Combination of Lithium Chloride and Hexafluoroisopropanol for Friedel–Crafts Reactions

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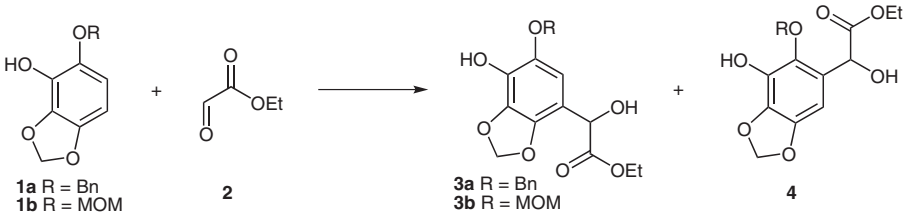
Abstract: A combination of weak Lewis acid (LiCl) and weak Brønsted acid (hexafluoroisopropanol, HFIP) promotes efficiently the Friedel–Crafts reaction of electron-rich aromatic compounds with ethyl glyoxylate.

Key words: Friedel–Crafts reaction, glyoxylate, lithium chloride, hexafluoroisopropanol, Lewis acid, Brønsted acid

The Friedel–Crafts (F–C) reaction is one of the most important C–C bond-forming transformations.[1] It encompasses a wide set of reactions including acylation,[2] alkylation,[3] and hydroxyalkylation of aromatic compounds. Among them, the latter reactions involving electron-rich aromatics and glyoxylate or pyruvate derivatives have attracted recent attention due to the importance of the resulting adducts as building blocks in the synthesis of complex molecules and as ligands in asymmetric synthesis. Consequently, reaction conditions[4] including some that are catalyst- and solvent-free[5] have been developed allowing the synthesis of numerous functionalized aromatics. Enantioselective versions have also been reported using either chiral Lewis acids[6] or small organomolecules as catalysts.[7] In connection with our research program centering on the synthesis of tetrahydroisoquinoline-containing polycyclic alkaloids,[8] we found that the combination of lithium chloride (LiCl) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) in toluene is highly efficient for promoting the Pictet–Spengler reaction of acid-sensitive substrates.[9] We report herein that these conditions are also very effective for performing the Friedel–Crafts reactions between electron-rich aromatics and ethyl glyoxylate.

Table 1 Survey of Reaction Conditions between Phenol **1** and Ethyl Glyoxylate (**2**)



1a R = Bn
1b R = MOM

2

3a R = Bn
3b R = MOM

4

Entry	Acid	Solvent	Temp (°C)	Yield (%) of **3**, **4**
1[a]	AcOH	CH_2Cl_2	r.t.	0, 0[b]
2[a]	TFA	CH_2Cl_2	r.t.	47, 47
3[c]	$Sc(OTf)_3$	CH_2Cl_2	r.t.	0, 0[d]
4[c]	$Yb(OTf)_3$	CH_2Cl_2	r.t.	0, 0[d]
5[c]	LiCl	toluene	r.t.	0, 0[b]
6[c]	LiCl	toluene–HFIP (16:1)[e]	70	55, 0
7[c]	LiCl	toluene–HFIP (6:1)[e]	40	95, 0
8[c]	LiCl	toluene–HFIP (4:1)[e]	r.t.	97, 0

[a] R = Bn.
[b] Phenol **1** was recovered.
[c] R = MOM.
[d] $Ln(OTf)_3$ (0.1 equiv), phenol **1** decomposed.
[e] LiCl (2.0 equiv), in the presence of 3 Å MS.

