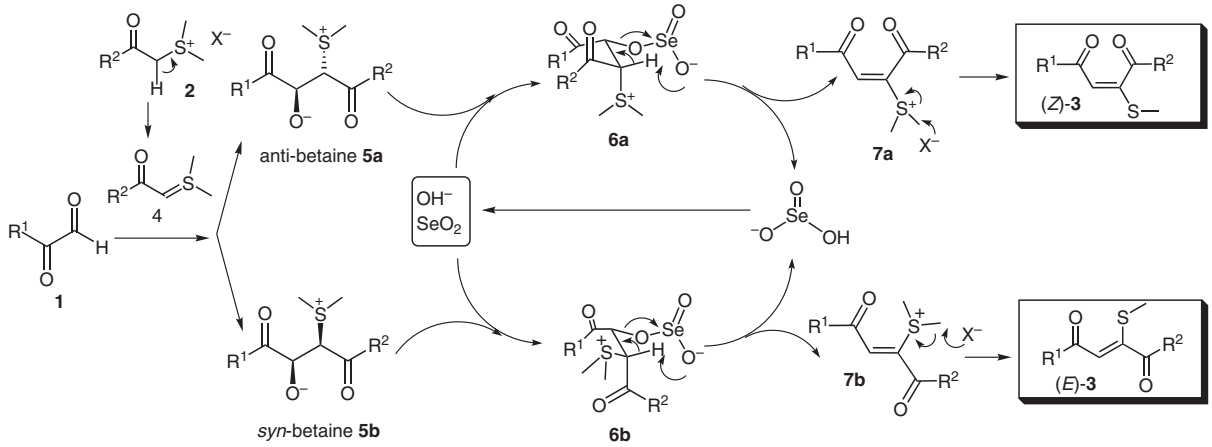
Scheme 2 Decomposition of betaine **I** from stable ylide[8]

It is known that sulfonium ylides react with aldehydes to give epoxides via betaine intermediates[4] (Scheme 1). It has also been reported that the formation of betaines from stabilized ylides is reversible.[5] In addition, stabilized sulfur ylides, such as dimethylsulfonium phenacylide (R^1 = PhCO) react only with the very electrophilic carbonyl centres of α,β-diketones[6] and aromatic aldehydes[7] to form corresponding epoxides.

An early report also demonstrated that, following its independent generation, betaine **I** decomposes to give only benzaldehyde and the stabilized ylide (R^1 = PhCO), the epoxide is not formed (Scheme 2).[8] Thus, while it is clear that the betaine formed upon reaction of aldehydes with nonstabilized sulfur ylides undergoes elimination of sulfide faster than it reverts to ylide and aldehyde, it is difficult for the betaine from a stable ylide to undergo elimination of sulfide. In fact, without SeO_2, neither epoxide nor expected olefin was formed in our experiments (entry 8, Table 1).

Based on these facts, a plausible reaction mechanism is proposed in Scheme 3. The sulfonium salt **2** is deprotonated by the hydroxide or the basic salt (Na_2SeO_3) to generate the sulfur ylide **4**, which then attack the phenyl glyoxal (**1**) to give the *anti*- or *syn*-betaine intermediates **5a** or **5b**. Since these betaine intermediates cannot eliminate sulfide immediately, **5a** and **5b** could then react with selenium dioxide to give the intermediates **6a** and **6b**, respectively, which release hydrogenselenite ion via a six-membered cyclic transition state to give **7a** and **7b** followed by the products (*Z*/*E*)-**3**. The released hydrogenselenite ion can then regenerate the hydroxide ion and selenium dioxide.

In conclusion, we have developed a simple and efficient procedure to produce α-alkylthio-substituted α,β-unsaturated 1,4-dicarbonyl compounds in good to high yields from glyoxal hydrates and sulfonium salts catalyzed by a



Scheme 3 Plausible mechanism of Na_2SeO_3 (SeO_2 and Na_2CO_3)-catalyzed condensation of sulfonium salt and glyoxal hydrate

combination of SeO_2 and Na_2CO_3 or mineral salt Na_2SeO_3. The reaction conditions are milder than the procedures reported before. Additionally, to our knowledge, this is the first use of selenium dioxide or sodium selenite as a condensation catalyst.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank NSFC (20572078) and TMSTC (05YFGPGX07500) for financial support.

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(9) **Typical Procedure for Preparing Compound 3**
A mixture of **1a** (152 mg, 1.0 mmol), **2a** (261 mg, 1.0 mmol), SeO_2 (4.4 mg, 0.04 mmol), and Na_2CO_3 (10.6 mg, 0.1 mmol) in MeCN (10 mL) was stirred for 4.5 h at r.t. After complete consumption of starting material (TLC), MeCN was removed in vacuum to give yellow syrup. The residue was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (10 mL) and dried over anhyd Na_2SO_4. The extracts were then concentrated under reduced pressure, and the residue was purified by column chromatography (eluent: PE–EtOAc) on SiO_2 to give an 81% yield of **3a** [(*Z*)-**3a**, 129 mg; (*E*)-**3a**, 100 mg].
Compound (*Z*)-**3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.5 Hz, 2 H), 7.95 (d, *J* = 8.5 Hz, 2 H), 7.69–7.44 (m, 6 H), 7.10 (s, 1 H), 2.17 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.9, 188.2, 160.6, 137.8, 134.9, 134.8, 132.7, 130.0, 129.1, 128.6, 128.1, 116.0, 15.4. IR (KBr): ν = 2926, 1670, 1635, 1596, 1537, 1246, 1023, 699 cm^{-1}.
Compound (*E*)-**3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 2 H), 7.89 (d, *J* = 8.0 Hz, 2 H), 7.57–7.43 (m, 6 H), 7.04 (s, 1 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.7, 185.1, 160.8, 137.2, 134.9, 133.6, 133.0, 128.8, 128.7, 128.6, 128.4, 115.8, 14.9. IR (KBr): ν = 3413, 1674, 1637, 1540, 1220, 781, 703, 632 cm^{-1}. Spectral data were in agreement with those previously reported.[3]