Convenient and robust one-pot synthesis of symmetrical and unsymmetrical benzyl thioethers from benzyl halides using thiourea

Kevin S. Eccles,[a] Curtis J. Elcoate,[a] Simon E. Lawrence,[a] and Anita R. Maguire*[b]

[a]Department of Chemistry, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland
[b]Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland
E-mail: a.maguire@ucc.ie

Abstract
A series of symmetrical and unsymmetrical benzyl thioethers have been synthesised using a one-pot reaction from benzyl halides and thiourea. This procedure avoids the isolation or handling of malodorous thiols and generates high yields of benzyl thioethers in excellent purity.

Keywords: Symmetrical and unsymmetrical benzyl thioethers

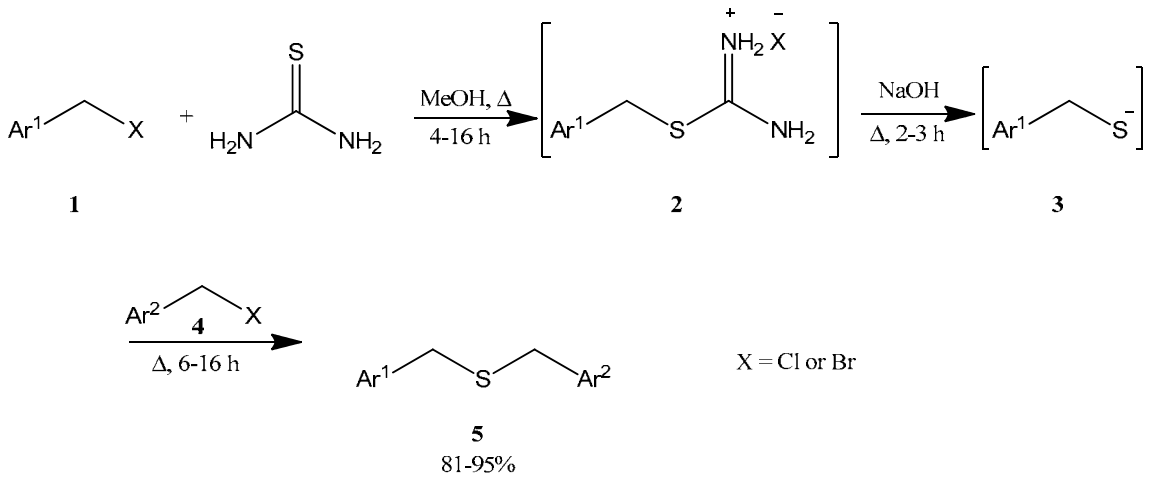
Introduction

Thioethers are useful synthetic intermediates in many aspects of organic and medicinal chemistry, with applications in bio-organic, inorganic, medicinal, heterocyclic synthesis and as key intermediates for the synthesis of biologically active compounds.[1] Generally the synthesis of thioethers employs the condensation of a thiol (or disulfide) with a halide in the presence of a base.[2] This method is robust but requires the handling of malodorous thiols. Novel synthetic methodology for formation of thioethers avoiding the use or intermediate isolation of thiols has clear advantages.

Thiols are generally synthesised from halides using a source of sulfur, typically sodium hydrosulfide or thiourea derivatives.[3,4] Sodium hydrosulfide can also be used for the generation of symmetrical benzyl thioethers but often accessing good quality products with decent yields is challenging using this reagent.[3,4] Reaction of thiourea (and derivatives thereof) with alkyl halides followed by basic hydrolysis and protonation provides thiols. Kajigaeshi and co-workers[5] reported a process whereupon addition of an alkyl halide and an alcohol to tetramethylthiourea in DMF followed by the addition of Na / NaH allows access to both unsymmetrical and symmetrical thioethers (alkyl and benzyl) in moderate to good yields. Emerson and co-workers[6] reported a one-pot reaction for the synthesis of alkyl-thioethers using thiourea but only described

one example with moderate yields (59%). Recently there has been interest in using related procedures for formation of aryl thioethers but these reactions require more forcing conditions such as use of a metal catalyst,[7,8] or photochemical activation.[9] Takido and Itabashi[10] reported the synthesis of unsymmetrical thioethers using a similar process to the one described in this manuscript. However, in their report, the 1-alkylthioethaniminium halide salt of benzyl bromide and thioacetamide is isolated before being reacted with other halides under phase transfer conditions (benzene and aqueous sodium hydroxide) with tetrabutylammonium bromide as the catalyst. This series of reactions generated yields between 77- 100%.

Herein we describe a robust and convenient procedure for the synthesis of not only symmetrical but also unsymmetrical benzyl thioethers in a one pot reaction from halides using thiourea (Scheme 1). It is shown that the isolation of the intermediate thiol or isothiuronium salt is not required, thereby significantly increasing the ease of this synthetic method. Instead the thiolate is generated using one benzyl halide, and reacted *in-situ* with a second benzyl halide, obviating the need for isolation of the malodorous thiol.



Scheme 1

Reaction of the benzyl halide **1** with thiourea affords the isothiuronium salt **2** which upon basic hydrolysis generates the thiolate **3**. This intermediate is further reacted *in situ* with a substituted benzyl halide **4** to generate the benzyl thioether **5**. This process is not limited to symmetrical benzyl thioethers but is readily employed for synthesis of unsymmetrical benzyl thioethers. Extension to alkyl derivatives was briefly explored.