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The Friedel–Crafts reaction between phenol **1** and ethyl glyoxylate (**2**) leading to adduct **3** was needed in our synthesis of ecteinascidin 743 (Yondelis®),[10] an anticancer drug. As shown in Table 1, neither Brønsted acids (AcOH, TFA), nor Lewis acids [($Sc(OTf)_3$, $Yb(OTf)_3$] were effective for promoting this transformation. As expected, only starting materials were recovered when a weak Lewis acid (LiCl) was used as a promoter (entry 5). Interestingly, by adding hexafluoroisopropanol (HFIP)[11] as co-solvent (toluene–HFIP = 16:1 by volume), the desired alkylation took place at 70 °C, although conversion remained incomplete, to afford **3** in 55% yield (entry 6). Increasing the amount of HFIP allowed the reaction to take place at lower temperature and under optimized conditions: LiCl (2 equiv), toluene–HFIP = 4:1, 3 Å MS, r.t.), the reaction between phenol **1b** and **2** proceeded smoothly to afford single regioisomer **3** in 97% yield.[12] It is interesting to note that the same reaction performed in the presence of trifluoroacetic acid provided two regioisomers **3** and **4** in a 1:1 ratio (entry 2).

The generality of these conditions were next examined varying the nature of aromatic compounds and the results are summarized in Table 2. The reaction took place exclusively at the position *ortho* to the phenol group (entries 1–4) or at the *para* position if the *ortho* position is occupied (compound **3b**, Table 1). However, the presence of a free hydroxy group is not an obligation since 1,3-dimethoxybenzene (**1g**) was converted to adduct **3g** in 69% yield (entry 5). In accordance with the literature precedents, the hydroxyalkylation of *N*,*N*-dimethylaniline (**1h**) occurred at the *para* position to furnish **3h** in 73% yield (entry 6). As expected, indole (**1i**) participated in the reaction to afford **3i** in 74% yield (entry 7). However, double F–C reaction occurred in these two cases to furnish bisadducts **5** and **6** in 26% and 27% yields, respectively.[13] Finally, unactivated pyrrole **1j** was also transformed to the corresponding F–C adduct **3j** in 38% yield (entry 8), together with a 2,5-bisalkylated product **7** (37%, Figure 1).

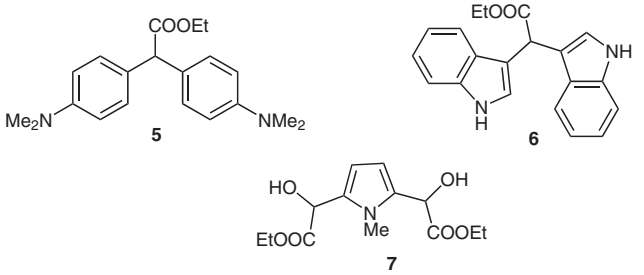
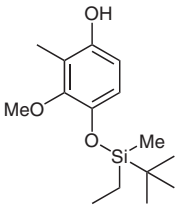
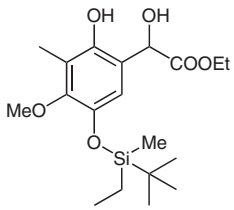
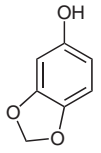
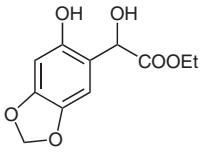
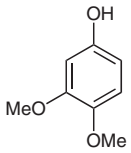
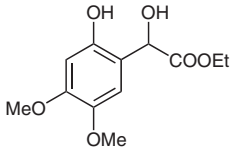
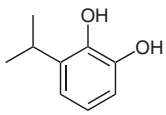
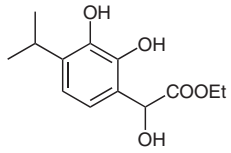
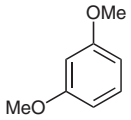
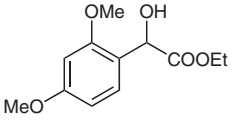
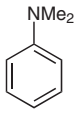
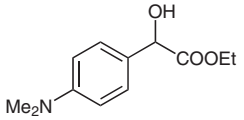
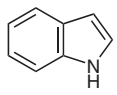
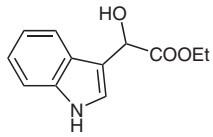
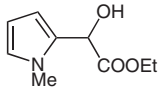


