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High-Yielding Cleavage of (Aryloxy)acetates

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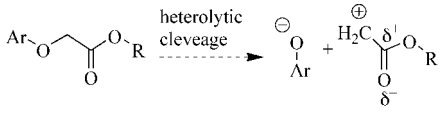
A reliable and high-yielding one-pot sequence for the removal of *O*-carboxymethyl moieties from phenols is presented. When diethylphosphoryl azide is employed as the azide transfer reagent in the Curtius rearrangement and glycerol in the subsequent hydrolytic workup, the protocol can be reliably applied to a very broad scope of substrates.

Introduction

(Aryloxy)acetates are a common motif in plant growth modulators.[1–3] This particular class of compounds exhibits an exceptional stability towards electrophilic conditions. The strong electron-withdrawing effect of the carbonyl system onto the methylene group makes it less susceptible to heterolytic cleavage, as this would destabilize the resulting cationic intermediate (Scheme 1). Consequently, most transformations on the aryl moiety do not affect this particular side chain. Under electrophilic conditions, a methoxy group on the arene moiety undergoes cleavage rather than the acetate skeleton of **1**.[4]



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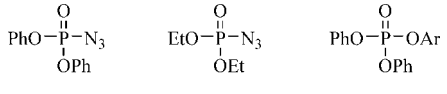
Scheme 1. Electronic effects in (aryloxy)acetates.

The robust character of the phenoxy derivatives of this class of compounds led to the development of some deprotection protocols involving harsh and prolonged reaction conditions.[5] Other methods involve very high temperatures (>270 °C),[6] gas-phase chemistry,[7] electrochemical[8] or photochemical[9] procedures, or irradiation techniques.[10] Because alkoxycarbonylmethoxy moieties turned out to be beneficial for oxidative processes involving strong Lewis acids,[11,12] a mild and reliable method for its removal is desired. This would allow exploitation of this particularly stable and transformation-directing moiety[13] as a protecting group for phenols. Initial studies led to a strategy for the cleavage.[14] That protocol involved saponification to yield the carboxymethoxy substituent, which was subsequently degraded in a Curtius rearrangement by employing diphenyl phosphoryl azide (DPPA) as the azide transfer reagent.[15] This approach also gave access to labile iodo-substituted phenols.

However, the yield for the individual cleavage sequence did not exceed 60%. Therefore, multiple deprotection reactions led to an unacceptable loss of material. Because the saponification works almost quantitatively, the side reactions occur in the subsequent steps. Initially, triaryl phosphates **2** were identified as byproducts by using spectrometric and spectroscopic means.[14] However, the formation of **2** could not be avoided by employing smaller amounts of DPPA. Furthermore, the purification of low molecular weight phenols turned out to be tedious, as the DPPA reagent liberates phenol upon workup. Therefore, we developed a significantly ameliorated cleavage sequence that overcomes all these preparative hurdles. With the use of DEPA (Figure 1) as the azide transfer reagent, only ethanol was produced as a low-boiling byproduct. Addition of glycerol during the workup converted intermediates like **2** into the desired phenols and water-soluble cyclic phosphates.



DPPA DEPA **2**

Figure 1. Azide transfer reagents and byproduct **2**.

Results and Discussion

The required substrates were prepared according to standard procedures starting from commercially available phenols. Alkylation with ethyl bromoacetate and subsequent saponification to **5** was performed in good-to-excellent yields (Scheme 2). The Curtius degradation and workup (Scheme 3) provided the alkyl-substituted phenols in excel-

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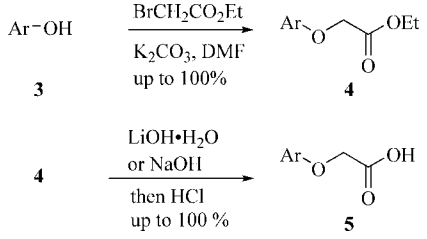
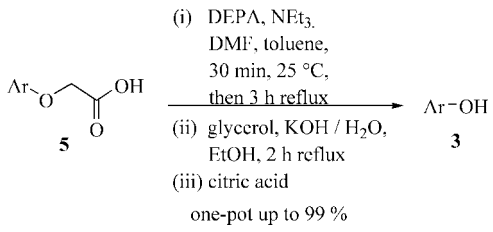
lent yields (Table 1, Entries 2 and 3). Small derivatives like *p*-cresol are more volatile and more soluble in the aqueous media. Therefore, the yield is slightly lower (Table 1, Entry 1). The same trend can be followed to phenol derivatives involving arenes as substituents (Table 1, Entries 4 and 5). Despite the large electron-donating effect of alkoxy substituents in the 4-position, these substrates are still compatible and provide good-to-excellent results (Table 1, Entries 6 and 7).



Scheme 2. Preparation of starting materials.



Scheme 3. Reliable deblocking sequence.