Results and Discussion

Initial experiments were undertaken using benzyl bromide **1a** for formation of the isothiuronium ion **2** and thiolate **3** followed by alkylation with a series of mono-substituted benzyl bromides **4**

leading to a series of known thioethers **5a, b, e, f** which had identical spectroscopic features to those described in the literature. The optimum reaction conditions involve reaction of 1.1 equivalents of thiourea with 1 equivalent of benzyl bromide in refluxing methanol typically overnight, but reactions are generally complete within 3-4 h. Three equivalents of solid sodium hydroxide is then added, followed by further heating under reflux (2-3 h), cooling to room temperature, addition of 0.85 equiv. of the second benzyl halide, then heating under reflux for 8-16 h. Partitioning between aqueous sodium hydroxide and dichloromethane provides the thioethers which, in most instances, were sufficiently pure by ^{1}H NMR to use synthetically. However, for consistency the yields reported in the Table refer to analytically pure samples purified by chromatography. Using the optimised conditions a series of 27 differently substituted benzyl thioethers were produced as summarised in the Table, 16 of which are novel. Methyl, methoxy and chloro substituents in *ortho, meta* or *para* positions and one pyridine derivative were employed with no detectable effect on the efficiency of the process.

The reaction steps proved relatively robust and prolonged heating in methanol for up to 48 h at each step did not have any notable effect on the outcome of the reactions. These reactions can also be carried out in ethanol without any noticeable effects in yield, reaction times or quality of the product (see entries **5b**, **5g**, and **5t**).

During the optimisation process the stoichiometries of **1**, thiourea and **4** were varied in the synthesis of **5k**. It was found that the use of 1 equiv of the electrophile **4** resulted in the presence of unreacted **4,** 4-methylbenzyl bromide, and other side products in the final product **5k**, and, in practice the use of just 0.85 equiv of the electrophile led more readily to the clean thioether.

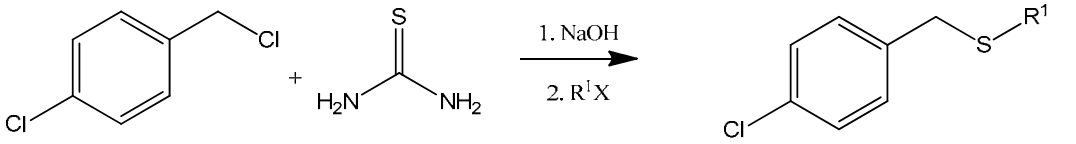
When generating symmetrical thioethers, a simpler single step protocol can be employed in place of the two step process outlined above. Thus, 2 equiv of 2-methylbenzyl chloride (**1**), and 1.1 equiv of thiourea were refluxed in ethanol (6 h), solid sodium hydroxide (3 equiv.) was added and reflux continued for an additional 2 h. Upon work up the clean symmetrical thioether **5g** was isolated in 94% yield.

Table 1. Synthesis of symmetrical and unsymmetrical benzyl thioethers

Ar^1	Ar^2	Thioether	Yield[a] (%)
Ph	2'-Tol	**5a** [11]	94
Ph	4'-Tol	**5b** [10,12,13]	90 / 91[d]
Ph	2'-$MeOC_6H_4$	**5c**	91
Ph	3'-ClC_6H_4	**5d**	94
Ph	4'-ClC_6H_4	**5e** [10,12]	88
Ph	3'-Tol	**5f** [12]	92
2-Tol	2'-Tol	**5g** [14]	93 / 94[b,d]
2-Tol	4'-ClC_6H_4	**5h**	83
2-Tol	2'-$MeOC_6H_4$	**5i**	94
2-Tol	4'-$MeOC_6H_4$	**5j** [11]	93
2-Tol	4'-Tol	**5k** [11]	89
4-Tol	4'-Tol	**5l** [10,15]	95
4-Tol	3'-Tol	**5m**	95
4-Tol	3'-$MeOC_6H_4$	**5n**	87
4-C_4H_4N	4-Tol	**5o**	71[c, d]
3-ClC_6H_4	4'-$MeOC_6H_4$	**5p**	86
3-ClC_6H_4	2'-Tol	**5q**	87
3-ClC_6H_4	4'-Tol	**5r**	90
3-ClC_6H_4	3'-ClC_6H_4	**5s** [16]	91
3-Tol	3'-Tol	**5t** [15,17]	93, 92[d]
3-Tol	2'-Tol	**5u**	94
3-Tol	2'-ClC_6H_4	**5v**	89
3-Tol	4'-$MeOC_6H_4$	**5w**	81
3-Tol	3'-$MeOC_6H_4$	**5x**	85
3-$MeOC_6H_4$	2'-Tol	**5y**	86
3-$MeOC_6H_4$	2'-ClC_6H_4	**5z**	90
3-$MeOC_6H_4$	3'-$MeOC_6H_4$	**5aa** [17]	91

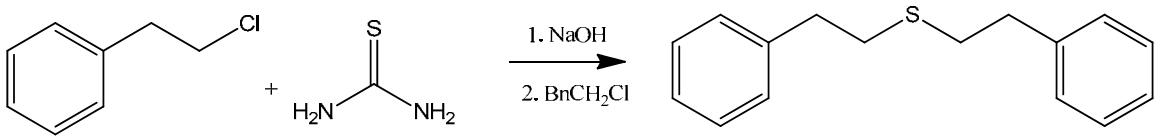
[a]Yield of thioether from benzyl halide **4** following chromatographic purification. Reactions conducted in methanol unless otherwise stated.
[b]Yield using single step method.
[c]Recrystallised yield from hexane.
[d] Reaction conducted in ethanol.

We have also demonstrated that the reaction works well using a primary or a secondary alkyl halide (Scheme 2) as the electrophile generating benzyl alkyl thioethers, as well as a symmetrical phenylethylthioether (Scheme 3) leading to the sulfides **6a, 6b** and **7** in good yields and purity.



