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3-Ethenyl, 3-Ethynyl, 3-Aryl, and 3-Cyclopropyl-2,4,5-Trifluorobenzoic Acids: Useful Intermediates In The Synthesis Of Quinolone Antibacterials

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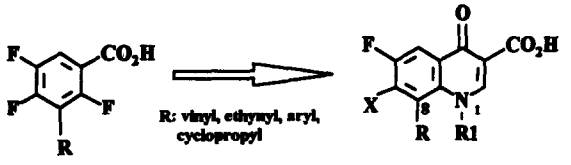
Abstract: The synthesis of 3-ethenyl, 3-ethynyl, 3-aryl, and 3-cyclopropyl-2,4,5-trifluorobenzoic acids from 1-bromo-2,4,5-trifluorobenzene and 2,4,5-trifluoro-3-hydroxybenzoic acid is described. These compounds are useful intermediates for the synthesis of quinolone antibacterials.

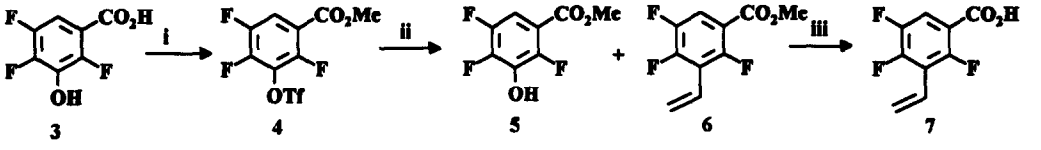
As part of our investigation of the electronic and steric effects of the 8-position of the quinolones **2** (**Scheme 1**) on antibacterial activity, we wanted to prepare the 3-ethenyl, 3-ethynyl, 3-aryl, and 3-cyclopropyl-2,4,5-trifluorobenzoic acids **1**, which are precursors to the target quinolones through well established procedures.[1] The 8-position of the quinolone antibiotics has not been well explored,[2] mainly due to the lack of published routes to 3-substituted-2,4,5-trifluorobenzoic acids **1**, particularly with carbon substitution. We now report the synthesis of several of these pentasubstituted trifluorobenzoic acid intermediates.[3]



1 **Scheme 1** **2**

We originally thought that the triflate ester **4** (**Scheme 2**), obtained from the readily available 3-hydroxybenzoic acid **3**[4] by esterification followed by triflation, would readily undergo Pd-catalyzed coupling with monosubstituted ethynes[5] and appropriate vinyl-, aryl-, and cyclopropylstannanes[6] to give our desired intermediates **1**. However, we observed primarily detriflation to give phenol **5** under a variety of conditions and Pd-catalysts.

The synthesis of our first objective, ethenyl acid **7** (**Scheme 2**), exemplified the difficulties we



3 **4** **5** **6** **7**

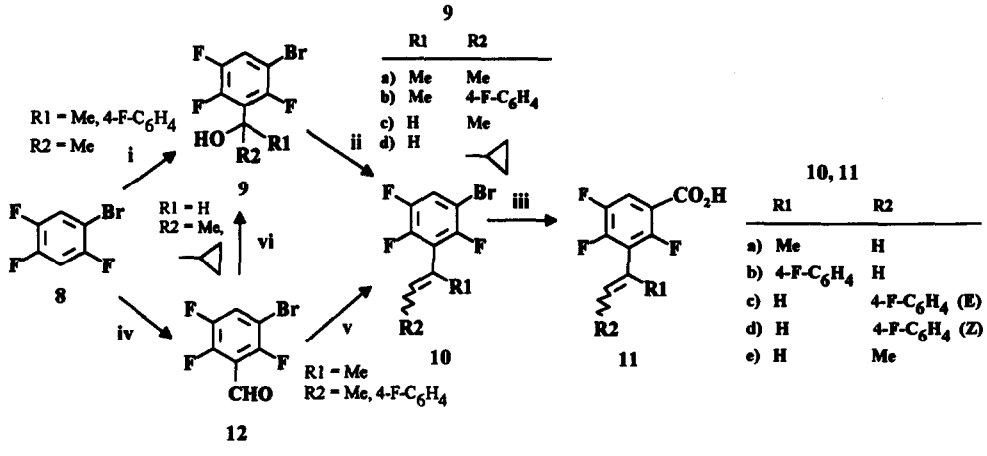
Reagents: (i) a) $(COCl)_2$, CH_2Cl_2, DMF (cat.), 0°-20° b) MeOH, 0° c) $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine, 0° (ii) n-Bu_3Sn-C_2H_3 (1.05 equiv.), LiCl (6 equiv.), 2,6-di-t-butyl-4-methylphenol (trace), $Pd(PPh_3)_4$ (1.5 mole %), N_2, dioxane, 98°, 12h (iii) a) MeOH, 1N NaOH b) H

