Facile Synthesis of *o*- and *p*-(1-Trifluoromethyl)-alkylated Phenols via Generation and Reaction of Quinone Methides

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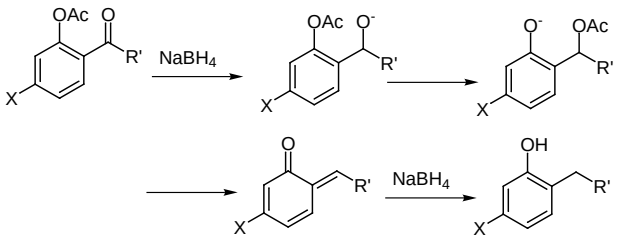
Received 11 December 2001

Abstract: Several *ortho*- and *para*-(1-chloro-2,2,2-trifluoroethyl)phenols were prepared from the corresponding alcohols and thionyl chloride in the presence of pyridine. They reacted smoothly with sodium borohydride and Grignard reagents under mild conditions, forming 2,2,2-trifluoroethyl- or 1-trifluoromethylalkylphenols in high yields.

Key words: trifluoroalkyl, phenol, sodium borohydride, Grignard reagent, quinone methide

Introduction of fluorine atoms into bioactive organic molecules is of interest because of the characteristic effect on their physical-chemical and biological properties.[1] Phenols with *ortho*-functional groups are well-known bioactive compounds and ubiquitous among natural products. They are usually prepared by regioselective electrophilic aromatic substitution[2] or the Claisen rearrangement,[3] but lithiation or halogenation followed by a metal-mediated coupling process sometimes is used.[4] Formation of *ortho*-alkylated phenols also occurs during the reduction of phenolic ketones.[5] This reductive removal of the side-chain oxygen from O-acylated phenones has been used to prepare such mono-alkylated polyhydroxyl aromatics as resorcinols, in which process the generation of reactive quinone methide intermediate was proposed[6] (Scheme 1). There are few reports, however, on the preparation of fluoroalkylated phenols.[7] To our knowledge, no convenient method for introducing a fluoroalkyl group specifically into the *ortho*-position of phenol has been reported. Development of a new way of constructing *ortho*-fluoroalkylated phenols therefore is important.



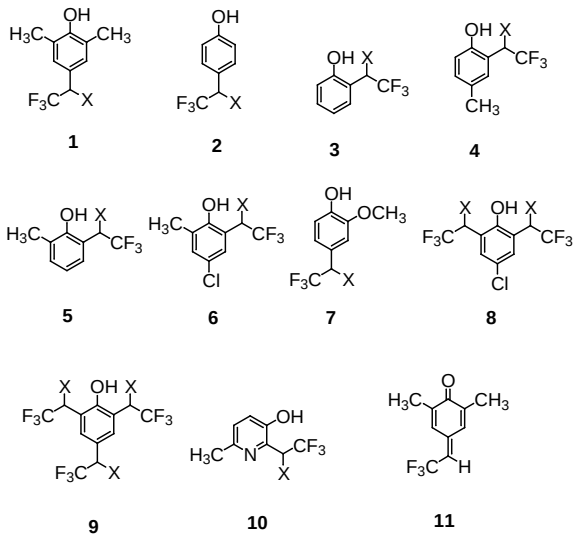
Scheme 1

Our recent work shows that 2- and 4-(1-hydroxy-2,2,2-trifluoroethyl)phenols are easily prepared through the reaction of phenols with trifluoroacetaldehyde ethyl hemiacetal in the presence of ZnI_2 or K_2CO_3.[8] We thought that these α-trifluoromethyl alcohols might be useful starting materials in the preparation of 2- and 4-fluoroalkylated phenols. Based on the process outlined in Scheme 1, we proposed a possible mechanistic pathway (Scheme 2) for the selective removal of side-chain hydroxyl. The key problem is how to selectively convert the side-chain hydroxyl into a good leaving group, because simultaneously the phenolic hydroxyl and the side-chain hydroxyl are easily O-acylated in acetic anhydride. We here report a convenient synthetic method for obtaining 2- and 4-fluoroalkylated phenols. It consists of selective conversion of the side-chain hydroxyl to chlorine and subsequent nucleophilic replacement.