R[1] = *n*-PrBr (**6a**, 88%) or *i*-PrI (**6b**, 91%)

Scheme 2



7, 98%

Scheme 3

Use of a secondary benzylic halide as the electrophile led to sulfide formation but it proved difficult to obtain the product clean of by-products. Use of alkyl halides 1-bromopropane and (bromomethyl)cyclohexane in the first step to generate the isothiuronium ion proved unsatisfactory with sulfides formed in very low yields.

In conclusion a practical approach to the synthesis of benzyl thioethers is described which is applicable to both symmetrical and unsymmetrical benzyl thioethers. While most of the examples involve benzylic sulfides the reaction can be extended to alkyl derivatives in some instances.

Experimental Section

General. All reagents were supplied from Sigma-Aldrich and were used without further purification. Benzyl bromide, 3-methylbenzyl chloride, 2-methylbenzyl chloride, 2-chlorobenzyl bromide, 4-methylbenzyl bromide, 3-chlorobenzyl bromide, 1-bromopropane, 2-iodopropane and (2-chloroethyl)benzene were used as the sources of halides. 2-Methoxybenzyl chloride, 3-methoxybenzyl chloride and 4-methoxybenzyl chloride were synthesised according to the literature procedure[18] from the corresponding alcohol and purified by distillation. Solvents were of laboratory grade and distilled prior to use, except methanol and ethanol which were of HPLC grade and distilled over CaH_2 under a nitrogen atmosphere. All reactions were conducted under an inert atmosphere.

Infrared spectra for solids were recorded as KBr discs; for oils were recorded as a film on NaCl plates on a Perkin Elmer FT-IR spectrophotometer interfaced with Spectrum version 6.3.2 using KBr / NaCl as the background over the range 400-4000 cm^{-1}.

^{1}H (400 MHz) NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer and ^{1}H (300 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer in proton coupled mode. ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker Avance 400 NMR spectrometer. All spectra were recorded at 20 °C in deuterated chloroform ($CDCl_3$) using trimethylsilane (TMS) as an internal standard. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to the TMS signal and coupling constants are expressed in Hertz (Hz).
Elemental analysis was performed by the Microanalysis Laboratory, University College Cork, on a Perkin-Elmer 240 and Exeter Analytical CE440 elemental analysers.
Melting points were measured on an Electrothermal 9100-Melting Point apparatus and are uncorrected.

General Procedure (Scheme 1)
1.1 equiv of thiourea is added to 1 equiv of benzyl halide **1** in dry degassed methanol (1 g of halide in 10 mL MeOH or EtOH) and refluxed overnight. 3 equiv of NaOH is added and the reaction mixture refluxed for 2-3 h. The reaction is cooled to room temperature followed by the addition of 0.85 equiv of benzyl halide **4** and refluxed overnight. Upon cooling 2 M NaOH (3 × volume of MeOH or EtOH) is added to the reaction mixture followed by extraction with CH_2Cl_2 (3 × 50 mL). The combined organic phases are washed with 2 M NaOH (2 × 50 mL), water (50 mL) and brine (50 mL). The organic phase is dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure. All products were purified by vacuum liquid column chromatography[19] (60 H silica gel) using hexane / methylene chloride (85 : 15) as the eluent, except Entry 5o which was recrystallised from hexane after chromatography.
Single step method for the synthesis of (5g). Thiourea (167 mg , 2.2 mmol) was added to 2-methylbenzyl chloride (281mg, 2.00 mmol) in dry degassed ethanol (10 mL) followed by reflux for 6 h. Solid sodium hydroxide (240 mg, 6 mmol) was added and reflux continued for an additional 2 h. Upon cooling NaOH (2 M, 30 mL) was added to the reaction mixture followed by extraction with CH_2Cl_2 (3 × 25 mL). The combined organic phases are washed with NaOH (2 M, 2 × 25 mL), water (25 mL) and brine (25 mL). The organic phase is dried over anhydrous $MgSO_4$, filtered and the solvent removed under reduced pressure to give **5g** (227 mg, 94%) which did not require chromatographic purification.
Entry 5a [11] (Ar^1 = Ph Ar^2 = 2'-Tol). Colourless solid, mp 31-32 ºC; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.30 (3H, s, Ar-CH_3), 3.61 (2H, s, Ar-CH_2), 3.66 (2H, s, Ar-CH_2), 7.12 – 7.17 (4H, m, Ar-H), 7.30 -7.34 (5H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.2, 136.8, 135.7 (3 × quaternary aromatic C), 130.6, 129.6, 128.9, 128.5, 127.2, 127.0, 125.8 (7 × aromatic CH), 36.2, 33.8 (2 × Ar-CH_2) and 19.0 (Ar-CH_3)
I.R (KBr) ν cm^{-1} = 3026, 2917, 1493 (s), 1452 (s), 767 (s), 731 (s), 697 (s). Anal. Calcd. for $C_{15}H_{16}S$: C, 78.90; H, 7.06. Found C, 78.38 and H, 7.03
Entry 5b [10,12,13] (Ar^1 = Ph Ar^2 = 4'-Tol). Colourless oil that solidified upon prolonged standing mp 29 – 31 ºC (Lit. [10, 12, 13] 29 – 31 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-

CH_3), 3.57 (2H, s, Ar-CH_2), 3.60 (2H, s, Ar-CH_2), 7.12 (2H, d, Ar-H, *J* = 8.1 Hz), 7.18 (2H, d, Ar-H, *J* = 8.1 Hz), 7.21 – 7.34 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.2, 136.6, 135.0 (3 × quaternary aromatic C), 129.1, 129.0, 128.9, 128.4, 126.9 (5 × aromatic CH), 35.6, 35.3 (2 × Ar-CH_2), 21.1 (Ar-CH_3). I.R (film) ν cm^{-1} = 3027 (s), 2916 (s), 1602, 1513(s), 1494(s), 1453(s) and 700(s). Anal. Calcd. for $C_{15}H_{16}S$: C, 78.90; H, 7.06. Found C, 78.69 and H, 7.05. From ethanol satisfactory ^{1}H NMR, ^{13}C NMR and melting point were achieved.

