Pergamon

Tetrahedron 56 (2000) 6541–6548

TETRAHEDRON

Regiospecific Synthesis of α-Diones, α,α-Dialkoxyketones and α-Alkoxy-α-sulfenylated Ketones

Kourosch Abbaspour Tehrani,[a,†] Marc Boeykens,[a] Vladimir I. Tyvorskii,[b] Oleg Kulinkovich[b] and Norbert De Kimpe[a,*]

[a]*Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, University of Gent, Coupure Links 653, B-9000 Gent, Belgium*

[b]*Department of Chemistry, Belarussian State University, Fr. Scorina Avenue 4, 220050 Minsk, Belarus*

Dedicated to Professor Dr Richard Neidlein on the occasion of his 70th birthday

Received 6 March 2000; revised 13 June 2000; accepted 29 June 2000

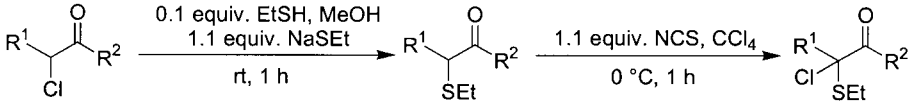
Abstract—A convenient synthesis of α-diones and their monoprotected acetals, i.e. α-ketoacetals, was developed by mercury induced solvolysis of regiospecifically formed α-chloro-α-(alkylthio)ketones. Analogously, α-alkoxy-α-sulfenylated ketones were formed when reacting α-chloro-α-sulfenylated ketones with an alkaline alcoholic medium. α-Alkoxy-α-sulfenylated ketones themselves could be transformed into α-diones or α-ketoacetals, which in turn were hydrolyzed under anhydrous conditions into the corresponding α-diones.

Introduction

The chemistry of α-diones thus far has always been the subject of intense research efforts. Undoubtedly this is due to their synthetic potential and the numerous applications associated with their chemistry.[1] As a consequence, α-diones and their protected forms have enjoyed a similar pronounced attention. In the food industry α-diones are used as a synthetic flavor additive of candies, ice cream and pudding because of their characteristic sweet and butter-like flavor. Despite the wealth of synthetic methodologies available, ready access to α-diones and their monoprotected forms, especially in a regiospecific way, remains problematic. Here we would like to report a more general convenient synthesis of the title compounds in a short and efficient way.

Results and Discussion

For the synthesis of α-diones and monoprotected derivatives, α-chloroketones **1** were used as starting material. The regiospecific α-chlorination of ketones is a difficult problem, but is overcome by a method disclosed recently, avoiding a direct chlorination of the parent ketone.[2] α-Chloroketones **1** can be generated conveniently (multigram scale) in a regiospecific way via a strategy involving alkylation of methyl acetoacetate, monochlorination and subsequent demethoxycarbonylation.[2] Starting from these α-chloroketones **1**, the α-chloro-β-ketosulfides **3** were synthesized for further solvolysis reactions (Scheme 1). The presence of chlorine and sulfur, attached to the same carbon, generates a reactive intermediate which offers



1a $R^1 = R^2 = Me$
1b $R^1 = Et$, $R^2 = Me$
1c $R^1 = Me$, $R^2 = Et$
1d $R^1 = n\text{-Bu}$, $R^2 = Me$

2a-d (71 - 94 %)

3a-d (quant.)

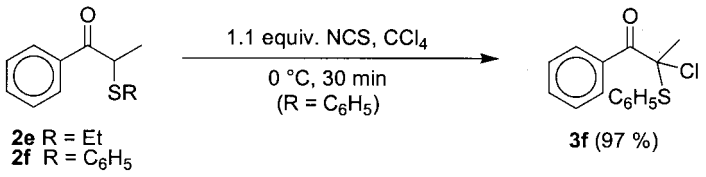
Scheme 1.

Keywords: α-diones; solvolysis; ketoacetals.

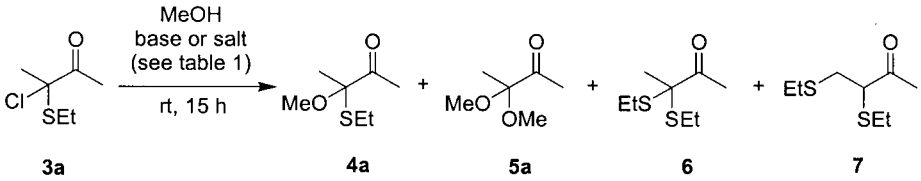
* Corresponding author. Tel.: +32-9-264-59-51; fax: +32-9-264-62-43; e-mail: norbert.dekimpe@rug.ac.be

† Postdoctoral Fellow of the F.W.O.-Flanders (Belgium).

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00604-9



Scheme 2.



Scheme 3.

Table 1. Behavior of 3-chloro-3-(ethylthio)-2-butanone **3a** under different types of solvolysis conditions in methanol (all reactions were performed in absolute methanol at room temperature for a period of 15 h; the figures illustrate the relative amount of each compound obtained in % (^{1}H NMR and GC))