The slightly lower yield for the benzyloxy-substituted system might be attributed to the sensitivity of this group towards the acidic workup conditions. When even more electron-rich substrates were converted, for example, derivatives of sesamol, only moderate results were obtained. Methylsulfanyl-substituted phenols also represent suitable targets for the deblocking sequence (Table 1, Entry 8). Halogen atoms in the substitution pattern do not interfere with the transformations (Table 1, Entries 9–11). The yields correspond to the stability of the individual phenol derivative. Organic azides like DPPA or DEPA are capable of 1,3-dipolar cycloaddition.[38] However, treatment of **5l** under the given conditions did not result in the formation of heterocycles nor in the isomerization to styrene derivatives (Table 1, Entry 12). Substrates containing carbonyl or carbonyl-analogous moieties can also be used under this protocol (Table 1, Entries 13–15). No significant side reactions of the oxidation-prone and base-labile carbaldehyde moiety were found. The better solubilities in water of resulting phenols **3m**–**o** − with additional polar groups − result in a lower but still practical yield. Application of this one-pot protocol to heterocyclic substrates involving benzothiazoles or coumarins provided the deprotected hydroxy compounds in moderate yields, which is also attributed to solubility in water (Table 1, Entries 16 and 17). Multiple deprotection reactions can be performed by this one-pot procedure for lipophilic product **3r** by using DPPA or DEPA (Table 1, Entries 18–20). Apparently, multiple deprotection reactions can be performed in the presence of additional functional groups in good yield. This makes it to an attractive and practical transformation.

Table 1. Yields for deblocking sequence.[16–37]

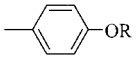
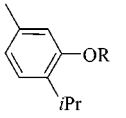
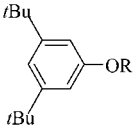
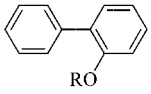
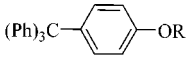
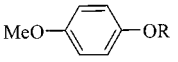
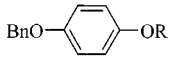
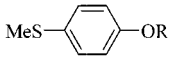
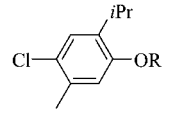
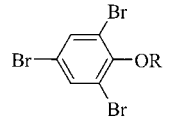
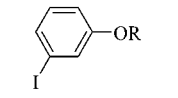
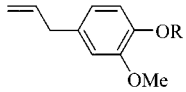
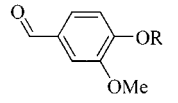
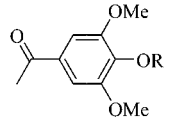
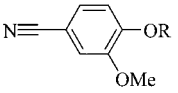
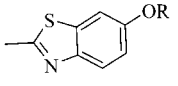
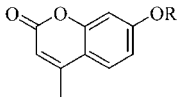
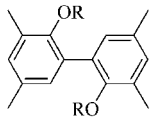
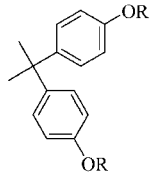
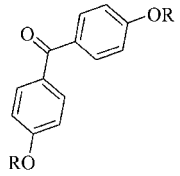
		Yield [%]		
		R = CH_2CO_2X		R = H
Entry	ArOR	X = Et	X = H	
1		82[16] (**4a**)	99 (**5a**)	83 (**3a**)
2		88[17] (**4b**)	100[18] (**5b**)	99 (**3b**)
3		94 (**4c**)	80[19] (**5c**)	96 (**3c**)
4		67[20] (**4d**)	80[21] (**5d**)	83 (**3d**)
5		93 (**4e**)	55[22] (**5e**)	91 (**3e**)
6		63[23] (**4f**)	92 (**5f**)	94 (**3f**)
7		99[24] (**4g**)	87[25] (**5g**)	83 (**3g**)
8		91[26] (**4h**)	81[27] (**5h**)	85 (**3h**)
9		90[17] (**4i**)	70[28] (**5i**)	98 (**3i**)
10		73[29] (**4j**)	73[27] (**5j**)	82[a] (**3j**)
11		90[30] (**4k**)	53[31] (**5k**)	75 (**3k**)
12		63[32] (**4l**)	91[32] (**5l**)	84 (**3l**)
13		90[16] (**4m**)	78[33] (**5m**)	70 (**3m**)
14		90 (**4n**)	96 (**5n**)	70 (**3n**)
15		85 (**4o**)	90[34] (**5o**)	70 (**3o**)
16		63 (**4p**)	63 (**5p**)	54 (**3p**)

Table 1. *(continued)*

Entry	ArOR	Yield [%] R = CH_2CO_2X X = Et	Yield [%] R = CH_2CO_2X X = H	Yield [%] R = H
17		54[35] (**4q**)	77[36] (**5q**)	44 (**3q**)
18		77 (**4r**)	80 (**5r**)	90[b] (**3r**)
19		100[37] (**4s**)	80[37] (**5s**)	72 (**3s**)
20		99 (**4t**)	76 (**5t**)	51 (**3t**)

[a] (i) DEPA, Et_3N, DMF, toluene 1 h, 25 °C then 3 h reflux; (ii) KOH, H_2O, 8 min, 25 °C; (iii) citric acid, H_2O; (iv) KOH, H_2O, EtOH, glycerol 2 h reflux; (v) citric acid, H_2O. [b] (i) DPPA, Et_3N, DMF, toluene, 1 h, 25 °C, then 3 h reflux, (ii) KOH, H_2O, 8 min, 25 °C; (iii) citric acid, H_2O.

