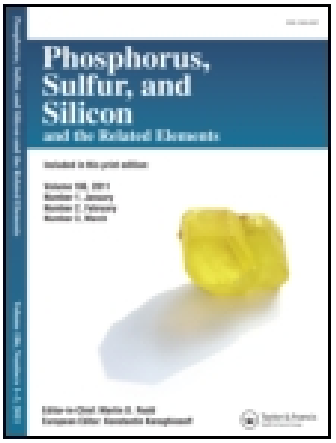


Phosphorus, Sulfur, and Silicon and the Related Elements

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# Microwave-Assisted Pd-Catalyzed Desulfitative C—S Coupling of Arylsulfinate Metal Salts and Alkanethiols

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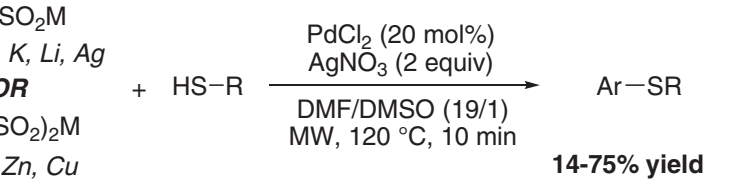
# MICROWAVE-ASSISTED PD-CATALYZED DESULFITATIVE C−S COUPLING OF ARYLSULFINATE METAL SALTS AND ALKANETHIOLS

**Junchen Li, Xiaojing Bi, Hongmei Wang, and Junhua Xiao**
*State Key Laboratory of NBC Protection for Civilian, Beijing, P. R. China*

## GRAPHICAL ABSTRACT




**Abstract** *This paper reports a palladium-catalyzed C-S coupling of arylsulfinate metal salts and alkanethiols via liberation of sulfur dioxide. The use of $PdCl_2$ as the catalyst in combination with $AgNO_3$ as the oxidant under microwave irradiation results in the synthetically and biologically important aryl alkyl sulfides. A variety of arylsulfinate metal salts, such as sodium, potassium, lithium, silver, zinc, and copper salts, are tolerated well in this reaction.*

**Keywords** Desulfitative coupling; C-S coupling; arylsulfinate metal salts; thiols

## INTRODUCTION

Aryl alkyl sulfide moieties represent one of the most important molecules that are widely used in many pharmaceuticals, such *asthloridazine*,[1] *diltiazem*,[2] *nelfinavir*,[3] and *bicalutamide*.[4] Though great achievements have been made in recent years, current synthetic methodologies of aryl alkyl sulfide are restricted to the Michael addition of $\alpha,\beta$-unsaturated compounds[5] or the coupling of halide substrates with thiols/disulfides.[6] The narrow scope of the $\alpha,\beta$-unsaturated compounds and the relatively high reactivity of halide substrates impedes their further application. Therefore, development of environment-benign and inexpensive alternatives for the synthesis of aryl alkyl sulfides is still a great challenge. Liu reported a convenient decarboxylative C−S coupling using a bimetallic catalytic system (Scheme 1a).[7] However, only electron-deficient aromatic carboxylic acids were employed in this reaction. Although aromatic boronic acids exhibit good functional group tolerance,

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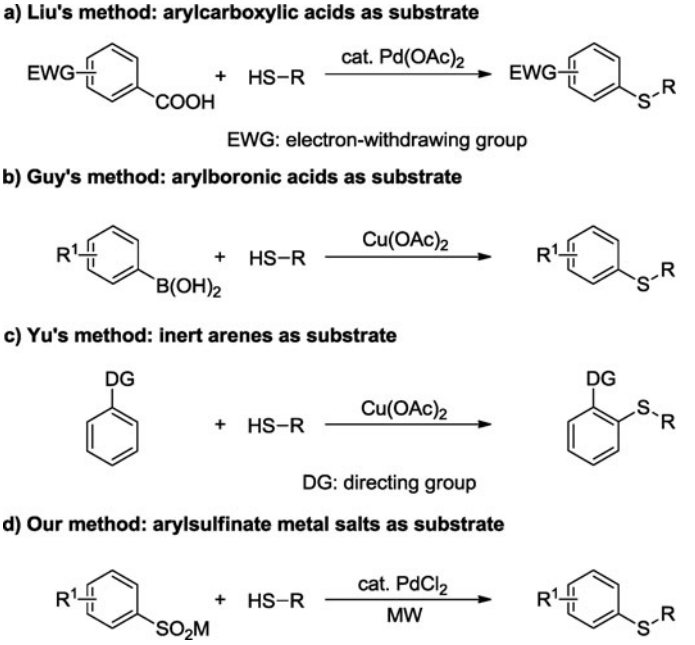