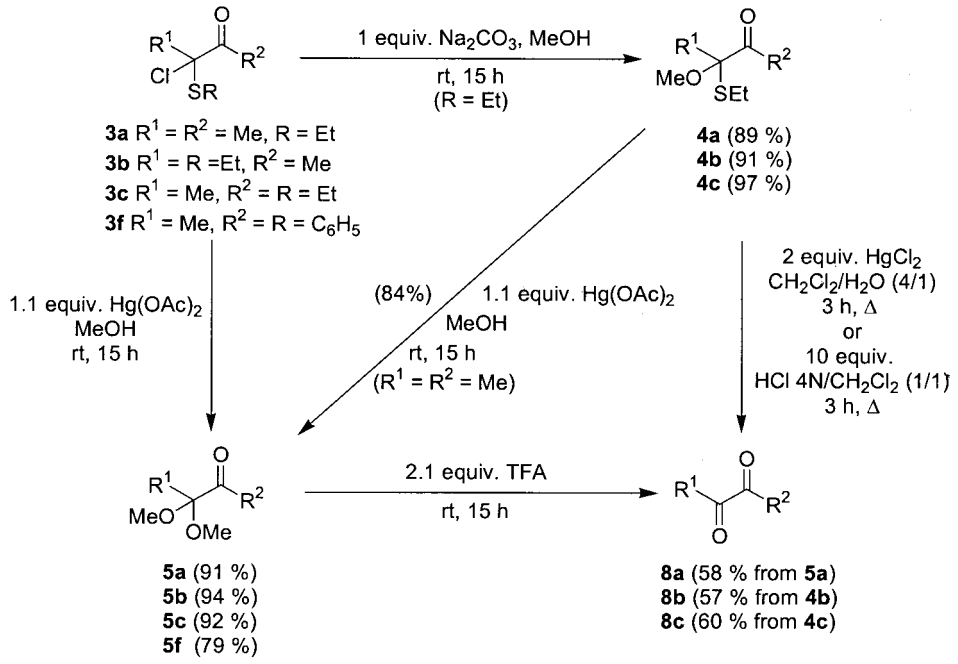
Entry	Reaction conditions	4a	5a	6	7
1	1 equiv. Na_2CO_3	94	6		
2	3 equiv. NaOMe 2 M	94	6		
3	2 equiv. $Pb(OAc)_2$	48	13	7	
4	2 equiv. $Cu(OAc)_2$	22	37	6	
5	1 equiv. Ag_2CO_3	24	68	8	
6	1.1 equiv. $Hg(OAc)_2$		100		
7	MeOH neat		52	38	10

several attractive features. This effect is even more pronounced in the vicinity of a carbonyl group.

Substitution of the α-chloro atom of compounds **1** with sodium ethylthiolate in methanol is an obvious choice for the synthesis of the corresponding α-sulfenylated ketones **2a–d**. The reaction is well known and can be performed according to a general procedure.[3] It proceeds smoothly to give the α-sulfenylated ketones **2a–d** in 71–94% yield. Initially, the chlorination of 3-(ethylthio)-2-butanone **2a** was executed using sulfuryl chloride in carbon tetrachloride.[4,5] The reaction proceeded rapidly and cleanly, but the corresponding α-chlorosulfide **3a** did not withstand an aqueous workup. Chlorination was further executed using *N*-chlorosuccinimide in the same solvent.[4] Under these conditions, α-chlorosulfides **3** can be obtained as relatively pure (purity >95%) yellow oils after filtration of succinimide and evaporation of the solvent in vacuo. In all cases, these α-chlorosulfides were used as such in the following solvolysis reactions. The α-chloro-β-ketosulfides **3** can themselves be regarded as monoprotected, but reactive and thus unstable forms of α-diones. 3-Chloro-3-(ethylthio)-2-butanone **3a** decomposed quite readily even when stored at low temperature (−20°C) while none of the α-chlorosulfides **3** was stable at room temperature for a long period of time. For the same reason, this methodology could not be applied to aromatic α-chloro-α-(ethylthio)-ketones. When treating 2-(ethylthio)-1-phenyl-1-propanone **2e** with *N*-chlorosuccinimide in carbon tetrachloride, elimination of hydrogen chloride was already observed even before the chlorination was completed (Scheme 2). α-Chlorosulfides of type **3a–d** are of limited occurrence. Only compound **3a** was prepared before as a mixture (purity 72%) resulting from the reaction of ethanesulfenyl chloride and 2,2,2,4,5-pentamethyl-1,3,2λ^5-dioxaphosphole.[6] 3-Chloro-3-(methylthio)-2-pentanone was reported as an intermediate for the synthesis of the corresponding 3-(methylthio)-3-penten-2-one.[7] It is worth noting that the presence of an asymmetric center causes the methylene protons adjacent to sulfur to be diastereotopic and therefore to appear as a somewhat more complex AB×q spin system (ABX-splitting) in ^{1}H NMR. More common and easy to handle are these α-chlorosulfides, bearing an aryl group on sulfur or α-chlorosulfides derived from α-ketoaldehydes (monoprotected at the aldehyde function).[8] In accordance with these findings, α-bromo propiophenone was substituted with sodium phenylthiolate to give compound **2f**. The increase in electron withdrawing effect of the aromatic substituent then indeed allowed the chlorination of the sulfenylated aromatic ketone to give rise to 2-chloro-2-(phenylthio)propiophenone **3f** (Scheme 2).

In a next stage, the exact reaction conditions for the solvolysis of the sulfur and/or chloro substituent were determined. α-Acetoxy-β-ketosulfides[9] and especially α-chloro-β-ketoselenides[10] were evaluated before in a related way. The results obtained for α-chlorosulfides, however, are scattered throughout the literature and in most cases are limited to one or a restricted class of compounds. 3-Chloro-3-(ethylthio)-2-butanone **3a** was used as a test substrate to examine the influence of different solvolysis conditions on the reaction course.

The results of these experiments are summarized in Scheme 3 and Table 1. In the presence of sodium carbonate[11] or sodium methoxide in methanol (entries 1 and 2), the α-chloro atom is selectively replaced by the solvent to afford 3-(ethylthio)-3-methoxy-2-butanone **4a** in 94% yield. Using mercuric acetate, a metal ion induced solvolysis of both the chloro atom and the sulfur substituent was achieved with complete selectivity (entry 6), affording α-ketoacetal **5a** quantitatively.[12] On the basis of these promising results, α-chlorosulfides **3b,c** were also treated



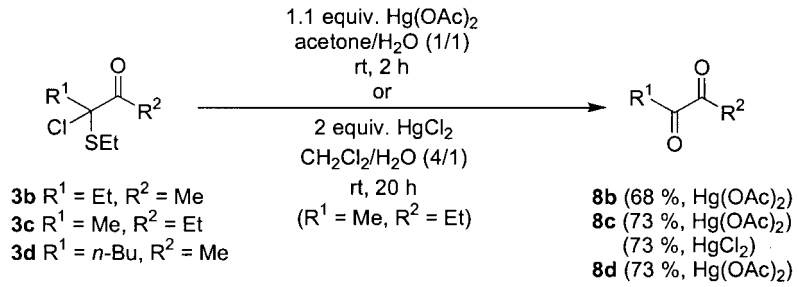
Scheme 4.

