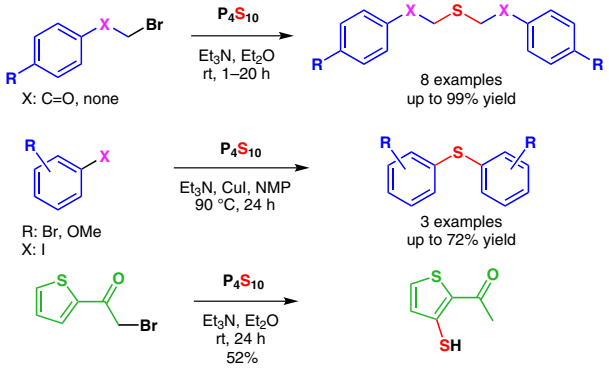
Synthesis G. Turkoglu et al. Paper

Synthesis of Thioethers Using Triethylamine-Activated Phosphorus Decasulfide (P_4S_{10})

Gulsen Turkoglu[a]
M. Emin Cinar*[a,b]
Turan Ozturk*[a,c]

[a] Istanbul Technical University, Science Faculty, Chemistry Department, Organic Chemistry, 34469 Maslak, Istanbul, Turkey
[b] Universität Siegen, Department Chemie-Biologie, OC1, Adolf-Reichwein-Str., 57068 Siegen, Germany
emin.cinar@uni-siegen.de
[c] TUBITAK-UME, Chemistry Group Laboratories, PO Box 54, 41471 Gebze, Kocaeli, Turkey
ozturktur@itu.edu.tr



Received: 22.02.2016
Accepted after revision: 05.05.2016
Published online: 13.06.2016
DOI: 10.1055/s-0035-1561673; Art ID: ss-2016-t0127-op

Abstract The synthesis of thioethers in excellent yields was achieved under mild conditions via the displacement reaction of halogens by sulfur. The cross-reaction of 2-(α-bromoacetyl)thiophene with triethylamine-activated phosphorus decasulfide ($Et_3N–P_2S_5$) was elaborated by utilizing DFT calculations.

Key words thioethers, phosphorus decasulfide, triethylamine activation, DFT, mechanism

Organic compounds possessing a sulfur heteroatom have attracted scientific interest not only regarding their utility in syntheses but also for their applications.[1] Among such compounds, thioethers, especially aryl-substituted examples, are important scaffolds for materials chemistry[2] and important for medicinal chemistry due to their biological activities.[3]

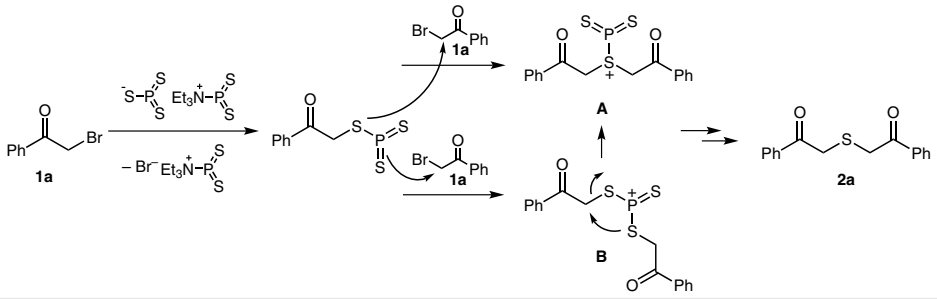
The classical C–S coupling between aryl/alkyl halides and thiols or other sulfur sources often requires harsh reaction conditions, such as strong bases, elevated temperatures, transition-metal catalysts,[4,5] and addition of organometallic reagents to disulfides.[6] Migita and co-workers[7] first reported cross-coupling reactions of aryl halides with thiols in the presence of $Pd(PPh_3)_4$. Recently, nickel,[8] palladium,[9] iron,[10] and cobalt[11] catalysts have emerged as appealing catalysts for such reactions. Copper salts have also been used as alternative and promising catalysts for many organic transformations including the C–S bond-formation reaction.[12] As sulfur sources, $S=C(NH_2)_2$, KSCN, CuSCN, Na_2S, KSAc, elemental sulfur, $H_2NC(=S)NHNH_2$, S_2Cl_2, and MeSH have generally been utilized for this transformation.[12c,13]

Phosphorus decasulfide, P_4S_{10} (also known as phosphorus pentasulfide, P_2S_5, or Berzelius reagent),[14,15] and Lawesson's reagent[16,17] are the most common chemicals used for thionation, for building heterocycles, and also in industrial applications including additives for lubricants, oil, and insecticides.[18] The first nucleophilic displacement of halogens located on heterocycles (pyrizadines) by sulfur was performed by Castle and Kaji with P_4S_{10}, leading to the formation of the corresponding thiols.[19] Thiols have also been obtained by using hydrosulfide-exchange resin,[20] sodium hydrosulfide hydrate,[21] and H_2S.[22]

In this work, P_4S_{10} was used to obtain thioethers via nucleophilic displacement reactions of halogens (Br) under milder conditions and in shorter reaction times. The effects of carbonyl, aromatic/heteroaromatic, and alkyl subunits were investigated. To shed more light on the reactions involving an aryl-containing reactant, electronic effects of a para substituent (OMe, Me, H, Br, CN, NO_2) were taken into consideration.

