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Operationally Simple and Selective One-Pot Synthesis of Hydroxyphenones: A Facile Access to SNARF Dyes

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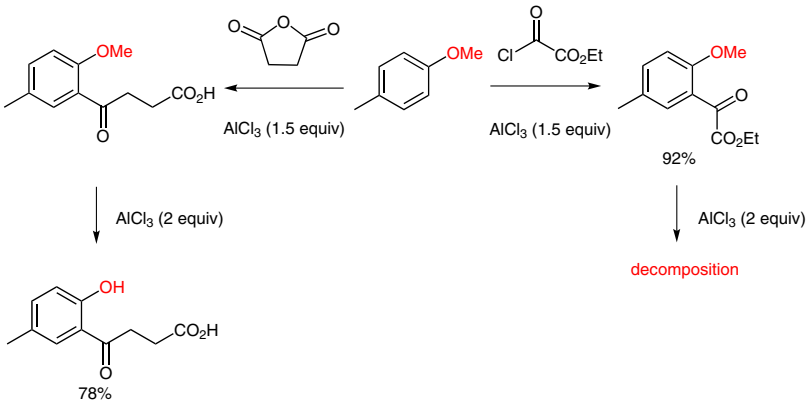

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Abstract High selectivity is observed during a Friedel–Crafts acylation/demethylation cascade. In contrast to this cascade, oxygen-containing acylating reagents do not undergo the demethylation step. By the methodology elaborated here, an access is provided to important intermediates for the total synthesis of seminaphthorhodafluor (SNARF) dyes.

Key words Friedel–Crafts acylation, demethylation cascade, aluminum chloride, selectivity

Xanthene-based ratiometric pH-probes are often utilized for imaging pH changes in cells and biofilms.[1] Investigation on a time-resolved picosecond scale demands a dual emission band, reflecting the protonated as well as the deprotonated state of the fluorophore. Seminaphthorhodafluor (SNARF) homologues offer this property together with a wide excitation range and a pK_a in the physiological range.[2] In a previous article, two SNARF-derivatives for measurements in cells or linked to protein surfaces have been reported.[3]

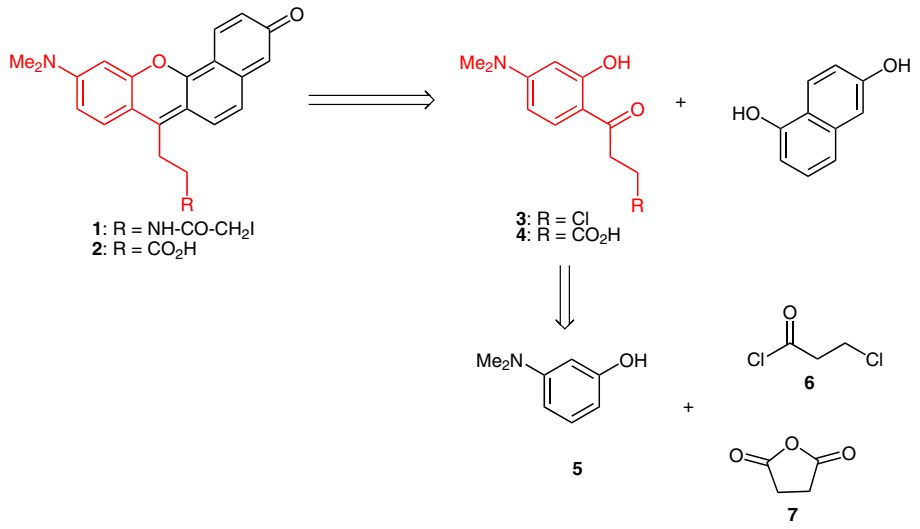
To construct the SNARF-dyes **1** and **2** we followed the classic synthetic route to unsymmetric benzoxanthenes (Scheme 1).[1] For this approach the well-defined, highly substituted 3-chloro-1-[4-(dimethylamino)-2-hydroxyphenyl]propan-1-one (**3**) and 4-[4-(dimethylamino)-2-hydroxyphenyl]-4-oxobutanoic acid (**4**) are needed. By retrosynthetic evaluation, the 3-aminophenols **3** and **4** should be accessible by Friedel–Crafts acylation of the corresponding 3-dimethylaminophenol (**5**) (Scheme 1).

Unfortunately, the conditions for the common Friedel–Crafts acylation of unprotected phenols are not compatible with a simple and direct acylation of 3-dimethylaminophenol (**5**).[4] The formation of the acylated products **3** or **4** was not observed when 3-dimethylaminophenol (**5**) was used under these conditions.

Acyl chlorides or anhydrides often react with phenols to the corresponding phenyl esters to a more or less extent under the conditions of a Friedel–Crafts acylation.[5] To avoid this yield-diminishing side reaction several different multistep approaches have been developed to isolate the required acylated target molecule in high yields.[6]

In general, a three-step sequence is used: protection of the hydroxyl group as the methyl ether, Friedel–Crafts acylation, and subsequent final deprotection. This stepwise strategy is exemplified by the synthesis of several cytosporones,[7] chromanones,[8] and flavonoides.[9] In addition, some authors have described a one-pot acylation/deprotection procedure of protected phenols in the presence of aluminum and boron halides. This approach was mostly accomplished by acetylation of methoxybenzenes as a starting sequence in a great many total syntheses of flavones, benzophenones, chalcones, or catechols.[10] This phenomenon – the concomitant deprotection during the acylation step – is a very old one and goes probably back to an observation made by Karl von Auwers in 1909.[11] A systematic study of substrates used in this simplified procedure does not exist so far.

