

Full Paper

***L*-Proline Catalyzed Michael Additions of Thiophenols to α,β -Unsaturated Compounds, Particularly α -Enones, in the Ionic Liquid [bmim]PF₆**

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Abstract: *L*-Proline catalyzed additions of 13 different thiols to 11 different α -enone Michael acceptors in [bmim] PF₆ are reported. Reasonable to high yields of the reaction products were isolated in most cases.

Keywords: Thiols, Enones, Michael Addition, Organocatalysis, Ionic Liquids

Introduction

Addition reactions of thiols to unsaturated ketones have been studied quite frequently, in particular the stereoselective version where chiral metal complexes are often used as catalysts [1,2]. Asymmetric reactions catalyzed by small molecule organic catalysts have become very attractive in recent years [3-8]. *L*-Proline, quinine and ephedrine, as well as 2-(*S*)-phenylaminomethyl-4-(*S*)-hydroxypyrrolidine and 2-(*S*)-(diphenylhydroxymethyl)piperidine and its 1-Boc derivatives have all previously been used as the catalysts for additions of thiols to unsaturated ketones, but they gave only moderate e.e. values [9-14].

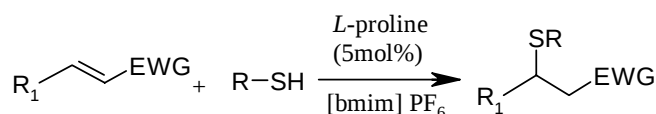
Ionic liquids have emerged in recent years as “green” solvents for many organic reactions, including transition metal-catalyzed reactions [15-23], but they have been less frequently used as the media for organocatalyst catalyzed reactions. We [24] and Loh *et al.* [25] have simultaneously described the excellent results observed for *L*-proline catalyzed aldol reactions in ionic liquids. We have also reported [26] *L*-proline catalyzed additions of carbonyl compounds to β -nitrostyrenes. These

reactions took place with high yields and with high e.e. using just 5 mol % of *L*-proline. Rasalkar very recently described [27] *L*-proline catalysed Michael additions of ketones to nitrostyrene. He tested several ionic liquids for this purpose and the best was found to be 1-methoxyethyl-3-methylimidazolium methanesulfonate ([MOEMIM]OMs), although to achieve good yields it was necessary to prolong the reaction times for up to 60 hours and use up to 40 mol % of the catalyst to achieve 75 % e.e. Hagiwara has recently described [28] organocatalyst catalysed additions of aliphatic aldehydes to methyl vinyl ketone in the ionic liquid [bmim]PF₆. 2-(*S*)-(1-Morpholinomethyl)piperidine was found to be the best catalyst, but the yields of the product were only average and the e.e. values were just 11–51 %. Yadav *et al.* have disclosed [29] the results of Michael additions of thiols to α,β -unsaturated ketones in [bmim]BF₄/H₂O and [bmim]PF₆/H₂O (2:1) mixtures. Similarly Ranu has reported [30] Michael addition of thiols and thiophosphate to α,β -unsaturated carbonyl compounds in [pmim]Br as the reaction medium as well as the catalyst. Salunkhe [31] has used ionic liquids as the medium for the quinidinium bromide catalyzed addition of dimethyl malonate to chalcone. The main aim of our current work was to examine the range of *L*-proline catalysed Michael additions of different thiophenols and thiols to several Michael acceptors.

Results and Discussion

The Michael addition of thiophenol to chalcone catalyzed by 5 mol % of *L*-proline went smoothly when 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) was used as the solvent and nearly quantitative yields of the addition product were isolated after extraction of the ionic liquid with diethyl ether and quick chromatography on a short silica gel column. The possibility of re-use of the ionic liquid/catalyst system was also checked. The yields of the product were practically the same over four experiments (95%–90%), but dropped to 82% in the fifth experiment and to 74% at the sixth experiment. Our next aim was to explore the limits of Michael additions of thiols to substrates with activated double bonds (Scheme 1). The substrate structures are shown in Figure 1, those of the thiols in Figure 2 and those of the products in Figure 3. Results are summarized in Table 1.