The reaction conditions were explored in depth by varying several parameters such as temperature, solvent, reagent, and stoichiometry. In order to initiate the reaction, P_4S_{10} had to be activated either chemically[23] or with heat. As the reaction was aimed to be performed under mild conditions, the activation of P_4S_{10} was undertaken using reagents such as Et_3N and HCl. Several solvents, including *n*-hexane, diethyl ether, 1,4-dioxane, and ethanol, were tested to find the most appropriate for obtaining the best yield in the shortest reaction time. The temperature factor was also checked, namely whether a higher yield of thioether could be achieved at higher temperatures.

Activation of P_4S_{10} was achieved using Et_3N via formation of the complex $Et_3N–P_2S_5$ (PS_3^- $^+NEt_3–PS_2$).[15] Reaction of α-bromoacetophenone (**1a**) with P_4S_{10} in the presence of excess Et_3N, also used as the solvent, resulted in symmetrical thioether **2a** (Scheme 1). The whole process could start with an S_N2 reaction of PS_3^- $^+NEt_3–PS_2$ with **1a**, leading to the formation of PS_3-substituted ketone, followed by an intermolecular S_N2 reaction with another equivalent of **1a**.



Scheme 1 Reaction of α-bromoacetophenone (**1a**) with Et_3N-activated P_4S_{10} providing thioether **2a** via proposed intermediates **A** and **B**

The reaction might follow two pathways involving an attack either from the α-sulfur atom providing cationic intermediate **A** or from the other sulfur atoms generating a phosphorous cation **B**, where **A** is afforded with a relative energy of 17.8 kcal·mol^{-1} [(CPCM:Et_2O)-MPW1PW91/6-31+G(d)] with respect to **B** via an intramolecular S_N2 mechanism. Then, hydrolysis of **A** would provide **2a**. P_4S_{10} as a sulfur source was also an effective nucleophile under these reaction conditions, with the ketones remaining intact.

The best yield of **2a** (77%) was obtained from the reaction of **1a** performed with 0.5 equivalents of P_4S_{10} and 10 equivalents of Et_3N in diethyl ether for 4 hours. In the absence of Et_3N no reaction was observed, while decreasing the amount of P_4S_{10} resulted in longer reaction times with lower yields (Table 1).

Table 1 Optimization of the Reaction Conditions for α-Bromoacetophenone (**1a**) and P_4S_{10} at Room Temperature[a]

Entry	P_4S_{10} (equiv)	Et_3N (equiv)	Solvent	Time (h)	Yield (%) of **2a**
1	1.00	–	Et_3N	4	50
2	0.50	–	Et_3N	6	62
3	0.25	–	Et_3N	18	29
4	0.12	–	Et_3N	18	31
5	1.00	–	toluene	19	–
6	0.25	0.5	THF	1.5	–
7	0.12	5.0	*n*-hexane	19	40
8	0.50	10	*n*-hexane	70	47
9	0.50	5.0	Et_2O	3	62
10	0.50	10	Et_2O	4	77
11	0.50	5.0	CH_2Cl_2	4	73
12	0.50	10	CH_3Cl	24	–
13	0.50	10	1,4-dioxane	1	74

[a] Reactions were performed on a 100 μmol scale.

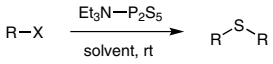
To elaborate this transformation, a series of reactants with carbonyl, aryl, and alkyl units were subjected to the reaction with the Et_3N–P_2S_5 complex in different solvents (Table 2).

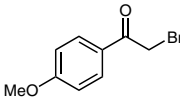
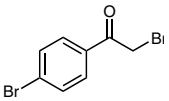
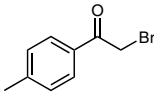
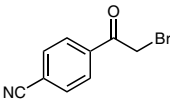
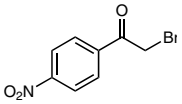
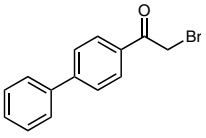
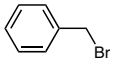
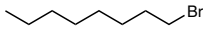
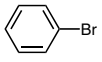
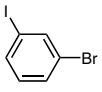
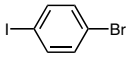
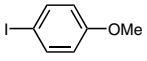
While the reaction of benzyl bromide in diethyl ether in the presence of 10 equivalents of Et_3N provided thioether **2h** in 75% yield (Table 2, entry 7), its reaction in neat Et_3N gave a quantitative yield (99%). When a reactant with an alkyl chain, *n*-octyl bromide, was subjected to reaction with the complex, the corresponding thioether **2i** was obtained in 90% yield (Table 2, entry 8). The presence of only a ketone group did not change the result, with the corresponding thioether **2j** obtained in moderate yield. The electronic effects of a substituent at the para position of a phenyl group were examined. Unlike the electron-withdrawing NO_2 group, which furnished **2f** in the highest yield of 83% in diethyl ether, the other substituents (OMe, Br, Me, CN) provided **2b**–**2e** in yields between 62% and 71%, indicating that the substituent group mainly had no effect on the transformation (Table 2, entries 1–5).