**Scheme 1** Metal-catalyzed methods for the construction of C-S bond.

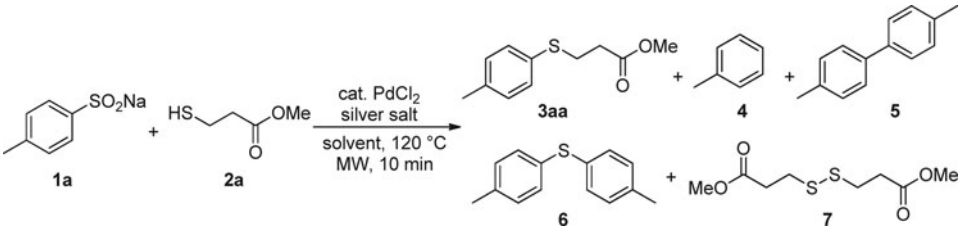
the alkanethiol scope is restrained (Scheme 1b).[8] The C−H activation method is undoubtedly the most green and direct approach to aryl alkyl sulfides. The drawback is that present arene substrates require a directing group or electron-rich substituents (Scheme 1c).[9]

Recently, increasing attention has been attracted to the desulfitative C−C couplings via extrusion of sulfur dioxide from sulfinate metal salts, $RSO_2Na$[10] or $(RSO_2)_2Zn$.[11] In analogy to decarboxylative couplings that carboxylates could be employed as sources of carbon nucleophiles and electrophiles,[12] we anticipated that arylsulfinate metal salts might have a similar potential. Besides present desulfitative carbon–carbon coupling methods, we would like to use arylsulfinate metal salts as a potential carbon electrophile to react with nucleophiles to construct carbon–heteroatom bond. Langler and co-workers reported that *p*-nitrobenzenesulfonates could undergo desulfinative C−S coupling with *p*-methylbenzenethiol in the presence of sodium hydride to give aryl sulfides through nucleophilic aromatic substitution.[13] Inspired by this pioneering work and in view of the significance of aryl alkyl sulfides, we report herein a desulfitative C−S coupling using $PdCl_2$ as a catalyst and alkanethiols as nucleophiles under microwave irradiation (Scheme 1d).

## RESULTS AND DISCUSSION

Initial investigations focused on the $PdCl_2$-catalyzed desulfitative C−S coupling of sodium *p*-toluenesulfinate **1a** with methyl 3-mercaptopropanoate **2a** under microwave irradiation. Due to the reductive properties of thiols,[7] we selected Ag(I) salts as oxidants which are known to be efficient oxidants in Pd-catalyzed oxidative couplings.[14] As shown in Table 1, we were pleased to find that the desired C−S coupling product **3aa** was