Scheme 1



The results proved that addition of different thiols to chalcone is possible and high yields of the products were isolated. Exceptions were **2k**, **2l** and **2m**, which did not afford any Michael addition products, possibly because all of them exist in their thione form. This was substantiated by the fact that **2h** gave 27% of the product. High yields of the products were also achieved in additions to **1g** and **1i**, while low yields were observed in the addition to **1h**, due to the steric hindrance. We were pleased to find that additions with **1e** and **1f** took place, albeit with low yields, because Ranu had previously claimed that additions of thiols to **1e** are not possible [14]. Surprisingly, no product was isolated in the attempted additions of thiophenol to **2j**, **2k** and **2l**, which is in accord with findings of Ranu [30]. A possible explanation for this could be the competitive reversible addition of thiophenol to the functional group.

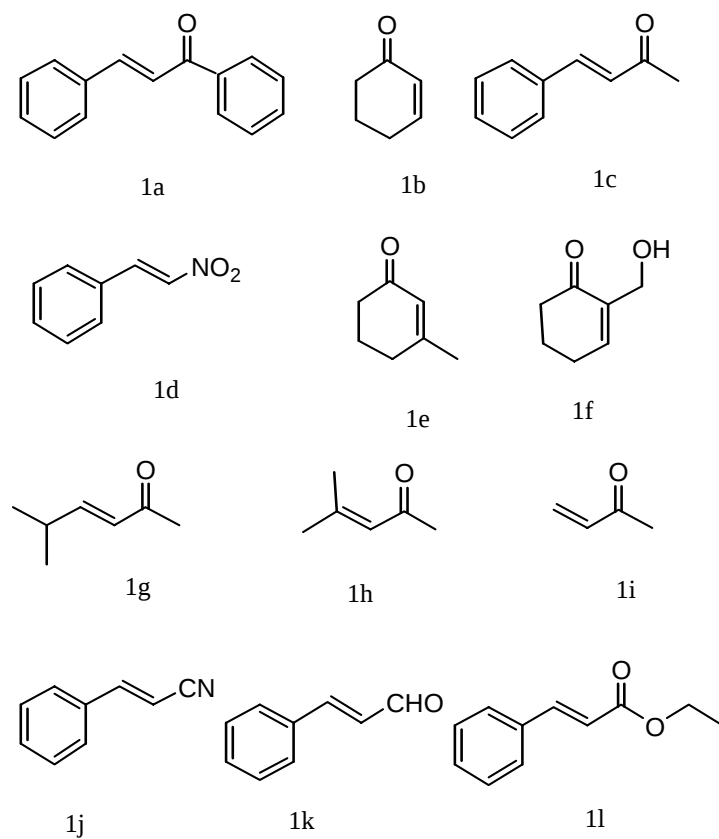
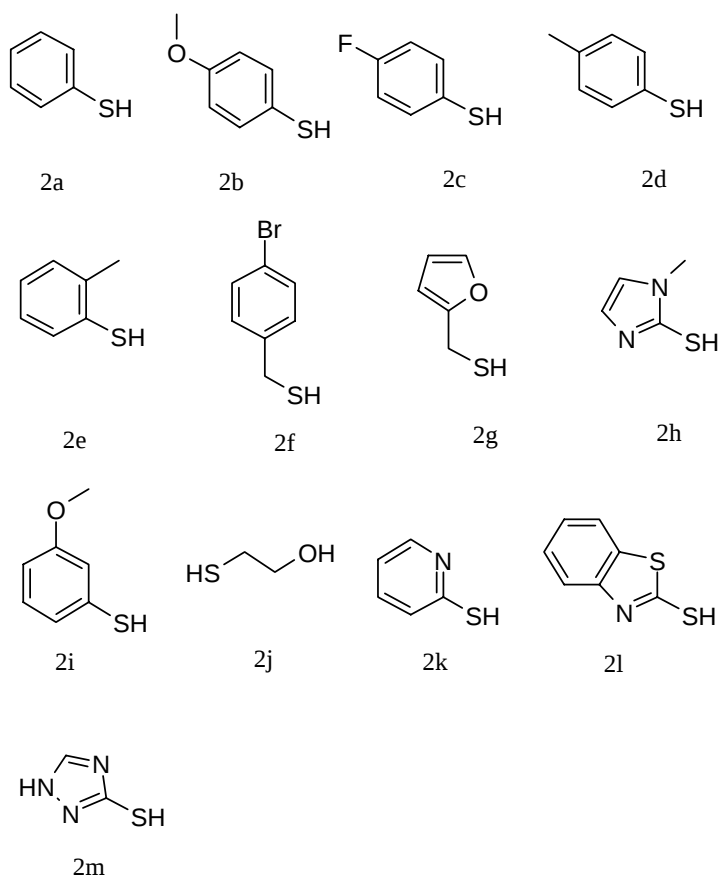
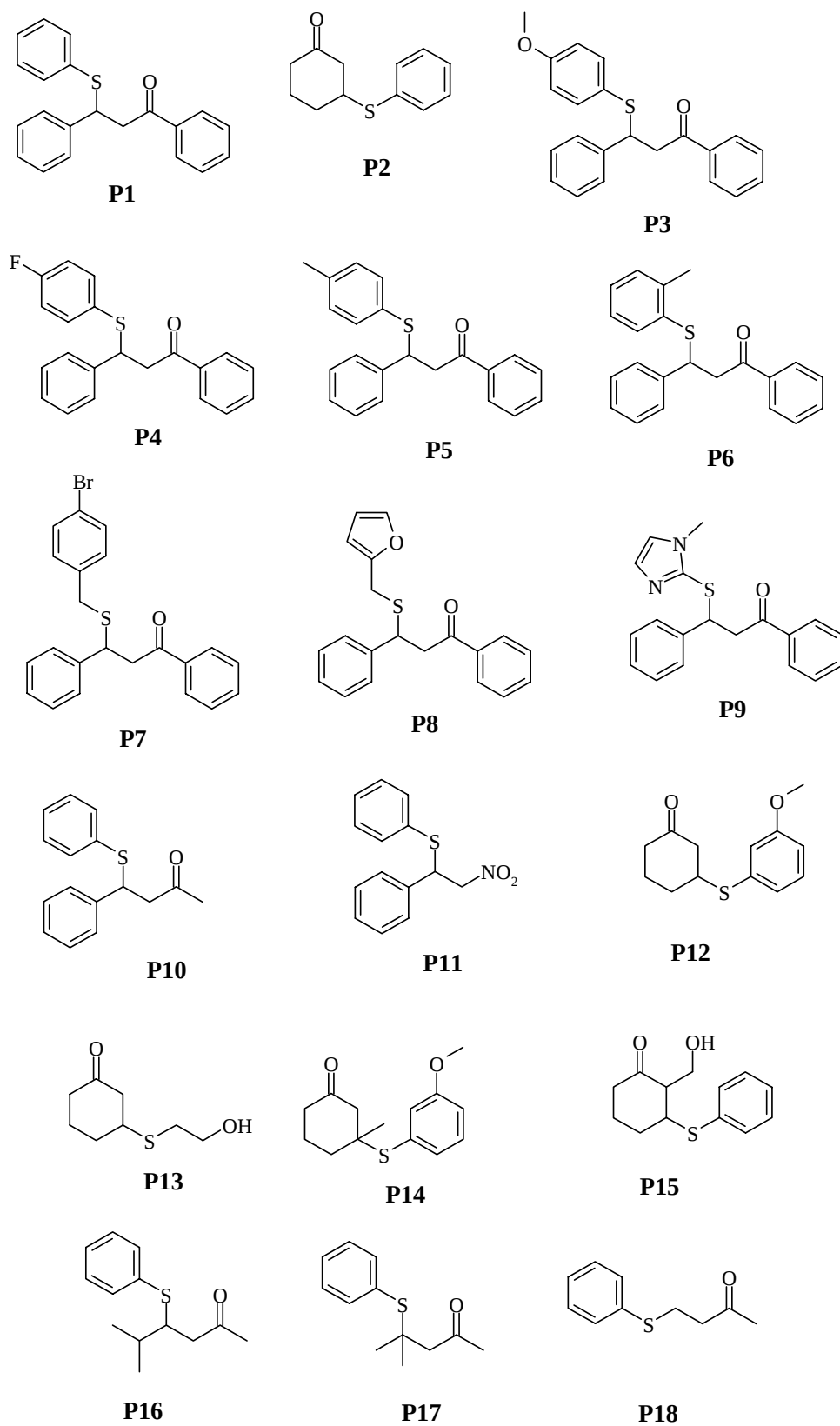
Figure 1. Structures of substrates**Figure 2.** Structures of thiols

Figure 3. Structures of products

We were sorry to find that practically no stereoselectivity was observed for the *L*-proline catalysed additions of different thiols to neither chalcone or cyclohexene-1-one, although this is in accord with the results of Agami [11].