Following this simplified synthetic route we tested 3-dimethylaminoanisole (**8**) and 3-chloropropionyl chloride (**6**) as substrates. The expected Friedel–Crafts product **9** was isolated from the reaction of 3-dimethylaminoanisole (**8**) with 3-chloropropionyl chloride (**6**) in the presence of 1.5 equivalents of aluminum chloride in 11% yield. In addition



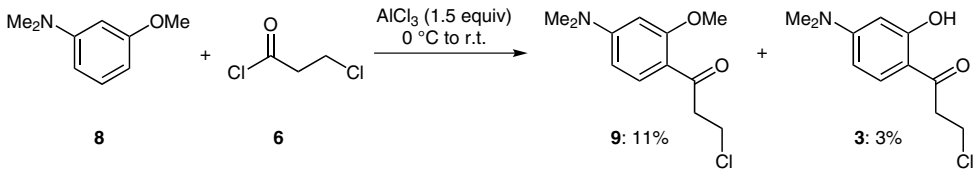
Scheme 1 Retrosynthetic map of SNARF-derivatives

to the methyl ether **9** the formation of small amounts of the acylated unprotected phenol **3** was observed (yield: 3%, Scheme 2).

This operationally simple and direct access to the demethylated Friedel–Crafts product **3** was subjected to further investigation, since the acylated phenol **3** represents a valuable intermediate in the total synthesis of SNARF dye **1** (Scheme 1). It has been demonstrated, that the demethylation occurs only via the acylated methyl ether **9**.[12] A demethylation of the starting aminoanisole **8** was not observed under these conditions. Also, a direct acylation of the unprotected 3-dimethylaminophenol (**5**) could not be accomplished under the described reaction conditions or by Fries rearrangement. In a further series, several different Lewis acids were tested in these reactions. A clear formation of the *ortho*-acylated phenol **3** was observed only by the deployment of aluminum chloride. Use of aluminum bromide, boron halides, or titanium(IV) chloride led only to the formation of the methyl ether **9** or decomposition products. Both 1.5 and 3.5 equivalents of the corresponding Lewis acids were tested in these experiments. No reactions were observed by using boron trifluoride etherate and the starting material was recovered quantitatively. The formation of the corresponding and undesired ester was detected by application of trifluoromethanesulfonic acid in acylation reactions of unprotected 3-dimethylaminophenol **5** with chloropropionic acid. A Fries rearrangement did not occur. The optimization of these results ends up in the following one-pot procedure. Only the acylated phenol **3** was detected when an excess of 3.5 equivalents of aluminum chloride was used, although in low yields (18%). Approximately 30% of the starting 3-dimethylaminoanisole (**8**) was recovered. By-products could not be detected by thin layer chromatography in the organic phase.

In a first series of experiments, further substrates were tested under the conditions as they were elaborated for the reaction of 3-dimethylaminoanisole (**8**) and chloropropionyl chloride (**6**) (Scheme 2).

This systematic optimization process appeared necessary because many different protocols exist (reaction time, reaction temperature, substrates, equivalents of Lewis acids).[13] Even conflicting results have been reported for this reaction.[14] A set of different aryl methyl ethers, **8** and **10**–**12** were reacted with different acyl halides **6**, **13**, and succinic anhydride (**7**) under the described conditions (Scheme 3). The yields of these reactions strongly depend on the substrates employed. These results were obtained independently of the performance of the experiments. Similar yields were obtained by successive addition of 1.5 equivalents followed by a further addition of 2 equivalents of alu-