**Table 1** Optimization of the reaction between sodium *p*-toluenesulfinate **1a** and 3-mercaptopropanoate **2a**[a]




| Entry | Silver salt (equivalent) | Solvent | Power (W) | Yield of **3aa** (%)[b] | **3aa: 4: 5: 6: 7** (%)[b,c] |
|---|---|---|---|---|---|
| 1 | $Ag_2CO_3$ (2) | dioxan | 180 | 68 | 83: 6: 1: 5: 5 |
| 2 | $Ag_2CO_3$ (2) | toluene | 180 | ~0 | — |
| 3 | $Ag_2CO_3$ (2) | THF | 120 | 76 | 83: 2: 3: 6: 6 |
| 4 | $Ag_2CO_3$ (2) | DMF | 40 | 34 | 56: 5: 37: 0: 2 |
| 5 | $Ag_2CO_3$ (2) | DMSO | 40 | 46 | 69: 1: 23: 2: 5 |
| 6 | $Ag_2CO_3$ (2) | DMF/DMSO[d] | 40 | 25 | 45: 1: 52: 0 : 1 |
| 7 | $Ag_2O$ (2) | DMF/DMSO[d] | 40 | 53 | 74: 9: 15: 2: 0 |
| 8 | AgOAc (2) | DMF/DMSO[d] | 40 | 50 | 70: 7: 13: 2: 8 |
| 9 | $Ag_2MoO_4$ (2) | DMF/DMSO[d] | 40 | 58 | 79: 4: 4: 11: 2 |
| 10 | $AgNO_3$ (2) | DMF/DMSO[d] | 40 | 95 (75)[e] | 98: 0: 0: 0: 2 |
| 11 | — | DMF/DMSO[d] | 40 | 8 | 14: 36: 0: 10: 40 |
| 12[f] | $AgNO_3$ (2) | DMF/DMSO[d] | 40 | 3 | 6: 12: 2: 74: 6 |
| 13[f] | — | DMF/DMSO[d] | 40 | 0 | 0: 0: 0: 4: 96 |
| 14 | $AgNO_3$ (1) | DMF/DMSO[d] | 40 | 37 | 45: 9: 1: 7: 38 |
| 15[g] | $AgNO_3$ (2) | DMF/DMSO[d] | 40 | 88 | 92: 0: 0 2: 6 |

[a]Reaction conditions: **1a** (0.36 mmol), **2a** (0.3 mmol), $PdCl_2$ (20 mol%), silver salt, solvent (2 mL), MW irradiation at 120 °C for 10 min.

[b]Yields were determined by GC-MS.

[c]Ratio of these peaks was determined by the area normalization method.

[d] DMF/DMSO = 19/1 (v/v).

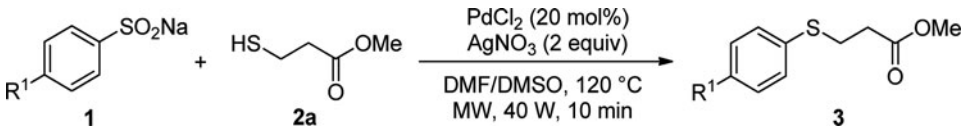
[e] Isolated yield in parenthesis.

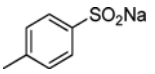
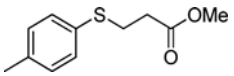
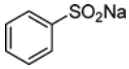
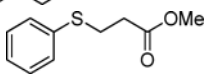
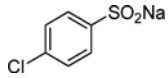
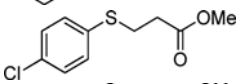
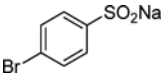
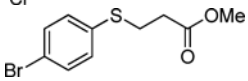
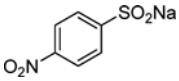
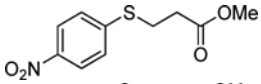
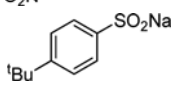
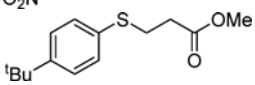
[f] In the absence of $PdCl_2$.

[g]10 mol% of $PdCl_2$ was used.

formed in 68% yield at 120°C with 20 mol% $PdCl_2$ and two equivalents of $Ag_2CO_3$ in dioxan (Table 1, entry 1). At the same time, the desulfitative protonation product **4**, the desulfitative homocoupling product **5**,[10i,10j] the reduction/desulfitative coupling product **6**, and the homocoupling product of **2a** were generated. The reaction was almost interrupted when toluene was used as the solvent (Table 1, entry 2). Moderate to good yields could be obtained when THF, DMF, and DMSO were used as the solvent (Table 1, entries 3–5). By employing Myers's solvent system,[15] a lower yield of 25% was gained (Table 1, entry 6). But the side-product distribution was simpler. Further optimization experiments of silver salts showed that $AgNO_3$ was the ideal oxidant in this catalytic system (Table 1, entries 7–10). When the reaction was carried out in the absence of $PdCl_2$ or $AgNO_3$, only a small amount of the desired product was generated (Table 1, entries 11–12), whereas the protonation product **4** and the reduction/desulfitative coupling product **6** were produced. No desulfitative products (**3aa**, **4**, **5**, and **6**) were obtained when both $PdCl_2$ and $AgNO_3$ were not present (Table 1, entry 13), suggesting that $PdCl_2$ and $AgNO_3$ might play a synergetic