Table 1. Michael additions of thiols to substrates containing activated double bonds

Entry	Substrate	Reagent	Time (min)	Yield (%)	Product
1	1a	2a	10	99	P1
2	1a	2b	5	89.8	P3
3	1a	2c	20	86	P4
4	1a	2d	10	91.5	P5
5	1a	2e	65	74	P6
6	1a	2f	30	74	P7
7	1a	2g	40	83	P8
8 ^a	1a	2h	480	27	P9
9	1b	2a	30	98	P2
10	1b	2i	30	94	P12
11	1b	2j	30	96	P13
12	1c	2a	120	93	P10
13	1d	2a	30	89	P11
14	1e	2i	60	19	P14
15 ^b	1f	2a	60	18	P15
16	1g	2a	30	75	P16
17	1h	2a	30	30	P17
18	1i	2a	30	95	P18

^a Reaction was performed at 90 °C. No product was detected at r.t./24 h.

^b The yield was determined from the ¹H-NMR spectrum.

Conclusions

Our examination proved that ionic liquid is a solvent of choice for Michael additions of different thiols to a range of Michael acceptors catalyzed by *L*-proline. Products are isolated in reasonable to high yields by simple extraction into organic solvent.

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Experimental

General

NMR spectra were measured on a Varian Gemini 2000 spectrometer operating at 300 MHz for ^1H and 75 MHz for ^{13}C , respectively. Deuteriochloroform was used as solvent and tetramethylsilane was used as an internal standard.

General experimental procedure

L-Proline (5.75 mg, 5 mol%) and the chosen acceptor (1 mmol) was added to degassed [bmim] PF₆ ionic liquid (1 mL) and the mixture was stirred for 10 min at r.t.. Thiol (1.1 mmol) was then added and the reaction mixture was stirred vigorously for the chosen time and at the chosen temperature (see Tables). The product was extracted with several portions of diethyl ether and the extract was chromatographed on a SiO₂ column using 9 : 1 hexane/ethyl acetate in all cases. Products were isolated as pure materials and their structure was proven by ^1H -NMR and ^{13}C -NMR spectra and, in the case of new compounds, also by microanalysis.

Characterization of the products

1,3-Diphenyl-3-(phenylsulfanyl)propan-1-one (P1) ^1H -NMR: 7.89 (d, 2H, $J=6.9\text{Hz}$), 7.54-7.34 (m, 6H), 7.28-7.21 (m, 7H), 4.95 (dt, 1H, $J=8.1\text{Hz}$, $J=6\text{Hz}$), 3.61 (dd, 2H, $J=8.1\text{Hz}$, $J=6\text{Hz}$), which is in accord with the literature values [32].

3-(Phenylsulfanyl)cyclohexan-1-one (P2) ^1H -NMR: 7.44-7.28 (m, 5H), 3.43 (m, 1H), 2.27 (2d, 1H, $J=4.8\text{Hz}$), 2.42 (m, 3H-cycl.), 2.17 (m, 2H-cycl.), 1.17 (m, 2H-cycl.), which is in accord with [33].

3-(4-Methoxyphenylsulfanyl)-1,3-diphenylpropan-1-one (P3) ^1H -NMR: 7.87 (d, 2H), 7.66-7.22 (m, 10H), 6.75 (d, 2H), 4.78 (t, 1H), 3.77 (s, 3H), 3.59 (m, 2H), which is in accord with [34].

3-(4-Fluorophenylsulfanyl)-1,3-diphenylpropan-1-one (P4) ^1H -NMR: 7.89 (d, 2H), 7.66-7.24 (m, 10H), 6.90 (t, 2H), 4.84 (t, 1H), 3.60 (m, 2H); ^{13}C -NMR: 197.0, 164.5, 161.3, 145.0, 141.3, 136.9, 136.2, 136.1, 133.5, 132.9, 130.7, 129.2, 128.9, 128.6, 128.2, 127.9, 127.6, 116.2, 115.9, 49.3, 44.5.

1,3-Diphenyl-3-(p-tolylsulfanyl)propan-1-one (P5) ^1H -NMR: 8.04 (d, 2H), 7.66-7.20 (m, 12H), 4.88 (dt, 1H, $J=6.3\text{Hz}$, $J=1.8\text{Hz}$), 3.60 (m, 2H), 2.29 (s, 3H), which is in accord with [35]

1,3-Diphenyl-3-(o-tolylsulfanyl)propan-1-one (P6) ^1H -NMR: 7.87 (d, 2H), 7.55-7.12 (m, 12H), 4.89 (dt, 1H, $J=6\text{Hz}$, $J=1.8\text{Hz}$), 3.63 (m, 2H), 2.33 (s, 3H); ^{13}C -NMR: 196.7, 151.5, 142.3, 141.6, 136.9, 133.4, 128.8, 128.7, 128.3, 128.3, 127.6, 110.6, 107.8, 45.3, 44.3, 28.1; Microanalysis: for C₂₂H₂₀OS (M.W.= 332.22) calc.: C, 79.48%; H, 6.06%; S, 9.64%; found: C, 79.51%; H, 6.11%; S, 9.49%.