with both sodium carbonate and mercuric acetate in methanol to give the corresponding hemithioacetals **4** (89–97%) and α-ketoacetals **5** (79–94%) (Scheme 4). Also for the aromatic ketone **3f** the solvolysis proceeds nicely giving 2,2-dimethoxypropiophenone **5f** as the sole product (Scheme 4). Thus, it seems that the α-chloro-α-(ethyl- or phenylthio)ketones lend themselves perfectly for the α-alkoxylation process put forward. As α-chlorosulfides, they are rapidly ionized, leaving behind a sulfur stabilized α-acyl carbenium ion, which is trapped by a solvent molecule in a S_N1-reaction. The resulting α-methoxy-α-(ethylthio)ketone is then isolated as such or reacts further in the presence of Hg^{2+}-ions via an oxygen stabilized α-acyl carbenium ion (push and pull mechanism) to form the corresponding α-ketoacetal **5**. The latter is shown clearly by the solvolysis of 3-(ethylthio)-3-methoxy-2-butanone **4a** to 2,3-butanedione monodimethyl acetal **5a** in methanol in the presence of $Hg(OAc)_2$. Important is that other metal ions with a high affinity for chlorine and/or sulfur, such as Pb^{2+}, Cu^{2+} or Ag^{+} ions, only lead to less attractive results. In these cases the sulfur substituent is not scavenged completely and interferes on adding to the intermediate carbenium ion, generating the dithioacetal **6**. The relative amounts of ketoacetal **5a** and dithioacetal **6** formed (Table 1, entries 3–6) nicely reflect the 'soft acid character' of the metal ion concerned. The metal–sulfur complexation is a soft acid–soft base interaction and increases from Pb^{2+} over Cu^{2+} and Ag^{+} to Hg^{2+}. The same interaction is also illustrated by the solubility constants of the corresponding sulfides, decreasing in the same order.

Divergent from a mechanistic viewpoint is the reaction of 3-chloro-3-(ethylthio)-2-butanone **3a** with methanol itself, without added base or heavy metal salt. Next to S_N1, the formation of hydrogen chloride also occurs on dehydrochlorination. While it is not neutralized or trapped by a metal ion, it creates a more acidic environment. In turn, relatively more free ethanethiol is generated via a S_NlcA process. In the presence of the α-sulfenylated-α,β-unsaturated ketone formed, Michael addition occurs, leading to the vicinal disulfide **7**. Under these conditions, thioacetalization to afford compound **6** is also a substantial process.

The regiospecificity of the synthesis described here originates from the α-chloroketones **1**, which themselves can be generated in a regiospecific way. Combined with the straightforward action of the different reactions involved, it enables the regiospecific synthesis of the title compounds **4** and **5** starting from α-chloroketones **1** with the same carbon skeleton. No rearrangements, either intramolecular or via an elimination–addition sequence, are involved. However, conversions of α-chloro-α-phenylthio aldehydes to α-methoxy-α-phenylthio ketones in the presence of sodium methoxide have been reported in literature.[8e,16] Somewhat surprisingly, looking at their relatively simple structure, all three mixed acetals **4a–c** are reported here for the first time. Thus far, the synthesis and hydrolysis of hemithioacetals derived from aliphatic and aromatic aldehydes has been emphasized.[13] Most commonly known is the (methylthio)methyl ether protective group.

Having in hand some monoprotected forms of α-diones, attempts were made for their transformation (deprotection) into the parent α-dicarbonyl compounds **8**. Aqueous hydrolysis of α-ketoacetals **5a–c** could not be established in a selective way as for the aromatic compound **5f**.[14] In all three cases the corresponding α-diones were obtained in a more or less complicated reaction mixture. In the presence of 2N hydrogen chloride (5 equiv.) and dichloromethane as a second phase, 2,2-dimethoxy-3-pentanone **5c** was hydrolyzed after 1 h at reflux to afford a reaction mixture consisting of 2,3-pentanedione **8c** (73%) and starting acetal **5c** (27%). On prolonged heating (3 h at reflux) the reaction mixture became complicated substantially. Performing the



Scheme 5.

hydrolysis at room temperature, a slower but analogous reaction course was observed. Stirring for one day yielded a reaction mixture of 2,3-pentanedione **8c** (66%), remaining ketoacetal **5c** (10%) and some unidentified material. Changing the concentration or type of acid (*p*-TsOH/acetone[15]) also was not satisfying. In another approach, the α-ketoacetal **5a** was treated in anhydrous acid conditions by dissolving it in a small excess (2.1 equiv.) of trifluoroacetic acid (TFA). Monitoring the reaction by ^{1}H NMR spectroscopy showed a complete and selective conversion of the starting material into the dione on standing overnight. Next to methyl trifluoroacetate, the α-dione **8a** was formed as the sole product in 58% yield (Scheme 4). The corresponding hemithioacetals **4** seemed more prone to aqueous hydrolysis. Both under acidic conditions (4N hydrogen chloride) and in the presence of mercuric chloride[16] they can be deprotected to the parent α-diones **8** (Scheme 4). Both reactions lead to considerably better results when executed at reflux for a shorter period of time. At room temperature the final result is less attractive. The hydrolysis of α-chlorosulfides for the generation of carbonyl compounds is widespread, decomposing readily in water.[17] Concerning α-dicarbonyl equivalents, this transformation is limited to some cyclic structures and phenylglyoxal.[18] For the desired transformation two necessary conditions are the presence of H_2O and a reagent to sequester the thiol liberated during the reaction. Otherwise, dithioacetal formation next to carbonyl product is a typical undesirable feature.

These requirements are met perfectly by stirring α-chlorosulfides **3b–c** at room temperature in 50% aqueous acetone in the presence of $Hg(OAc)_2$ (Scheme 5). Mercuric chloride in a biphase liquid system of water and dichloromethane also gave satisfactory results (Scheme 5). Under these conditions α-diones **8** were produced nicely without side reactions. Only the aromatic α-chlorosulfide **3f** failed to give the desired outcome.