Conclusions

A reliable and high yielding deblocking sequence for (aryloxy)acetates was established. The whole transformation sequence was performed in one pot. The Curtius degradation can be performed in a practical manner when diethylphosphoryl azide (DEPA) as the azide transfer reagent and glycerol in the acidic hydrolytic workup are used. The sequence is a valuable tool for a broad scope of substrates and allows even multiple deprotections. As a potent and easily applicable method for their cleavage is now established, alkoxycarbonylmethoxy moieties can be considered as protecting groups for aromatic and heteroaromatic hydroxy functions. This class of protecting groups is particularly useful under strong electrophilic conditions.

Experimental Section

General Procedure for the Cleavage Sequence: (Aryloxy)acetic acid (1.20 mmol) was dissolved in anhydrous toluene (5 mL) and anhydrous *N*,*N*-dimethylformamide (0.50 mL). After the addition of NEt_3 (1.01 equiv.) and diethylphosphoryl azide (DEPA; 1.1 equiv.), the mixture was stirred for 30 min at ambient temperature and then brought to reflux for 3 h. A potassium hydroxide solution (50 wt.-% in H_2O, 2 mL), ethanol (5 mL), and glycerol (2.5 mL) were then added, and the reaction mixture was heated at reflux for 2 h. For workup, the reaction mixture was brought to pH = 5 by the addition of a saturated citric acid solution. Subsequently, the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layer was washed with water (50 mL) and brine (50 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Purification was performed by column chromatography.

General Procedure for Ethyl Phenoxyacetates: Phenol derivative **3** (46 mmol) and potassium carbonate (69 mmol, 1.5 equiv.) were suspended in *N*,*N*-dimethylformamide (120 mL). After the addition of ethyl bromoacetate (5.65 mL, 8.52 g, 51 mmol, 1.1 equiv.) the reaction mixture was stirred for 18 h at ambient temperature. For workup, H_2O (300 mL) was added, and the aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic layer was washed with H_2O (3 × 100 mL) and brine (2 × 50 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Purification of ethyl phenoxyacetates **4** was performed by crystallization (cyclohexane/ethyl acetate) or distillation. Analytical data are only given if the compounds are new, differ significantly from literature, or are less detailed.

Ethyl (2-Isopropyl-5-methylphenoxy)acetate (4b): 2-Isopropyl-5-methylphenol (thymol) (**3b**; 6.00 g, 40.0 mmol), potassium carbonate (8.29 g, 60.0 mmol), ethyl bromoacetate (4.87 mL, 7.35 g, 44.0 mmol). Ethyl (2-isopropyl-5-methylphenoxy)acetate (**4b**) was obtained after distillation (95 °C; 2.7 × 10^2 mbar)[17] as a colorless oil in 8.35 g (88%) yield. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 1.23 [d, ^3J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 1.31 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.31 (s, 3 H, Ar-CH_3), 3.38 [sept, ^3J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 4.27 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.63 (s, 2 H, OCH_2CO), 6.58 (s, 1 H, Ar-H), 6.79 (d, ^3J = 7.7 Hz, 1 H, Ar-H), 7.12 (d, ^3J = 7.7 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 14.1, 21.3, 22.7, 26.6, 61.1, 65.7, 112.4, 122.2, 126.2, 134.6, 136.2, 155.0, 169.2 ppm. MS (EI, 70 eV): *m*/*z* (%) = 236 (74) $[M]^+$, 221 (100) $[M - CH_3]^+$, 149 (70) $[M - C_4H_7O_2]^+$, 147 (84) $[M - CH_3 - C_3H_4O_2 - H]^+$. HRMS (EI): calcd. for $C_{14}H_{20}O_3$ $[M]^+$ 236.1412; found 236.1409.