This transformation was also applied to the synthesis of diaryl thioethers **3a**–**3d** which, however, required treatment of the aryl halides with Et_3N–P_2S_5 in the presence of 0.2 equivalents of CuI and *N*-methyl-2-pyrrolidinone (NMP) at 90 °C to form **3a**–**3d** in 25–72% yield (Table 2, entries 10–13). All attempts with other copper catalysts (CuO, CuCl, CuBr) and other solvents (e.g., DMF, pyridine) ended with failure. In the case of 2-bromo-1-(4-bromophenyl)ethanone, 3-bromoiodobenzene, and 4-bromoiodobenzene, good chemoselectivity was observed not only with the iodide and bromide functional groups but also with the aliphatic and aromatic bromide units (Table 2, entries 2, 11, 12). In addition, under these reaction conditions, carbonyl groups remained intact (Table 2, entries 1–6, 9).

A possible mechanism for this transformation is illustrated in Scheme 2, based on Phukan's work[24] in which diaryl thioether synthesis was achieved via CuI-catalyzed dominothiolation of aryl halides in the presence of 4-(dimethylamino)pyridine as a ligand. Firstly, the reaction between aryl halide and Et_3N–P_2S_5 (PS_3^- $^+NEt_3$–PS_2) forms

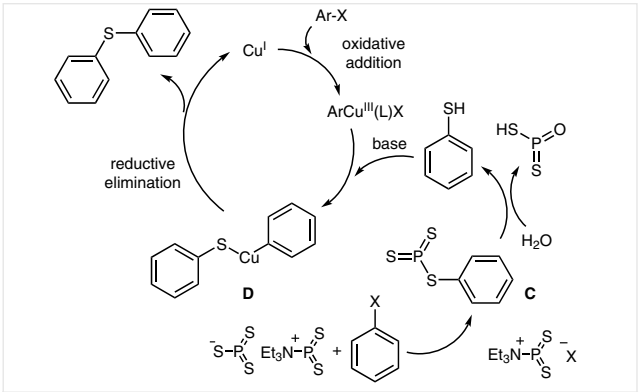
Table 2 Reaction of Et_3N-Activated P_4S_{10} with a Variety of Alkyl and Aryl Halides



Entry	Reactant	Solvent	Time (h)	Product	Yield (%)
1		Et_2O 1,4-dioxane	4 1	**2b**	66 58
2		Et_2O 1,4-dioxane	4 1	**2c**	71 49
3		Et_2O 1,4-dioxane	1 1.5	**2d**	68 46
4		Et_2O 1,4-dioxane	4 0.5	**2e**	62 67
5		Et_2O 1,4-dioxane	5 1	**2f**	83 46
6		Et_2O 1,4-dioxane	4 1.5	**2g**	74 76
7		Et_2O Et_3N	20 20	**2h**	75 99
8		Et_3N	20	**2i**	90
9		Et_2O	1.5	**2j**	65
10[a]		Et_3N	48	**3a**	25
11[a]		Et_3N	24	**3b**	72
12[a]		Et_3N	24	**3c**	43
13[a]		Et_3N	24	**3d**	62

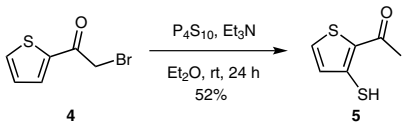
[a] Reaction was performed with CuI (0.2 equiv) and NMP (0.2 equiv) at 90 °C.

$ArPS_3$ species **C**. Then, hydrolysis of **C** produces the corresponding thiol. Treatment of thiol with $ArCu^{III}(L)X$ (X: halide), generated in situ from oxidative addition of Cu(I) to ArX in the presence of ligand NMP, furnishes Cu(III) intermediate **D**. Lastly, reductive elimination from **D** produces the diaryl thioether.



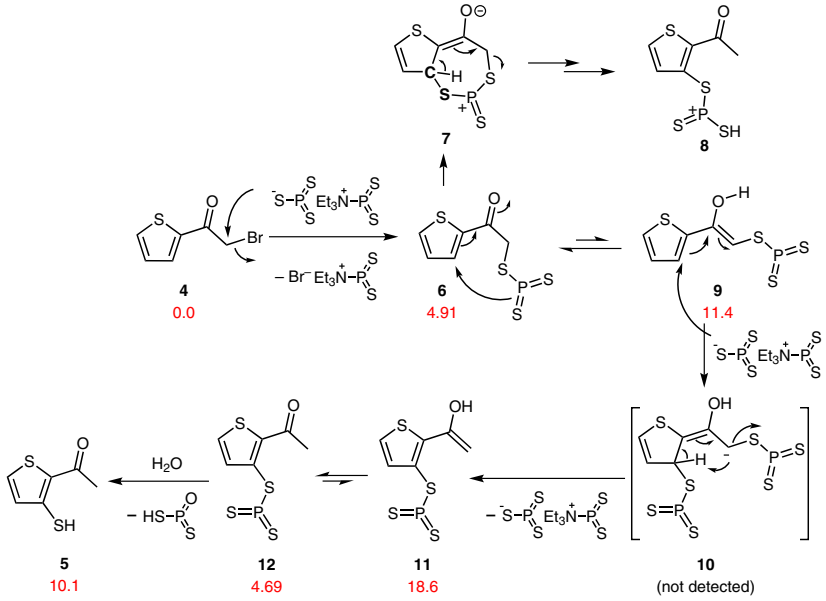
Scheme 2 Proposed mechanism for CuI-catalyzed thioether formation from aryl halides

Thiophene as a heteroaromatic compound was also considered for the transformation. Thionation of 2-(α-bromoacetyl)thiophene (**4**) was performed in the presence of Et_3N in diethyl ether at room temperature for 1 day, which surprisingly led to the formation of 2-acetyl-3-sulfanylthiophene (**5**), the structure of which was confirmed by ^1H and ^{13}C NMR spectroscopy (Scheme 3).