Scheme 2

encountered. The Pd-catalyzed coupling of the triflate **4** with tri-*n*-butylvinylstannane was very sensitive to catalyst, solvent, and temperature. $(MeCN)_2PdCl_2$ or $Pd(PPh_3)_2Cl_2$ in DMF (20° - 100°C) gave primarily triflate cleavage to phenol **5**; only traces of **6** were formed. Likewise $Pd(PPh_3)_4$ at 80°C in dioxane gave less than 10% **6**, however, under reflux it yielded **6** in 80% yield. Distillation separated **6** from the small amount of **5**. Hydrolysis of ester **6** to acid **7** was conducted under basic conditions since acidic hydrolysis caused polymerization. The acid **7** was obtained most easily by hydrolysis of crude **6** since the crystalline acid was separated more readily from tin by-products.

The coupling conditions which successfully led to **7** failed for the other derivatives we desired and thus

prompted the investigation of other synthetic methods. It is known that lithiation of 2,4,5-trifluorobromobenzene **8** (**Scheme 3**) with LDA at -78°C in THF occurs at the 3-position.[7] Addition of this

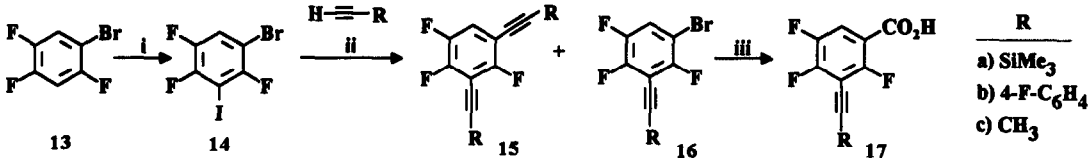


Reagents: (i) a) LDA, THF, -78° b) Acetone (or 4-fluoroacetophenone), THF, -78° c) H^+ (ii) Toluene, p-toluenesulfonic acid (iii) a) n-BuLi, THF, -78° b) CO_2 c) H^+ (iv) a) LDA, THF, -78° b) PhNMeCHO, THF, -78° c) H^+, -78°, THF (v) $Ph_3P^+CH_2CH_3Br^-$ (or $Ph_3P^+CH_2$(4-F-Ph)), ether, -78°, n-BuLi (vi) a) MeMgBr (or C_3H_5MgBr), ether, -78° b) H^+

Scheme 3

anion to appropriate ketones and aldehydes (**Scheme 3**) followed by dehydration would lead to substituted ethenyl acids. Thus, the tertiary alcohols **9a-b** were easily formed from acetone and 4-fluoroacetophenone and dehydrated with p-toluenesulfonic acid in toluene to give the α-substituted ethenyl bromobenzenes **10a-b**. No polymerization was observed. Finally, the acids **11a-b** were obtained by bromine-lithium exchange in ether followed by carboxylation.[8]

The analogous reaction of lithiated **8** with aldehydes (e.g., acetaldehyde) failed to yield the expected alcohols and compound **8** was recovered. We then supposed that the ß-ethenyl acids **11c-e** could be procured from aldehyde **12** (**Scheme 3**) either by coupling with the appropriate Wittig reagents or by condensation with Grignard reagents and subsequent dehydration of the secondary alcohols. The formylation of **8**, however, proved to be problematical and presented difficulties. The standard formyl equivalent, DMF, gave very poor yields. Several other formylating agents also gave low yields (DMF, 3%; triethylorthoformate, 30%; N-formylpiperidine, 80% conversion as monitored by GC).The best results (90% distilled product) were obtained by quick addition of an equivalent of N-formyl-N-methylaniline at -78°C followed by quenching with acid at -78°C as soon as the reaction was finished (monitoring by GC). Compound **8** was never completely consumed. In all cases examined, elevated temperatures, increased reaction time, or addition of more formylating equivalents resulted in poorer yields. Finally, reaction of aldehyde **12** with appropriate Wittig reagents in THF