**Table 2** Desulfitative C−S coupling of **2a** with various sodium arylsulfinates[a,b]




| Entry | Sodium arylsulfinate | | Product | Yield |
|---|---|---|---|---|
| 1 |  | **1a** |  **3aa** | 75 |
| 2 |  | **1b** |  **3ba** | 52 |
| 3 |  | **1c** |  **3ca** | 44 |
| 4 |  | **1d** |  **3da** | 50 |
| 5 |  | **1e** |  **3ea** | 25 |
| 6 |  | **1f** |  **3fa** | 60 |

[a]Reaction conditions: **1** (0.36 mmol), **2a** (0.3 mmol), $PdCl_2$ (20 mol%), $AgNO_3$ (2 equiv), DMF/DMSO (v/v = 19/1, 2 mL), MW irradiation at 120 °C for 10 min.
[b]Isolated yield.

role in the desulfination. Either decreasing the catalyst loading or the amount of oxidant resulted in lower yields (Table 1, entries 14–15).

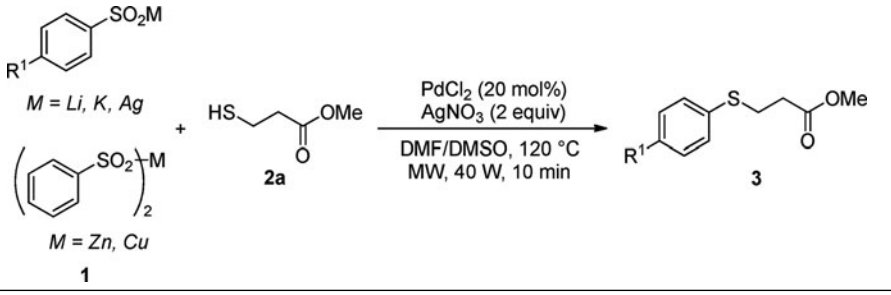
With the optimized reaction conditions in hand, we examined the scope of the sodium arylsulfinate (Table 2). Electron-donating and electron-withdrawing substituents on the arylsulfinate were well tolerated in this coupling (Table 2, entries 1–6). In addition, halide and nitro groups were compatible with the reaction conditions (Table 2, entries 3–5). The good tolerance of the bromo substituent provided further elaborations in synthesis.

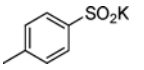
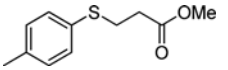
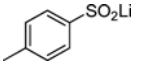
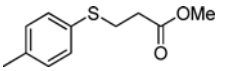
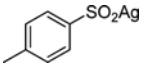
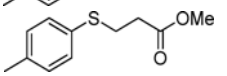
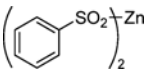
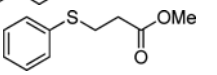
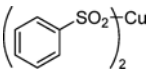
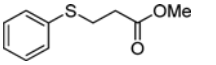
This desulfitative C−S coupling was also effective for other arylsulfinate metal salts, including K, Li, Ag, Zn, and Cu (Table 3, entries 1–5). The arylsulfinate zinc salt showed high reactivity to give the coupling product in 62% yield (Table 3, entry 4).

We then explored the use of other alkanethiols in these transformations. As depicted in Table 4, the desulfitative C−S coupling proceeded well with electron-deficient thiols (**2b** and **2c**) and relatively sterically hindered thiol (**2d**).