Entry 5c (Ar^1 = Ph Ar^2 = 2'-MeOC_6H_4). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.66 (2H, s, Ar-CH_2), 3.68 (2H, s, Ar-CH_2), 3.83 (3H, s, Ar-OCH_3), 6.84 – 6.93 (2H, m, Ar-H), 7.18 – 7.34 (7H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 157.4, 138.5, 126.7 (3 × quaternary aromatic C), 130.3, 129.0, 128.4, 128.2, 126.8, 120.3, 110.7 (7 × aromatic CH), 55.4 (Ar-OCH_3), 36.2 and 30.1 (2 × Ar-CH_2). I.R (film) ν cm^{-1} = 3028, 2835, 1600, 1494(s), 1247(s), 1029, 753(s), 698(s). Anal. Calcd. for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found C, 73.59 and H, 6.42.

Entry 5d (Ar^1 = Ph Ar^2 = 3'-ClC_6H_4). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.55 (2H, s, Ar-CH_2), 3.60 (2H, s, Ar-CH_2), 7.13 – 7.17 (1H, m, Ar-H), 7.20 – 7.35 (8H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 140.3, 137.8, 134.3 (3 × quaternary aromatic C), 129.7, 129.1, 129.0, 128.5, 127.17, 127.12, 127.10 (7 × aromatic CH), 35.2 and 35.1 (2 × Ar-CH_2). I.R (film) ν cm^{-1} = 3061, 3028, 2915, 1598(s), 1574(s), 1494(s), 1475(s), 1453(s), 1431(s), 1234, 1076, 786, 723(s), 693(s). Anal. Calcd. for $C_{14}H_{13}ClS$: C, 67.59; H, 5.27. Found C, 67.65 and H, 5.29.

Entry 5e [10,12] (Ar^1 = Ph Ar^2 = 4'-ClC_6H_4). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.55 (2H, s, Ar-CH_2), 3.59 (2H, s, Ar-CH_2), 7.18 – 7.34 (9H, m, Ar-H)

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 137.8, 136.7, 129.4 (3 × quaternary aromatic C), 130.3, 129.0, 128.6, 128.5, 127.1 (5 × aromatic CH), 35.6 and 34.9 (2 × Ar-CH_2)

I.R (film) ν cm^{-1} = 3028, 2915, 1600, 1490(s), 1453, 1092(s), 1015, 833 and 698(s)

Anal. Calcd. for $C_{14}H_{13}ClS$: C, 67.59; H, 5.27. Found C, 67.24 and H, 5.20.

Entry 5f [12] (Ar^1 = Ph Ar^2 = 3'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.57 (2H, s, Ar-CH_2), 3.61 (2H, s, Ar-CH_2), 7.02 – 7.12 (3H, m, Ar-H), 7.16 – 7.34 (6H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.2, 138.1, 138.0 (3 × quaternary aromatic C), 129.7, 129.0, 128.4, 128.3, 127.7, 126.9, 126.0 (7 × aromatic CH), 35.7, 35.6 (2 × Ar-CH_2) and 21.4 (Ar-CH_3). I.R (film) ν cm^{-1} = 3028, 2916, 1607, 1493(s), 1453 (s), 1089, 1071, 787 and 702. Anal. Calcd. for $C_{15}H_{16}S$: C, 78.90; H, 7.06. Found C, 78.80 and H, 7.19.

Entry 5g [14] (Ar^1 = 2-Tol Ar^2 = 2'-Tol). White solid mp 83-85 °C (Lit. [14] 82 – 83 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.30 (6H, s, Ar-CH_3), 3.66 (4H, s, Ar-CH_2), 7.10 – 7.24 (8H, m, Ar-H) ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.8, 135.8 (2 × quaternary aromatic C), 130.6, 129.6, 127.2, 125.8 (4 × aromatic CH), 34.3 (Ar-CH_2) and 19.0 (Ar-CH_3). I.R (KBr) ν cm^{-1} = 3018, 2953, 2916, 1492(s), 1459(s), 1419(s), 1372, 1235, 1098(s), 1034, 942, 772(s), 732(s), 690(s) and 590. Anal. Calcd. for $C_{16}H_{18}S$: C, 79.29; H, 7.49. Found C, 79.19 and H, 7.49. From ethanol satisfactory ^{1}H NMR, ^{13}C NMR and melting point were achieved.

Entry 5h (Ar^1 = 2-Tol Ar^2 = 4'-ClC_6H_4). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (3H, s, Ar-CH_3), 3.60 (2H, s, Ar-CH_2), 3.61 (2H, s, Ar-CH_2), 7.11 – 7.16 (4H, m, Ar-H), 7.22 – 7.31 (4H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 137.0, 135.4, 132.7 (3 × quaternary aromatic C), 130.7, 130.2, 129.6, 128.6, 127.3, 125.8 (6 × aromatic CH), 35.4, 33.8 (2 × Ar-CH_2) and 19.1 (Ar-CH_3). I.R (film) ν cm^{-1} = 3019, 2918, 1490(s), 1092(s), 1015(s), 832, and 732(s). Anal. Calcd. for $C_{15}H_{15}ClS$: C, 68.55; H, 5.94. Found C, 68.64 and H, 5.94.