Experimental

^{1}H NMR spectra were recorded at 60 MHz (JEOL PMX 60 SI) or 270 MHz (JEOL JNM-EX 270) with $CDCl_3$ or C_6D_6 as solvent. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) with $CDCl_3$ or C_6D_6 as solvent. Mass spectra were obtained on a mass spectrometer (VARIAN MAT 112, 70 eV) using a GC-MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas). IR spectra were measured with a Perkin–Elmer 1310 spectrophotometer or a Spectrum One FT-IR. Tetrachloromethane and dichloromethane were dried over calciumhydride. Other solvents were used as received from the supplier.

α-Haloketones **1b**[2], **1c**[2,16] and **1d**[2] were prepared according to a known procedure. 3-Chloro-2-butanone **1a** is commercially available. α-Bromopropiophenone was prepared by the addition of bromine (1 molar equivalent) to a 10% solution of propiophenone in CH_2Cl_2 at room temperature (2 h, yield 95%).

General procedure for the synthesis of α-sulfenylated ketones 2a–f

To an ice cooled solution of 2N sodium methoxide in methanol (82.5 mL, 0.165 mol) was added in one portion ethanethiol (11.18 g, 0.18 mol). After stirring for 10 min, α-haloketones **1** (0.15 mol) were added dropwise in order to ensure a smooth reaction (exothermic reaction!). Already while adding the α-chloroketone **1**, a white precipitate was formed. The suspension was stirred additionally for 1 h, poured into water (250 mL) and extracted with dichloromethane (4×80 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo. Small amounts of diethyl disulfide present were removed by distillation or evaporation in high vacuum, resulting in α-sulfenylated ketones as colorless or yellow oils (purity >95%). Distillation or evaporation in high vacuum of the β-ketosulfides formed is advisable in order to remove traces of diethyl disulfide, the presence of which is difficult to avoid. Simple disulfides, such as diethyl disulfide, are known to react with *N*-chlorosuccinimide (vide infra).[19] This way, it can impede a correct analysis of the reaction course of the chlorination reaction, easy to monitor by ^{1}H NMR spectroscopy.

3-(Ethylthio)-2-butanone 2a. Compound **2a** was obtained as a yellow oil in 94% yield. This compound has been synthesized before, however no spectra have been published.[20a,b] For the sake of completeness spectroscopic data are reported here. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.22 (3H, t, J=7.4 Hz, SCH_2CH_3); 1.39 (3H, d, J=7.2 Hz, CH_3CH); 2.28 (3H, s, CH_3CO); 2.38–2.51 (2H, m, SCH_2); 3.37 (1H, q, J=7.2 Hz, CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.45 (CH_2CH_3); 15.87 (CH_3CH); 24.10 (CH_3CO); 25.50 (CH_2); 48.21 (CH); 205.50 (C=O). IR (NaCl, cm^{-1}): ν=1709 (C=O). MS (70 eV) *m/z* (%): 132(M^+; 35); 91(5); 89(100); 72(8); 61(57); 59(7); 55(5); 45(5); 43(20).

3-(Ethylthio)-2-pentanone 2b. Compound **2b** was obtained

as a light yellow oil in 81% yield; bp 70–74°C/15 Torr. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.3 Hz, SCH_2CH_3); 1.21 (3H, t, J=7.4 Hz, CH_3CH_2); 1.68 (1H, d×q, J=7.3, 22.0 Hz, $CH_3C(H)H$); 1.83 (1H, d×q, J=7.4, 22.0 Hz, $CH_3C(H)H$); 2.27 (3H, s, CH_3CO); 2.35–2.51 (2H, m, SCH_2); 3.13 (1H, t, J=7.6 Hz, CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 12.00 (SCH_2CH_3); 14.47 (CH_3CH_2); 23.38 (CH_3CO); 24.24; 25.71; 55.78 (CH); 205.22 (C=O). IR (NaCl, cm^{-1}): ν=1702 (C=O). MS (70 eV) m/z (%): 146(M^+; 27); 105(5); 103(100); 86(6); 75(26); 73(3); 71(4); 61(19); 59 (3); 47(9); 45(6); 43(22); 41(25). Anal. Calcd for $C_7H_{14}OS$: C 57.49%; H 9.65%. Found: C 57.63%; H 9.76%.

2-(Ethylthio)-3-pentanone 2c. Compound **2c** was obtained as a light yellow oil in 79% yield; bp 59–62°C/12 Torr. Lit. bp 72–73°C/11 Torr.[20a] ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.03 (3H, t, J=6.9 Hz, $COCH_2CH_3$); 1.17 (3H, t, J=7.5 Hz, CH_3CH_2S); 1.34 (3H, d, J=6.9 Hz, $CHCH_3$); 2.22–2.82 (4H, m, SCH_2 and CH_2CH_3); 3.32 (1H, q, J=6.9 Hz, CH). IR (NaCl, cm^{-1}): ν=1705 (C=O).

3-(Ethylthio)-2-heptanone 2d. Compound **2d** was obtained as a yellow oil in 71% yield; bp 87–88°C/12 Torr. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.90 (3H, t, J=6.9 Hz, CH_2CH_3); 1.21 (3H, t, J=7.4 Hz, CH_3CH_2S); 1.38–1.48 (4H, m); 1.52–1.70 (1H, m,); 1.72–1.88 (1H, m,), 2.26 (3H, s, CH_3CO); 2.38–2.51 (2H, m, SCH_2); 3.19 (1H, t, J=7.6 Hz, CH). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.71 (CH_3); 14.29 (CH_3); 22.28 (CH_3CO); 24.24 (CH); 25.43; 29.44; 29.71 (CH_2) 53.96 (CH); 205.43 (C=O). IR (NaCl, cm^{-1}): ν=1705 (C=O). MS (70 eV) m/z (%): 174(M^+; 26); 133(5); 131(97); 114(11); 89(9); 77(5); 75(100); 73(3); 71(7); 69(65); 67(3); 61(8); 60(5); 59(5); 55(6); 47(5); 43(30); 41(19).