Based on the above observations and previous work,[10,12] the arylsulfinate metal salts should cause desulfination directly in the presence of the Pd/Ag catalytic system to give an aryl-metal intermediate which then undergoes further transformations. This type of reaction is disparate from the arylsulfonates-based desulfitative C−S coupling which proceeds via a nucleophilic aromatic substitution mechanism.[13]

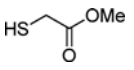
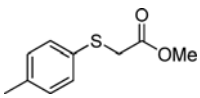
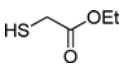
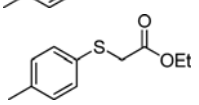
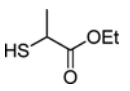
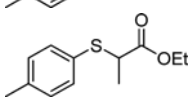
**Table 3** Desulfitative C−S coupling of **2a** with other arylsulfinate metal salts[a,b]




| Entry | Arylsulfinate metal salt | | Product | | Yield |
|---|---|---|---|---|---|
| 1 |  | **1g** |  | **3ga** | 33 |
| 2 |  | **1h** |  | **3ha** | 54 |
| 3 |  | **1i** |  | **3ia** | 42 |
| 4 |  | **1j** |  | **3ja** | 62 |
| 5 |  | **1k** |  | **3ka** | 14 |

[a]Reaction conditions: **1** (0.36 mmol or 0.18 mmol), **2a** (0.3 mmol), $PdCl_2$ (20 mol%), $AgNO_3$ (2 equiv), DMF/DMSO (v/v = 19/1, 2 mL), MW irradiation at 120 °C for 10 min.
[b]Isolated yield.

**Table 4** Desulfitative C−S coupling of **1a** with other alkanethiols[a,b]


| Entry | Alkanethiol | | Product | | Yield |
|---|---|---|---|---|---|
| 1 |  | **2b** |  | **3ab** | 48 |
| 2 |  | **2c** |  | **3ac** | 38 |
| 3 |  | **2d** |  | **3ad** | 63 |

[a]Reaction conditions: **1a** (0.36 mmol or 0.18 mmol), **2** (0.3 mmol), $PdCl_2$ (20 mol%), $AgNO_3$ (2 equiv), DMF/DMSO (v/v = 19/1, 2 mL), MW irradiation at 120 °C for 10 min.
[b]Isolated yield.

## CONCLUSION

We have developed a Pd-catalyzed desulfitative C−S coupling for the synthesis of aryl alkyl sulfides under microwave irradiation. The reaction is shown to be amenable to halide and nitro substituents on the arylsulfinate metal salts. Further efforts are focused on expanding the substrate scope and understanding the mechanism of the transformation.

## EXPERIMENTAL

All commercially obtained reagents for the desulfitative C−S coupling reaction were used as received; sodium arylsulfinates and potassium arylsulfinates were prepared according to the literature;[16] silver arylsulfinates were prepared according to the literature.[17] Dichloromethane, hexane, and ethyl acetate (EA) were distilled prior to use. All reactions were carried out in the air. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent. Qingdao haiyang silica gel (200–300 mesh) was used for flash column chromatography. NMR spectra of $CDCl_3$ solutions were recorded on Bruker Advance III-400 instruments at 400 MHz ($^1$H) or 100 MHz ($^{13}$C) and calibrated using residual undeuterated solvent as an internal reference (TMS @ 0.00 ppm $^1$H NMR, $CHCl_3$ @ 77.16 ppm $^{13}$C NMR). The following abbreviations (or combinations thereof) were used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on Polaris Q using an electron impact ion source (70 eV).

The reactions involving microwave irradiation were conducted under air in heavy walled glass vessels purchased from CEM. The microwave heating was performed in a CEM DISCOVER SCLASS autofocus coupling single-mode microwave cavity using a *dynamic method*. The reaction mixtures were stirred with a magnetic stir bar at high speed during the irradiation. The temperature, pressure, and irradiation power were monitored during the course of the reactions using the provided software.

### General Procedure for the Preparation of Aryl Alkyl Sulfides

Arylsulfinate metal salt (0.36 mmol or 0.18 mmol), $PdCl_2$ (0.06 mmol), $AgNO_3$ (0.6 mmol), DMF/DMSO (v/v = 19/1, 2 mL), and thiol (0.3 mmol) were added to the microwave tube. The tube was sealed and stirred for 5 min at ambient temperature. The tube was then heated at 40 W for 10 min at 120°C. After cooling down, the resulting suspensions were filtered off and washed with $CH_2Cl_2$. A small amount of silica gel was added into the filtrate, and then evaporated. The residue was purified by flash chromatography on silica with hexane/EA to provide the desired product.