Figure 1 Bis-Friedel–Crafts adducts

Although the exact role of HFIP was unclear, the synergetic effect of LiCl and HFIP in promoting the present Friedel–Crafts reaction is evident. The weak Brønsted acidity ($pK_a = 9.3$), strong ionizing power,[14] and hydrogen-bond donor ability[15] may be relevant to its unique role in this transformation. The polarity effect might not be important in this case since no reaction occurred when HFIP was replaced by EtOH or 2,2,2-trifluroethanol (TFE),[16] although the dielectric constant of these two polar protic solvents [ε (EtOH) = 24.3; ε (TFE) = 26.7] is higher than HFIP (ε = 16.7).[15a]

Table 2 Generality of LiCl–HFIP-Promoted Friedel–Crafts Reactions[a]

Entry	Substrate	Product	Yield (%)[b]
1	 **1c**	 **3c**	90
2	 **1d**	 **3d**	82
3	 **1e**	 **3e**	90
4	 **1f**	 **3f**	57
5	 **1g**	 **3g**	69
6	 **1h**	 **3h**	73
7	 **1i**	 **3i**	74
8	 **1j**	 **3j**	38

[a] General conditions: **1** (1.0 equiv), **2** (1.5 equiv), LiCl (2.0 equiv), toluene–HFIP = 4:1, *c* 0.9 M, r.t.
[b] Yield of chromatographically pure compound.

In summary, we demonstrated that a combination of a weak Lewis acid (LiCl) and a weak Brønsted acid (HFIP) is effective for promoting the Friedel–Crafts reactions between electron-rich aromatics and glyoxylate. The utility of these conditions is readily seen as one of the adduct **1b** has been employed as a key building block in our total synthesis of ecteinascidin 743.[10]

General Procedure

To a round-bottom flask containing dried LiCl (84.8 mg, 2.0 mmol, 2.0 equiv) and 3 Å MS (100.1 mg), a solution of compound **1b–j** (1.0 mmol) in dry toluene (1.8 mL), freshly distilled ethyl glyoxylate (**2**, 50% solution in toluene, 268 μL, 1.5 mmol, 1.5 equiv), and hexafluoroisopropanol (0.45 mL) were added successively. The reaction mixture was stirred at r.t. under argon atmosphere until the complete consumption of the starting phenol (7–36 h). The solution was then filtered, washed with CH_2Cl_2, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2, EtOAc in heptane) to afford compounds **3b–j**.

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(12) **Analytical Data**

Compound **3b**: IR (neat): 3428, 2904, 1734, 1654, 1499, 1461, 1370, 1215, 1046, 994, 931 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K): δ = 6.54 (s, 1 H), 6.26 (br s, 1 H), 5.96 (d, *J* = 1.1 Hz, 1 H), 5.91 (d, *J* = 1.1 Hz, 1 H), 5.12 (s, 1 H), 5.05 (s, 2 H), 4.23 (dq, *J* = 10.2, 7.2 Hz, 1 H), 4.18 (dq, *J* = 10.2, 7.2 Hz, 1 H), 3.49 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 173.0, 142.3, 141.5, 134.4, 132.3, 110.7, 108.3, 102.1, 97.6, 68.3, 62.2, 56.5, 14.0 ppm. HRMS (ESI^+): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{16}O_8$: 323.0743; found: 323.0745.