Scheme 2 Acylation of 3-dimethylaminoanisole

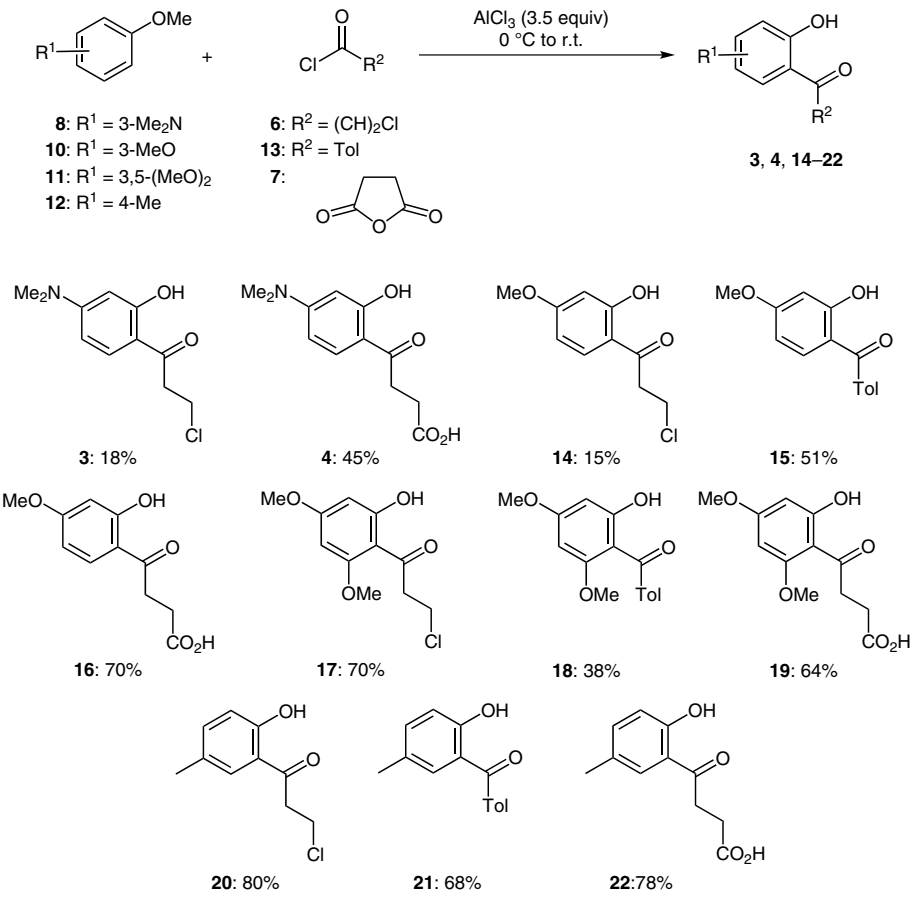
minum chloride or by a singular addition of 3.5 equivalents of aluminum chloride. The addition of aluminum chloride to the reactants was performed at 0 °C, whereas the reactions themselves were carried out at room temperature. The corresponding methyl ethers were not detected when 3.5 equivalents of aluminum chloride were used. By-products or doubly demethylated products were not observed.

In a second series of experiments, we tested oxygen-containing acyl halides as substrates in these reactions. There is a strong difference between the use of oxygen-containing halides and simple, unfunctionalized halides as shown in Scheme 3. In contrast to the results of Scheme 3, a demethylation was not observed when the acyl halides **23**–**25** were used (Scheme 4). The corresponding acylated aryl methyl ethers **26**–**37** can easily be accessed in good to high yields. Even when used with an additional excess of aluminum chloride (3.5 equiv) a demethylation does not occur. By further addition of aluminum chloride only decomposition of products was observed. Comparison of results from the second series to reactions described in the literature cannot be made, since the latter were carried out in the presence of equimolar amounts of aluminum chloride or other Lewis acids.[15]

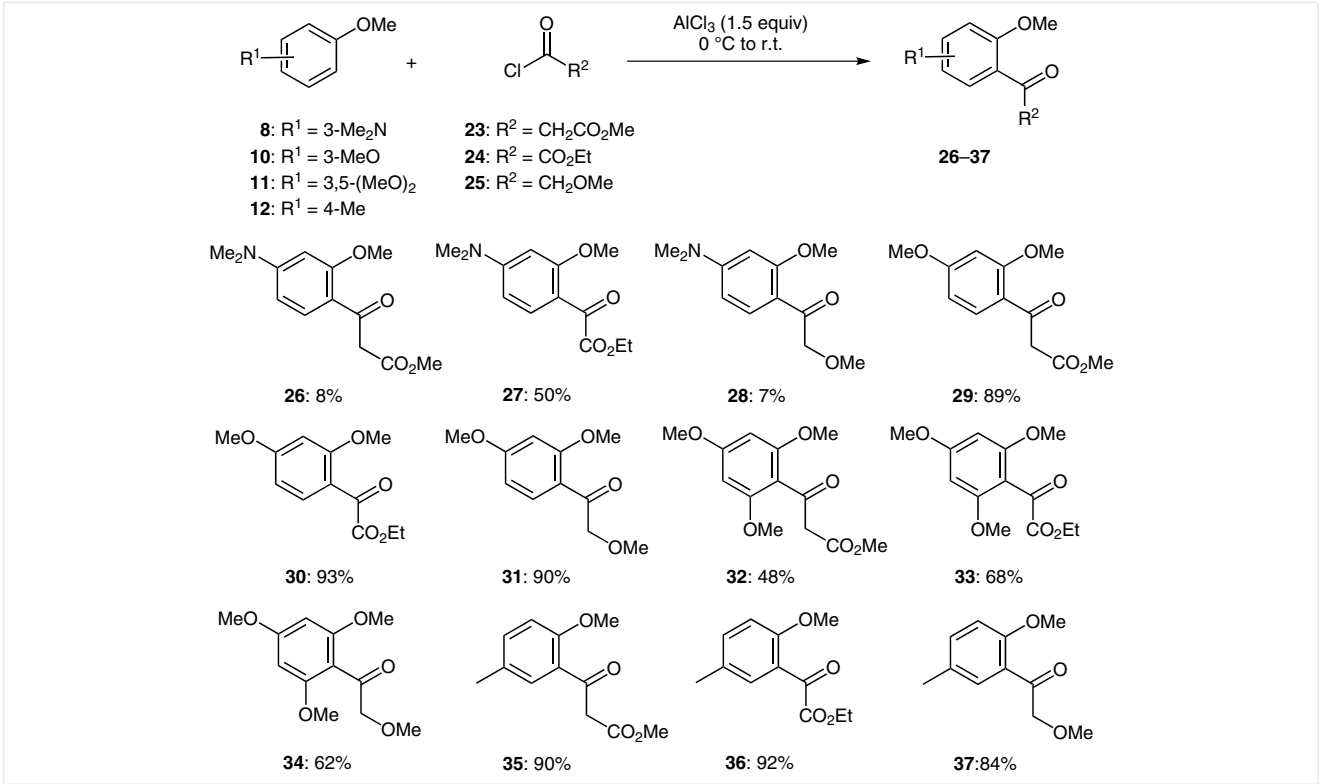
A first explanation for this high chemoselectivity is given by comparison of the corresponding complexation states. By acylation of anisoles with succinic anhydride (**7**) the complexation of aluminum chloride can occur within the succinic moiety (7-membered ring system **A** – unfavored) or via a 6-membered ring system, which includes the methyl ether **B** (Scheme 5)