Ethyl (3,5-Di-*tert*-butylphenoxy)acetate (4c): 3,5-Di-*tert*-butylphenol (**3c**, 8.60 g, 41.7 mmol), potassium carbonate (8.60 g, 62.6 mmol), ethyl bromoacetate (5.10 mL, 7.70 g, 45.9 mmol). Ethyl (3,5-di-*tert*-butylphenoxy)acetate (**4c**) was obtained after distillation (117 °C, 2.3 × 10^{-2} mbar) as a colorless oil in 11.5 g (94%) yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 1.19–1.23 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.25 [s, 18 H, $C(CH_3)_3$], 4.15–4.20 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.74 (s, 2 H, OCH_2CO), 6.70 (d, ^4J = 1.6 Hz, 2 H, Ar-H), 7.00 (m, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 14.0, 31.0, 34.5, 60.4, 64.7, 108.7, 114.8, 151.6, 157.1, 168.9 ppm. MS (EI, 70 eV): *m*/*z* (%) = 292 (56) $[M]^+$, 277 (100) $[M - CH_3]^+$, 219 (4) $[M - CO_2C_2H_5]^+$, 147 (7) $[M - CH_2CO_2C_2H_5 - C_4H_9]^+$, 57 (7) $[C_4H_9]^+$. HRMS (EI): calcd. for $C_{18}H_{28}O_3$ $[M]^+$ 292.2038; found 292.2038. $C_{18}H_{28}O_3$ (292.41): calcd. C 73.93, H 9.65; found C 73.52, H 9.57. GC: t_R = 11.07 min.

Ethyl (4-Tritylphenoxy)acetate (4e): 4-Tritylphenol (**3e**; 5.47 g, 16.3 mmol), potassium carbonate (3.40 g, 24.5 mmol), ethyl bromoacetate (2.00 mL, 3.00 g, 17.9 mmol). Ethyl (4-tritylphenoxy)-acetate (**4e**) was obtained as a light brown solid in 6.00 g (93%) yield. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 1.26–1.31 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 4.23–4.30 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.59 (s, 2 H, OCH_2CO), 6.67–6.79 (d, ^3J = 9.0 Hz, 2 H, Ar-H), 7.10–7.12 (d, ^3J = 9.0 Hz, 2 H, Ar-H), 7.17–7.26 (m, 15 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 14.2, 61.3, 64.3, 65.4, 113.5, 125.9, 127.4, 131.1, 132.2, 140.9, 146.1, 155.8, 169.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 422 (36) $[M]^+$, 345 (100) $[M - C_6H_5]^+$, 234 (8) $[M - OCH_2CO_2C_2H_5 - C_6H_5 + H]^+$, 165 (12) $[C(C_6H_5)_2]^+$. HRMS (EI): calcd. for $C_{29}H_{26}O_3$ $[M]^+$ 422.1882; found 422.1880. GC: t_R = 20.44 min.

Ethyl 2-(4-Methylsulfanylphenoxy)acetate (4h): 4-(Methylsulfanyl)-phenol (**3h**, 5.19 g, 37.0 mmol), potassium carbonate (7.66 g, 55.5 mmol), ethyl bromoacetate (4.50 mL, 6.80 g, 40.7 mmol). Product **4h** was obtained as a colorless oil (b.p. 133 °C, 4.2×10^{-2} mbar)[26] in 7.65 g (91%) yield. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 1.27 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.44 (s, 3 H, SCH_3), 4.24–4.29 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.59 (s, 2 H, OCH_2CO), 6.84–6.87 (d, ^3J = 8.9 Hz, 2 H, Ar-H), 7.24–7.26 (d, ^3J = 8.9 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 14.1, 17.5, 61.3, 65.5, 115.3, 129.6, 130.1, 156.2, 168.7 ppm. MS (EI, 70 eV): *m/z* (%) = 226 (100) $[M]^+$, 211 (2) $[M - CH_3]^+$, 198 (4) $[M - C_2H_6 + H]^+$, 153 (12) $[M - CO_2C_2H_5]^+$, 139 (92) $[M - CH_2CO_2C_2H_5]^+$, 125 (16) $[M - CH_2CO_2C_2H_5 - CH_3 + H]^+$, 108 (6) $[M - OCH_2CO_2C_2H_5 - CH_3]^+$, 77 $[C_6H_5]^+$, 73 (5) $[CO_2C_2H_5]^+$. HRMS (EI): calcd. for $C_{11}H_{14}O_3S$ $[M]^+$ 226.0664; found 226.0667. $C_{11}H_{14}O_3S$ (226.3): calcd. C 58.38, H 6.24; found C 58.30, H 6.19. GC: t_R = 10.10 min.

