General and Efficient Protocol for Formylation of Aromatic and Heterocyclic Phenols

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Abstract: A convenient, general procedure for formylation of diverse range of phenols with the Duff protocol has been developed. The procedure gives dialdehydes when possible.

Key words: aldehydes, arenes, electrophilic aromatic substitution, heterocycles, phenols

Aromatic aldehydes are one of the most important classes of reagents used in organic synthesis. Over the last decades many methods allowing direct formylation of aromatic rings have been developed with Vilsmeier–Haack,[1] Gattermann–Koch,[2] and Reimer–Tiemann[3] reactions being the most recognized, and few more that are less known.[4] All these well-established protocols suffer, however, from the same drawback: they allow only monosubstitution as a result of aromatic ring deactivation; and for many applications further formylation is needed, which involves tedious, multistep synthesis. Nevertheless, there are several reports on a successful multiple formylation in a single step using the Duff reaction. Diformylated phenols obtained in this process have been used as precursors for the synthesis of various drugs,[5] sensors,[6] receptors,[7] and protein inhibitors.[8] The Duff reaction, developed in the 1930s[9] and then modified by Smith,[10] requires the use of hexamethylenetetramine (HMTA) in strongly acidic media. As a consequence of its mechanism, involving a series of equilibrium reactions, with iminium ion intermediates that do not deactivate aromatic ring, a polysubstitution is achievable.[11] A survey of the literature reveals that various procedures, sometimes differing quite significantly, were proposed for diformylation of phenols. Recognizing the enormous utility of the Duff reaction, we set ourselves the goal to establish one universal procedure, which could be subsequently used for a broad range of demanding, aromatic substrates.

We decided to employ the transformation of 2-methylresorcinol (**1**) into dialdehyde **16** as a model reaction. Brief examination of various conditions used so far in the literature[12] followed by optimization of such parameters as temperature, time, and concentration of reagents, led us to the following protocol: a) phenol (10 mmol), TFA (7–8 mL), HMTA (20 mmol), 70 °C, 72 h, then 100 °C, 4 h; b) aq HCl, 100 °C, 1 h. Using this protocol we obtained dialdehyde **16** in 44% yield directly from the reaction mixture, without the need for any purification. The strength of the Duff reaction is well illustrated by direct comparison with the synthesis of aldehyde **16** published by Richter and Lash,[13] that required three steps and multiple chromatography.

Having a good procedure in hand, scope and limitations studies were conducted. First, it was decided to examine other monosubstituted resorcinols **2**–**4**. 4-Ethylresorcinol (**2**), 4-hexylresorcinol (**3**), and 2-nitroresorcinol (**4**) were successfully transformed into the corresponding dialdehydes **17**–**19** (Table 1). Strongly electron-withdrawing, nitro substituent in position 2 of resorcinol did not hamper the reaction outcome. Encouraged by these results the use of 4,6-disubstituted resorcinols **5** and **6** was considered. 4,6-Dichlororesorcinol (**5**) smoothly afforded monoaldehyde **12**. Interestingly, 4,6-di-*tert*-butylresorcinol (**6**) gave in addition to the expected aldehyde **13** also the dialdehyde **20** as an unexpected product of *ipso*-substitution, that to the best of our knowledge, was not reported so far for this reaction.

Subsequently, attention was turned to structurally and electronically demanding phenols. Sashidhara and coworkers found that subjecting 8-hydroxyquinoline to the Duff reaction results in the formation of 7-methylaminomethylene-8-oxo-7,8-dihydroquinoline-5-carbaldehyde instead of the expected dialdehyde.[14] This result was rationalized based upon existence of strong intramolecular hydrogen bond. To our delight, the formylation of the corresponding *N*-oxide **7** smoothly afforded dialdehyde **21** as the only isolable product (Table 1). It is worth mentioning that the synthesis of the analogous aldehyde was successfully accomplished by Fiedler using multistep approach.[15] Also two regioisomeric hydroxybenzofurans[16] **8** and **9** were successfully diformylated under optimized conditions to give the previously unknown aldehydes **22** and **23**. Monoformylation of identical hydroxybenzofuran was recently reported by Dubonosov.[17] Interestingly, al-