### Methyl 3-(*p*-tolylthio)propanoate (3aa)

Oil, $R_f$ = 0.44 ($V_{hexane}/V_{EA}$ = 4/1). $^1$H NMR: $\delta$ 7.28 (d, 2H, ArH, $J$ = 8.0 Hz), 7.10 (d, 2H, ArH, $J$ = 8.0 Hz), 3.66 (s, 3H, OC$H_3$), 3.11 (t, 2H, SC$H_2$, $J$ = 7.4 Hz), 2.59 (t, 2H, COC$H_2$, $J$ = 7.4 Hz), 2.31 (s, 3H, ArC$H_3$). $^{13}$C NMR: $\delta$ 172.2, 136.9, 131.4, $\delta$131.1 (2 × C), 129.3(2 × C), 51.8, 34.36, 29.83, 21.05. MS: *m/z* (%): 210 ($M^+$, 100), 179 (10), 150 (42), 135 (35).

### Methyl 3-(phenylthio)propanoate (3ba)

Oil, $R_f = 0.46$ ($V_{hexane}/V_{EA} = 4/1$). $^1$H NMR: $\delta$ 7.36 (d, 2H, ArH, $J = 7.2$ Hz), 7.29 (t, 2H, ArH, $J = 7.5$ Hz), 7.20 (t, 1H, ArH, $J = 7.5$ Hz), 3.67 (s, 3H, OC$H_3$), 3.16 (t, 2H, SC$H_2$, $J = 7.4$ Hz), 2.63 (t, 2H, COC$H_2$, $J = 7.4$ Hz). $^{13}$C NMR: $\delta$ 172.2, 136.3, 130.2 (2 × C), 129.1 (2 × C), 126.6, 51.8,34.3, 29.1. MS: *m/z* (%): 196 ($M^+$, 100), 165 (8), 136 (62).

### Methyl 3-(4-chlorophenylthio)propanoate (3ca)

Oil, $R_f = 0.47$ ($V_{hexane}/V_{EA} = 4/1$). $^1$H NMR: $\delta$ 7.28 (dd, 4H, ArH, $J = 7.8$ Hz, $J = 7.8$ Hz), 3.68 (s, 3H, OC$H_3$), 3.14 (t, 2H, SC$H_2$, $J = 7.3$ Hz), 2.62 (t, 2H, COC$H_2$, $J = 7.3$ Hz). $^{13}$C NMR: $\delta$ 172.1, 133.9, 132.8, 131.6 (2 × C), 129.3 (2 × C), 52.00, 34.2, 29.5. MS: *m/z* (%): 230 ($M^+-1$, 84), 199 (11), 170 (62), 157 (21), 143 (14), 135 (46).

### Methyl 3-(4-bromophenylthio)propanoate (3da)

Oil, $R_f = 0.43$ ($V_{hexane}/V_{EA} = 4/1$). $^1$H NMR: $\delta$ 7.41 (d, 2H, ArH, $J = 8.4$ Hz), 7.23 (d, 2H, ArH, $J = 8.4$ Hz), 3.68 (s, 3H, OC$H_3$), 3.15 (t, 2H, SC$H_2$, $J = 7.3$ Hz), 2.62 (t, 2H, COC$H_2$, $J = 7.3$ Hz). $^{13}$C NMR: $\delta$ 172.1, 134.6, 132.2 (2 × C), 131.7 (2 × C), 120.7, 52.0, 34.2, 29.3. MS: *m/z* (%): 276 ($M^+$+1, 100), 274 ($M^+-1$, 96), 245 (8), 216 (70), 203 (24), 189 (16), 135 (71).

### Methyl 3-(4-nitrophenylthio)propanoate (3ea)

Oil, $R_f = 0.26$ ($V_{hexane}/V_{EA} = 4/1$). $^1$HNMR:$\delta$ 8.14 (d, 2H, ArH, $J = 8.8$ Hz), 7.36 (d, 2H, ArH, $J = 8.8$ Hz), 3.72 (s, 3H, OC$H_3$), 3.32 (t, 2H, SC$H_2$, $J = 7.3$ Hz), 2.71 (t, 2H, COC$H_2$, $J = 7.3$ Hz).$^{13}$C NMR: $\delta$ 171.7, 146.4, 145.6, 126.9 (2 × C), 124.2 (2 × C), 52.2, 33.6, 27.8. MS: *m/z* (%): 241 ($M^+$, 84), 224 (42), 209 (53), 192 (18), 181 (100), 164 (31), 134 (50).