Ethyl (4-Chloro-2-isopropyl-5-methylphenoxy)acetate (4i): 4-Chlorothymol (**3i**; 3.50 g, 19.0 mmol), 3.93 g (28.5 mmol) potassium carbonate, 2.31 mL (3.48 g, 20.9 mmol) ethyl bromoacetate. Ethyl (4-chloro-2-isopropyl-5-methylphenoxy)acetate (**4i**) was obtained as colorless oil in 4.60 g (90%) yield. ^{1}H NMR (400 MHz, [D$_6$]-DMSO, 20 °C): δ = 1.15 [d, ^3J = 6.9 Hz, 6 H, $CH(CH_3)_2$], 1.20 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.25 (s, 3 H, Ar-CH_3), 3.25 [sept, ^3J = 6.9 Hz, 1 H, $CH(CH_3)_2$], 4.16 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.79 (s, 2 H, OCH_2CO), 6.88 (s, 1 H, Ar-H), 7.15 (s, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 13.9, 19.3, 22.1, 26.2, 60.5, 65.0, 114.4, 125.0, 126.0, 133.2, 136,0, 153.4, 162.1 ppm. MS (EI, 70 eV): *m/z* (%) = 270 (76) $[M]^+$, 255 (46) $[M - CH_3]^+$, 183 (100) $[M - C_4H_7O_2]^+$, 181 (80) $[M - CH_3 - C_3H_4O_2 - H]^+$, 169 (36) $[M - CH_3 - C_4H_6O_2]^+$. HRMS (EI): calcd. for $C_{14}H_{19}ClO_3$ $[M]^+$ 270.1023; found 270.1023. GC: t_R = 10.9 min.

Ethyl (3-Iodophenoxy)acetate (4k): 3-Iodophenol (**3k**; 3.00 g, 13.6 mmol), potassium carbonate (2.80 g, 20.4 mmol), ethyl bromoacetate (1.70 mL, 2.51 g, 15.0 mmol). Ethyl (3-iodophenoxy)-acetate (**4k**) was obtained as a colorless solid in 3.37 g (90%) yield. M.p. 42–43 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 1.28–1.33 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 4.24–4.31 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.59 (s, 2 H, OCH_2CO), 6.86–6.89 (dd, ^3J = 8.3 Hz, ^4J = 2.5 Hz, 1 H, Ar-H), 6.98–7.03 (m, ^3J = 8.3 Hz, 1 H, Ar-H), 7.26–7.27 (d, ^4J = 2.5 Hz, 1 H, Ar-H), 7.32–7.35 (d, ^3J = 7.7 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 14.1, 61.5, 65.4, 94.2, 114.2, 124.0, 130.8, 130.9, 158.3, 168.4 ppm. MS (EI, 70 eV): *m/z* (%) = 306 (100) $[M]^+$, 233 (40) $[M - CO_2C_2H_5]^+$, 220 (4) $[M - CH_2CO_2C_2H_5 + H]^+$, 203 (26) $[M - OCH_2CO_2C_2H_5]^+$, 106 (10) $[M - CO_2C_2H_5 - I]^+$, 92 (5) $[M - CH_2CO_2C_2H_5 - I]^+$, 76 (13) $[M - OCH_2CO_2C_2H_5 - I]^+$. HRMS (EI): calcd. for $C_{10}H_{11}O_3I$ $[M]^+$ 305.9753; found 305.9756. $C_{10}H_{11}IO_3$ (306.1): calcd. C 39.24, H 3.62; found C 39.10, H 3.32. GC: t_R = 10.24 min.

3,3′-Dimethoxy-4-ethoxycarbonylmethoxyacetophenone (4n): 3,5-Dimethoxy-4-hydroxyacetophenone (**3n**; 4.81 g, 24.5 mmol), potassium carbonate (5.10 g, 13.8 mmol), ethyl bromoacetate (3.00 mL, 4.51 g, 27.0 mmol). 3,3′-Dimethoxy-4-ethoxycarbonylmethoxyacetophenone (**4n**) was obtained as a light yellow solid in 6.22 g (90%) yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 1.18–1.21 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.56 (s, 3 H, $COCH_3$), 3.82 (s, 6 H, OCH_3), 4.11–4.16 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.63 (s, 2 H, OCH_2CO), 7.23 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]-DMSO, 20 °C): δ = 14.1, 26.7, 56.2, 60.5, 68.8, 106.0, 132.1, 140.0, 151.9, 168.7, 197.0 ppm. MS (EI, 70 eV): *m/z* (%) = 282 (100) $[M]^+$, 267 (26) $[M - CH_3]^+$, 209 (16) $[M - CO_2C_2H_5]^+$, 195 $[M - CH_2CO_2C_2H_5]^+$,167 (7) $[M - CH_2CO_2C_2H_5 - 2\ CH_3 + 2\ H]^+$, 149 (6) $[M - CH_2CO_2C_2H_5 - CH_3 - OCH_3]^+$, 137 (4) $[M - CH_2CO_2C_2H_5 - 2\ CH_3 - OCH_3]^+$. HRMS (EI): calcd. for $C_{14}H_{18}O_6$ $[M]^+$ 282.1103; found 282.1105. $C_{14}H_{18}O_6$ (282.3): calcd. C 59.57, H 6.43; found C 59.59, H 6.38. GC: t_R = 12.71 min.