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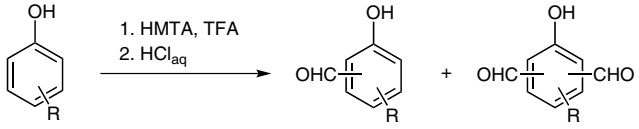
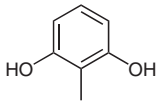
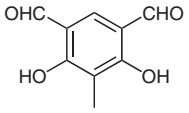
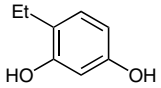
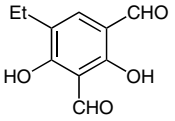
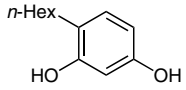
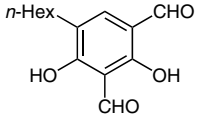
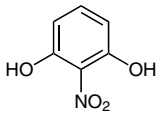
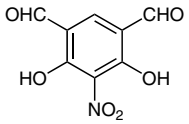
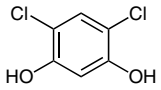
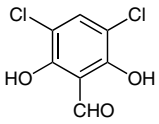
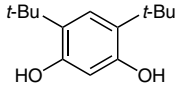
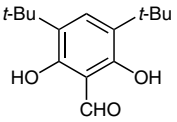
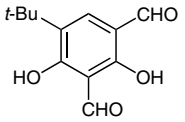
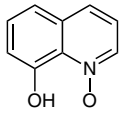
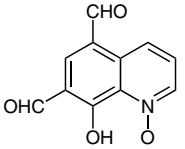
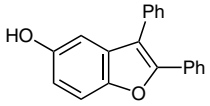
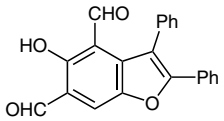
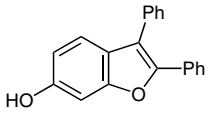
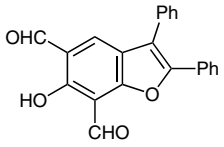
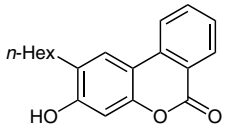
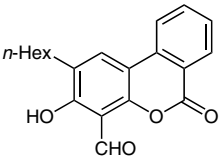
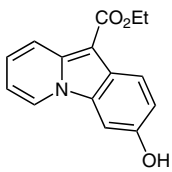
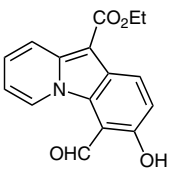
Table 1 Duff Formylation of Phenols



Phenol		Monoaldehyde		Yield (%)	Dialdehyde		Yield (%)
1		–	–	–	**16**		44
2		–	–	–	**17**		55
3		–	–	–	**18**		42
4		–	–	–	**19**		40
5		**12**		68	–	–	–
6		**13**		22	**20**		27
7		–	–	–	**21**		59
8		–	–	–	**22**		29
9		–	–		**23**		15
10		**14**		35	–	–	–
11		**15**		18	–	–	–

though simple hydroxyl-coumarins proved to be troublesome substrates in the Duff reaction, formylation of benzo[*c*]coumarin **10** smoothly afforded aldehyde **14** in 35% yield. Finally complex heterocyclic phenol **11** possessing indolizine skeleton was formylated to afford aldehyde **15** as the only regioisomer.

In conclusion, we have developed an efficient and versatile protocol for diformylation of phenols. Less reactive starting materials usually participate in this reaction, but monosubstitution dominates. This procedure, in many cases, allows isolation of the desired product by simple filtration, without chromatography and helps to avoid annoying multistep syntheses, as was shown by comparison with literature data. This facile procedure opens the way for a variety of complex aldehydes to be used in materials or medicinal chemistry.

All chemicals were used as received, unless otherwise noted. Reagent grade solvents (CH_2Cl_2, hexane, toluene) were distilled prior use. All reported NMR spectra were recorded on 400 or 500 MHz spectrometer unless otherwise noted. Chemical shifts (δ ppm) were determined with TMS as the internal reference; *J* values are given in Hz. Chromatography was performed on silica gel (Kieselgel 60, 200–400 mesh). Mass spectra were obtained via EI MS. Phenol **11** was prepared as described in literature.[18]

Duff Formylation of Phenols; General Procedure

To the phenolic substrate (1 equiv) dissolved in a minimum amount of TFA (7–8 mL for 10 mmol of phenol) was added HMTA (2 equiv) under argon atmosphere. Addition of the HMTA was done slowly as the reaction was very exothermic. The solution was stirred at 70 C for 72 h and then at 100 °C for another 4 h. Subsequently, aq HCl (10%, ~10 mL for 10 mmol of phenol) was added and the reaction mixture was kept at 100 °C for 1 h. The whole suspension was cooled down to r.t. and left overnight without stirring. In most cases, the formation of a precipitate was observed, which was filtered, washed extensively with H_2O, and dried overnight under high vacuum (Table 1).