Compound **3c**: IR (neat): 3386, 2930, 2857, 1731, 1482, 1335, 1251, 1126, 1006 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 293 K): δ (mixture of two diastereomers) = 6.89 (2 s, 1 H), 6.55 (s, 1 H), 5.18 (d, *J* = 3.1 Hz, 1 H), 4.30 (dq, *J* = 10.7, 7.2 Hz, 1 H), 4.20 (dq, *J* = 10.7, 7.2 Hz, 1 H), 3.74 (s, 3 H), 3.45 (d, *J* = 3.1 Hz, 1 H), 2.15 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.01 (s, 9 H), 0.96 (2 t, *J* = 7.6 Hz, 3 H), 0.72 (m, 2 H), 0.16 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 173.2, 150.4, 148.1, 142.1, 120.9, 117.7, 117.1, 72.7, 62.6, 60.1, 26.3 (3 C), 18.8, 14.1, 9.2, 7.5, 4.8, –6.5 ppm. MS (ESI^+): *m/z* = 791.3 $[2 M + Na]^+$, 407.1 $[M + Na]^+$, 367.2 $[M - H_2O + H]^+$. HRMS (ESI^+): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{32}O_6Si$: 407.1866; found: 407.1862.

Compound **3d**: IR (neat): 3349, 2983, 2903, 1722, 1628, 1485, 1442, 1169, 1033, 930 cm^{-1}. ^1H NMR (500 MHz,

$CDCl_3$, 293 K): δ = 6.64 (s, 1 H), 6.42 (s, 1 H), 5.90 (s, 1 H), 5.89 (s, 1 H), 5.19 (s, 1 H), 4.28 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.21 (dq, *J* = 10.8, 7.1 Hz, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 173.3, 150.4, 148.7, 141.5, 114.6, 107.8, 101.4, 99.8, 72.1, 62.7, 14.2 ppm. MS (ESI$^+$): *m/z* = 263.0 [M + Na]$^+$, 245.0 [M – H_2O + Na]$^+$, 223.1 [M – H_2O + H]$^+$. HRMS (ESI$^+$): *m/z* [M + Na]$^+$ calcd for $C_{11}H_{12}O_6$: 263.0532; found: 263.0497.

Compound **3e**: IR (neat): 3414, 2937, 2837, 1729, 1616, 1515, 1451, 1417, 1197, 1109, 997 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.21 (br s, 1 H), 6.67 (s, 1 H), 6.42 (s, 1 H), 5.22 (s, 1 H), 4.22 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.17 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.00 (s, 1 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 1.21 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 173.3, 150.2, 149.3, 142.7, 113.6, 111.9, 101.9, 71.8, 62.4, 56.6, 55.9, 14.1 ppm. MS (ESI$^+$): *m/z* = 279.1 [M + Na]$^+$. HRMS (ESI$^+$): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_6$: 279.0845; found: 279.0840.

Compound **3f**: IR (neat): 3418, 2961, 2871, 1724, 1625, 1460, 1368, 1222, 1059, 1024, 935 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.63 (br s, 1 H), 6.77 (d, *J* = 8.2 Hz, 1 H), 6.71 (d, *J* = 8.2 Hz, 1 H), 5.72 (br s, 1 H), 5.30 (s, 1 H), 4.33 (dq, *J* = 10.7, 7.1 Hz, 1 H), 4.24 (dq, *J* = 10.7, 7.1 Hz, 1 H), 3.39 (br s, 1 H), 3.27 (hept, *J* = 7.0 Hz, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 1.24 (t, *J* = 7.0 Hz, 3 H), 1.23 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 173.4, 143.0, 141.8, 135.5, 119.9, 118.8, 118.0, 72.7, 62.9, 27.3, 22.5, 22.4, 14.1 ppm. MS (ESI$^+$): *m/z* = 277.1 [M + Na]$^+$. HRMS (ESI$^+$): *m/z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_5$: 277.1052; found: 277.1034.

Compound **3g**: IR (neat): 3482, 2939, 2839, 1731, 1612, 1589, 1507, 1207, 1157, 1065, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.15 (d, *J* = 8.5 Hz, 1 H), 6.45 (m, 2 H), 5.19 (d, *J* = 5.8 Hz, 1 H), 4.19 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.18 (dq, *J* = 10.8, 7.1 Hz, 1 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.53 (d, *J* = 5.8 Hz, 1 H), 1.19 (t, *J* = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 174.0, 161.2, 158.3, 130.2, 119.9, 104.4, 99.0, 69.8, 61.7, 55.5, 55.4, 14.1 ppm. MS (ESI$^+$): *m/z* = 263.1 [M + Na]$^+$. HRMS (ESI$^+$): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_5$: 263.0895; found: 263.0893.