4-Ethoxycarbonylmethoxy-3-methoxybenzonitrile (4o): 4-Hydroxy-3-methoxybenzonitrile (**3o**; 4.66 g 31.3 mmol), potassium carbonate (6.48 g, 47.0 mmol), ethyl bromoacetate (3.80 mL, 5.74 g, 34.4 mmol). 4-Ethoxycarbonylmethoxy-3-methoxybenzonitrile (**4o**) was obtained as a colorless solid in 6.24 g (85%) yield. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ = 1.27 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 3.91 (s, 3 H, OCH_3), 4.23–4.31 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.74 (s, 2 H, OCH_2CO), 6.80–6.83 (d, ^3J = 8.4 Hz, 1 H, Ar-H), 7.12–7.13 (d, ^4J = 1.8 Hz, 1 H, Ar-H), 7.23–7.26 (dd, ^3J = 8.4 Hz, ^4J = 1.8 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ = 14.1, 56.2, 61.7, 65.9, 105.4, 113.4, 114.8, 118.9, 126.0, 149.6, 151.0, 167.9 ppm. MS (EI, 70 eV): *m/z* (%) = 235 (100) $[M]^+$, 162 (40) $[M - CO_2C_2H_5]^+$, 147 (34) $[M - CO_2C_2H_5 - CH_3]^+$, 134 (5) $[M - CH_2CO_2C_2H_5 - CH_3 + H]^+$, 117 (11) $[M - OCH_2CO_2C_2H_5 - CH_3]^+$, 102 (8) $[C_7H_4N]^+$, $[C_6H_5]^+$. HRMS (EI): calcd. for $C_{12}H_{13}NO_4$ $[M]^+$ 235.0845; found 235.0848. GC: t_R = 11.30 min.

5-Ethoxycarbonylmethoxy-2-methylbenzothiazole (4p): 5-Hydroxy-2-methylbenzothiazole (**3p**; 3.00 g, 18.2 mmol), potassium carbonate (3.77 g, 27.3 mmol), ethyl bromoacetate (2.20 mL, 3.34 g, 20.0 mmol). Product **4p** was obtained after distillation (2.1×10^{-1} mbar, 127 °C) as a colorless oil in 2.88 g (63%) yield. M.p. 43 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 1.20–1.23 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.76 (s, 3 H, CCH_3), 4.15–4.20 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.86 (s, 2 H, OCH_2CO), 7.04–7.07 (dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz, 1 H, Ar-H), 7.42–7.43 (d, ^4J = 2.5 Hz, 1 H, Ar-H), 7.88–7.91 (d, ^3J = 8.8 Hz, 1 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 13.9, 19.7, 60.6, 65.0, 106.0, 114.3, 122.3, 127.5, 154.0, 156.6, 168.3, 168.6 ppm. MS (EI, 70 eV): *m/z* (%) = 251 (100) $[M]^+$, 178 (40) $[M - CO_2C_2H_5]^+$, 164 (26) $[M - CH_2CO_2C_2H_5]^+$, 148 (32) $[M - OCH_2CO_2C_2H_5]^+$, 136 (5) $[C_7H_4OS]^+$, 107 $[C_6H_3S]^+$. HRMS (EI): calcd. for $C_{12}H_{13}NO_3S$ $[M]^+$ 251.0616; found 251.0620. $C_{12}H_{13}NO_3S$ (251.3): calcd. C 57.35, H 5.21, N 5.57; found C 57.32, H 5.01, N 5.53. GC: t_R = 12.23 min.

Ethyl (2′-Ethoxycarbonylmethoxy-3,5,3′,5′-tetramethylbiphenyl-2-yloxy)acetate (4r): 3,3′,5,5′-Tetramethylbiphenyl-2,2′-diol (**3r**; 3.61 g, 14.9 mmol), potassium carbonate (6.20 g, 44.7 mmol), ethyl bromoacetate (3.60 mL, 5.47 g, 32.8 mmol). Ethyl (2′-ethoxycarbonylmethoxy-3,5,3′,5′-tetramethylbiphenyl-2-yloxy)acetate (**4r**) was obtained as a colorless solid in 4.78 g (77%) yield. M.p. 38–39 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 1.20 (t, J = 7.1 Hz, 6 H, CH_2CH_3), 2.27 (s, 6 H, Ar-CH_3), 2.33 (s, 6 H, Ar-CH_3), 4.11 (q, J = 7.1 Hz, 4 H, CH_2CH_3), 4.15 (s, 4 H, OCH_2CO), 6.96–6.97 (s, 2 H, Ar-H), 6.97 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 14.0, 16.5, 20.6, 60.8, 69.5, 129.6, 130.8, 130.9, 131.3, 133.3, 152.4, 169.1 ppm. MS (EI, 70 eV): *m/z* (%) = 414 (100) $[M]^+$, 341 (6) $[M - C_3H_5O_2]^+$, 267 (8) $[M - C_6H_{11}O_4]^+$, 253 (36) $[M - C_7H_{13}O_4]^+$. HRMS (EI): calcd. for $C_{24}H_{30}O_6$ $[M]^+$ 414.2042; found 414.2044. $C_{24}H_{30}O_6$ (414.20): calcd. C 69.54, H 7.30; found C 69.27, H 7.39. GC: t_R = 15.5 min.