2-(Ethylthio)-1-phenyl-1-propanone 2e. Compound **2e** was obtained as a yellow oil in 85% yield. This compound has been synthesized before, however, no spectra have been published.[21] For the sake of completeness spectroscopic data are reported here; bp 146–150°C/15 Torr. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.17 (3H, t, J=7.4 Hz, SCH_2CH_3); 1.57 (3H, d, J=6.9 Hz, CH_3CH); 2.41 (1H, d×q, J=12.1, 7.4 Hz, $SC(H)HCH_3$); 2.56 (1H, d×q, J=12.1, 7.4 Hz, $SC(H)HCH_3$); 4.34 (1H, q, J=6.9 Hz, CH); 7.4–7.6 (3H, m, $=CH_{meta,para}$); 7.99–8.02 (2H, m, $=CH_{ortho}$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 14.32 (SCH_2CH_3); 16.44 (CH_3CH); 22.80 (SCH_2); 41.51 (CH_3CH); 128.53 and 128.57 (2×HC=); 132.94 ($=CH_{para}$); 135.70 (C_{quat}); 196.17 (C=O). IR (NaCl, cm^{-1}): ν=1678 (C=O). MS (70 eV) m/z (%): 194(M^+; 7); 134(85); 133(5); 115(2); 105(86); 89(100); 77(52); 61(22); 59(4); 55(4); 51(13); 45(2).

1-Phenyl-2-(phenylthio)-1-propanone 2f. Compound **2f** was obtained as a yellow oil in 83% yield. The spectrometric data of compound **2f** (bp 126–135°C/0.01 Torr) are in accordance with the literature data.[22] ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.53 (3H, d, J=6.9 Hz, CH_3); 4.62 (1H, q, J=6.9 Hz, CH); 7.2–7.6 (8H, m, SC_6H_5 and $=CH_{meta,para}$); 7.9–8.0 (2H, m, $=CH_{ortho}$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 17.00 (CH_3); 46.13 (CH); 127.42 (C_q); 128.52; 128.59 and 128.88 (3×HC=); 129.02 (C_q); 132.99 ($=CH_{para}$); 134.48 (=CH); 135.65 (C_{quat}); 196.13 (C=O). IR (NaCl, cm^{-1}): ν=1680 (C=O). MS (70 eV) m/z (%): 194(M^+; 7); 134(85); 133(5); 115(2); 105(86); 89(100); 77(52); 61(22); 59(4); 55(4); 51(13); 45(2).

General procedure for the synthesis of α-chloro-α-sulfenylated ketones 3a–d,f

To an ice cooled solution of α-sulfenylated ketones **2** (0.10 mol) in 100 mL of carbon tetrachloride was added *N*-chlorosuccinimide (14.69 g, 0.11 mol). The resulting suspension is stirred for 1 h, filtered and evaporated to give pure α-chloro-α-sulfenylated sulfides in quantitative yield. α-Chloro-α-sulfenylated ketones **3** were used as such in the next step.

3-Chloro-3-(ethylthio)-2-butanone 3a. Compound **3a** was obtained as a yellow oil in quantitative yield. ^{1}H NMR (270 MHz, C_6D_6): δ 0.97 (3H, t, J=7.6 Hz, SCH_2CH_3); 1.79 (3H, s, CH_3CSEt); 2.17 (3H, s, CH_3CO); 2.42 (2H, ~q, J=7.6 Hz, SCH_2CH_3). ^{13}C NMR (68 MHz, C_6D_6): δ 13.46 (SCH_2CH_3); 23.63; 25.44 and 28.30 (CH_3CO and CH_3CSCH_2); 79.69 (CCl); 197.46 (C=O). IR (NaCl, cm^{-1}): ν=1720 (C=O). The lability of this compound did not allow the obtention of correct mass spectra1 data or elementary analyses. Upon GC-MS analysis hydrogen chloride was eliminated yielding the corresponding vinyl sulfide.

3-Chloro-3-(ethylthio)-2-pentanone 3b. Compound **3b** was obtained as a yellow oil in quantitative yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.09 and 1.23 (2×3H, 2×t, J=7.3 Hz and 7.6 Hz, CH_2CH_3 and SCH_2CH_3); 2.1–2.3 (2H, m, CH_2CH_3); 2.41 (3H, s, CH_3CO); 2.5–2.7 (2H, m, SCH_2CH_3). ^{13}C NMR (68 MHz, $CDCl_3$): δ 9.38 and 13.37 (CH_2CH_3 and SCH_2CH_3); 24.22 (CH_3CO); 24.83 and 32.67 (CH_2CH_3 and SCH_2CH_3); 85.01 (CCl); 197.98 (C=O). IR (NaCl, cm^{-1}): ν=1715 (C=O). The lability of this compound did not allow the obtention of correct mass spectral data or elementary analyses. Upon GC-MS analysis hydrogen chloride was eliminated yielding the corresponding vinyl sulfide.

2-Chloro-2-(ethylthio)-3-pentanone 3c. Compound **3c** was obtained as a yellow oil in quantitative yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14 and 1.25 (each 3H, each t, J=7.26 and 7.56 Hz, CH_2CH_3 and SCH_2CH_3); 1.98 (3H, s, CH_3CCl); 2.6–2.7 and 2.7–3.0 (4H, each m, CH_2CH_3 and SCH_2CH_3). ^{13}C NMR (68 MHz, $CDCl_3$): δ 8.77 and 13.46 (CH_2CH_3 and SCH_2CH_3); 25.18, 28.21 and 28.93 (SCH_2, CH_3CCl and $COCH_2$); 78.85 (CCl); 200.70 (C=O).). IR (NaCl, cm^{-1}): ν=1715 (C=O). MS (70 eV) m/z (%): 180/182(M^+; 7); 145(15); 144(8); 123/125(13); 95/7(10); 87(100); 85(10); 83(9); 61(15); 60(90); 59(28); 57(100); 55(20); 45(15); 44(20).