Compound **3h**: IR (neat): 3442, 2891, 1727, 1614, 1523, 1354, 1180, 1074, 1012, 800 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 7.25 (d, *J* = 8.7 Hz, 2 H), 6.70 (d, *J* = 8.7 Hz, 2 H), 5.06 (s, 1 H), 4.26 (dq, *J* = 10.9, 7.0 Hz, 1 H), 4.16 (dq, *J* = 10.9, 7.0 Hz, 1 H), 3.27 (br s, 1 H), 2.95 (s, 6 H), 1.23 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 174.3, 150.8, 127.7 (2 C), 126.3, 112.5 (2 C), 72.9, 62.0, 40.6 (2 C), 14.2 ppm. MS (ESI$^+$): *m/z* = 246.1 [M + Na]$^+$, 224.1 [M + H]$^+$, 206.1 [M – H_2O + H]$^+$. HRMS (ESI$^+$): *m/z* [M + H]$^+$ calcd for $C_{12}H_{17}NO_3$: 224.1287; found: 224.1270.

Compound **3i**: IR (neat): 3399, 2981, 1724, 1548, 1457, 1423, 1198, 1077, 1037, 743 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 8.40 (br s, 1 H), 7.71 (d, *J* = 7.9 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 1 H), 7.20 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1 H), 7.14 (ddd, *J* = 8.2, 7.0, 0.9 Hz, 1 H), 7.08 (d, *J* = 2.3 Hz, 1 H), 5.46 (d, *J* = 5.5 Hz, 1 H), 4.28 (dq, *J* = 10.8, 7.0 Hz, 1 H), 4.16 (dq, *J* = 10.8, 7.0 Hz, 1 H), 3.51 (m, 1 H), 1.20 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 174.1, 136.5, 125.4, 123.5, 122.5, 120.1, 119.4, 113.6, 111.6, 67.4, 62.1, 14.1 ppm. MS (ESI$^+$): *m/z* = 242.1 [M + Na]$^+$, 202.1 [M – H_2O + H]$^+$. HRMS (ESI$^+$): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{13}NO_3$: 242.0793; found: 242.0805.

Compound **3j**: IR (neat): 3369, 2981, 1730, 1492, 1368, 1299, 1203, 1052, 1018, 714 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 293 K): δ = 6.61 (t, *J* = 2.1 Hz, 1 H), 6.05 (d, *J* = 2.1 Hz, 2 H), 5.20 (d, *J* = 7.0 Hz, 1 H), 4.31 (dq, *J* = 10.9, 7.0 Hz, 1 H), 4.27 (dq, *J* = 10.9, 7.0 Hz, 1 H), 3.66 (s, 3 H), 3.15 (d, *J* = 7.0 Hz, 1 H), 1.29 (t, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 172.9, 129.2, 124.1, 108.5, 107.0, 66.4, 62.1, 34.1, 14.2 ppm. MS (ESI$^+$): *m/z* = 206.1 [M + Na]$^+$, 166.1 [M – H_2O + H]$^+$. HRMS (ESI$^+$): *m/z* [M + Na]$^+$ calcd for $C_9H_{13}NO_3$: 206.0793; found: 206.0791.

(13) Formation of bisindolylalkanes, see for examples: (a) Gibbs, T. J. K.; Tomkinson, N. C. O. *Org. Biomol. Chem.* **2005**, *3*, 4043. (b) Nair, V.; Abhilash, K. G.; Vidya, N. *Org. Lett.* **2005**, *7*, 5857.

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