4,4′-Bis(ethoxycarbonylmethoxy)benzophenone (4t): 2,6-Dihydroxybenzophenone (**3t**; 6.24 g, 29.1 mmol), potassium carbonate (12.10 g, 87.3 mmol), ethyl bromoacetate (7.10 mL, 10.70 g, 64.0 mmol). 4,4′-Bis(Ethoxycarbonylmethoxy)benzophenone (**4t**) was obtained as a colorless solid in 11.24 g (99%) yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 1.20–1.24 (t, ^3J = 7.1 Hz, 6 H, CH_2CH_3), 4.16–4.21 (q, ^3J = 7.1 Hz, 4 H, CH_2CH_3), 4.90 (s, 4 H, OCH_2CO), 7.06–7.09 (d, ^3J = 8.9 Hz, 4 H, Ar-H), 7.69–7.71 (d, ^3J

= 8.9 Hz, 4 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 14.0, 60,7, 64.6, 114.3, 130.5, 131.7, 160.8, 168.3, 193.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 386 (100) [M]$^+$, 313 (13) [M – $CO_2C_2H_5$]$^+$, 271 (4) [M – $CH_2CO_2C_2H_5$ – C_2H_5 + H]$^+$, 207 (54) [M – $C_6H_4OCH_2CO_2C_2H_5$]$^+$, 196 (12) [M – $OCH_2CO_2C_2H_5$ – $CH_2CO_2C_2H_5$]$^+$, 179 (6) [$C_6H_4OCH_2CO_2C_2H_5$]$^+$, 121 (4) [CO-C_6H_4OH]$^+$. HRMS (EI): calcd. for $C_{21}H_{22}O_7$ [M]$^+$ 386.1366; found 386.1368. $C_{21}H_{22}O_7$ (386.4): calcd. C 65.28, H 5.74; found C 65.19, H 5.83. GC: t_R = 19.15 min.

General Procedure for Aryloxy Acids

Method A: Ethyl (aryloxy)acetate **4** (35 mmol) was dissolved in tetrahydrofuran (40 mL) and sodium hydroxide solution (20 wt.-% in H_2O, 20 mL). The mixture was brought to reflux for 3 h. For workup, the reaction mixture was adjusted to pH = 1 by the addition of hydrochloric acid. Subsequently, the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with brine (2 × 75 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Purification was performed by crystallization (ethanol/H_2O, 9:1).

Method B: Ethyl (aryloxy)acetate **4** (18 mmol) and lithium hydroxide monohydrate (36 mmol, 2 equiv.) were dissolved in tetrahydrofuran (30 mL). The mixture was stirred at ambient temperature for 1 d. For workup, the reaction mixture was adjusted to pH = 1 by the addition of hydrochloric acid. Subsequently, the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layer was washed with brine (2 × 75 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Purification was performed by crystallization (ethanol/H_2O, 9:1).

3,3′-Dimethoxy-4-carboxymethoxyacetophenone (5n): Prepared according to general procedure B by using: 3,3′-dimethoxy-4-ethoxycarbonylmethoxyacetophenone (**4n**; 3.25 g, 11.5 mmol), lithium hydroxide monohydrate (0.97 g, 23.0 mmol). 3,3′-Dimethoxy-4-carboxymethoxyacetophenone (**5n**) was obtained as a light brown solid in 2.79 g (96%) yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 2.57 (s, 3 H, CH_3CO), 3.84 (s, 6 H, OCH_3), 4.56 (s, 2 H, OCH_2CO), 7.24 (s, 2 H, Ar-H), 12.94 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 26.5, 56.1, 68.4, 105.9, 131.9, 140.0, 151.8, 169.9, 196.7 ppm. MS (EI, 70 eV): *m*/*z* (%) = 254 (100) [M]$^+$, 239 (26) [M – CH_3]$^+$, 195 (72) [M – CH_2CO_2H]$^+$, 181 (15) [M – CH_3 – CH_2CO_2H + H]$^+$, 152 (4) [M – 3 CH_3 – CH_2CO_2H + 2 H]$^+$. HRMS (EI): calcd. for $C_{12}H_{14}O_6$ [M]$^+$ 254.0790; found 254.0794. $C_{12}H_{14}O_6$ (254.2): calcd. C 56.69, H 5.55; found C 56.63, H 5.39.