3-Chloro-3-(ethylthio)-2-heptanone 3d. Compound **3d** was obtained as a yellow oil in quantitative yield. ^{1}H NMR (270 MHz, C_6D_6): δ 0.79 and 0.96 (2×3H, 2×t, J=7.25 Hz and 7.59 Hz, $(CH_2)_3CH_3$ and SCH_2CH_3); 1.1–1.5 and 1.5–1.7 (4H, 2×m, $CH_2(CH_2)_2CH_3$); 2.0–2.2 (2H, m, $CClCH_2$), 2.17 (3H, s, CH_3CO); 2.3–2.5 (2H, m, SCH_2CH_3). ^{13}C NMR (68 MHz, C_6D_6): δ 13.42 and 13.91 (SCH_2CH_3 and $(CH_2)_3CH_3$); 22.68; 24.22; 25.16; 27.48 and 39.62 (CH_3CO, SCH_2 and $(CH_2)_3$); 84.82 (CCl); 197.28

(C═O).). IR (NaCl, cm^{-1}): ν=1710 (C═O). MS (70 eV) *m/z* (%): 208/210(M^+, 24); 173(14); 172(16); 165/167(45); 130(62); 103(49); 101(57); 75(45); 67(47); 43(100); 42(27).

2-Chloro-2-(phenylthio)-1-phenyl-1-propanone 3f. The lability of this light brown α-chlorosulfide did not allow its isolation in a pure state. As a result it was used as such in solution after filtering off succinimide.

General procedure for the synthesis of α-(ethylthio)-α-methoxyketones 4a–c

To an ice cooled suspension of sodium carbonate (10.60 g, 0.10 mol) in 150 mL of methanol were added dropwise α-chloro-α-sulfenylated sulfides (**3a–c**, 0.10 mol). After complete addition, the ice bath was removed and the reaction mixture was stirred for 15 h at room temperature. The resulting suspension was poured into water (300 mL) and extracted with dichloromethane (4×60 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo. The residual oils were distilled in vacuo to give pure α-(ethylthio)-α-methoxyketones **4**.

3-(Ethylthio)-3-methoxy-2-butanone 4a. Compound **4a** was obtained as a colorless oil in 89% yield; bp 92–94°C/18 Torr. ^{1}H NMR (60 MHz, CCl_4): δ 1.19 (3H, t, J=7.2 Hz, CH_2CH_3); 1.53 (3H, s, CH_3CCl); 2.19 (3H, s, $COCH_3$); 2.43 (2H, q, J=7.2 Hz, CH_2CH_3); 3.39 (3H, s, OMe). IR (NaCl, cm^{-1}): ν=1715 (C═O). MS (70 eV) *m/z* (%): no M^+; 119(36); 101(15); 91(12); 73(14); 61(5); 60(3); 59(64); 58(3); 57(3); 45(4); 44(3); 43(100); 42(6); 41(4). Anal. Calcd for $C_7H_{14}O_2S$: C 51.82%; H 8.70%. Found: C 51.65%; H 8.76%.

3-(Ethylthio)-3-methoxy-2-pentanone 4b. Compound **4b** was obtained as a colorless oil in 91% yield; bp 100–102°C/16 Torr. ^{1}H NMR (60 MHz, CCl_4): δ 0.77 (3H, t, J=7.2 Hz, CH_3CH_2); 1.17 (3H, t, J=7.3 Hz, SCH_2CH_3); 1.7–2.2 (2H, m, CH_3CH_2); 2.16 (3H, s, $COCH_3$); 2.38 (2H, q, J=7.3 Hz, SCH_2CH_3); 3.34 (3H, s, OMe). IR (NaCl, cm^{-1}): ν=1720 (C═O). MS (70 eV) *m/z* (%): 176 (M^+, 0.2); 145(1); 135(5); 134(7); 133(100); 119(1); 116(2); 115(22); 114(1); 106(1); 105(17); 104(1); 103(1); 101(1); 99(1); 97(1); 87(3); 84(1); 83(1); 77(1); 75(4); 74(2); 73(44); 72(2); 71(5); 69(1); 67(1); 61(3); 59(4); 58(1); 57(2); 56(2); 55(5); 53(1); 49(1; 47(2); 46(1); 45(8); 44(5); 43(95); 42(2); 41(9). Anal. Calcd for $C_8H_{16}O_2S$: C 54.51%; H 9.15%. Found: C 54.69%; H 9.22%.

2-(Ethylthio)-2-methoxy-3-pentanone 4c. Compound **4c** was obtained as a colorless oil in 97% yield; bp 49–51°C/0.1 Torr. ^{1}H NMR (60 MHz, CCl_4): δ 1.03 and 1.17 (6H, each t, each J=7.4 Hz, CH_2CH_3 and SCH_2CH_3); 1.54 (3H, s, CH_3CCl); 2.39 and 2.62 (4H, each q, each J=7.4 Hz, CH_2CH_3 and SCH_2CH_3); 3.37 (3H, s, OMe). IR (NaCl, cm^{-1}): ν=1722 (C═O). MS (70 eV) *m/z* (%): 176 (M^+, 0.5); 145(2); 121(6); 120(8); 119(100); 115(19); 114(4); 91(26); 87(6); 84(3); 83(3); 77(3); 74(1); 73(2); 62(4); 61(6); 60(5); 59(54); 58(6); 57(33); 55(9); 49(2); 47(3); 45(4); 44(10); 43(57). Anal. Calcd for $C_8H_{16}O_2S$: C 54.51%; H 9.15%. Found: C 54.31%; H 9.23%.

General procedures for the synthesis of α,α-dimethoxyketones 5a–c,f

a. Mercury(II) acetate assisted methanolysis of α-chloro-α-sulfenylated ketones 3. To an ice cooled suspension of mercury(II) acetate (35.05 g, 0.11 mol) in 150 mL of methanol was added dropwise the α-chloro-α-sulfenylated ketone **3** (0.10 mol). After complete addition, the ice bath was removed and the reaction mixture was stirred for 15 h at room temperature. The resulting suspension was poured into water (300 mL) and extracted with dichloromethane (4×60 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo. The residual oils were distilled to give pure α,α-dimethoxyketones **5**.