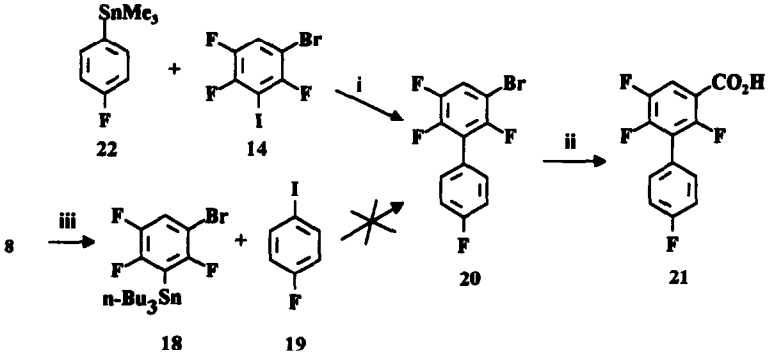


Reagents: (i) a) LDA, -78°, THF b) I_2 (ii) NEt_3, HC_2R, CuI (cat.), $Pd(Ph_3P)_2Cl_2$ (2 mole %), 20°, 4-24h (iii) a) MeLi, ether, -78° b) CO_2

Scheme 4

at -78°C gave the ß-ethenylbromobenzenes **10c-e** (**E/Z** = 1:1). The **E**-isomer **10c** was separated by fractional crystallization. The **Z**-isomer **10d** could not be separated chromatographically but was purified by crystallization of acid **11d**. The isomers of **10e** and **11e** could not be separated.

Conceivably, the ethenyl acid 7 could also be synthesized by the Wittig reaction of aldehyde 12 with a methyl phosphorane followed by carboxylation; however, reactions with methyl phosphoranes were unsuccessful. Alternatively, reaction of aldehyde 12 with methylmagnesium bromide gave the secondary alcohol 9c and dehydration of 9c would also lead to 7. However, 9c polymerized under the same conditions used to dehydrate the tertiary alcohols 9a-b. Dehydration was also unsuccessful for the cyclopropyl alcohol 9d.

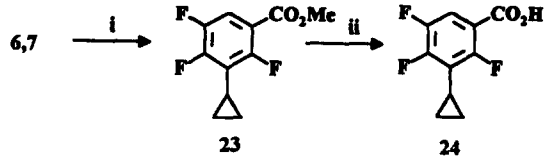


Reagents: (i) $Pd(PPh_3)_2Cl_2$ (2 mole %), toluene, 100°, 16h (ii) a) n-Butyllithium, ether, -78° b) CO_2
(iii) a) LDA, THF, -78° b) $n\text{-}Bu_3SnCl$

Scheme 5

As previously mentioned, the ethynyl acids could not be made by Pd-catalyzed coupling of ethynes with aryl triflate 4 since triflate cleavage[5] was the preponderant reaction. However, coupling of ethynes has also been accomplished on halo aromatics (Heck reaction[9]), and selectivity is in the order I > Br >> Cl.[6,9] Accordingly, we prepared the 3-iodo compound 14, expecting that coupling with ethynes would occur only at the iodine position (**Scheme 4**). This was indeed the case, and ethynyl coupling occurred readily with $(PPh_3)_2PdCl_2$ in triethylamine at 20°C. A small amount of bis-substitution occurred only with trimethylsilylethyne to give 15a. Carboxylation of 16 to give ethynyl acids 17 was then best achieved with methyl- rather than *n*-butyl-lithium. Since the methyl analog 16c could not be cleanly carboxylated, presumably due to the competing acidity of the methyl moiety for the base, this route is probably limited to ethynes without extractable hydrogens.

The Pd-catalyzed coupling of arylstannanes with aryl halides to give biphenyls is also well documented[10] and led to our synthesis of biphenyl 20 (**Scheme 5**). The Pd-catalyzed coupling of the easily prepared aryltributylstannane 18 to *p*-fluoroiodobenzene 19 was unsuccessful, possibly because of steric hindrance at the stannane position. However, the reverse coupling of the less bulky aryltrimethylstannane 22[11] with the 3-iodo compound 14 proceeded smoothly to give the desired biphenyl 20. Carboxylation of 20 gave the desired acid 21.



Reagents: (i) a) CH_2N_2, 0°-20°, 24h b) Xylenes, reflux, 2h
(ii) a) 1N NaOH, THF, 20° b) HCl, H_2O

Scheme 6

Finally, we pursued the cyclopropyl acid 24 (**Scheme 6**). Its unusual hybridization and relation of its electron donor-acceptor properties to its conformation relative to the aromatic ring[12] made it an interesting target for comparison with the ethenyl analogs. Since the Pd-catalyzed coupling of tri-*n*-butylstannylcyclopropane[13] with 5-bromopyrimidines does occur in low yield[14] we thought that the aromatic iodo compound 14 might also be cyclopropylated by Pd-catalyzed coupling with neat cyclopropylstannanes. Attempted couplings of neat tri-*n*-butylstannylcyclopropane with the 3-iodo analog 14 were unsuccessful. Coupling with tetracyclopropylstannane[13] was also unsuccessful with various solvents, temperatures, and palladium catalysts (including $(PPh_3)_2PdCl_2$, which is particularly effective for alkyl transfer[6]). Again, attempted introduction of the cyclopropyl moiety with these tin reagents on the triflate 4 led only to triflate cleavage to form phenol 5.