5-Carboxymethoxy-2-methylbenzothiazole (5p): Prepared according to general procedure B by using: 5-ethoxycarbonylmethoxy-2-methylbenzothiazole (**4p**; 2.59 g, 10.3 mmol), lithium hydroxide monohydrate (0.65 g, 15.5 mmol). 5-Carboxymethoxy-2-methylbenzothiazole (**5p**) was obtained as a colorless solid in 1.44 g (63%) yield. M.p. 149 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 2.76 (s, 3 H, CH_3), 4.76 (s, 2 H, OCH_2CO), 7.02–7.05 (dd, ^3J = 8.8 Hz, ^4J = 2.5 Hz, 1 H, Ar-H), 7.39–7.40 (d, ^4J = 2.5 Hz, 1 H, Ar-H), 7.87–7.90 (d, ^3J = 8.8 Hz, 1 H, Ar-H), 12.81 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 19.7, 64.8, 105.9, 114.3, 122.2, 127.3, 154.0, 156.8, 168.2, 170.0 ppm. MS (EI, 70 eV): *m*/*z* (%) = 223 (100) [M]$^+$, 178 (13) [M – CO_2H]$^+$, 164 (43) [M – CH_2CO_2H]$^+$, 148 (16) [M – OCH_2CO_2H]$^+$, 123 (7) [M – CH_2CO_2H – CH_3CN]$^+$, 107 (4) [M – OCH_2CO_2H – CH_3CN]$^+$, 95 (6) [C_5H_3S]$^+$, 63 (3) [C_5H_3]$^+$. HRMS (EI): calcd. for $C_{10}H_9NO_3S$ [M]$^+$ 223.0303; found 233.0305.

(2′-Carboxymethoxy-3,5,3′,5′-tetramethylbiphenyl-2-yloxy)acetic Acid (5r): Prepared according to general procedure A by using: (2′-ethoxycarbonylmethoxy-3,5,3′,5′-tetramethylbiphenyl-2-yloxy)-ethyl acetate (**4r**; 4.78 g 11.5 mmol). (2′-Carboxymethoxy-3,5,3′,5′-tetramethylbiphenyl-2-yloxy)acetic acid (**5r**) was obtained as a colorless solid in 3.29 g (80%) yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 2.23 (s, 6 H, Ar-CH_3), 2.25 (s, 6 H, Ar-CH_3), 4.04 (s, 4 H, OCH_2CO), 6.89 (s, 2 H, Ar-H), 7.00 (s, 2 H, Ar-H), 12.62 (s, 2 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 16.7, 20.7, 69.2, 129.8, 130.9, 131.1, 131.5, 132.8, 152.3, 170.4 ppm. MS (EI, 70 eV): *m*/*z* (%) = 358 (100) [M]$^+$, 300 (24) [M – CH_2CO_2H + H]$^+$, 253 [M – CH_2CO_2H – CO_2H – H]$^+$, 237 (34) [M – 2 CO_2H – 2 CH_3 – H]$^+$, 223 (24) [M – CH_2CO_2H – CO_2H – 2 CH_3 – H]$^+$, 209 (10) [M – CH_2CO_2H – CO_2H – 3 CH_3]$^+$. HRMS (EI): calcd. for $C_{20}H_{22}O_6$ [M]$^+$ 358.1416; found 358.1418.

4,4′-Bis(carboxymethoxy)benzophenone (5t): Prepared according to general procedure A by using: 4,4′-bis(ethoxycarbonylmethoxy)-benzophenone (**4t**; 10.64 g, 26.6 mmol). 4,4′-Bis(carboxymethoxy)-benzophenone (**5t**) was obtained as a light yellow solid in 7.13 g (76%) yield. ^{1}H NMR (400 MHz, [D$_6$]DMSO, 20 °C): δ = 4.80 (s, 2 H, OCH_2CO), 7.05–7.07 (d, ^3J = 8.8 Hz, 2 H, Ar-H), 7.69–7.71 (d, ^3J = 8.8 Hz, 2 H, Ar-H), 13.10 (s, 1 H, OH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO, 20 °C): δ = 64.5, 114.3, 130.4, 131.7, 161.0, 169.8, 193.1 ppm. MS (EI, 70 eV): *m*/*z* (%) = 330 (82) [M]$^+$, 285 (4) [M – CO_2H]$^+$, 271 (8) [M – CH_2CO_2H]$^+$, 243 (4) [M – 2 CO_2H + 3H]$^+$, 179 (100) [M – 2 OCH_2CO_2H – H]$^+$, 121 (12) [CO-C_6H_4OH]$^+$, 92 (4) [C_6H_4O]$^+$. HRMS (EI): calcd. for $C_{17}H_{14}O_7$ [M]$^+$ 330.0740; found 330.0745. $C_{17}H_{14}O_7$ (330.3): calcd. C 61.82, H 4.27; found C 61.68, H 4.48.

Supporting Information (see footnote on the first page of this article): General remarks and ^{1}H and ^{13}C NMR spectra.

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