3,3-Dimethoxy-2-butanone ***5a***. (91%) This compound was identical in all aspects (^{1}H NMR, IR, MS) with a commercial sample.[23]

3,3-Dimethoxy-2-pentanone ***5b***. bp 62–65°C/17 Torr (94%). This compound was identical in all aspects (^{1}H NMR, IR, MS) with an authentic sample obtained formerly.[1]

2,2-Dimethoxy-3-pentanone ***5c***. bp 54–57°C/16 Torr (92%). Lit. bp 162.5/760 Torr. This compound was identical in all aspects with a sample obtained formerly.[1]

1-Phenyl-2,2-dimethoxy-1-propanone ***5f***. (79%). This compound was identical in all aspects with a sample obtained formerly.[24]

b. Mercury(II) acetate assisted methanolysis of α-(ethylthio)-α-methoxyketone 4a. To an ice cooled suspension of mercury(II) acetate (1.05 g, 3.3 mmol) in methanol (10 mL) was added dropwise 3-(ethylthio)-3-methoxy-2-butanone **4a** (0.49 g, 3 mmol). After complete addition, the ice bath was removed and the reaction mixture was stirred for 15 h at room temperature. The resulting suspension was poured into water (50 mL) and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated in vacuo to give 3,3-dimethoxy-2-butanone **5a** as a colorless liquid. Yield: 0.33 g (84%).

General procedures for the synthesis of α-diones 8a–c

a. Mercury(II) acetate assisted hydrolysis of α-chloro-α-sulfenylated ketones 3. The solvolysis of 3-chloro-3-(ethylthio)-2-heptanone **3d** is representative. To an ice cooled suspension of $Hg(OAc)_2$ (11.45 g, 36 mmol) in 50% aqueous acetone (100 mL) was added dropwise 3-chloro-3-(ethylthio)-2-heptanone **3d** (6.24 g, 30 mmol) as to ensure a smooth reaction. The reaction mixture was stirred for 2 h at room temperature, neutralized with 5% aqueous $NaHCO_3$ (until neutral or slightly alkaline), filtered and extracted with diethylether (3×40 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo to yield 2.8 g (73%) of 2,3-heptanedione **8d**. If residual mercury salts were present, they could be removed easily by precipitation in pentane at −20°C. The ^{1}H NMR and IR spectra of this compound were identical with the

literature data.[25] The same workup accounts for the other procedures described below.

b. Mercury(II) chloride assisted hydrolysis of α-alkoxy-α-sulfenylated ketones 4b,c. To a mixture of CH_2Cl_2/H_2O (v/v: 4/1) was added $HgCl_2$ (1.63 g, 6 mmol) followed by 2-(ethylthio)-2-methoxy-3-pentanone **4c** (0.53 g, 3 mmol). The reaction mixture was stirred for 3 h at reflux, neutralized with $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated to yield 0.17 g (57%) of 2,3-pentanedione **8b**. Compound **8b** was identical in all aspects (^{1}H NMR, IR, MS) with a commercial sample.[26]

c. Mercury(II) chloride assisted hydrolysis of α-chloro-α-sulfenylated ketones 3b–d. The mercury(II) chloride assisted hydrolysis of 2-chloro-2-(ethylthio)-3-pentanone **3c** (0.53 g, 3 mmol) was performed in the same way as described for 2-(ethylthio)-2-methoxy-3-pentanone **4c**. In this case, the reaction mixture was stirred for 20 h at room temperature. Yield 0.22 g (73%) of α-dione **8c**.

d. Aqueous hydrolysis of α-alkoxy-α-sulfenylated ketones 4. To a biphase liquid system of CH_2Cl_2/4 N HCl (8.5 mL each) was added 2-(ethylthio)-2-methoxy-3-pentanone **4c** (0.53 g, 3 mmol). The suspension was treated in the same way as mentioned in the above procedure b. Yield: 0.18 g (60%).

e. Hydrolysis of α,α-dimethoxyketones 5. 3,3-Dimethoxy-2-butanone **5a** (6.6 g, 0.05 mmol) was dissolved in trifluoroacetic acid (12.54 g, 0.11 mmol) (exotherm reaction). The resulting dark brown solution was stirred at room temperature for 15 h, poured into 5% aqueous $NaHCO_3$, (until neutral or slightly alkaline) and extracted with dichloromethane. The combined organic extracts were filtered and evaporated in vacuo at 0°C to yield 2.50 g (58%) of 2,3-butanedione **8a** as a yellow oil. Before workup, the completion of the reaction can be verified by dissolving a small amount of the reaction mixture in $CDCl_3$. ^{1}H NMR analysis clearly shows the presence of two singlets at δ 2.35 and δ 4.07 belonging to 2,3-butanedione and methyl trifluoroacetate, respectively. Compound **8a** was identical in all aspects (^{1}H NMR, IR, MS) with a commercial sample.[27]

Reaction of 3-chloro-3-(ethylthio)-2-butanone 3a with methanol

3-Chloro-3-(ethylthio)-2-butanone **3a** (0.5 g, 3 mmol) was dissolved in methanol (5 mL) and stirred for 15 h at room temperature. The reaction mixture was then neutralized with a 5% aqueous solution of $NaHCO_3$ and extracted with dichloromethane (3×10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated. The residual oil was subjected to preparative GC showing the reaction mixture to consist of 3,3-dimethoxy-2-butanone **5a** (52%), 3,3-di(ethylthio)-2-butanone **6** (38%) and 3,4-di(ethylthio)-2-butanone **7** (10%).