### Methyl 3-(4-tert-butylphenylthio)propanoate (3fa)

Oil, $R_f = 0.46$ ($V_{hexane}/V_{EA} = 4/1$). $^1$HNMR: $\delta$ 7.32 (b, 4H, ArH), 3.67 (s, 3H, OC$H_3$), 3.13 (t, 2H, SC$H_2$, $J = 7.4$ Hz), 2.62 (t, 2H, COC$H_2$, $J = 7.4$ Hz), 1.30 (s, 9H, C(C$H_3$)$_3$). $^{13}$C NMR: $\delta$ 172.4, 150.2, 131.6, 130.7 (2 × C), 126.2 (2 × C), 51.9, 34.6, 31.4 (3 × C), 31.1, 29.7. MS: *m/z* (%): 252 ($M^+$, 47), 237 (100), 205 (19), 177 (18), 163 (28), 149 (18), 135 (10).

### Methyl 2-(*p*-tolylthio)acetate (3ab)

Oil, $R_f = 0.46$ ($V_{hexane}/V_{EA} = 4/1$). $^1$H NMR: $\delta$ 7.39 (t, 2H, ArH, $J = 8.5$ Hz), 7.01 (t, 2H, ArH, $J = 8.5$ Hz), 3.68 (s, 3H, OC$H_3$), 3.11 (t, 2H, SC$H_2$, $J = 7.3$ Hz), 2.59 (t, 2H, COC$H_2$, $J = 7.3$ Hz), 2.04 (s, 3H, ArC$H_3$). $^{13}$C NMR: $\delta$ 172.2, 133.6 (2 × C), 133.5 (2 × C), 130.1, 129.7, 51.9, 34.4, 21.2. MS: *m/z* (%): 196 ($M^+$, 100), 137 (54).

### Ethyl 2-(*p*-tolylthio)acetate (3ac)

Oil, $R_f = 0.49$ ($V_{hexane}/V_{EA} = 4/1$). $^1$H NMR: $\delta$ 7.33 (d, 2H, ArH, $J = 8.0$ Hz), 7.11 (d, 2H, ArH, $J = 8.0$ Hz), 4.15 (q, 2H, OC$H_2$, $J = 7.1$ Hz), 3.57 (s, 2H, SC$H_2$), 2.32 (s, 3H, ArC$H_3$), 1.22 (t, 3H, OCH$_2$C$H_3$, $J = 7.1$ Hz). $^{13}$C NMR: $\delta$ 169.9, 137.4, 131.3,

131.1 (2 × C), 129.9 (2 × C), 61.5, 37.6, 21.2, 14.2. MS: *m/z* (%): 210 ($M^+$, 100), 182 (5), 137 (60).

### Ethyl 2-(*p*-tolylthio)propanoate (3ad)

Oil, $R_f = 0.57$ ($V_{hexane}/V_{EA} = 4/1$). $^1$H NMR: $\delta$ 7.36 (d, 2H, ArH, $J = 8.0$ Hz), 7.11 (d, 2H, ArH, $J = 8.0$ Hz), 4.11 (q, 2H, OC$H_2$, $J = 7.0$ Hz), 3.70 (q, 1H, SC$H$, $J = 7.1$ Hz), 2.33 (s, 3H, ArC$H_3$), 1.45 (d, 3H, SCHC$H_3$, $J = 7.1$ Hz), 1.19 (t, 3H, $OCH_2CH_3$, J = 7.1 Hz). $^{13}$C NMR: $\delta$ 172.8, 138.5, 133.9 (2 × C), 129.8 (2 × C), 129.5, 61.2, 45.7, 21.3, 17.5, 14.2. MS: *m/z* (%): 224 ($M^+$, 75), 151 (100).

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