Scheme 3 Reaction of 2-(α-bromoacetyl)thiophene (**4**) with Et_3N-activated P_4S_{10} giving rise to 2-acetyl-3-sulfanylthiophene (**5**) via likely consecutive intramolecular reactions

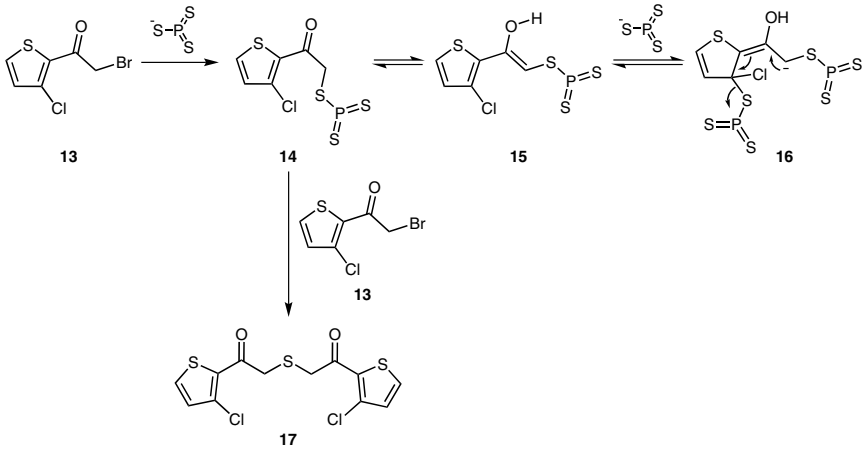
In order to understand the mechanism, DFT calculations were conducted using the Gaussian 09 program (Scheme 4).[25] Optimization of the geometries was performed at the MPW1PW91[26] level with an augmented polarized double-zeta basis set (aug-cc-pVDZ), unless otherwise stated, owing to the fact that it provides reasonable results for structures possessing phosphorus and sulfur atoms.[27] A double-zeta quality basis set (LANL2DZ)[28] containing Hay and Wadt's effective core potential (ECP) was applied on the bromine atom, as implemented in Gaussian 09. The solvent effect (Et_2O) was incorporated by using a self-consistent reaction field (SCRF) with a UFF (universal force field) parametrization of the polarizable continuum model (PCM).[29] The minima of the calculated structures were verified by analyzing the harmonic vibrational frequencies, using analytical second derivatives, which gave NImag = 0.



Scheme 4 Reaction of 2-(α-bromoacetyl)thiophene (**4**) with $Et_3N–P_2S_5$ affording 2-acetyl-3-sulfanylthiophene (**5**) [(CPCM:Et_2O)-MPW1PW91/aug-cc-pVDZ level, relative Gibbs free energies including unscaled ZPE are given in kcal·mol^{-1}]

Based on DFT calculations, S_N2 reaction of activated P_4S_{10} ($Et_3N–P_2S_5$, PS_3^- $^+NEt_3–PS_2$) with 2-(α-bromoacetyl)thiophene (**4**) resulted in an endothermic product **6** (Scheme 4). All calculation attempts to undergo an intramolecular ring-closure reaction of **6** to form zwitterionic seven-membered ring **7**, which could lead to **8** via a rearrangement, were unfortunately failed by a ring-opening reaction and rendering compound **6** back. Optimization of **7** was also performed by freezing the newly generated C–S single bond (in bold) which, however, led to cleavage of the S–P bond and the formation of a thiocyclopropane-fused dihydrothiophene molecule. Then, the calculation was continued with keto–enol tautomerization of **6**, furnishing **9**, which had a 6.5 kcal·mol^{-1} higher energy than **6**. This was followed by attack of PS_3^- $^+NEt_3–PS_2$ at the thiophene ring giving rise to the corresponding enol **11** with energy of 18.6 kcal·mol^{-1}. The possible carbanion intermediate **10**, expected from the reaction of **9** with a second PS_3^-, could not be located, indicating successive electron delocalization and simultaneous proton abstraction, and consequently cleavage of the PS_3^- unit. Keto–enol tautomerization provided the corresponding ketone **12**, with 13.9 kcal·mol^{-1} less energy than enol **11**. Finally, hydrolysis resulted in mercapto product **5** and $HPOS_2$ (Scheme 4).

The reaction of thiophene **13** (Scheme 5), possessing Cl in place of the hydrogen atom proximate to the carbonyl



Scheme 5 Reaction of 2-(α-bromoacetyl)-3-chlorothiophene (**13**) with $Et_3N–P_2S_5$ providing 2,2′-thiobis(1-(3-chlorothiophen-2-yl)ethanone) (**17**)

group in compound **4**, with $Et_3N–P_2S_5$ in diethyl ether was realized to unveil whether the reaction proceeds via the proposed mechanism depicted in Scheme 4. Indeed, the expected anion **16**, generated from the second PS_3^- attack at the Cl-substituted carbon atom, brought about cleavage of the second PS_3 unit due to the weaker C–S bond with respect to the C–Cl bond, and resulted in formation of **14** after keto–enol tautomerization. As a result, **14** undergoes an intermolecular reaction with **13** leading to the corresponding thioether **17**.