We were thus led to attempt formation of the cyclopropyl ring via annellation on the ethenyl compounds **6** and **7** (**Scheme 6**). Standard Simmons-Smith conditions failed with **6**. A small scale reaction with η^5-$C_5H_5(CO)_2FeCH_2S^+(CH_3)_2KBF_4^-$ [15] afforded **23** in 34% yield; but scale up of the reaction failed, presumably (since GC showed formation of **23**) due to decomposition of **23** as it was formed under the reaction conditions. However, diazomethane[16] smoothly reacted with **6** or **7** and thermal decomposition of the intermediate pyrazoline in refluxing xylenes gave **23** in 70% overall yield. Basic hydrolysis of **23** gave the desired acid **24**.

The synthesis of quinolones derived from the intermediates described in this paper and their biological activity will be reported elsewhere.

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   7: M.p. 108-110°C; ^{1}H-NMR ($CDCl_3$) 5.75 (d, 1H, J=11.8 Hz), 6.14 (d, 1H, J=18.2 Hz), 6.71 (dd, 1H, J=11.9, 18.1 Hz), 7.76(m, 1H), 12.0 (broad s, 1H); MS 202 (M^+). **11a**: M.p. 95-97°C; ^{1}H-NMR ($CDCl_3$) 2.11 (s, 3H), 5.17 (s,1H), 5.52 (s, 1H), 7.79 (m, 1H), 12.6 (broad s, 1H, disappears with D_2O); MS 216 (M^+, 68), 151 (100). **11b**: M.p. 153-155°C; ^{1}H-NMR ($CDCl_3$) 5.44 (s, 1H), 6.01 (s, 1H), 7.02 (t, 1H, J=6.4 Hz), 7.26 (m, 1H), 7.89 (m, 1H); MS 296 (M^+, 100). **11c**: M.p. 144-147°C; ^{1}H-NMR ($CDCl_3$) 2.00 (d, 3H, J=6.0 Hz), 6.27 (m, 1H), 6.64 (m, 1H), 7.68 (m, 1H), 10.50 (broad s, 1H, disappears with D_2O); MS 216 (M^+, 100). **11d**: M.p. 175-177°C; ^{1}H-NMR (DMSO-d_6) 7.08 (d, 1H, J=16.8 Hz), 7.26 (m, 2H), 7.44 (d, 1H, J=16.8 Hz), 7.77 (m, 3H), 13.7 (broad s, 1H); MS 296 (M^+, 53), 66 (100). **11e**: M.p. 134-135°C; ^{1}H-NMR (DMSO-d_6) 6.40 (d, 1H, J=12.1), 7.0-7.3 (m, 5H), 7.80 (m, 1H), 13.70 (broad s, 1H); MS 296 (M^+, 100). **12**: B.p. 63-68°C (0.2 torr); ^{1}H-NMR ($CDCl_3$) 7.71 (m, 1H), 10.20 (s, 1H); MS 237.9 (M-1, 100), 238.9 (M^+, 82). 17a: M.p. 175-179°C; ^{1}H-NMR ($CDCl_3$) 0.30 (s, 9H), 7.80 (m, 1H); MS 272 (M^+, 12), 257 (100). **17b**: M.p. 167-169°C; ^{1}H-NMR ($CDCl_3$+DMSO-d_6) 7.10 (t, 2H), 7.56 (m, 2H), 7.79 (m, 1H); MS 294 (M^+, 100). **21**: M.p. 201-203°C; 1H-NMR (DMSO-d_6) 7.39 (t, 2H, J=8.8 Hz), 7.60 (m, 2H), 7.95(m, 1H), 13.70 (broad s, 1H, disappears with D_2O); MS 216 (M^+, 100). **24**: M.p. 95-97°C; ^{1}H-NMR ($CDCl_3$) 1.05 (d, 4H, J=6.9 Hz), 1.91 (q, 1H, J=6.9 Hz), 7.65 (m, 1H); MS 215 (M^+ ,100).
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