Result of this kind of complexation is the demethylation. In contrast, by carrying out the acylation of anisoles with methyl malonyl chloride (**23**), a preferred complexation of aluminum chloride via a 6-membered ring system **C** can be assumed (Scheme 5). A demethylation is not observed under these conditions.

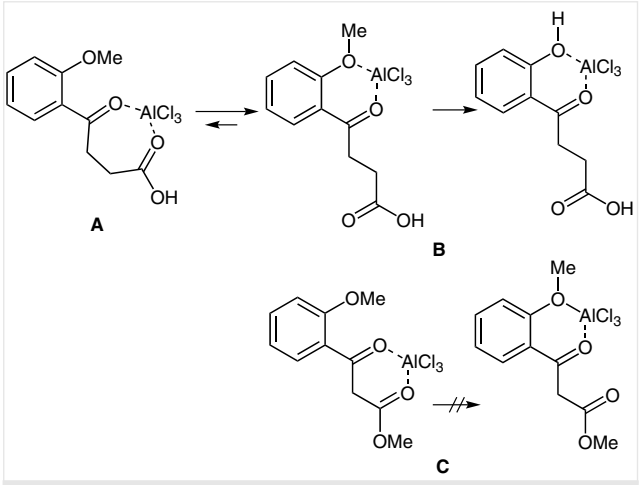
Note that high regio- and chemoselectivity were observed in all transformations. The acylation occurs only at the *ortho*-position to the methoxy groups. Moreover, a second Friedel–Crafts acylation was not observed in all the reactions carried out, even when an excess of 10 equivalents of aluminum chloride or acyl chloride was used. Several products of our investigations are rarely described in the lit-



Scheme 3 One-pot Friedel–Crafts acylation/demethylation reactions



Scheme 4 Friedel–Crafts acylation with oxygen-containing acyl halides



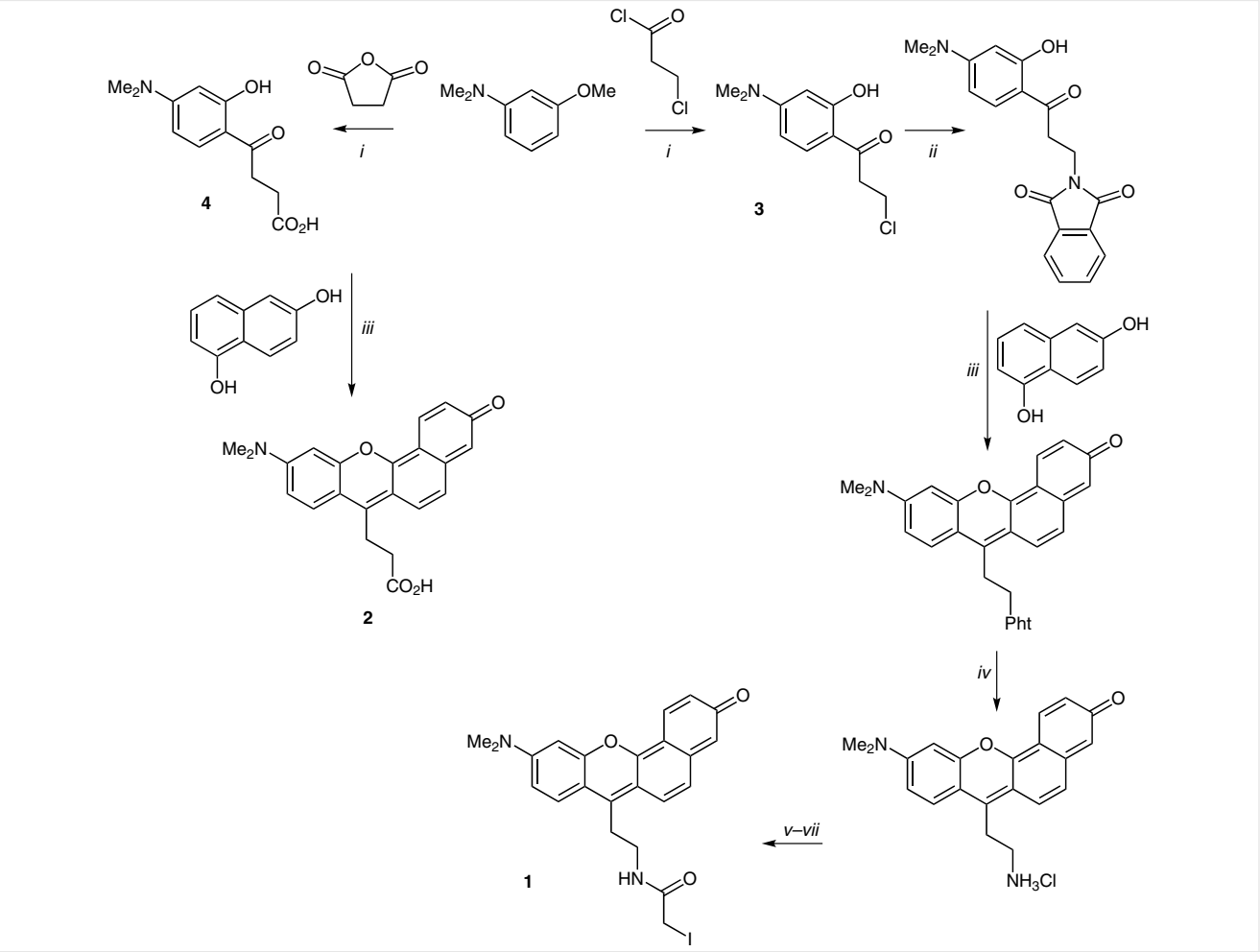
Scheme 5 Different aluminum chloride complexation states