In conclusion, we have described a useful and simple methodology to synthesize various thioethers possessing alkyl, benzyl, aryl, and carbonyl groups. This methodology provides mild conditions for the displacement of halogens by sulfur using the commercially available, inexpensive, easy-to-handle, and chemically stable sulfur source P_4S_{10} under noninert conditions. The important applicability of this procedure was demonstrated with various substrates which provided the corresponding thioethers in excellent yields and with a good functional group tolerance. Moreover, an intriguing reaction of 2-(α-bromoacetyl)thiophene (**4**) with activated P_4S_{10} ($Et_3N–P_2S_5$) was also supported by DFT calculations. Treatment of thiophene **13**, containing a neighboring Cl atom, with $Et_3N–P_2S_5$ resulted in the corresponding thioether **17**, which is a strong experimental backup for inclusion of the follow-up reactions of intermediate **10**. Further exploration of this methodology and extension to the synthesis of unsymmetrical and other heteroaromatic thioethers are currently in progress in our laboratory.

All reagents were used as received from commercial sources, without further purification. Analytical TLC was performed using Merck silica gel G F_{254} plates. Flash column chromatography was performed with silica gel (200–300 mesh). IR measurements were performed on a Nicolet 6700 FT-IR instrument (ATR, diamond). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian NMR spectrometer (500 MHz); proton and carbon chemical shifts are reported in ppm downfield from TMS. Mass spectra were recorded on Bruker micrOTOF-Q and Thermo LCQ Deca ion trap mass spectrometers.

Alkyl Thioethers 2; General Procedure

A mixture of P_4S_{10} (0.5 equiv) and Et_3N (10 mL) was stirred at rt for 30 min and then alkyl bromide (1.0 equiv) was added. The reaction mixture was allowed to stir until the alkyl bromide was completely consumed, as monitored by TLC. Then, it was quenched with saturated aqueous NH_4Cl solution and extracted with Et_2O (3 × 10 mL). After successive washing with water and brine, the organic layer was dried over Na_2SO_4. The product was purified by column chromatography over silica gel (*n*-hexane–EtOAc). The NMR data of **2a**–**d**[30] and **2f**–**j**[31–35] align well with the corresponding literature values.

2-(2-Oxo-2-phenylethylsulfanyl)-1-phenylethanone (2a)[30]

White needless; yield: 106 mg (77%; Table 1, entry 10).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 4 H), 7.47 (t, *J* = 8.0 Hz, 4 H), 7.59 (t, *J* = 8.0 Hz, 2 H), 7.97 (d, *J* = 8.0 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.6, 128.6, 128.7, 133.5, 135.3, 194.2.

1-(4-Methoxyphenyl)-2-[2-(4-methoxyphenyl)-2-oxo-ethylsulfanyl]ethanone (2b)[30]

Pale yellow solid; yield: 102 mg (66%; Table 2, entry 1).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.85 (s, 6 H), 3.92 (s, 4 H), 6.92 (d, *J* = 9.0 Hz, 4 H), 7.94 (d, *J* = 9.0 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.4, 55.4, 113.8, 128.3, 130.9, 163.8, 192.9.

1-(4-Bromophenyl)-2-[2-(4-bromophenyl)-2-oxoethylsulfanyl]ethanone (2c)[30]

White solid; yield: 115 mg (71%; Table 2, entry 2).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92 (s, 4 H), 7.62 (dd, *J* = 8.5, 2.0 Hz, 4 H), 7.82 (dd, *J* = 8.5, 2.0 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.4, 128.9, 130.1, 132.1, 134.0, 193.0.

2-(2-Oxo-2-*p*-tolylethylsulfanyl)-1-*p*-tolylethanone (2d)[30]

Off-white solid; yield: 96 mg (68%; Table 2, entry 3).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 3.95 (s, 4 H), 7.25 (d, *J* = 8.0 Hz, 4 H), 7.86 (d, *J* = 8.5 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 37.6, 128.7, 129.4, 132.9, 144.4, 193.9.

1-(4-Cyanophenyl)-2-[2-(4-cyanophenyl)-2-oxoethylsulfanyl]ethanone (2e)

Light brown solid; yield: 97 mg (67%; Table 2, entry 4); mp 126–128 °C.

IR (ATR, diamond): 2961 (m), 2918 (m), 2890 (m), 2849 (m), 2231 (m, C≡N), 1684 (s, C=O), 1605 (m), 1401 (m), 1259 (s), 1012 (s), 794 (s), 570 cm^{-1} (m, C–S).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.95 (s, 4 H), 7.78 (d, *J* = 8.5 Hz, 4 H), 8.04 (d, *J* = 8.5 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.5, 116.9, 117.7, 129.0, 132.6, 138.2, 192.4.

HRMS (EI): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{13}N_2O_2S$: 321.06922; found: 321.06915.

1-(4-Nitrophenyl)-2-[2-(4-nitrophenyl)-2-oxoethylsulfanyl]ethanone (2f)[31]

Light red solid; yield: 123 mg (83%; Table 2, entry 5).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 4 H), 8.12 (d, *J* = 8.4 Hz, 4 H), 8.33 (d, *J* = 8.4 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.7, 124.0, 129.7, 139.7, 150.6, 192.2.

1-(1,1′-Biphenyl-4-yl)-2-[2-(1,1′-biphenyl-4-yl)-2-oxoethylsulfanyl]ethanone (2g)[32]

Off-white solid; yield: 117 mg (76%; Table 2, entry 6).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.03 (s, 4 H), 7.42 (t, *J* = 7.5 Hz, 2 H), 7.48 (t, *J* = 7.5 Hz, 4 H), 7.62 (d, *J* = 7.5 Hz, 4 H), 7.70 (d, *J* = 8.5 Hz, 4 H), 8.03 (d, *J* = 8.5 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.7, 127.3, 127.4, 128.3, 129.0, 129.3, 134.1, 139.7, 146.3, 193.8.

Dibenzyl Sulfide (2h)[33]

Pale yellow liquid; yield: 125 mg (99%; Table 2, entry 7).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.70 (s, 4 H), 7.38 (d, *J* = 8.8 Hz, 4 H), 8.20 (d, *J* = 8.8 Hz, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 42.2, 123.8, 130.0, 144.7, 147.3, 160.6.

Di-*n*-octyl Sulfide (2i)[34]

Colorless liquid; yield: 121 mg (90%; Table 2, entry 8).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.5 Hz, 6 H), 1.40–1.75 (m, 24 H), 2.88 (t, *J* = 7.2 Hz, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.5, 28.8, 29.1, 31.8, 38.9, 39.2.

1-(2-Oxopropylsulfanyl)propan-2-one (2j)[35]

Pale yellow solid; yield: 60 mg (65%; Table 2, entry 9).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (s, 6 H), 3.42 (s, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 41.6, 202.6.

Aryl Thioethers 3; General Procedure

A mixture of P_4S_{10} (1.11 g, 2.50 mmol) and Et_3N (5.0 mL) was stirred at rt for 15 min and then aryl halide (halide: Br, I) (1.00 mmol), CuI (38.1 mg, 0.2 mmol), and NMP (19.8 mg, 0.2 mmol) were added. The reaction mixture was stirred at 90 °C until the aryl halide was completely consumed, as monitored by TLC. Then, it was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was washed with water and brine, and dried over Na_2SO_4. The product was purified by column chromatography over silica gel (*n*-hexane–CH_2Cl_2, 5:1). The NMR data of **3a**–**d**[13b,e,36] match well with reported data.

Diphenyl Sulfide (3a)[13b]

Colorless liquid; yield: 60 mg (25%; Table 2, entry 10).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 7.5 Hz, 4 H), 7.28 (d, *J* = 7.5 Hz, 2 H), 7.50 (dd, *J* = 8.2, 1.2 Hz, 4 H).

Bis(3-bromophenyl) Sulfide (3b)[13e]

Yellow liquid; yield: 87 mg (72%; Table 2, entry 11).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.16 (dt, *J* = 7.2, 1.25 Hz, 2 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.43 (dd, *J* = 8.0, 1.25 Hz, 2 H), 7.63 (d, *J* = 1.25 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 128.7, 128.8, 129.3, 132.8, 144.4.

Bis(4-bromophenyl) Sulfide (3c)[13b]

White solid; yield: 52 mg (43%; Table 2, entry 12).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.5 Hz, 4 H), 7.45 (d, *J* = 8.5 Hz, 4 H).

Bis(4-methoxyphenyl) Sulfide (3d)[13b,36]

Yellow liquid; yield: 65 mg (62%; Table 2, entry 13).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (s, 6 H), 6.88 (d, *J* = 7.5 Hz, 4 H), 7.45 (d, *J* = 7.5 Hz, 4 H).

2-Acetyl-3-sulfanylthiophene (5)[37]

2-(α-Bromoacetyl)thiophene (**4**) (100 mg, 488 µmol) was added to a solution of P_4S_{10} (109 mg, 244 µmol) and Et_3N (247 mg, 2.44 mmol) in Et_2O (10 mL) at rt. After the reaction mixture had been stirred for 24 h, it was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layer was dried over Na_2SO_4. Removal of the solvent furnished **5** as a dark yellow oil; yield: 40.0 mg (253 µmol, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.49 (s, 3 H), 2.56 (s, 1 H), 7.08 (d, *J* = 4.0 Hz, 1 H), 7.41 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.2, 122.7, 131.2, 132.5, 145.9, 189.5.

2,2′-Thiobis(1-(3-chlorothiophen-2-yl)ethanone) (17)

2-(α-Bromoacetyl)-3-chlorothiophene (**13**) (100 mg, 417 µmol) was added to a solution of P_4S_{10} (92.8 mg, 209 µmol) and Et_3N (211 mg, 2.09 mmol) in Et_2O (10 mL) at rt. After the reaction mixture had been stirred for 18 h, it was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layer was dried over Na_2SO_4. Removal of the solvent was followed by column chromatography over silica gel (*n*-hexane–CH_2Cl_2, 1:1) to furnish **17** as an orange oil; yield: 50.0 mg (143 µmol, 69%).

IR (ATR, diamond): 3102 (m), 2902 (m), 2890 (m), 2849 (m), 1639 (s, C=O), 1496 (s), 1403 (s), 1273 (s), 1185 (s), 726 (s, C–Cl), 556 cm^{-1} (m, C–S).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.03 (s, 4 H), 7.02 (d, *J* = 5.5 Hz, 2 H), 7.58 (d, *J* = 5.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.4, 129.0, 130.7, 132.5, 135.8, 186.1.