3,3-Di(ethylthio)-2-butanone 6. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.23 (6H, t, J=7.5 Hz, $(SCH_2CH_3)_2$); 1.75 (3H, s, $CH_3C(SEt)_2$); 2.41 (3H, s, CH_3CO); 2.54 (4H, q, J=7.5 Hz, $(SCH_2CH_3)_2$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 13.73 ($C(SCH_2CH_3)_2$); 23.87 (CH_3CO); 23.94 ($CH_3(SCH_2CH_3)_2$); 23.99 ($CH_3(SCH_2CH_3)_2$); 64.94 ($C(SCH_2CH_3)_2$); 202.41 (C=O). IR (NaCl, cm^{-1}): ν=1705 (C=O). MS (70 eV) m/z (%): 192 (M^+, 0.5); 151(3); 150(3); 149(33); 131(3); 121(2); 103(6); 75(7); 61(9); 60(5); 59(100); 58(4); 47(3); 45(5); 44(2); 43(45); 41(7); 40(7). Anal. Calcd for $C_8H_{16}OS_2$: C 49.96%; H 8.38%. Found: C 49.72%; H 8.49%.

3,4-Di(ethylthio)-2-butanone 7. This compound was isolated as a minor compound (10%) and as such no ^{13}C spectra and elemental analysis have been obtained. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.1–1.5. (6H, ~2×t, 2×CH_2CH_3); 2.33 (3H, s, CH_3CO); 2.3–2.7 (6H, m, CH_2SCH_2 and SCH_2), 3.2–3.7 (1H, m, SCH). IR (NaCl, cm^{-1}): ν=1708 (C=O). MS (70 eV) m/z (%): 192 (M^+, 7); 149(15); 132(8); 131(34); 130(6); 121(4); 101(5); 93(6); 91(4); 90(5); 89(63); 88(57); 87(16); 75(57); 71(20); 62(6); 61(25); 60(40); 59(30); 58(5); 55(10); 47(23); 46(3); 45(11); 44(13); 43(100); 41(7).

Acknowledgements

The authors are indebted to the 'Fund for Scientific Research—Flanders (Belgium)' (F.W.O.-Vlaanderen) and the I.W.T. for financial support.

References

1. For an overview concerning the synthesis and use of α-diones and their protected forms, see: De Kimpe, N.; Stanoeva, E.; Boeykens, M. *Synthesis* **1994**, 427–431.
2. De Kimpe, N.; Brunet, P. *Synthesis* **1990**, 595–596.
3. Horstmann, H. H. Herstellung und Umwandlung von Mercaptoketonen. In *Methoden der Organischen Chemie (Houben-Weyl)*, Müller, E. Ed.; Georg Thieme: Stuttgart, 1977; Vol. 7/2c, pp 2317–2429.
4. Dilworth, B. M.; McKervey, M. A. *Tetrahedron* **1986**, *42*, 3731–3752.
5. Leyendecker, F.; Comte, M.-T. *Tetrahedron Lett.* **1982**, 5031–5034.
6. Harpp, D. N.; Mathiaparanam, P. *J. Org. Chem.* **1972**, *37*, 1367–1374.
7. Iriuchijima, S.; Tanokuchi, K.; Tadokoro, K.; Tsuchihashi, G. *Agric. Biol. Chem.* **1976**, *40*, 1031–1034.
8. (a) Kaydos, J. A.; Smith, D. L. *J. Org. Chem.* **1983**, *48*, 1096–1099. (b) Lee, T. V.; Galan, A. A.; Chapleo, C. B. *Tetrahedron Lett*. **1987**, 2301–3202. (c) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1983**, 117–120. (d) Ishibashi, H.; Ikeda, M. *Rev. Heteroat. Chem.* **1992**, *7*, 191–213. (e) Duhamel, L.; Chauvin, J.; Messier, A. *Tetrahedron Lett.* **1980**, 4171–4174.
9. Buckley, D. J.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2193–2200.
10. Trost, B. M.; Massiot, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 4405–4412.
11. Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900–6902.
12. Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687–4690.
13. (a) Wimmer, P. O/S-Acetale. In *Methoden der Organischen Chemie (Houben-Weyl)*; Hagemann, H., Klamann, D., Eds.; Georg

Thieme: Stuttgart, 1991; Vol. E14a/l, pp 785–831. (b) Jensen, J. L.; Maynard, D. F.; Shaw, G. R.; Smith, T. W., Jr. *J. Org. Chem.* **1992**, *57*, 1982–1986. (c) Satchell, D. P. N.; Satchell, R. S. *Chem. Soc. Rev.* **1990**, *19*, 55–81.
14. De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1978**, *43*, 2933–2935.
15. Muxfeldt, H.; Weigele, M.; Van Rheenen, V. *J. Org. Chem.* **1965**, *30*, 3573–3574.
16. Duhamel, L.; Chauvin, J. *Tetrahedron Lett.* **1982**, 1665–1668.
17. (a) Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261–3264. (b) Mura, A. J.; Majetich, G.; Grieco, P. A.; Cohen, T. *Tetrahedron Lett.* **1975**, 4437–4440.
18. (a) Carre, M. C.; Caubere, P. *Tetrahedron Lett.* **1985**, 3103–3106. (b) Gassman, P. G.; Cue, B. W., Jr.; Tien-Yau, L. *J. Org. Chem.* **1977**, *42*, 1344–1348.
19. Tuleen, D. L.; Stephens, T. B. *J. Org. Chem.* **1969**, *34*, 31–35.
20. (a) Thiel, M.; Asinger, F.; Schäfer, W. *Liebigs Ann. Chem.* **1958**, *613*, 120–127. (b) Rothstein, E.; Stanbank, D. J.; Whiteley, R. *J. Chem. Soc. C* **1968**, 753–760.
21. (a) Nagao, Y.; Kaneko, K.; Fujita, E. *Tetrahedron Lett.* **1978**, 4115–4116. (b) Braun, M. *Tetrahedron Lett.* **1978**, 3695–3698. (c) Liu, Y; Glass, R. S. *Tetrahedron Lett.* **1997**, *38*, 8615–8618.
22. Katritzky, A. R.; Xie, L.; Serduyk, L. *J. Org. Chem.* **1996**, *61*, 7564–7570.
23. Aldrich, product number 34 355-2.
24. De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1980**, *45*, 2803–2813.
25. Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1991**, *56*, 5768–5773.
26. Aldrich, product number 24 196-2.
27. Aldrich, product number B 8 530-2.