erature, or they are described with insufficient characterization. To this end a complete set of analytic data is given in the experimental section.

Based on these results we successfully completed the synthesis of the SNARF dyes **1** and **2**.[3] These reaction sequences are depicted in Scheme 6.

In conclusion, we have investigated an operationally simple one-pot procedure for a Friedel–Crafts acylation/demethylation cascade. By an optimization process of the substrates employed, high selectivity was obtained. Using simple acyl halides or anhydrides a simultaneous demethylation process is observed. However, this demethylation failed to appear in the cases of oxygen-containing acyl halides. Using 3-dimethylaminoanisole (**8**) as aromatic substrate in these transformations, important intermediates for the total synthesis of several SNARF-dyes are accessible.

^{1}H NMR, ^{13}C NMR, DEPT, and correlation experiments ^{1}H, ^{1}H-^{1}H-COSY, HSQC, NOESY, and JRES were carried out at 500 MHz or 300 MHz for ^{1}H and 125 MHz or 75 MHz for ^{13}C, respectively, using a Bruker Avance-300 or Bruker-500 spectrometer. Chemical shifts are given in ppm, coupling constants in Hz. High-resolution mass spectroscopy was performed on a LTQ-FT-ICR spectrometer (Finnigan) (ESI). Purification of products was accomplished by flash chromatography (Merck silica gel 60, particle size 0.04–0.063 mm). The solvent mixture of hexane and EtOAc in ratio 90:10 to 1:1 was used as eluent. Yields were determined after column chromatography. TLC was performed with Merck Silica Gel 60 F_{254} TLC plates. Development was performed with cerium(IV) sulfate/phosphormolybdic acid. Solvents were purchased from Sigma-Aldrich and used, unless otherwise mentioned, without further purification or drying.



Scheme 6 Syntheses of SNARF-dyes **1** and **2**. *Reagents and conditions*: *i*. $AlCl_3$, CH_2Cl_2 0 °C → r.t.; *ii*. potassium phthalimide, DMF; *iii*. H_3PO_4, 145 °C, 6 h; *iv*. HCl/AcOH; *v*. chloroacetyl chloride; *vi*. NaOH, MeOH; *vii*. NaI, acetone.

Friedel–Crafts Reactions of Aryl Methyl Ethers 8, 10–12 with Acyl Chlorides 6, 7, and 13; General Procedure A

$AlCl_3$ (467 mg, 3.5 mmol) was suspended in CH_2Cl_2 (10 mL) in a round-bottom flask. The corresponding aryl methyl ether **8** or **10**–**12** (1.0 mmol) was added to this suspension and the mixture was cooled down to 0 °C. After stirring for 5 min, the corresponding acyl chloride **6**, **7**, or **13** (1.5 mmol) was added dropwise and the resulting mixture was stirred at r.t. The progress of the reaction was monitored by TLC (hexane/EtOAc, 8:2). At the end of the reaction (5–10 h), the mixture was poured into aq 1 N HCl and extracted with CH_2Cl_2 (4 ×). The combined organic phases were washed with aq 1 N HCl, aq $NaHCO_3$ (with the exception of reactions with **7**) and H_2O, and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the remaining residue was purified by column chromatography.