The 2- and 4-(1-hydroxy-2,2,2-trifluoroethyl)phenols **1a**–**10a** used are listed in the Figure. Selective chlorination was first done by refluxing **1a** and an excess of $SOCl_2$ under solvent-free conditions. As a consequence, a good yield of α-chlorinated product 2,6-dimethyl-4-(1-chloro-2,2,2-trifluoroethyl)phenol, **1b**,[9] was obtained (Table 1, entry 1). Only about 9% of 4-(1-chloro-2,2,2-trifluoroethyl)phenol **2b**, however, was obtained under the same conditions (entry 2) due to formation of a large amount of a white insoluble precipitate. The addition of hexane as solvent somewhat improved the yield of **2b** (entry 3). Alternative reaction conditions therefore were tried in the presence of pyridine. The reaction of **1b** with $SOCl_2$ in the presence of pyridine is exothermic at room temperature. To avoid a violent reaction, equivalent amount of $SOCl_2$ was dropped into the mixture of **1b** and pyridine in toluene set in an ice water bath. Under these improved conditions, the yield of **2b** increased markedly (entry 4). An ideal yield of **2b** was obtained when an excess of $SOCl_2$ was used (entry 5). Therefore, that procedures were followed for the corresponding reactions of **1a** and **3a**–**7a**, which gave 2- or 4-(1-chloro-2,2,2-trifluoroethyl)phenols in high yields (entries 6–11). This method also was used to prepare the bis-(1-chloro-2,2,2-trifluoroethyl)- and tris-(1-chloro-2,2,2-trifluoroethyl)phenols, **8b** (entry 12) and **9b** (entry 13). In addition, 6-methyl-2-(1-chloro-2,2,2-trifluoroethyl)pyridin-3-ol (**10b**) was obtained in good yield without additional pyridine (entry 14).

Synlett 2002, No. 3, 04 03 2002. Article Identifier:
1437-2096,E;2002,0,03,0431,0434,ftx,en;Y24001ST.pdf.

ISSN 0936-5214



a: X = OH; b: X = Cl; c: X = H; d: X = allyl; e: X = vinyl; f: X = ethyl

Figure

Table 1 Reaction of (2,2,2-Trifluoro-1-hydroxyethyl)phenol with $SOCl_2$

Entry	Substrate (mmol)	$SOCl_2$ (mmol)	Pyridine (mmol)	Product (Yield %)[a]
1	**1a** (2.0)	6.0	none[b]	**1b** (76)
2	**2a** (2.0)	6.0	none[b]	**2b** (9)
3	**2a** (2.0)	6.0	none[c]	**2b** (22)
4	**2a** (2.0)	2.0	2.0[d]	**2b** (66)
5	**2a** (2.0)	2.8	2.0[d]	**2b** (91)
6	**1a** (2.0)	2.8	2.0[d]	**1b** (95)
7	**3a** (2.0)	2.8	2.0[d]	**3b** (90)
8	**4a** (2.0)	2.8	2.0[d]	**4b** (81)
9	**5a** (2.0)	2.8	2.0[d]	**5b** (90)
10	**6a** (2.0)	2.8	2.0[d]	**6b** (86)
11	**7a** (2.0)	2.8	2.0[d]	**7b** (95)
12	**8a** (2.0)	5.6	4.0[d]	**8b** (69)
13	**9a** (2.0)	9.0	6.0[d]	**9b** (70)
14	**10a** (2.0)	2.8	none[d]	**10b** (79)

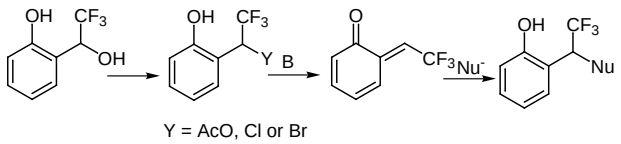
[a] Isolated yields.
[b] No solvent, reflux 4 h.
[c] Hexane (10 mL), reflux 1 h.
[d] Toluene (10 mL), 0 °C, 1 h then 70 °C, 2 h.

