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Regioselective Synthesis of Trifluoromethyl Substituted Quinolines from Trifluoroacetyl Acetylenes

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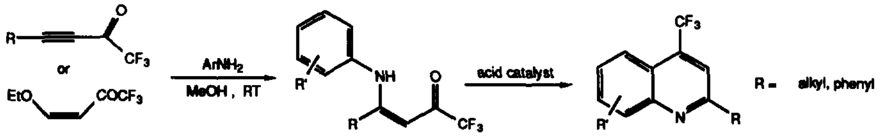
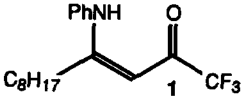
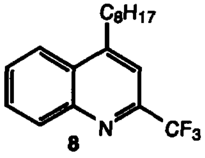
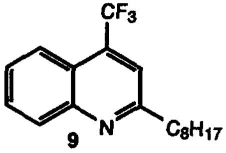
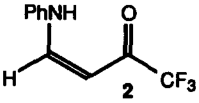
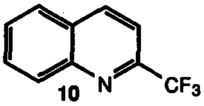
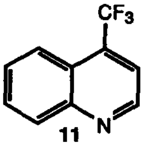
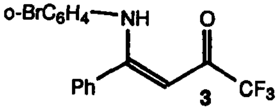
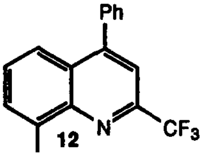
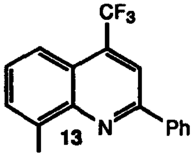
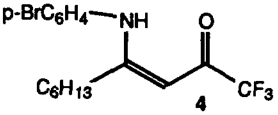
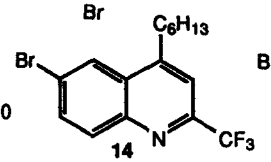
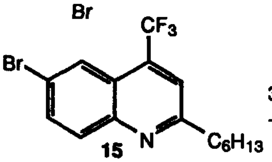
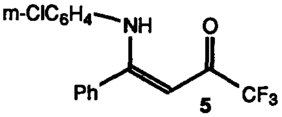
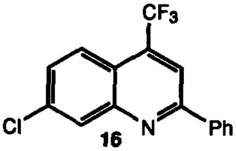
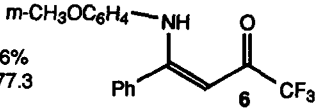
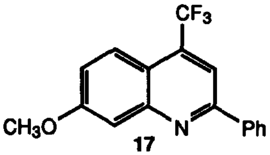
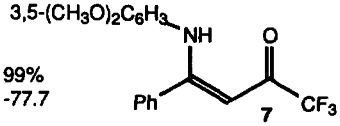
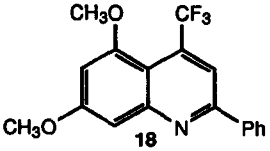
Abstract: Trifluoromethyl substituted quinolines have been prepared by 1, 2- or 1, 4- addition of anilines to trifluoroacetyl acetylenes followed by intramolecular acid catalyzed ring closure.

Recently considerable interest has been directed toward the synthesis of trifluoromethyl substituted heteroaromatic compounds[1], due in part to the unique biological properties imparted by fluorine.[2] For example, mefloquine, a trifluoromethylated quinoline, has been developed as an antimalarial agent in response to increased resistance to existing drugs.[3] Several non-regiospecific approaches to CF_3 substituted quinolines are known, typically providing access to 2-CF_3 substituted quinolines[4] or quinolones[5] in modest yields. More recently, Pastor and co-workers[6] achieved improved yields for 2-R_f substituted quinolines from R_f alkynyl esters. Methods for the regioselective synthesis of 4-CF_3 substituted quinolines have not been reported. We now wish to report preliminary data on the regiocontrolled synthesis of 4-CF_3 substituted quinolines from trifluoroacetyl (TFA) acetylenes. Significantly, the CF_3 group ultimately is derived from trifluoroacetic acid rather than an expensive CF_3 substituted aniline.



Regioselective 1, 4- addition of a wide variety of anilines to TFA acetylenes is a facile reaction, providing the β-TFA enamine in good yield, see Table. Only the Z-isomer was observed for 1° amines, while 2° amines or thiols produced a mixture of E and Z isomers.[7a] Hojo et al[7b] recently reported an addition/elimination sequence leading to β-TFA enamines from β-TFA enol ethers. To prepare α-unsubstituted enamines such as **2**, we also employed the addition/elimination sequence.[7] The yields for isomerically pure enamines **1-7** are given in the Table.