Friedel–Crafts Reactions of Aryl Methyl Ethers 8, 10–12 with Acyl Chlorides 23–25; General Procedure B

$AlCl_3$ (200 mg, 1.5 mmol) was suspended in CH_2Cl_2 (10 mL) in a round-bottom flask. The corresponding aryl methyl ether **8** or **10**–**12** (1.0 mmol) was added to this suspension and the mixture was stirred at 0 °C. After 5 min, the corresponding acyl chloride **23**–**25** (1.5 mmol) was added dropwise and the resulting mixture was stirred at r.t. The progress of the reaction was monitored by TLC (hexane/EtOAc, 8:2). At the end of the reaction (5–10 h), the mixture was poured into aq 1 N HCl and extracted with CH_2Cl_2 (4 ×). The combined organic phases were washed with aq 1 N HCl, aq $NaHCO_3$ and H_2O, and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the remaining residue was purified by column chromatography.

3-Chloro-1-[4-(dimethylamino)-2-hydroxyphenyl]propan-1-one (3)

Yield: 40 mg (18%); white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.68 (s, 1 H), 7.52 (d, *J* = 9.1 Hz, 1 H), 6.22 (dd, *J* = 9.1, 2.6 Hz, 1 H), 6.09 (d, *J* = 2.6 Hz, 1 H), 3.90 (t, *J* = 6.9 Hz, 2 H), 3.33 (t, *J* = 6.9 Hz, 2 H), 3.05 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 165.1, 156.2, 131.6, 109.8, 104.3, 97.9, 40.1, 39.9, 39.4.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{15}ClNO_2$: 228.0786; found: 228.0787.

4-[4-(Dimethylamino)-2-hydroxyphenyl]-4-oxobutanoic Acid (4)

Yield: 105 mg (45%); white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.68 (s, 1 H), 12.14 (s, 1 H), 7.69 (d, J = 9.2 Hz, 1 H), 6.31 (dd, J = 9.2, 2.5 Hz, 1 H), 6.02 (d, J = 2.5 Hz, 1 H), 3.13 (t, J = 6.4 Hz, 2 H), 3.00 (s, 6 H) 2.54 (t, J = 6.4 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 201.1, 173.9, 163.9, 155.7, 131.9, 109.0, 104.3, 97.0, 39.6, 31.8, 27.9.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{16}NO_4$: 238.1074; found: 238.1074.

3-Chloro-1-(2-hydroxy-4-methoxyphenyl)propan-1-one (14)[16]

Yield: 31 mg (15%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 12.42 (s, 1 H), 7.79 (d, J = 8.8 Hz, 1 H), 6.76 (d, J = 2.2 Hz, 1 H), 6.70 (dd, J = 8.8, 2.2 Hz, 1 H), 3.81 (t, J = 6.3 Hz, 2 H), 3.38 (s, 3 H), 3.23 (t, J = 6.3 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.1, 145.8, 144.3, 131.7, 114.8, 112.9, 111.3, 59.2, 38.8, 38.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{12}ClO_3$: 215.0469; found: 215.0470.

(2-Hydroxy-4-methoxyphenyl)(*p*-tolyl)methanone (15)[17]

Yield: 122 mg (51%); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.73 (s, 1 H), 7.55 (d, J = 8.1 Hz, 2 H), 7.53 (d, J = 9.0 Hz, 1 H), 7.29 (d, J = 7.8 Hz, 2 H), 6.52 (d, J = 2.5 Hz, 1 H), 6.41 (dd, J = 9.0, 2.5 Hz, 1 H), 3.86 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.0, 166.4, 166.2, 142.3, 135.6, 135.3, 129.2, 129.1, 113.4, 107.3, 101.2, 55.7, 21.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{15}O_3$: 243.1016; found: 243.1017.

4-(2-Hydroxy-4-methoxyphenyl)-4-oxobutanoic Acid (16)[18]

Yield: 156 mg (70%); white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.40 (s, 1 H), 12.18 (s, 1 H), 7.89 (d, J = 9.0 Hz, 1 H), 6.54 (dd, J = 9.0, 2.5 Hz, 1 H), 6.48 (d, J = 2.5 Hz, 1 H), 3.82 (s, 3 H), 3.26 (t, J = 6.2 Hz, 2 H), 2.58 (t, J = 6.2 Hz, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 203.0, 173.8, 165.6, 163.8, 132.4, 113.5, 107.3, 100.8, 55.7, 32.9, 27.6.

HRMS (ESI): m/z [M – H]$^+$ calcd for $C_{11}H_{11}O_5$: 223.0612; found: 223.0612.

3-Chloro-1-(2-hydroxy-4,6-dimethoxyphenyl)propan-1-one (17)[19]

Yield: 170 mg (70%); yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 13.70 (s, 1 H), 6.06 (d, J = 2.4 Hz, 1 H), 5.92 (d, J = 2.4 Hz, 1 H), 3.87 (s, 3 H), 3.86 (t, J = 6.9 Hz, 2 H), 3.82 (s, 3 H), 3.48 (t, J = 6.8 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.3, 167.8, 166.5, 162.8, 105.7, 93.8, 91.0, 55.8, 55.7, 46.7, 39.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{14}ClO_4$: 245.0575; found: 245.0574.