HRMS (EI): *m*/*z* $[M + 1]^+$ calcd for $C_{12}H_9O_2Cl_2S_3$: 350.9136; found: 350.9137.

Acknowledgment

G.T. and M.E.C. thank the Scientific and Technological Research Council of Turkey (TUBITAK) for Postdoctoral Research Fellowships BIDEB 2218 and 2216 programs, respectively. We thank Okan Demirel (MS) for his help with the work related to compound **17**. We are indebted to the National Center for High Performance Computing (UYBHM) (project: tvddvb) and the High-Performance-Computing (HPC) Linux Cluster HorUS of the University of Siegen for the computer time provided. Unsped Global Logistics is gratefully acknowledged for financial support.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561673. Included are copies of ^{1}H and ^{13}C NMR spectra, and computed Cartesian coordinates.

References

(1) (a) Cinar, M. E.; Ozturk, T. *Chem. Rev.* **2015**, *115*, 3036. (b) Cinar, M. E.; Ozturk, T. In *Thiophenes*; Joule, J. A., Ed.; Springer-Verlag: Berlin, Heidelberg, **2014**, 161.

(2) (a) Lee, D.; Kim, G.; Yin, J.; Yoon, J. *Chem. Commun.* **2015**, *51*, 6518. (b) Okamoto, T.; Mitsui, C.; Yamagishi, M.; Nakahara, K.; Soeda, J.; Hirose, Y.; Miwa, K.; Sato, H.; Yamano, A.; Matsushita, T.; Uemura, T.; Takeya, J. *Adv. Mater.* **2013**, *25*, 6392. (c) Mori, T.; Nishimura, T.; Yamamoto, T.; Doi, I.; Miyazaki, E.; Osaka, I.; Takimiya, K. *J. Am. Chem. Soc.* **2013**, *135*, 13900.

(3) (a) Liu, G.; Huth, J. R.; Olejniczak, E. T.; Mendoza, R.; DeVries, P.; Leitza, S.; Reilly, E. B.; Okasinski, G. F.; Nielsen, E.; Fesik, S. W.; von Geldern, T. W. *J. Med. Chem.* **2001**, *44*, 1202. (b) Beletskaya,