Reductive removal of the α-chlorine atom from 2- or 4-(1-chloro-2,2,2-trifluoroethyl)phenols **1b**–**10b** was done in THF with $NaBH_4$ as the reducing reagent. Product analysis indicated the formation of 2- or 4-(2,2,2-trifluoroethyl)phenols **1c**–**10c** in excellent yields, for details see Table 2. A parallel experiment showed that no reaction took place between (1-chloro-2,2,2-trifluoroethyl)benzene and $NaBH_4$, indicative that the S_N2 substitution of chlorine with hydride is difficult. Based on these findings, we consider that reductive removal of the α-chlorine atom occurred via generation of quinone methide followed by preferential reaction with hydride, as in Scheme 2.

Table 2 Reduction of (1-Chloro-2,2,2-trifluoroethyl)phenol with $NaBH_4$ in THF

Entry	Substrate (mmol)	$NaBH_4$ (mmol)	Conditions	Product (Yield %)[a]
1	**1b** (2.0)	3.0	r.t., 12 h	**1c** (97)
2	**2b** (2.0)	3.0	r.t., 12 h	**2c** (95)
3	**3b** (2.0)	3.0	r.t., 12 h	**3c** (89)
4	**4b** (2.0)	3.0	r.t., 12 h	**4c** (94)
5	**5b** (2.0)	3.0	r.t., 12 h	**5c** (88)
6	**6b** (2.0)	3.0	r.t., 12 h	**6c** (93)
7	**7b** (2.0)	3.0	r.t., 12 h	**7c** (93)
8	**8b** (2.0)	4.5	r.t., 24 h	**8c** (91)
9	**9b** (2.0)	7.0	r.t., 48 h	**9c** (80)
10	**10b** (2.0)	3.0	r.t., 12 h	**10c** (95)

[a] Isolated yields.



Y = AcO, Cl or Br

Scheme 2

Next, the reactions of **1b**–**4b** and **10b** with Grignard reagents were examined. An addition of allylmagnesium bromide (4.0 mL) in ether to **1b** (2.0 mmol) in toluene (10 mL) at –10 °C produced the corresponding compound **1d** with α-branched alkyl chains and an amount of *p*-quinone methide **11** (Table 3, entry 1). Compound **11** was stable enough to be isolated by silica gel column chromatography and identified by spectrometry. Addition of a large excess of allylmagnesium bromide (6.0 mL) caused the disappearance of **11** and the formation of **1d** in high yield (entry 2). This finding strongly supports the above suggestion that nucleophilic replacement of the α-chlorine atom proceeded via the mechanistic pathway in Scheme 3. Under the same conditions, the corresponding reaction with **2b** gave 4-(2,2,2-trifluoroethyl)phenol **2d** but only in 38% yield (entry 3). This low yield mainly was due to the formation of side products caused by competitive substitution of the α-chlorine atom with the phenolate anion generated in situ during the reaction. In contrast, high yields of phenols *ortho*-substituted with α-branched alkyl chains, **3d**, **4d** and **3e**, **4e**, were obtained by adding allylmagnesium bromide (6.0 mL) in ether or vinylmag-

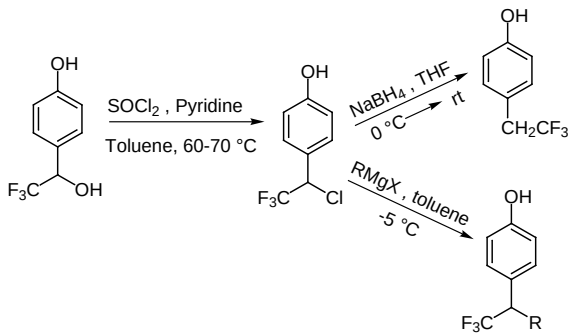
nesium bromide (6.0 mL) in THF (entries 4, 5 and 7, 8). In the case of ethylmagnesium bromide, reductive products **3c** and **4c** were detected besides the normal products with α-branched alkyl chains, **3f** and **4f** (entries 6 and 9). In addition, the corresponding reaction of allylmagnesium bromide with **10b** produced 6-methyl-2-(1-trifluoromethyl-but-3-enyl)pyridin-3-ol (**10d**) in moderate yield (entry 10).