Entry 5i (Ar^1 = 2-Tol Ar^2 = 2'-$MeOC_6H_4$). White solid mp 36 – 37 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (3H, s, Ar-CH_3), 3.68 (2H, s, Ar-CH_2), 3.72 (2H, s, Ar-CH_2), 3.83 (3H, s, Ar-OCH_3), 6.85-6.94 (m, 2H, Ar-H), 7.10 – 7.16 (3H, m, Ar-H), 7.19 – 7.28 (3H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 157.4, 136.8, 136.1 (3 × quaternary aromatic C), 130.5, 130.2, 129.6, 128.2, 127.1, 125.8, 120.4, 110.7 (8 × aromatic CH), 55.5 (Ar-OCH_3), 34.3, 30.5(2 × Ar-CH_2) and 19.1 (Ar-CH_3). I.R (KBr) ν cm^{-1} = 3018, 2922, 2835, 1600, 1494(s), 1463(s), 1290, 1247(s), 1102, 1050, 1030(s), 752(s) and 731(s). Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found C, 74.32 and H, 7.07.

Entry 5j [11] (Ar^1 = 2-Tol Ar^2 = 4'-$MeOC_6H_4$). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (3H, s, Ar-CH_3), 3.60 (2H, s, Ar-CH_2), 3.62 (2H, s, Ar-CH_2), 3.81 (3H, s, Ar-OCH_3), 6.85 (2H, d, Ar-H, *J* = 8.7 Hz), 7.10 – 7.18 (4H, m, Ar-H), 7.24 (2H, d, Ar-H, *J* = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.6, 136.8, 135.8, (3 × quaternary aromatic C), 130.6 (aromatic CH), 130.2 (quaternary aromatic C), 130.0, 129.6, 127.2, 125.8, 113.9 (5 × aromatic CH), 55.3 (Ar-OCH_3), 35.5, 33.7 (2 × Ar-CH_2) and 19.1 (Ar-CH_3).I.R (film) ν cm^{-1} = 2913 (br), 2834, 1610, 1511(s), 1248(s), 1174, 1035, 832 and 729. Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found C, 73.94 and H, 7.07.

Entry 5k [11] (Ar^1 = 2-Tol Ar^2 = 4'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (3H, s, Ar-CH_3), 2.34 (3H, s, Ar-CH_3), 3.60 (2H, s, Ar-CH_2), 3.63 (2H, s, Ar-CH_2), 7.09 – 7.17 (6H, m, Ar-H), 7.18 – 7.24 (2H, m, Ar-H), ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.8, 136.6, 135.8, 135.1 (4 × quaternary aromatic C), 129.6, 129.1, 128.8, 127.2, 125.8(5 × aromatic CH), 35.9, 33.8 (2 × Ar-CH_2), 21.1 and 19.1 (2 × Ar-CH_3). I.R (film) ν cm^{-1} = 3019, 2919, 1513(s), 1492, 1461, 1237, 1099, 1049, 817 and 730(s). Anal. Calcd. for $C_{16}H_{18}S$: C, 79.29; H, 7.49. Found C, 79.07 and H, 7.57.

Entry 5l [10,15] (Ar^1 = 4-Tol Ar^2 = 4'-Tol). White solid mp 76-78 °C (Lit. [10, 15] 76 °C).
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.33 (6H, s, Ar-CH_3), 3.56 (4H, s, Ar-CH_2), 7.11 (4H, d, Ar-H, *J* = 8.0 Hz), 7.18 (4H, d, Ar-H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 136.5, 135.1 (2 × quaternary aromatic C), 129.1, 128.9 (2 × aromatic CH), 35.3 (2 × Ar-CH_2), 21.1 (2 × Ar-CH_3). I.R (KBr) ν cm^{-1} = 3022, 2921, 1906, 1511(s), 1416(s), 1179, 1111(s), 818(s), 730(s), 680(s), 659(s) and 527(s). Anal. Calcd. for $C_{16}H_{18}S$: C, 79.29; H, 7.49. Found C, 78.86 and H, 7.51.

Entry 5m (Ar^1 = 4-Tol Ar^2 = 3'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (6H, s, Ar-CH_3), 3.57 (2H, s, Ar-CH_2), 3.58 (2H, s, Ar-CH_2), 7.23 – 7.01 (8H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.11, 138.08, 136.6, 135.1, (4 × quaternary aromatic C), 129.7, 129.1, 128.9, 128.3, 127.7, 126.0 (6 × aromatic CH), 35.6, 35.4 (2 × Ar-CH_2), 21.4

and 21.1(2 × Ar-CH_3). I.R (film) ν cm^{-1} = 3021, 2917, 1608, 1513(s), 1488, 1455, 1421, 1228, 1108, 1021, 818, 787, 726 and 712.

Entry 5n (Ar^1 = 4-Tol Ar^2 = 3'-$MeOC_6H_4$). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.57 (2H, s, Ar-CH_2), 3.58 (2H, s, Ar-CH_2), 3.81 (3H, s, Ar-OCH_3), 6.78 (1H, dd, Ar-H, *J* = 8.0 Hz, 2.4 Hz), 6.83 – 6.90 (2H, m, Ar-H), 7.12 (2H, d, Ar-H, *J* = 8.0 Hz), 7.15 – 7.25 (3H, m, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 159.7, 139.8, 136.6, 135.0 (4 × quaternary aromatic C) , 129.4, 129.1, 128.9, 121.4, 114.4, 112.6 (6 × aromatic CH) , 55.2 (Ar-OCH_3), 35.6, 35.4 (2 × Ar-CH_2) and 21.1 (Ar-CH_3). I.R (film) ν cm^{-1} = 2917, 2834, 1600(s), 1514(s), 1489(s), 1455(s), 1435(s), 1267(s), 1151, 1048(s), 819, 783, and 726. Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found C, 74.83 and H, 7.03.