3-(4-Bromobenzylsulfanyl)-1,3-diphenylpropan-1-one (P7) $^1\text{H-NMR}$: 7.84 (d, 2H), 7.54-7.05 (m, 12H), 4.42 (t, 1H), 3.48 (m, 4H); $^{13}\text{C-NMR}$: 196.8, 141.7, 137.2, 136.8, 133.4, 131.7, 130.8, 128.8, 128.2, 128.2, 127.6, 121.0, 45.4, 44.4, 35.4; Microanalysis: calc. for $\text{C}_{22}\text{H}_{19}\text{BrOS}$ (M.W.= 411.36) C, 64.24%; H, 4.66%; Br, 19.42%; O, 3.89%; S 7.79%; found: C, 64.41%; H, 4.63%; Br, 19.18%; S, 7.71%.

3-(Furan-2-ylmethylsulfanyl)-1,3-diphenylpropan-1-one (P8) $^1\text{H-NMR}$: 7.86 (d, 2H), 7.54-7.22 (m, 9H), 6.29 (dt, 1H, $J=1.8\text{Hz}$, $J=1.2\text{Hz}$), 6.11 (d, 1H, $J=3.3\text{Hz}$), 4.57 (dd, 1H, $J=6.3\text{Hz}$, $J=1.8\text{Hz}$), 3.54 (m, 2H); $^{13}\text{C-NMR}$: 197.4, 141.7, 140.9, 137.2, 133.9, 133.6, 133.5, 130.7, 129.0, 128.8, 128.5, 128.1, 128.0, 127.8, 126.8, 47.9, 45.1, 21.0; Microanalysis: calc. for $\text{C}_{20}\text{H}_{18}\text{O}_2\text{S}$ (M.W.= 322.43): C, 74.50%; H, 5.63%; S, 9.94%; found: C, 75.28%; H, 5.82%; S, 10.49%.

3-(1-Methyl-1H-imidazol-2-ylsulfanyl)-1,3-diphenylpropan-1-one (P9) $^1\text{H-NMR}$: 8.00 (d, 2H), 7.58-7.21 (m, 8H), 6.65 (d, 1H, $J=3.3\text{Hz}$), 6.57 (d, 1H, $J=2.1\text{Hz}$), 4.07 (d, 1H, $J=6\text{Hz}$), 4.03 (d, 1H, $J=6\text{Hz}$), 3.84 (dd, 1H, $J=9\text{Hz}$, $J=8.7\text{Hz}$), 3.62 (s, 3H); $^{13}\text{C-NMR}$: 196.4, 137.9, 136.7, 133.8, 129.3, 129.1, 128.7, 128.7, 128.2, 118.3, 115.4, 57.4, 42.0, 35.4; Microanalysis: calc. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{OS}$ (M.W.=322.43): C, 70.78%; H, 5.63%; N, 8.69%; S, 9.94%; found: C, 70.62%; H, 5.52%; N, 8.56%; S, 9.69%.

4-Phenyl-4-Phenylsulfanylbutan-2-one (P10) $^1\text{H-NMR}$: 7.30-7.19 (m, 10H), 4.71 (t, 1H), 3.04 (m, 2H), 2.06 (s, 3H), which is in accord with [36].

(2-Nitro-1-phenylethyl)phenyl sulfide (P11) $^1\text{H-NMR}$: 7.41-7.26 (m, 10H), 4.91-4.76 (m, 2H), 4.71 (dd, 1H, $J=6.6\text{Hz}$, $J=4.5\text{Hz}$), which is in accord with [37].

3-(3-Methoxyphenylsulfanyl)cyclohexanone (P12) $^1\text{H-NMR}$: 7.23 (m, 2H), 7.01 (d, 1H, $J=18.5\text{Hz}$), 6.96 (d, 1H, $J=7.8\text{Hz}$), 6.83 (dd, 1H, $J=2.7\text{Hz}$, $J=2.1\text{Hz}$), 3.81 (s, 3H), 3.46 (m, 1H), 2.73 (dd, 1H, $J=4.8\text{Hz}$, $J=3\text{Hz}$), 2.41-2.22 (m, 3H), 2.17 (m, 2H), 1.75 (m, 2H), which is in accord with [10].

