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Mild and reliable cleavage sequence for phenoxy acetates

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Abstract—A novel combination of reliable transformations like ester saponification and subsequent *Curtius*-rearrangement employing mild reaction conditions, offers the first synthetically interesting strategy for the removal of methoxycarbonylmethyl groups from phenolic oxygens. This methodology gives also access to labile iodosubstituted phenols.

Phenoxy acetates are very robust moieties towards various harsh reaction conditions. The stability is documented by numerous transformations on the aryl system without affecting the side chain. This alkoxy moiety turned out to be beneficial for oxidative transformations with strong Lewis acids like $MoCl_5$[1] or hypervalent iodine reagents[2] and can be exploited as a directing side chain for chlorination processes.[3] However, in both transformations this particular moiety serves as splendid and superior permanent protective group for the phenolic oxygen without having any tool for the cleavage of the phenoxy alkyl bond.[4,5]

The strong electron withdrawing effect of the carbonyl system on the methylene group (Fig. 1) makes it less prone for a heterolytic removal of the phenoxy system and may explain the stability especially under cationic conditions. Therefore, rather a methoxy group undergoes the cleavage than the corresponding carboxy methoxy moiety on the arene system.[6]

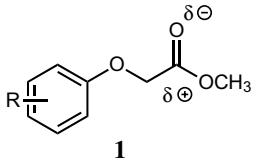

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Figure 1. Polarization of methyl phenoxy acetates.

Due to the robust character of the phenoxy derivatives the cleavage occurs only as a side reaction under harsh and prolonged reaction conditions.[7] Other methods involve very high temperatures (>270 °C),[8] gas phase chemistry,[9] electrochemical procedures,[10] or irradiation techniques.[11] *Fries*-rearrangements on the aromatic moiety and a broad product distribution result in synthetically unattractive yields.[12] The displacement of a carboxy methoxy group on a very electron deficient arene can be realized by a nucleophilic aromatic substitution reaction.[13] For simple systems a reductive cleavage with sodium in liquid ammonia might be successful.[14]

Apparently, arenes with sensitive substituents and complex molecular structures are not anticipated to be compatible with the reported methods. Therefore, we developed a reliable and easy to perform two-step sequence for the removal of the alkoxy carbonyl methyl group under mild conditions giving access to the corresponding phenols (Scheme 1). Starting from known substrates,[15] except for **1f**,[16] we applied this protocol on a variety of different substituted phenoxy acetates (Table 1).

The first step of the reaction sequence is the saponification of the ester moieties to the corresponding carboxylic acids **2** under standard conditions.[17] The isolated yields of the products were excellent in almost all the cases, even the biscarboxylic acid **2g** is obtained quantitatively. For **2a–e** the structures were proven by NMR techniques and mass spectrometry and the analytical data match with the data given in literature;[18] **2f** and **2g** are novel compounds and therefore fully characterized.[19]

Keywords: Deprotection; Phenoxy acetates; Protecting groups; Cleavage; *Curtius*-rearrangement; Azide.
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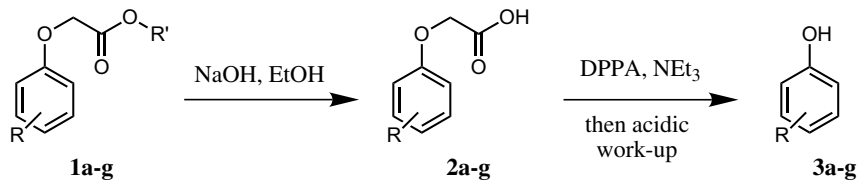
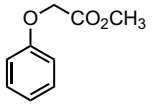
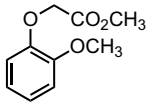
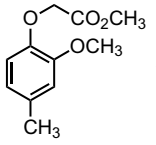
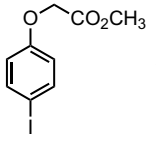
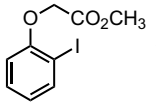
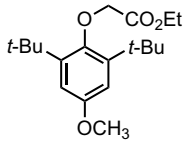
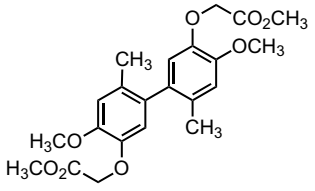


Scheme 1. Deprotection sequence.