Entry 5o (**Ar^1 = 4-C_5H_4N Ar^2 = 4-Tol).** Reaction conducted in ethanol. White solid, mp 63 – 65 °C decomposes to a brown solid upon prolonged standing at ambient conditions.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.66 (2H, 2, Ar-CH_2), 3.74 (2H, s, Ar-CH_2), 7.10 (4H, s, Ar-H), 7.71 (2H, br s, Ar-H), 8.66 (2H, br s, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.9, 137.7, 133.1(3x quaternary aromatic C), 140.6, 129.5, 128.9, 126.9 (4 × aromatic CH), 36.2, 34.8 (2 × Ar-CH_2) and 21.1 (Ar-CH_3)

I.R (film) ν cm^{-1} = 2962, 2359, 1490, 1272, 1092, 1015 and 826.

Entry 5p (Ar^1 = 3-ClC_6H_4 Ar^2 = 4'-$MeOC_6H_4$). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.56 (2H, s, Ar-CH_2), 3.57 (2H, s, Ar-CH_2), 3.81 (3H, s, Ar-OCH_3), 6.85 (2H, d, Ar-H, *J* = 8.4 Hz), 7.12 – 7.25 (6H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.7, 140.4, 134.2, (3 × quaternary aromatic C), 130.0 (1 signal for 2 × aromatic CH), 129.69, (quaternary aromatic C), 129.65, 129.0, 127.1, 113.9 (4 × aromatic CH), 55.3 (Ar-OCH_3), 35.1 and 35.0 (2 × Ar-CH_2). I.R (film) ν cm^{-1} = 2911, 2834, 1610 (s), 1512(s), 1464, 1431, 1302, 1250(s), 1175, 1035, 833 and 692. Anal. Calcd. for $C_{15}H_{15}ClOS$: C, 64.62; H, 5.42. Found C, 64.29 and H, 5.39.

Entry 5q (Ar^1 = 3-ClC_6H_4 Ar^2 = 2'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (3H, s, Ar-CH_3), 3.61 (4H, s, Ar-CH_2), 7.12 – 7.26 (7H, m, Ar-H), 7.30 (1H, br s, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 140.4, 136.8, 135.4, 134.3 (4 × quaternary aromatic C), 130.7, 129.7, 129.6, 129.0, 127.4, 127.2, 127.1, 125.8 (8 × aromatic CH), 35.6, 33.8 (2x Ar-CH_2) and 19.1 (Ar-CH_3). I.R (film) ν cm^{-1} = 3063, 3018, 2920, 1598(s), 1574(s), 1475(s), 1431(s), 1237, 1077, 872, 786, 733(s) and 691

Anal. Calcd. for $C_{15}H_{15}ClS$: C, 68.55; H, 5.75. Found C, 68.17 and H, 5.80.

Entry 5r (Ar^1 = 3-ClC_6H_4 Ar^2 = 4'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.54 (2H, s, Ar-CH_2), 3.57 (2H, s, Ar-CH_2), 7.09 – 7.24 (8H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 140.4, 136.7, 134.6, 134.2 (4 × quaternary aromatic C), 129.6, 129.2, 129.1, 128.9, 127.12, 127.11 (6 × aromatic CH), 35.4, 35.0 (2 × Ar-CH_2) and 21.1 (Ar-CH_3). I.R (film) ν cm^{-1} = 3049, 3021, 2918, 1598(s), 1574(s), 1514(s), 1475(s), 1431(s), 1235, 1077, 870, 818, 787 and 692

Anal. Calcd. for $C_{15}H_{15}ClS$: C, 68.55; H, 5.75. Found C, 68.16 and H, 5.77.

Entry 5s [16] (Ar^1 = 3-ClC_6H_4 Ar^2 = 3'-ClC_6H_4). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.56 (4H, s, Ar-CH_2), 7.12 – 7.16 (2H, m, Ar-H), 7.21 – 7.28 (6H, m, Ar-H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ (ppm) = 139.9, 134.4 (2 × quaternary aromatic C), 129.7, 129.1, 127.3, 127.1 (4 × aromatic CH) and 35.2 (Ar-CH_2). I.R (film) ν cm^{-1} = 3060, 2916, 1597(s), 1574(s), 1475(s), 1431(s), 1230, 1202, 1077(s), 874, 787(s), and 691(s). Anal. Calcd. for $C_{14}H_{12}Cl_2S$: C, 59.37; H, 4.27. Found C, 58.96 and H, 4.28.

Entry 5t [15,17] (Ar[1] = 3-Tol Ar[2] = 3'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (6H, s, Ar-CH_3), 3.58 (4H, s, Ar-CH_2), 7.02 – 7.12 (6H, m, Ar-H), 7.20 (2H, t, Ar-H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.1 (1 signal for 2 × quaternary aromatic C) 129.7, 127.7, 126.0, 128.3 (4 × aromatic CH), 35.7 (Ar-CH_2) and 21.4 (Ar-CH_3). I.R (film) ν cm^{-1} = 3022, 2916(s), 1608(s), 1489(s), 1224, 1089, 787(s), 712(s) and 691(s). Anal. Calcd. for $C_{16}H_{18}S$: C, 79.29; H, 7.49. Found C, 79.31 and H, 7.48. From ethanol satisfactory ^{1}H NMR, ^{13}C NMR and melting point were achieved.

Entry (5u Ar[1] = 3-Tol Ar[2] = 2'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (2H, s, Ar-CH_3), 2.34 (3H, s, Ar-CH_3), 3.61 (2H, s, Ar-CH_2), 3.63 (2H, s, Ar-CH_2), 7.03 – 7.23 (8H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.1, 136.8, 135.8 (3 signals for 4 × quaternary aromatic C), 130.6, 129.7, 129.6, 128.3, 127.7, 127.2, 126.0, 125.8 (8 × aromatic CH), 36.2, 33.8 (2 × Ar-CH_2), 21.4 and 19.1 (2 × Ar-CH_3). I.R (film) ν cm^{-1} = 3018(s), 2918(s), 1608(s), 1492(s), 1462(s), 787 and 731(s).