(2-Hydroxy-4,6-dimethoxyphenyl)(*p*-tolyl)methanone (18)[20]

Yield: 102 mg (38%); yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.11 (s, 1 H), 7.46 (d, J = 8.2 Hz, 2 H), 7.18 (d, J = 8.2 Hz, 2 H), 6.16 (d, J = 2.3 Hz, 1 H), 5.94 (d, J = 2.3 Hz, 1 H), 3.83 (s, 3 H), 3.47 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.8, 166.2, 165.7, 161.9, 141.7, 138.8, 128.4, 128.3, 105.8, 93.7, 91.4, 55.6, 55.2, 21.7.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{17}O_4$: 273.1121; found: 273.1122.

4-(2-Hydroxy-4,6-dimethoxyphenyl)-4-oxobutanoic Acid (19)

Yield: 162 mg (64%); white solid.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 13.60 (s, 1 H), 6.09 (d, J = 2.4 Hz, 1 H), 6.06 (d, J = 2.4 Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H), 3.18 (t, J = 6.2 Hz, 2 H), 2.51 (t, J = 6.2 Hz, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 203.6, 174.1, 166.1, 165.9, 162.9, 105.3, 93.8, 90.9, 56.1, 55.8, 38.8, 28.1.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{15}O_6$: 255.0863; found: 255.0864.

3-Chloro-1-(2-hydroxy-5-methylphenyl)propan-1-one (20)[21]

Yield: 158 mg (80%); white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.85 (s, 1 H), 7.49 (d, J = 2.0 Hz, 1 H), 7.30 (dd, J = 8.5, 2.0 Hz, 1 H), 6.89 (d, J = 8.5 Hz, 1 H), 3.91 (t, J = 6.7 Hz, 2 H), 3.47 (t, J = 6.7 Hz, 2 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.4, 160.5, 138.0, 129.5, 128.4, 118.9, 118.5, 40.9, 38.3, 20.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{12}ClO_2$: 199.0520; found: 199.0520.

(2-Hydroxy-5-methylphenyl)(*p*-tolyl)methanone (21)[22]

Yield: 152 mg (68%); yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 11.73 (s, 1 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.28–7.25 (m, 1 H), 7.19 (d, J = 8.0 Hz, 2 H), 7.18 (d, J = 8.5 Hz, 1 H), 6.85 (d, J = 8.5 Hz, 1 H), 2.33 (s, 3 H), 2.13 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.4, 161.1, 142.7, 137.2, 135.5, 133.3, 129.5, 129.1, 127.8, 119.1, 118.2, 21.7, 20.6.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{15}O_2$: 227.1067; found: 227.1068.

4-(2-Hydroxy-5-methylphenyl)-4-oxobutanoic Acid (22)[23]

Yield: 161 mg (78%); white solid.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.17 (s, 1 H), 11.55 (s, 1 H), 7.71 (d, J = 1.7 Hz, 1 H), 7.33 (dd, J = 8.4, 1.7 Hz, 1 H), 6.87 (d, J = 8.4 Hz, 1 H), 3.47–3.10 (t, J = 6.3 Hz, 2 H), 2.58 (t, J = 6.3 Hz, 2 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 204.2, 173.8, 158.4, 136.8, 130.1, 127.9, 119.9, 117.5, 34.1, 27.7, 20.0.

HRMS (ESI): m/z [M – H]$^-$ calcd for $C_{11}H_{11}O_4$: 207.0663; found: 207.0663.

Methyl 3-[4-(Dimethylamino)-2-methoxyphenyl]-3-oxopropanoate (26)

Yield: 19 mg (8%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, J = 9.0 Hz, 1 H), 6.31 (dd, J = 9.0, 2.4 Hz, 1 H), 6.02 (d, J = 2.4 Hz, 1 H), 3.90 (s, 2 H), 3.86 (s, 3 H), 3.70 (s, 3 H), 3.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.1, 169.7, 161.8, 155.5, 134.4, 133.2, 104.8, 93.3, 67.9, 55.0, 52.0, 40.2.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{18}NO_4$: 252.1230; found: 252.1231.

Ethyl 2-[4-(Dimethylamino)-2-methoxyphenyl]-2-oxoacetate (27)

Yield: 124 mg (50%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 9.0 Hz, 1 H), 6.33 (dd, *J* = 9.0, 2.3 Hz, 1 H), 5.98 (d, *J* = 2.3 Hz, 1 H), 4.34 (q, *J* = 7.2 Hz, 2 H), 3.83 (s, 3 H), 3.07 (s, 6 H), 1.37 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.0, 167.0, 162.7, 156.5, 132.5, 110.5, 105.4, 93.1, 61.2, 55.6, 40.2, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{18}NO_4$: 252.1230; found: 252.1231.