Table 3 Reaction of (1-Chloro-2,2,2-trifluoroethyl)phenol with RMgX in Toluene

Entry	Substrate (mmol)	RMgBr[a] (mL)	Conditions[b]	Product (Yield %)[c]
1	**1b** (2.0)	allyl (4.0)	–5 °C, 8 h	**1d** (57), **11** (29)
2	**1b** (2.0)	allyl (6.0)	–5 °C, 8 h	**1d** (88)
3	**2b** (2.0)	allyl (6.0)	–5 °C, 8 h	**2d** (38)
4	**3b** (2.0)	allyl (6.0)	–5 °C, 8 h	**3d** (83)
5	**3b** (2.0)	vinyl (6.0)	–5 °C, 8 h	**3e** (70)
6	**3b** (2.0)	ethyl (6.0)	–5 °C, 8 h	**3f** (81), **3c** (7)
7	**4b** (2.0)	allyl (6.0)	–5 °C, 8 h	**4d** (90)
8	**4b** (2.0)	vinyl (6.0)	–5 °C, 8 h	**4e** (76)
9	**4b** (2.0)	ethyl (6.0)	–5 °C, 8 h	**4f** (73), **4c** (9)
10	**10b** (2.0)	allyl (6.0)	–5 °C, 8 h	**10d** (58)

[a] 1 Mol/L solution (allyl in ether and vinyl and Et in THF).
[b] Addition made at –10 °C.
[c] Isolated yields.

In conclusion, we consider selective chlorination of the side-chain hydroxyl of 2- or 4-(1-hydroxy-2,2,2-trifluoroethyl)phenols followed by nucleophilic replacement with sodium borohydride or Grignard reagents to be a useful method for the specific introduction of trifluoroethyl or 1-trifluoromethylalkyl groups to the *ortho*- or *para*- positions of phenols.



Scheme 3

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(9) **1b**: A colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.09 (2 H, s), 4.98 (1 H, q, *J* = 6.8 Hz), 4.52 (1 H, br, s), 2.25 (6 H, s). ^{19}F NMR ($CDCl_3$): δ = 88.68 (3 F, d, *J* = 6.8 Hz). MS: *m/z* (%) = 238(32) [M^+], 203(100), 169(41), 153(67). HRMS: Calcd: 238.0372; found: 238.0373. **2b**: A colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.37 (2 H, d, *J* = 8.4 Hz), 6.85 (2 H, d, *J* = 8.4 Hz), 5.76 (1 H, br, s), 5.06 (1 H, q, *J* = 6.8 Hz). ^{19}F NMR ($CDCl_3$): δ = 88.39 (3 F, d, *J* = 6.8 Hz). MS: *m/z* (%) = 210(39) [M^+], 175(100), 141(42), 125(67), 96(24). HRMS: Calcd: 210.0059; found: 210.0059. **3b**: A colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.59 (1 H, d, *J* = 7.5 Hz), 7.20 (1 H, m), 7.02 (1 H, m), 6.82 (1 H, d, *J* = 8.1 Hz), 6.17 (1 H, br, s), 5.82 (1 H, q, *J* = 7.0 Hz). ^{19}F NMR ($CDCl_3$): δ = 88.80 (3 F, d, *J* = 7.0 Hz). MS: *m/z* (%) = 210(68) [M^+], 175(60), 155(30), 145(60), 141(74), 127(100), 96(39). HRMS: Calcd: 210.0059; found: 210.0061. **1c**: Colorless needles, mp 86–87 °C. ^{1}H NMR ($CDCl_3$): δ = 6.89 (2 H, s), 4.62 (1 H, s), 3.21 (2 H, q, *J* = 10.8 Hz), 2.23 (6 H, s). ^{19}F NMR ($CDCl_3$): δ = 95.53 (3 F, t, *J* = 10.8 Hz). MS. *m/z* (%) = 204(57) [M^+], 135(100), 109(7), 91(25). Anal. Calcd for $C_{10}H_{11}F_3O$: C, 58.82; H, 5.43. Found: C, 58.72; H, 5.42. **2c**: Colorless needles, mp 56–58 °C. ^{1}H NMR ($CDCl_3$): δ = 7.15 (2 H, d, *J* = 8.2 Hz), 6.81 (2 H, d, *J* = 8.2 Hz), 5.95 (1 H, br, s), 3.27 (2 H, q, *J* = 11.0 Hz). ^{19}F NMR ($CDCl_3$): δ = 95.48 (3 F, t, *J* = 11.0 Hz). MS: *m/z* (%) = 176(40) [M^+], 157(3), 107(100). Anal. Calcd for $C_8H_7F_3O$: C, 54.55; H, 4.01. Found: C, 54.50; H, 4.02. **3c**: A colorless oil. ^{1}H NMR ($CDCl_3$): δ =7.25 (1 H, d, *J* = 7.5 Hz), 6.92–7.22 (2 H, m), 6.79 (1 H, d, *J* = 7.9 Hz), 5.12 (1 H, br, s), 3.46 (2 H, q, *J* = 10.8 Hz). ^{19}F NMR ($CDCl_3$): δ = 96.33 (3 F, t, *J* = 10.8 Hz). MS: *m/z* (%) = 176(72) [M^+], 156(42), 107(100). Anal. Calcd for $C_8H_7F_3O$: C, 54.55; H, 4.01. Found: C, 54.47; H, 4.00. **1d**: Colorless needles, mp 109–110 °C. ^{1}H NMR ($CDCl_3$): δ = 6.87 (2 H, s), 5.60 (1 H, m), 5.00 (1 H, d, *J* = 18.0 Hz), 4.96 (1 H, d, *J* = 9.2 Hz), 4.67 (1 H, s), 3.14 (1 H, m), 2.66 (2 H, m), 2.21 (6 H, s). ^{19}F NMR ($CDCl_3$): δ = 91.99 (3 F, d, *J* = 9.4 Hz). MS: *m/z* (%) = 244(10) [M^+], 203(100), 153(27), 91(12). Anal. Calcd for $C_{13}H_{15}F_3O$: C, 63.93; H, 6.19. Found: C, 63.73; H, 6.16. **11**: Colorless