4,6-Dihydroxy-5-methylisophthalaldehyde (16)

Following the general procedure, 2-methylresorcinol (**1**; 10.00 g, 80 mmol) was treated with HMTA (29.00 g, 207 mmol) in TFA (70 mL); yield: 6.4 g (44%); white crystalline solid; mp 182–183 °C (Lit.[19] mp 185–185.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.13 (s, 3 H), 7.71 (s, 1 H), 9.78 (s, 2 H), 12.03 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.56, 113.4, 115.0, 140.0, 166.2, 194.2.

HRMS (EI): *m*/*z* calcd for $C_9H_8O_4$ [$M^{+\bullet}$]: 180.0423; found: 180.0417.

5-Ethyl-2,4-dihydroxyisophthalaldehyde (17)

Following the general procedure, 4-ethylresorcinol (**2**; 1.00 g, 7.2 mmol) was treated with HMTA (2.03 g, 14.5 mmol) in TFA (5 mL). After stirring at r.t. overnight, the formation of a precipitate was observed at the bottom of the flask. The solvents were poured out and the remaining solid was dissolved in CH_2Cl_2 (75 mL). The organic layer was washed with H_2O (2 × 10 mL), dried (Na_2SO_4), and evaporated; yield: 0.78 g (55%); white crystalline solid; mp 71–74 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (d, *J* = 7.5 Hz, 3 H), 2.62 (q, *J* = 7.5 Hz, 2 H), 7.49 (s, 1 H), 9.70 (s, 1 H), 10.39 (s, 1 H), 12.39 (s, 1 H), 12.96 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 21.6, 108.9, 113.0, 125.0, 140.0, 165.8, 167.9, 193.9, 194.6.

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}O_4$ [$M^{+\bullet}$]: 194.0579; found: 194.0588.

Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.79; H, 5.12.

5-Hexyl-2,4-dihydroxyisophthalaldehyde (18)

Following the general procedure, 4-hexylresorcinol (**3**; 1.00 g, 5.1 mmol) was treated with HMTA (1.44 g, 10.3 mmol) in TFA (6 mL). The precipitated crystals were filtered and recrystallized from EtOH to afford a light orange crystalline solid; yield: 0.54 g (42%); mp 60–61 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H), 1.32 (q, *J* = 4.5 Hz, 6 H), 1.58 (t, *J* = 7.5 Hz, 2 H), 2.57 (t, *J* = 7.5 Hz, 2 H), 7.47 (s, 1 H), 9.69 (s, 1 H), 10.39 (s, 1 H), 12.39 (s, 1 H), 12.95 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 28.3, 29.0, 29.1, 31.6, 108.8, 112.8, 123.6, 140.6, 165.6, 167.8, 193.6, 194.4.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{18}O_4$ [$M^{+\bullet}$]: 250.1205; found: 250.1199.

4,6-Dihydroxy-5-nitroisophthalaldehyde (19)

Following the general procedure, 2-nitroresorcinol (**4**; 1.00 g, 6.5 mmol) was treated with HMTA (2.34 g, 16.7 mmol) in TFA (6 mL). The precipitated crystals were filtered, washed with H_2O (40 mL) and recrystallized from EtOH to afford **19** as a yellow crystalline solid; yield: 0.54 g (40%); mp 195–196 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.20 (s, 1 H), 9.79 (br s, 2 H), 9.98 (s, 2 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 116.2, 131.6, 136.9, 158.9, 191.0, 191.0.

HRMS (EI): *m*/*z* calcd for $C_8H_5NO_6$ [$M^{+\bullet}$]: 211.0117; found: 211.0110.

3,5-Dichloro-2,6-dihydroxybenzaldehyde (12)

Following the general procedure, 4,6-dichlororesorcinol (**5**; 12.14 g, 68 mmol) was treated with HMTA (9.52 g, 68 mmol) in TFA (64 mL). The precipitated crystals were filtered and washed extensively with H_2O. After 12 h, the supernatant was filtrated one more time giving a second portion of the product. The yellow crystals obtained were dried overnight under vacuum; yield: 9.65 g (68%); mp 168–169 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55 (s, 1 H), 9.21 (br s, 2 H), 10.35 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 110.4, 111.7, 136.3, 155.3, 193.4.