2-Methoxy-1-[4-(dimethylamino)-2-methoxyphenyl]ethanone (28)

Yield: 15 mg (7%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 9.0 Hz, 1 H), 6.33 (dd, *J* = 9.0, 2.3 Hz, 1 H), 6.05 (d, *J* = 2.3 Hz, 1 H), 4.60 (s, 2 H), 3.92 (s, 3 H), 3.50 (s, 3 H), 3.06 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.4, 161.6, 155.1, 134.2, 132.6, 104.7, 93.2, 78.8, 59.2, 55.0, 40.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}NO_3$: 224.1281; found: 224.1280.

Methyl 3-(2,4-Dimethoxyphenyl)-3-oxopropanoate (29)[24]

Yield: 211 mg (89%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.8 Hz, 1 H), 6.52 (dd, *J* = 8.8, 2.3 Hz, 1 H), 6.41 (d, *J* = 2.3 Hz, 1 H), 3.90 (s, 2 H), 3.83 (s, 3 H), 3.83 (s, 3 H), 3.68 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 191.3, 169.2, 165.5, 161.3, 133.3, 119.4, 105.8, 98.1, 55.7, 55.4, 52.1, 40.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_5$: 239.0914; found: 239.0914.

Ethyl 2-(2,4-Dimethoxyphenyl)-2-oxoacetate (30)[25]

Yield: 220 mg (93%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.8 Hz, 1 H), 6.59 (dd, *J* = 8.8, 2.3 Hz, 1 H), 6.43 (d, *J* = 2.3 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.88 (s, 3 H), 3.84 (s, 3 H), 1.38 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.2, 166.9, 166.0, 133.1, 116.1, 106.8, 98.3, 61.7, 56.1, 55.9, 14.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_5$: 239.0914; found: 239.0914.

2-Methoxy-1-(2,4-dimethoxyphenyl)ethanone (31)

Yield: 188 mg (90%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.8 Hz, 1 H), 6.54 (dd, *J* = 8.8, 2.3 Hz, 1 H), 6.43 (d, *J* = 2.3 Hz, 1 H), 4.58 (s, 2 H), 3.89 (s, 3 H), 3.84 (s, 3 H), 3.48 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6, 165.1, 161.3, 133.0, 118.6, 105.7, 98.2, 79.1, 59.4, 55.7, 55.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}O_4$: 211.0965; found: 211.0966.

Methyl 3-(2,4,6-Trimethoxyphenyl)-3-oxopropanoate (32)[26]

Yield: 128 mg (48%); white solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.06 (s, 2 H), 3.79 (s, 3 H), 3.78 (s, 2 H), 3.76 (s, 6 H), 3.67 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 194.1, 168.2, 163.3, 159.4, 111.7, 90.6, 55.9, 55.5, 52.0, 50.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}O_6$: 269.1020; found: 269.1021.

Ethyl 2-(2,4,6-Trimethoxyphenyl)-2-oxoacetate (33)

Yield: 181 mg (68%); white solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.00 (s, 2 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 3.74 (s, 3 H), 3.70 (s, 6 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 184.2, 165.7, 164.5, 162.4, 106.6, 90.6, 61.4, 55.9, 55.4, 14.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}O_6$: 269.1020; found: 269.1020.

Methoxy-1-(2,4,6-trimethoxyphenyl)ethanone (34)

Yield: 148 mg (62%); yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.01 (s, 2 H), 3.73 (s, 3 H), 3.73 (s, 2 H), 3.70 (s, 6 H), 3.62 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 194.0, 163.2, 159.3, 111.6, 90.5, 55.7, 55.4, 51.9, 50.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}O_5$: 241.1071; found: 241.1070.

Methyl 3-(2-Methoxy-5-methylphenyl)-3-oxopropanoate (35)[23]

Yield: 199 mg (90%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 2.4 Hz, 1 H), 7.28 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 3.94 (s, 2 H), 3.83 (s, 3 H), 3.69 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 193.1, 168.7, 157.3, 135.4, 131.2, 130.2, 125.8, 111.7, 55.5, 52.0, 50.4, 20.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_4$: 223.0965; found: 223.0966.

Ethyl 2-(2-Methoxy-5-methylphenyl)-2-oxoacetate (36)

Yield: 203 mg (92%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, *J* = 2.1 Hz, 1 H), 7.29 (ddd, *J* = 8.5, 2.4, 0.6 Hz, 1 H), 6.81 (d, *J* = 8.5 Hz, 1 H), 4.30 (q, *J* = 7.1 Hz, 2 H), 3.74 (s, 3 H), 2.22 (s, 3 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 186.59, 165.30, 158.33, 137.04, 130.54, 130.28, 122.09, 112.04, 61.54, 55.91, 19.98, 13.94.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}O_4$: 223.0965; found: 223.0964.

2-Methoxy-1-(2-methoxy-5-methylphenyl)ethanone (37)

Yield: 162 mg (84%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 2.2 Hz, 1 H), 7.27 (dd, *J* = 8.6, 2.2 Hz, 1 H), 6.85 (d, *J* = 8.6 Hz, 1 H), 4.62 (s, 2 H), 3.87 (s, 3 H), 3.47 (s, 3 H), 2.28 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.6, 157.3, 135.0, 130.8, 130.3, 124.9, 111.5, 79.2, 59.3, 55.6, 20.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{15}O_3$: 195.1016; found: 195.1015.

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Supporting Information

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