plates, mp 57–58 °C. ^{1}H NMR ($CDCl_3$): δ = 6.51 (1 H, s), 5.97 (1 H, s), 5.20 (1 H, q, *J* = 8.1 Hz), 1.97 (3 H, s), 1.95 (3 H, s). ^{19}F NMR ($CDCl_3$): δ = 106.96 (3 F, d, *J* = 8.1 Hz). MS: *m/z* (%) = 203(100) [M^+], 153(26). Anal. Calcd for $C_{10}H_9F_3O$: C, 59.41; H, 4.49. Found: C, 59.60; H, 4.50. **2d**: A colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.15 (2 H, d, *J* = 8.4 Hz), 6.81 (2 H, d, *J* = 8.4 Hz), 5.60 (1 H, m), 5.21 (1 H, s), 5.00 (1 H, d, *J* = 16.9 Hz), 4.96 (1 H, d, *J* = 10.3 Hz), 3.23 (1 H, m), 2.67 (2 H, m). ^{19}F NMR ($CDCl_3$): δ = 91.67 (3 F, d, *J* = 9.4 Hz). MS: *m/z* (%) = 216(15) [M^+], 175(100), 127(6), 125(51). Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 61.03; H, 5.11. **3d**: A colorless oil. ^{1}H NMR ($CDCl_3$): δ = 7.31 (1 H, d, *J* = 8.3 Hz), 6.94–7.18 (2 H, m), 6.87 (1 H, d, *J* = 7.7 Hz), 5.60 (1 H, m), 5.07 (1 H, s), 4.99 (1 H, d, *J* = 15.4 Hz), 4.95 (1 H, d, *J* = 9.01 Hz), 4.10 (1 H, m), 2.70 (2 H, m). ^{19}F NMR ($CDCl_3$): δ = 92.49 (3 F, d, *J* = 9.2 Hz). MS: *m/z* (%) = 216(39) [M^+], 215(44), 195(17), 175(62), 155(61), 127(100), 115(28), 107(31). Anal. Calcd for $C_{11}H_{11}F_3O$: C, 61.11; H, 5.13. Found: C, 61.09; H, 5.10.