3-(2-Hydroxyethylsulfanyl)cyclohexanone (P13) $^1\text{H-NMR}$: 3.74 (m, 2H), 3.12 (m, 1H), 2.78 (m, 2H), 2.71 (m, 1H), 2.44-2.32 (m, 3H), 2.19-2.05 (m, 3H), 1.78-1.69 (m, 2H); $^{13}\text{C-NMR}$: 208.7, 61.1, 48.5, 42.9, 41.1, 33.9, 32.0, 24.3; Microanalysis: calc. for $\text{C}_8\text{H}_{14}\text{O}_2\text{S}$ (M.W.=174.26): C, 55.14%; H, 8.10%; S, 8.40%; found: C, 55.19%; H, 8.14%; S, 8.49%.

3-(3-Methoxyphenylsulfanyl)-3-methylcyclohexanone (P14) $^1\text{H-NMR}$: 7.27 (t, 1H); 7.09 (m, 2H); 7.95 (dd, 1H, $J=2.4\text{Hz}$, $J=0.9\text{Hz}$); 3.83 (s, 3H); 2.53 (d, 1H); 2.35-2.15 (m, 4H); 1.95-1.80 (m, 3H); 1.30 (s, 3H); $^{13}\text{C-NMR}$: 209.6, 160.4, 123.3, 120.0, 115.7, 113.5, 112.9, 55.8, 53.6, 52.3, 40.8, 37.2, 28.9, 22.5; Microanalysis: calc. for $\text{C}_{14}\text{H}_{18}\text{O}_2\text{S}$ (M.W.=250.36): C, 67.17%; H, 7.25%; S, 12.81%; found: C, 67.10%; H, 7.21%; S, 12.90%.

2-Hydroxymethyl-3-phenylsulfanylcyclohexanone (P15) $^1\text{H-NMR}$: 7.50-7.46 (m, 2H), 7.34-7.31 (m, 3H), 4.23-4.20 (dd, 1H, $J=6\text{Hz}$, $J=2.1\text{Hz}$), 4.09-3.99 (dd, 1H, $J=6.1\text{Hz}$, $J=2.9\text{Hz}$), 3.25 (dt, 1H, $J=4.2\text{Hz}$), 2.56 (bs, 1H), 2.49 (m, 2H), 2.30 (m, 2H), 2.09 (m, 1H), 1.84 (m, 1H), 1.63 (m, 1H); ^{13}C -

NMR: 198.4, 138.9, 137.7, 137.2, 136.9, 136.7, 135.3, 62.4, 60.1, 56.8, 48.8, 32.8, 25.8; Microanalysis: calc. for C₁₃H₁₆O₂S (M.W.=236.34): C, 66.07%; H, 6.82%; S, 13.57%; found: C, 66.16%; H, 6.87%; S, 13.65%.

5-Methyl-4-phenylsulfanylhexas-2-one (P16) ¹H-NMR: 7.43 (d, 2H), 7.30-7.20 (m, 3H), 3.61 (m, 1H), 2.69 (d, 2H, *J*=6.6Hz), 2.14 (s, 3H), 1.97 (m, 1H), 1.01 (d, 3H), 0.96 (d, 3H); ¹³C-NMR: 206.8, 135.7, 131.6, 128.9, 126.7, 50.7, 45.9, 31.9, 30.7, 19.5, 18.9; Microanalysis: calc. for C₁₃H₁₈OS (M.W.=222.35): C, 70.22%; H, 8.16%; S, 14.42%; found: C, 70.18%; H, 8.10%; S, 14.39%.

4-Methyl-4-phenylsulfanyl-pentan-2-one (P17) ¹H-NMR: 7.38 (m, 2H), 7.20 (m, 3H), 2.52 (s, 2H), 1.98 (s, 3H), 1.22 (s, 6H), which is in accord with [38].

4-Phenylsulfanyl-butan-2-one (P18) ¹H-NMR: 7.38-7.28 (m, 4H), 7.24 (t, 1H), 3.17 (t, 2H), 2.77 (t, 2H), 2.17 (s, 3H), which is in accord with [39].

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Sample availability: Samples of the reaction products can be obtained from the author (P.K.)