HRMS (EI): *m*/*z* calcd for $C_7H_4Cl_2O_3$ [$M^{+\bullet}$]: 205.9537; found: 205.9528.

Anal. Calcd for $C_7H_4Cl_2O_3$: C, 40.61; H, 1.95. Found: C, 40.51; H, 1.91.

3,5-Di-*tert*-butyl-2,6-dihydroxybenzaldehyde (13) and 5-(*tert*-Butyl)-2,4-dihydroxyisophthalaldehyde (20)

Following the general procedure, 4,6-di-*tert*-butylresorcinol (**6**; 1.00 g, 4.5 mmol) was treated with HMTA (1.63 g, 11.6 mmol) in TFA (6 mL). The solid obtained contained two products **13** and **20**, which were separated by column chromatography on silica gel using CH_2Cl_2–hexanes (2:1) as eluent.

13

Yield: 0.25 g (22%); yellow crystalline solid; mp 123–124 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.34 (s, 18 H), 7.34 (s, 1 H), 10.21 (s, 1 H), 11.26 (s, 2 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 30.22, 34.71, 113.19, 127.77, 134.14, 158.85, 196.64.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{22}O_3$ [M + H]$^+$: 251.1647; found: 251.1648.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.75; H, 8.90.

20
Yield: 0.27 g (27%); white crystalline solid; mp 109–110 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 7.59 (s, 1 H), 9.70 (s, 1 H), 10.40 (s, 1 H), 12.39 (s, 1 H), 13.50 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2, 34.3, 109.1, 112.4, 130.6, 138.3, 165.7, 169.2, 194.0, 194.7.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{13}O_4$ [M – H]$^-$: 221.0814; found: 221.0815.

Anal. Calcd for $C_{12}H_{13}O_4$: C, 64.85; H, 6.35. Found: C, 64.72; H, 6.40.

5,7-Diformyl-8-hydroxyquinoline 1-Oxide (21)
Following the general procedure, 8-hydroxyquinoline 1-oxide (**7**; 1.00 g, 6.2 mmol) was treated with HMTA (2.25 g, 16.1 mmol) in TFA (7 mL). The precipitated crystals were filtered, washed with H_2O (40 mL), and recrystallized from EtOH to afford **21** as a yellow crystalline solid; yield: 0.79 g (59%); mp 205–206 °C (EtOH).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.95 (dd, *J* = 8.5, 6.5 Hz, 1 H), 8.46 (s, 1 H), 8.87 (dd, *J* = 6.0, 1.0 Hz, 1 H), 9.40 (dd, *J* = 9.0, 1.0 Hz, 1 H), 10.11 (s, 1 H), 10.43 (s, 1 H), 19.63 (s, 1 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 118.7, 119.5, 127.1, 129.2, 129.4, 132.3, 136.9, 138.4, 165.8, 186.8, 192.0.

HRMS (EI): *m*/*z* calcd for $C_{11}H_7NO_4$ [M$^{+\bullet}$]: 217.0375; found: 217.0371.

Anal. Calcd for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.68; H, 3.08; N, 6.49.

5-Hydroxy-2,3-diphenylbenzofuran-4,7-dicarbaldehyde (22)
Following the general procedure, 2,3-diphenylbenzofuran-5-ol (**8**; 1.00 g, 3.5 mmol) was treated with HMTA (1.26 g, 9.0 mmol) in TFA (7 mL). The solid obtained was purified by column chromatography on silica gel using CH_2Cl_2 and CH_2Cl_2–MeOH (99:1) as eluent; yield: 0.35 g (29%); yellow crystalline solid; mp 202–203 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.37 (m, 3 H), 7.44–7.48 (m, 2 H), 7.51–7.59 (m, 5 H), 8.25 (s, 1 H), 9.56 (s, 1 H), 10.56 (s, 1 H), 12.70 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 113.1, 117.5, 117.7, 120.9, 127.3, 128.7, 129.0, 129.3, 129.9, 130.0, 130.2, 133.1, 136.8, 147.3, 158.0, 163.4, 188.0, 193.5.

HRMS (EI): *m*/*z* calcd for $C_{22}H_{14}O_4$ [M$^{+\bullet}$]; 342.0892; found: 342.0880.