Table Synthesis of Trifluoromethyl Substituted Quinolines

Yield,%[a] ^{19}F-NMR[b]	β - TFA Enamine	Yield,%[a] ^{19}F-NMR[b]	CF$_3$ Substituted Quinoline		Yield,%[a] ^{19}F-NMR[b]
89% -77.2	 **1**	not detected	 **8**	 **9**	55% -62.7
82% -78.0	 **2**	21% -68.3	 **10**	 **11**	trace
86% -77.7	 **3**	14% -68.3	 **12**	 **13**	26% -61.7
87% -77.0	 **4**	-69.0	 **14**	 **15**	39%[c] -62.3
77% -77.7	 **5**			 **16**	73% -62.7
96% -77.3	 **6**			 **17**	77% -62.3
99% -77.7	 **7**			 **18**	93% -60.0

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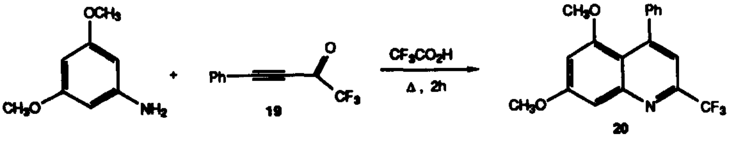
[a] Isolated yield of analytically pure material. [b] ^{19}F-NMR shifts reported in ppm relative to CFCl$_3$ (0 ppm). Upfield shifts are designated as negative. [c] Total yield of **14** and **15** isolated as a 4:96 inseparable mixture

Initial attempts at cyclization of β-TFA enamine **1** using a variety of Lewis acids failed,[8] resulting in only recovered starting material or significant material loss. Reaction of **1** in neat sulfuric acid at room temperature did provide the 4-CF_3 substituted quinoline **9**, albeit in 29% yield. The reaction was substantially improved by carrying out the cyclization step in polyphosphoric acid (165°, 3h), leading to the isolation of a single regiosomer (NMR and GC analysis) in 55% yield. The regiosomer was assigned structure **9** based on the observed ^{19}F-NMR signal at -62.7 ppm and ^{13}C-NMR signals at 124.2 ppm (CF_3, J_{CF} = 275.9 Hz) and 134.8 ppm (C4, J_{CF} = 31.7 Hz). Isomer **8** was not detected in the crude reaction mixture. Interestingly, attempts to cyclize enamine **2** under the same reaction conditions resulted in the isolation of only the 2-CF_3 substituted quinoline **10** with only a trace of the 4-CF_3 isomer **11**. The 2-CF_3 isomer **10** is clearly distinguished from the 4-CF_3 isomer by a ^{19}F-NMR signal at -68.3 ppm and ^{13}C-NMR signals at 122.3 ppm (CF_3, J_{CF} = 275.9 Hz) and 148.5 ppm (C2, J_{CF} = 34.2 Hz). In an earlier study on the regiospecific synthesis of isoxazoles via acid or base catalyzed 1,2- or 1,4-addition of hydroxylamine to TFA acetylenes, we determined that acidic reaction conditions favored 1,2-addition of a nitrogen nucleophile.[9] In the reaction of β-TFA enamine **2**, retro-1, 4- addition would produce the aniline and TFA acetylene. Subsequent 1,2-addition of the aniline would produce an acetylenic imine which would ultimately lead to quinoline **10**.[10] It is interesting to note that this reaction pathway is not observed for the more substituted β-TFA enamine **1**. In support of this assumption, 3,5-dimethoxy aniline and TFA acetylene **19**[9] were combined in neat trifluoroacetic acid and heated to reflux for 2h. Only the 2-CF_3 quinoline **20** was isolated in 48% (unoptimized) yield. The ^{19}F-NMR chemical shift of -68.3 ppm for **20** confirmed the regiochemical assignment. This approach to 2-CF_3 quinolines is completely regiospecific, providing a useful alternative to existing methods.



In a comprehensive study of the Combes quinoline synthesis, Roberts and Turner[11] noted that anilines substituted in the *meta* position by electron donating groups readily cyclized, generally leading exclusively to the 7-substituted quinoline, while *ortho* or *para* electron donating group substituents inhibited or prevented cyclization. This is also the case for the β-TFA enamines examined. β-TFA enamines 3 and 4 (derived from *ortho* and *para* bromoaniline respectively) both provided regiochemical mixtures of the 2- and 4-CF_3 quinolines (**12**, **13**, **14**, **15**). In contrast, enamines derived from *meta* substituted anilines (**5**, **6**, **7**) undergo cyclization to only the 4-CF_3 quinolines (**16**, **17**, **18**) in very good yield. The reaction conditions required reflect the activation of the aniline benzene ring. Quinoline **16** was obtained using the standard reaction conditions (PPA, 165°, 3h), while the 7-OCH_3 quinoline **17** was obtained by cyclization of **6** in refluxing trifluoroacetic acid. The 3, 5-dimethoxy derivative **7** provided quinoline **18** in 93% yield after only 30 minutes in refluxing trifluoroacetic acid.

In summary, we have reported methods for the regiospecific synthesis of 2-CF_3 or (more noteworthy) 4-CF_3 substituted quinolines by choice of the reaction conditions. As in our previous approach to isoxazoles,[9] the regiochemistry of the reaction can be controlled using basic or acidic reaction conditions. A novel acid catalyzed retro-1, 4- addition reaction was observed which places a limitation on this methodology in the preparation of 4-CF_3 quinolines which are not substituted in the 2-position. The approaches to fluorinated quinolines reported herein should find direct application in the synthesis of pharmaceuticals and agrochemicals.[1]

References and Footnotes

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