Entry 5v (Ar[1] = 3-Tol Ar[2] = 2'-ClC_6H_4). Colourless oil that precipitated upon standing to give a white solid mp < 25°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.66 (2H, s, Ar-CH_2), 3.74 (2H, s, Ar-CH_2), 7.02 – 7.14 (3H, m, Ar-H), 7.16 – 7.24 (3H, m, Ar-H), 7.29 – 7.39 (2H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 138.1, 137.8, 136.0, 134.1 (4 × quaternary aromatic C), 130.7, 129.8, 129.7, 128.4, 128.3, 127.8, 126.7, 126.0 (8 × aromatic CH), 36.2, 33.4 (2 × Ar-CH_2) and 21.4 (Ar-CH_3)
I.R (film) ν cm^{-1} = 3021, 2917(s), 1608(s), 1513(s), 1489, 1109, 1089, 818, 788 and 712
Anal. Calcd. for $C_{15}H_{15}ClS$: C, 68.55; H, 5.75. Found C, 68.53 and H, 5.94

Entry 5w (Ar[1] = 3-Tol Ar[2] = 4'-$MeOC_6H_4$). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.56 (2H, s, Ar-CH_2), 3.57 (2H, s, Ar-CH_2), 3.80 (3H, s, Ar-OCH_3), 6.85 (2H, d, Ar-H, *J* = 8.4 Hz), 7.02 – 7.11 (3H, m, Ar-H), 7.16 – 7.24 (3H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 158.6, 138.1, 138.1, 130.1 (4 × quaternary aromatic C), 130.0, 129.7, 128.3, 127.7, 126.0, 113.9 (6 × aromatic CH), 55.3 (Ar-OCH_3), 35.6, 35.1 (2 × Ar-CH_2) and 21.4 (Ar-CH_3). I.R (film) ν cm^{-1} = 2912, 2834, 1610(s), 1512(s), 1301, 1250(s), 1175(s), 1035(s), and 833. Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found C, 74.46 and H, 7.16.

Entry 5x (Ar[1] = 3-Tol Ar[2] = 3'-$MeOC_6H_4$). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.34 (3H, s, Ar-CH_3), 3.58 (2H, s, Ar-CH_2), 3.59 (2H, s, Ar-CH_2), 3.80 (3H, s, Ar-OCH_3), 6.79 (1H, dd, Ar-H, *J* = 8.4 Hz and 2.7 Hz), 6.83 – 6.91 (2H, m, Ar-H), 7.02 – 7.13 (3H, m, Ar-H), 7.16 – 7.24 (2H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.7, 139.8, 138.1, 138.0 (4 × quaternary aromatic C), 129.7, 129.4, 128.3, 127.7, 126.0, 121.4, 114.4, 112.6 (8 × aromatic CH), 55.2 (Ar-OCH_3), 35.7, 35.6 (2 × Ar-CH_2) and 21.4 (Ar-CH_3). I.R (film) ν cm^{-1} = 3003,

2939, 2916, 2834, 1600(s), 1489(s), 1454, 1436, 1266(s), 1151, 1047, 786 and 690. Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found C, 74.42 and H, 7.02.

Entry 5y (Ar^1 = 3-$MeOC_6H_4$ Ar^2 = 2'-Tol). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 2.31 (3H, s, Ar-CH_3), 3.61 (2H, s, Ar-CH_2), 3.64 (2H, s, Ar-CH_2), 3.80 (3H, s, Ar-OCH_3), 6.76 – 6.82 (1H, m, Ar-H), 6.87 – 6.93 (2H, m, Ar-H), 7.10 – 7.24 (5H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.7, 139.8, 136.8, 135.7 (4 × quaternary aromatic C), 130.6, 129.7, 129.4, 127.3, 125.8, 121.3, 114.3, 112.6 (8 × aromatic CH), 55.2 (Ar-OCH_3), 36.2, 33.8 (2 × Ar-CH_2) and 19.1 (Ar-CH_3). I.R (film) ν cm^{-1} = 3016, 2940, 2917, 2834, 1600(s), 1489(s), 1435(s), 1266(s), 1151(s), 1048(s), 779, 732(s), and 690. Anal. Calcd. for $C_{16}H_{18}OS$: C, 74.38; H, 7.02. Found C, 73.98 and H, 7.03.

Entry 5z (Ar^1 = 3-$MeOC_6H_4$ Ar^2 = 2'-ClC_6H_4). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.67 (2H, s, Ar-CH_2), 3.74 (2H, s, Ar-CH_2), 3.80 (3H, s, Ar-OCH_3), 6.76-6.82 (1H, m, Ar-H), 6.87 – 6.93 (2H, m, Ar-H), 7.14 – 7.24 (3H, m, Ar-H), 7.27 – 7.39 (2H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.8, 139.5, 135.9, 134.1 (4 × quaternary aromatic C) 130.7, 129.8, 129.4, 128.3, 126.7, 121.3, 114.3, 112.8 (8 × aromatic CH) 55.2 (Ar-OCH_3), 36.2, 33.4 (2 × Ar-CH_2). I.R (film) ν cm^{-1} = 2937, 2834, 1600(s), 1489(s), 1471(s), 1444(s), 1267, 1151, 1050(s), 744 (s) and 688. Anal. Calcd. for $C_{15}H_{15}ClOS$: C, 64.62; H, 5.42. Found C, 64.64 and H, 5.44.