Table 1. Isolated yields following the deprotection sequence (Scheme 1)

Entry	Substrate	**2**: Yield (%)	**3**: Yield (%)
1	 **1a**	97 (**2a**)	63 (**3a**)
2	 **1b**	93 (**2b**)	62 (**3b**)
3	 **1c**	95 (**2c**)	59 (**3c**)
4	 **1d**	99 (**2d**)	55 (**3d**)
5	 **1e**	88 (**2e**)	43 (**3e**)[a]
6	 **1f**	99 (**2f**)	60 (**3f**)
7	 **1g**	99 (**2g**)	31 (**3g**)[b]

[a] Formation of a by-product.
[b] 62% yield corresponds to one hydroxy moiety.

The second step of the deprotection sequence for the phenolic oxygen involves a *Curtius*-degradation. The carboxylic acid **2** was transformed into a carbonyl azide, which directly undergoes the rearrangement forming the corresponding isocyanate using diphenylphosphoryl azide (DPPA) and triethylamine under reflux conditions.[20] The *Curtius*-rearrangement is performed with DPPA, a mild and less harmful azide transfer reagent that is available in large scale.[21] Addition of water to the reaction mixture and acidic work-up leads to phenoxy methylamines, which are not stable in aqueous media. Subsequent hydrolysis of the aminal moiety provides the free phenol **3** in good to moderate isolated yields.

This two-step sequence allows a variety of sensitive substituents on the arene. The parent phenol derivative **1a** undergoes the deprotection protocol as well as electron rich derivatives, involving additional methoxy and alkyl moieties (entries 2 and 3). Even two *tert*-butyl groups adjacent to the hydroxy function are compatible with this sequence in spite of their steric hindrance and acid lability (entry 6). Interestingly, a valuable iodo substituent is not lost during the transformation (entries 4 and 5). Applying this methodology on the dimeric acid **2g** results the corresponding biaryl **3g**, offering an unusual substitution pattern on the aromatic scaffold exhibiting hydroxy substituents in the position *meta* to the aryl–aryl bond. The deprotection of a single phenol moiety occurs in 62%. Compound **3g** is not known in literature so far and therefore fully characterized.[22] Analytical data of phenols **3a–f** correspond to the data of samples of the commercially available phenols.

The amount of DPPA has to be carefully controlled since an excess of the reagent leads to the formation of a triphenyl phosphate derivative **4** (Fig. 2), which was identified by ^{31}P NMR and mass spectrometry and diminishes the yield significantly. This might explain the lower yield of **3e**, wherein the formation of this particular by-product could not be avoided even when using less amounts of DPPA.[23]

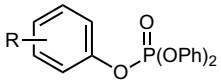


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Figure 2. Triphenyl phosphate derivatives **4**.

In conclusion, we developed the first reliable deprotection strategy for methoxycarbonylmethyl moieties. This methodology results the corresponding phenols in good and synthetically interesting yields and allows a large variety in the aromatic substitution pattern. This two-step protocol is easy to perform under mild reaction conditions and offers a broad application in the selective deprotection of phenolic oxygens. Moreover, sensitive substituents on the aromatic core like iodo or *tert*-butyl moieties are fully compatible with the herein presented

cleavage sequence whereas oxidative or reductive methods fail.