Anal. Calcd for $C_{22}H_{14}O_4$: C, 77.18; H, 4.12. Found: C, 76.96; H, 4.13.

6-Hydroxy-2,3-diphenyl-1-benzofuran-5,7-dicarbaldehyde (23)
Following the general procedure, phenol **9** (0.80 g, 2.8 mmol) was treated with HMTA (1.00 g, 7.2 mmol) in TFA (10 mL). The resulting oil was initially recrystallized (CH_2Cl_2–hexanes), followed by chromatography (SiO_2, CH_2Cl_2) to afford pure aldehyde **23** as orange crystals; yield: 144 mg (15%); mp 160–163 °C; R_f = 0.51 ($CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37 (m, 3 H), 7.49 (m, 3 H), 7.53 (m, 2 H), 7.68 (m, 2 H), 8.14 (s, 1 H), 10.37 (br s, 1 H), 10.72 (s, 1 H), 12.09 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 107.7, 117.4, 120.1, 124.3, 126.8 (2 signals), 128.5 (2 signals), 128.7 (2 signals), 129.2 (2 signals), 129.4 (2 signals), 129.6 (2 signals), 130.8, 152.2, 157.6, 163.2, 190.1 (2 signals).

HRMS (EI): *m*/*z* calcd for $C_{22}H_{14}O_4$ [M$^{+\bullet}$]: 342.0892; found: 342.0899.

4-Formyl-2-hexyl-3-hydroxy-6*H*-dibenzo[*b*,*d*]pyran-6-one (14)
Following the general procedure, benzo[*c*]coumarin **10** (0.53 g, 1.8 mmol) was treated with HMTA (0.70 g, 5.0 mmol) in TFA (10 mL). CH_2Cl_2 (10 mL) was added to the crude reaction mixture and phases were separated. The aqueous phase was extracted with CH_2Cl_2 (10 mL) and the organic layers were combined, and dried (Na_2SO_4). Drying agent was filtered, and the supernatant was evaporated with silica gel (10 g). Chromatography (SiO_2, CH_2Cl_2) afforded **14** as a colorless solid; yield: 204 mg (35%); R_f = 0.58 (CH_2Cl_2); mp 115–117 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.1 Hz, 3 H), 1.36 (m, 4 H), 1.43 (m, 2 H), 1.69 (quint, *J* = 7.3 Hz, 2 H), 2.74 (t, *J* = 7.8 Hz, 2 H), 7.57 (dt, *J* = 7.8, 1.0 Hz, 1 H), 7.86 (dt, *J* = 8.1, 1.4 Hz, 1 H), 8.02 (m, 2 H), 8.39 (dd, *J* = 8.0, 1.4 Hz, 1 H), 10.67 (s, 1 H), 12.47 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.1, 29.3, 29.4, 31.7, 108.6, 108.7, 119.7, 121.0, 128.2, 128.5, 130.6, 130.8, 134.5, 135.3, 151.4, 159.9, 162.6, 193.8.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}O_4$ + Na [M + Na]$^+$: 347.1254, found: 347.1253.

Ethyl 4-Formyl-3-hydroxypyrido[1,2-*a*]indole-10-carboxylate (15)
Following the general procedure, ethyl 3-hydroxypyrido[1,2-*a*]indole-10-carboxylate (**11**; 1.00 g, 3.9 mmol) was treated with HMTA (1.42 g, 10.1 mmol) in TFA (10 mL). The solid obtained was purified by column chromatography on silica gel using toluene and toluene–acetone (99:1) as eluent; yield: 0.2 g (18%); orange crystalline solid; mp 172–173 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (t, *J* = 7.0 Hz, 3 H), 4.46 (q, *J* = 7.1 Hz, 2 H), 6.77–6.81 (m, 1 H), 7.07 (d, *J* = 9.1 Hz, 1 H), 7.14–7.19 (m, 1 H), 8.35 (d, *J* = 7.3 Hz, 1 H), 8.40 (dd, *J* = 9.4, 1.1 Hz, 1 H), 8.60 (d, *J* = 9.0 Hz, 1 H), 10.84 (s, 1 H), 12.49 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.6, 59.8, 97.1, 108.7, 112.9, 116.8, 121.4, 122.2, 124.8, 127.0, 127.4, 133.0, 139.9, 162.1, 164.9, 189.8.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{13}NO_4$ [M$^{+\bullet}$]: 283.0845; found: 283.0833.

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.64; H, 4.62; N, 4.98.

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