I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Stump, B.; Eberle, C.; Kaiser, M.; Brun, R.; Krauth-Siegel, R. L.; Diederich, F. *Org. Biomol. Chem.* **2008**, *6*, 3935.
(4) (a) Peach, M. E. In *The Chemistry of the Thiol Group*; Patai, S., Ed.; John Wiley & Sons: London, **1974**, 721. (b) Yin, J.; Pidgeon, C. *Tetrahedron Lett.* **1997**, *38*, 5953.
(5) (a) Beletskaya, I. P.; Ananikov, D. P. *Chem. Rev.* **2011**, *111*, 1596. (b) Eichman, C. C.; Stambuli, J. P. *Molecules* **2011**, *16*, 590. (c) Bichler, P.; Love, J. A. *Top. Organomet. Chem.* **2010**, *31*, 39. (d) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (e) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205.
(6) (a) Bordwell, F. G.; Boutan, P. J. *J. Am. Chem. Soc.* **1957**, *79*, 717. (b) Klose, W.; Schwarz, K. *J. Heterocycl. Chem.* **1982**, *19*, 1165. (c) Tazaki, M.; Nagahama, S.; Takagi, M. *Chem. Lett.* **1988**, 339. (d) Shimazaki, M.; Takahashi, M.; Komatsu, H.; Ohta, A.; Kajii, K.; Kodama, Y. *Synthesis* **1992**, 555.
(7) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385.
(8) (a) Percec, V.; Bas, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (b) Beletskaya, I. P.; Ananikov, V. P. *Eur. J. Org. Chem.* **2007**, 3431. (c) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495.
(9) (a) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253. (b) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (c) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397. (d) Li, G. Y. *Angew. Chem. Int. Ed.* **2001**, *40*, 1513. (e) Zheng, N.; McWilliams, J. C.; Fleitz, F. J.; Armstrong, J. D. III; Volante, R. P. *J. Org. Chem.* **1998**, *63*, 9606. (f) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205. (g) Eichman, C. C.; Stambuli, J. P. *J. Org. Chem.* **2009**, *74*, 4005. (h) Jiang, Z.; She, J.; Lin, X. *Adv. Synth. Catal.* **2009**, *351*, 2558.
(10) (a) Correa, A.; Carril, M.; Bolm, C. *Angew. Chem. Int. Ed.* **2008**, *47*, 2880. (b) Wu, W.-Y.; Wang, J.-C.; Tsai, F.-Y. *Green Chem.* **2009**, *11*, 326.
(11) Wong, Y. C.; Jayanth, T. T.; Cheng, C. H. *Org. Lett.* **2006**, *8*, 5613.
(12) (a) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (b) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (c) Taniguchi, N. *Synlett* **2005**, 1687. (d) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 5583. (e) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (f) Bhadra, S.; Sreedhar, B.; Ranu, B. C. *Adv. Synth. Catal.* **2009**, *351*, 2369. (g) Wang, H.; Jiang, L.; Chen, T.; Li, Y. *Eur. J. Org. Chem.* **2010**, 2324. (h) Kabir, M. S.; Lorenz, M.; Van Linn, M. L.; Namjoshi, O. A.; Ara, S.; Cook, J. M. *J. Org. Chem.* **2010**, *75*, 3626.
(13) (a) Kamal, A.; Srinivasulu, V.; Murty, J. N. S. R. C.; Shankaraiah, N.; Nagesh, N.; Reddy, T. S.; Rao, A. V. S. *Adv. Synth. Catal.* **2013**, *355*, 2297. (b) Ke, F.; Qu, Y.; Jiang, Z.; Li, Z.; Wu, D.; Zhou, X. *Org. Lett.* **2011**, *13*, 454. (c) Li, Y.; Nie, C.; Wang, H.; Li, X.; Verpoort, F.; Duan, C. *Eur. J. Org. Chem.* **2011**, 7331. (d) Park, N.; Park, K.; Jang, M.; Lee, S. *J. Org. Chem.* **2011**, *76*, 4371. (e) Wu, X. M.; Hu, W. Y. *Chin. Chem. Lett.* **2012**, *23*, 391. (f) Hartman, W. W.; Smith, L. A.; Dickey, J. B. *Org. Synth.* **1934**, *14*, 36. (g) Taniguchi, N. *Tetrahedron* **2012**, *68*, 10510. (h) Roy, S.; Phukan, P. *Tetrahedron Lett.* **2015**, *56*, 2426. (i) Liu, Y.-C.; Lee, C.-F. *Synlett* **2013**, *24*, 2320. (j) Dubbaka, S. R.; Atthunuri, A. R.; Prakash, K. C.; Rangabashyam, P.; Gadde, S.; Kothandaraman, R. *Synthesis* **2016**, *48*, 1246.
(14) (a) Henry, L. *Ann. Chem. Pharm.* **1869**, *148*, 152. (b) Wislicenus, J. *Z. Chem.* **1869**, 324. (c) Polshettiwar, V. *Synlett* **2004**, 2245.
(15) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2010**, *110*, 3419.
(16) (a) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229. (b) Pedersen, B. S.; Scheibye, S.; Nilson, N. H.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 223. (c) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 299. (d) Pedersen, B. S.; Scheibye, S.; Nilson, N. H.; Clausen, K.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293.
(17) Ozturk, T.; Ertas, E.; Mert, O. *Chem. Rev.* **2007**, *107*, 5210.
(18) Hoffman, H.; Becke-Goehring, M. *Phosphorus Sulfides*, In *Topics in Phosphorus Chemistry*; Vol. 6; Griffith, E. J.; Grayson, M., Eds.; John Wiley and Sons: New York, **1976**, 193.
(19) (a) Castle, R. N.; Kaji, K. *Tetrahedron Lett.* **1962**, 393. (b) Castle, R. N.; Kaji, K.; Gerhardt, G. A.; Guither, W. D.; Weber, C.; Malm, M. P.; Shoup, R. R.; Rhoads, W. D. *J. Heterocycl. Chem.* **1966**, *3*, 79.
(20) Choi, J.; Yoon, N. M. *Synthesis* **1995**, 373.
(21) Gaywood, A. P.; McNab, H. *J. Org. Chem.* **2009**, *74*, 4278.
(22) Hofmann, T.; Schieberle, P. *J. Agric. Food Chem.* **1995**, *43*, 2187.
(23) Bergman, J.; Pettersson, B.; Hasimbegovic, V.; Svensson, P. H. *J. Org. Chem.* **2011**, *76*, 1546.
(24) (a) Roy, S.; Phukan, P. *Tetrahedron Lett.* **2015**, *56*, 2426. (b) Ramana, T.; Saha, P.; Das, M.; Punniyamurthy, T. *Org. Lett.* **2010**, *12*, 84. (c) Sahoo, S. K.; Jamir, L.; Guin, S.; Patel, B. K. *Adv. Synth. Catal.* **2010**, *352*, 2538. (d) Manivel, P.; Prabakaran, K.; Krishnakumar, V.; Khan, F.-R. N.; Maiyalagan, T. *Ind. Eng. Chem. Res.* **2014**, *53*, 7866. (e) Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 1971.
(25) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09, Revision D.01*; Gaussian Inc: Wallingford CT, **2010**.
(26) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664.
(27) Rotter, C.; Evangelisti, C.; Schönberger, S.; Klapötke, T. M.; Karaghiosoff, K. *Chem. Commun.* **2010**, *46*, 5024.
(28) (a) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270. (b) Wadt, W. R.; Hay, P. J. *J. Chem. Phys.* **1985**, *82*, 284. (c) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299.
(29) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.
(30) Karade, N. N.; Tiwari, G. B.; Gampawar, S. V.; Shinde, S. V. *Heteroat. Chem.* **2009**, *20*, 172.
(31) Miyahara, Y. *J. Heterocycl. Chem.* **1979**, *16*, 1147.
(32) Nakayama, J.; Konishi, T.; Ishii, A.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2608.
(33) Enthaler, S. *ChemCatChem* **2011**, *3*, 666.
(34) Wang, M.-L.; Tseng, Y.-H. *React. Kinet. Catal. Lett.* **2004**, *82*, 81.
(35) Böhme, H.; Pfeifer, H.; Schneider, E. *Ber. Dtsch. Chem. Ges.* **1942**, *75*, 900.
(36) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587.
(37) Paulmier, C. *Bull. Soc. Chim. Fr., Part. 2* **1979**, 237.