Acknowledgements

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15. Compound **1a**: Belleney, J.; Vebrel, J.; Cerutti, E. *J. Heterocycl. Chem.* **1984**, *21*, 1431–1435; Compound **1b**: Ahvonen, T.; Brunow, G.; Kristersson, P.; Lundquist, K. *Acta Chem. Scand. Ser. B* **1983**, *37*, 845–850; Compound **1c**: see Ref. 1; Compound **1d**: Baliah, V.; Gurumurthy, R. *Indian J. Chem. Sect. B* **1981**, *20*, 629–631; Compound **1e**: Green, S. P.; Whiting, D. A. *J. Chem. Soc. Perkin Trans. 1* **1998**, 193–202; Compound **1g**: see Ref. 1.
16. 2,6-Di-*tert*-butyl-4-methoxyphenol (9.45 g; 40.0 mmol) was dissolved in DMF (50 mL). K_2CO_3 (13.8 g; 100 mmol) and bromoacetic acid methyl ester (5.5 mL; 45.0 mmol) were added. After stirring at 25 °C overnight, Et_2O (200 mL) was added and the mixture was washed several times with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuum. 5.26 g (16.3 mmol; 41%) of **1f** were obtained as red oil, which was separated from solid starting material. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (t, 3H, $^3J_{7,8}$ = 7.2 Hz, CH_3); 1.44 (s, 18H, $C(CH_3)_3$); 3.77 (s, 3H, OCH_3); 4.29 (q, 2H, $^3J_{7,8}$ = 7.2 Hz, $COOCH_2$); 4.36 (s, 2H, OCH_2); 6.82 (s, 2H, Ar–H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.04 (CH_3); 31.87 ($C(CH_3)_3$); 35.84 ($C(CH_3)_3$); 55.01 (OCH_3); 60.68 ($COOCH_2$); 72.74 (OCH_2); 111.96 (C3); 144.27 (C2); 149.98 (C1); 154.82 (C4); 168.42 (CO). MS (EI, 70 eV): *m/z* (%) = 322 (100) [M^+]; 235 (72) [$M^+-CH_2CO_2CH_2CH_3$]; 207 (15) [235−CO]; 179 (67) [235−C_4H_9]; 57 (99) [$C_4H_9^+$]. Anal. Calcd for $C_{19}H_{30}O_4$ (322.44): C, 70.77; H, 9.38. Found: C, 70.65; H, 9.34.
17. General procedure: Substrate **1** was dissolved in a 1:1 mixture of EtOH and aqueous NaOH solution (20%) (20–60 mL) and stirred for 72 h at 25 °C. After adjusting to pH 1 the precipitated colorless carboxylic acids **2** were filtered off. If necessary the filtrate was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (2 × 50 mL), dried over anhydrous $MgSO_4$, and evaporated, yielding colorless or off-white, analytically pure solids.
18. Compound **2a**: Villemin, D.; Hammadi, M. *Synth. Commun.* **1996**, *26*, 4337–4342; Compound **2b**: Deffieux, D.; Fabre, I.; Courseille, C.; Quideau, S. *J. Org. Chem.* **2002**, *67*, 4458–4465; Compound **2c**: Freudenberg, K.; Müller, H. G. *Justus Liebigs Ann. Chem.* **1953**, *584*, 40–53; Compounds **2d** and **2e**: Koelsch, F. *J. Am. Chem. Soc.* **1931**, *53*, 304–305; Compound **2c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H, CH_3); 3.84 (s, 3H, OCH_3); 4.63 (s, 2H, OCH_2); 6.67 (dd, 1H, $^3J_{5,6}$ = 8.1 Hz, $^4J_{3,5}$ = 1.6 Hz, 5-H); 6.71 (d, 1H, $^4J_{3,5}$ = 1.6 Hz, 3-H); 6.79 (d, 1H, $^3J_{5,6}$ = 8.1 Hz, 6-H); 10.06 (br s, 1H, COOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.06 (CH_3); 55.82 (OCH_3); 67.78 (OCH_2); 113.24 (C6); 116.42 (C3); 121.25 (C5); 133.45 (C4); 144.95 (C1); 149.52 (C2); 173.21 (CO). MS (EI, 70 eV): *m/z* (%) = 196 (100) [M^+]; 137 (87) [M^+-CH_2COOH]; 123 (12) [$M^+-CH_2COOH-CH_2$]; 109 (39) [$M^+-CH_2COOH-CO$]; 91 (35) [$C_7H_7^+$]; 77 (22) [$C_6H_5^+$]; 65 (18) [$C_5H_5^+$]; 51 (10) [$C_4H_3^+$]. Compound **2d**: ^{1}H NMR (300 MHz, CD_3CN): δ = 4.75 (s, 2H, OCH_2); 6.86 (d, 2H, $^3J_{2,3}$ = 9.0 Hz, 2-H); 7.72 (d, 2H, $^3J_{2,3}$ = 9.0 Hz, 3-H); 9.36 (br s, 1H, COOH). ^{13}C NMR (75 MHz, CD_3CN): δ = 65.62 (OCH_2); 84.12 (C4); 117.78 (C2); 139.46 (C3); 159.00 (C1); 170.10 (CO). MS (EI, 70 eV): *m/z* (%) = 278 (100) [M^+]; 233 (31) [M^+-COOH]; 219 (21) [M^+-CH_2COOH]; 203 (31) [M^+-OCH_2COOH]. Compound **2e**: ^{1}H NMR (300 MHz, CD_3CN): δ = 4.73 (s, 2H, OCH_2); 6.78 (ddd, 1H, $^3J_{3,4}$ = $^3J_{4,5}$ = 7.7 Hz, $^4J_{4,6}$ = 1.2 Hz, 4-H); 6.85 (dd, 1H, $^3J_{5,6}$ = 8.3 Hz, $^4J_{4,6}$ = 1.2 Hz, 6-H); 7.34 (ddd, 1H, $^3J_{4,5}$ = 7.7 Hz; $^3J_{5,6}$ = 8.3 Hz, $^4J_{3,5}$ = 1.5 Hz, 5-H); 7.81 (dd, 1H, $^3J_{3,4}$ = 7.7 Hz, $^4J_{3,5}$ = 1.5 Hz, 3-H); 9.52 (br s, 1H, COOH). ^{13}C NMR (75 MHz, CD_3CN): δ = 66.44 (OCH_2); 86.39 (C2); 113.62 (C6); 124.50 (C4); 130.79 (C5); 140.77 (C3); 157.72 (C1); 169.88 (CO). MS (EI, 70 eV): *m/z* (%) = 278 (82) [M^+]; 233 (14) [M^+-COOH]; 203 (28) [M^+-OCH_2COOH]; 151 (100) [M^+-I]; 105 (49) [$C_8H_9^+$]; 77 (67) [$C_6H_5^+$].
19. Compound **2f**: Mp 117 °C (Et_2O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 18H, CH_3); 3.78 (s, 3H, OCH_3); 4.42 (s, 2H, OCH_2); 6.81 (s, 2H, 3-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.01 ($C(CH_3)_3$); 36.06 ($C(CH_3)_3$); 55.32 (OCH_3); 72.24 (OCH_2); 112.33 (C3); 144.37 (C2); 149.27 (C1); 155.21 (C4); 172.46 (CO). MS (EI, 70 eV): *m/z* (%) = 294 (92) [M^+]; 235 (54) [M^+-CH_2COOH]; 179 (46) [$M^+-CH_2COOH-C_4H_9$]; 57 (100) [$C_4H_9^+$]. Anal. Calcd for $C_{17}H_{26}O_4$ (294.39): C, 69.36; H, 8.90. Found: C, 69.19; H, 8.90. Compound **2g**: Mp 154 °C (Et_2O). ^{1}H NMR (300 MHz, CD_3CN): δ = 1.98 (s, 6H, CH_3); 3.85 (s, 6H, OCH_3); 4.60 (s, 4H, OCH_2); 6.59 (s, 2H, 3-H); 6.90 (s, 2H, 6-H). ^{13}C NMR (75 MHz, CD_3CN): δ = 19.61 (CH_3); 56.67 (OCH_3); 67.17 (OCH_2); 115.15 (C6); 117.36 (C3); 131.14 (C1); 134.10 (C2); 145.96 (C5); 149.60 (C4); 170.70 (CO). MS (EI, 70 eV): *m/z* (%) = 390 (100) [M^+]. HRMS: *m/z* Calcd for $C_{20}H_{22}NaO_8$ ($M+Na^+$): 413.1207. Found: 413.1224.
20. General procedure: Substrate **2** (500 mg) was dissolved in anhydrous toluene (30 mL) and DMF (3 mL). Et_3N (1.00–1.15 equiv) and DPPA (0.90–1.05 equiv) were added and the mixture was refluxed for 3 h and again for 1–2 h after addition of water (30 mL). The solution was acidified with 2 N HCl solution (50 mL) and extracted with EtOAc

(3×50 mL). The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Phenols **3** were purified via column chromatography on silica with cyclohexane and EtOAc as eluents.

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22. Compound **3g**: Mp 137–139 °C (Et_2O). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.99$ (s, 6H, CH_3); 3.90 (s, 6H, OCH_3); 5.48 (br s, 2H, OH); 6.68 (s, 2H, 3-H); 6.73 (s, 2H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 19.32$ (CH_3); 55.93 (OCH_3); 112.13 (C6); 115.83 (C3); 127.53 (C1); 134.05 (C2); 143.01 (C5); 145.39 (C4). MS (EI, 70 eV): *m/z* (%) = 274 (100) [M^+]. HRMS: *m/z* Calcd for $C_{16}H_{18}NaO_4$ ($M+Na^+$): 297.1097. Found: 297.1061.
23. Phenols **3** could not be separated from the by-products **4** by column chromatography. Therefore, **3e** was purified by distillation in high vacuum.