Entry 5aa [17] (Ar^1 = 3-$MeOC_6H_4$ Ar^2 = 3'-$MeOC_6H_4$). Colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 3.59 (4H, s, Ar-CH_2), 3.80 (6H, s, Ar-OCH_3), 6.79 (2H, dd, Ar-H, *J* = 8.1 Hz and 2.4 Hz), 6.83 – 6.91 (4H, m, Ar-H), 7.19-7.26 (2H, m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 159.7, 139.7 (2 × quaternary aromatic C), 129.4, 121.4, 114.4, 112.6 (4 × aromatic CH), 55.2 (Ar-OCH_3) and 35.7 (Ar-CH_2). I.R (film) ν cm^{-1} = 3000, 2940, 2915, 2834, 1600(s), 1488(s), 1455(s), 1435(s), 1267(s), 1151(s), 1048(s), 784 and 690. Anal. Calcd. for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61. Found C, 69.63 and H, 6.60.

Entry 6a (Ar^1 = 4-ClC_6H_4 R^1 = *n*-Pr). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 0.95 (3H, t, CH_3, *J* = 8.0 Hz), 1.51-1.62 (2H, m, CH_2-2), 2.38 (2H, t, CH_2-1, *J* = 8.0 Hz), 3.66 (2H, s Ar-CH_2), 7.22 – 7.30 (4H. m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 137.2, 132.6 (2 × quaternary aromatic C), 130.1, 128.5 (2 × aromatic CH), 35.5, 33.4, 22.5 (3x CH_2) and 13.5 (CH_3). I.R (film) ν cm^{-1} = 2962 (s), 1490 (s), 1457, 1236, 1093 (s), 1015, 826 and 738. Anal. Calcd. for $C_{10}H_{13}ClS$: C, 59.84; H, 6.53. Found C, 59.60 and H, 6.29

Entry 6b [12] (Ar^1 = 4-ClC_6H_4 R^1 = *i*-Pr). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 1.25 (6H, d. CCH_3, *J* = 6.8 Hz), 2.77 (1H, septet, CH, *J* = 6.8 Hz), 3.70 (2H, s, Ar-CH_2), 7.27 (4H, s, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 137.3, 132.5 (2 × quaternary aromatic C), 130.1, 128.6 (2 × aromatic CH), 34.5, 34.3 (2 × CH_2) and 23.1 (2 × CH_3). I.R (film) ν cm^{-1} = 2960 (s), 1490 (s), 1236, 1093 (s), 822.

Entry 7 [20, 21] ($BnCH_2$-S-CH_2Bn). Colourless oil that solidified upon standing to give a white solid mp 32 °C (Lit.[22] 92 °C, Lit. [23] 48 - 49 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.75 – 2.81 (4H, m, Ar-CH_2), 2.85 – 2.92 (4H, m, S-CH_2), 7.17 – 7.25 (6H, m, Ar-H), 7.27 – 7.33 (4H,

m, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 140.6 (quaternary aromatic C), 128.5, 126.4 (3 × aromatic CH), 36.4 and 33.8 (2 × CH_2)
I.R (film) ν cm^{-1} = 3027 (s), 2364, 1603, 1496 (s), 1453 (s), 1273, 1225, 1072, 1030, 731 and 698 (s).

Acknowledgements

This publication has emanated from research conducted with the financial support of Science Foundation Ireland under Grant Number 08/RFP/MTR1664 (KE), 07/SRC/B1158 (CE) and 05/PICA/B802/EC07.

References

1. Salvatore, R. N.; Smith, R. A.; Nischwitz, A. K.; Gavin, T. *Tetrahedron Lett.* **2005**, *46*, 8931.
2. Smith, M., B.; March, J. *Advanced Organic Chemistry: Reaction, Mechanism, and Structure*; 5th Ed.; John Wiley and Sons, Inc.: New York, 2001.
3. Cremlyn, R. J. *An Introduction to Organosulfur Chemistry*; John Wiley and Sons: New York, 1996.
4. Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*; Oxford University Press, 2001.
5. Fujisaki, S.; Fujiwara, I.; Norisue, Y.; Kajigaeshi, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2429.
6. Emerson, D. W.; Bennett, B. L.; Steinberg, Spencer M. *Synth. Commun.* **2005**, *35*, 631.
7. Takagi, K., *Chem. Lett.* **1986**, 1379.
8. Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* **2004**, *69*, 3236.
9. Argello, J. E.; Schmidt, L. C.; Peory, A. B. *Org. Lett.* **2003**, *5*, 4133.
10. Takido, T.; Itabashi, K. *Synthesis* **1987**, 817.
11. Nishimura, T.; Zhang, C.; Maeda, Y.; Shirai, N.; Ikeda, S; Sato, Y. *Chem. Pharm. Bull.* **1999**, *47*, 267.
12. Tuleen, D. L. *J. Org. Chem.* **1967**, *32*, 4006.
13. Baciocchi, E.; Del Giacco, T.; Lanzalunga, O.; Lapi, A. *J. Org. Chem.* **2007**, *72*, 9582.
14. Antebi, S.; Alper, H. *Tetrahedron Lett.* **1985**, *26*, 2609.
15. Voronkov, M. G.; Pereferkovich, A. N.; Mikhailova, S. V. *Zh. Prikl. Khim. (Leningrad)* **1969**, *42*, 1155.
16. Mitchell, R. H. *Tetrahedron Lett.* **1973**, 4395.
17. Wang, L.; Green, T. K. *Youji Huaxue* **1996**, *16*, 507.
18. Amin, S.; Hecht, S. S.; Hoffman, D. *J. Org. Chem.* **1981**, *46*, 2394.
19. Coll, J. C.; Bowden, B. F. *J. Nat. Prod.* **1986**, *49*, 934.
20. Bermejo, L.; Herrera, J. J. *IX Congr. intern. quim. pura aplicada* **1934**, *4*, 238.

21. Olah, G. A.; Fung A. P.; Gupta, B. G. B; Narang, S. C. *Synthesis* **1980**, *3*, 221.

