The Superacid Induced Condensation of Quinolinecarboxaldehydes with Arenes

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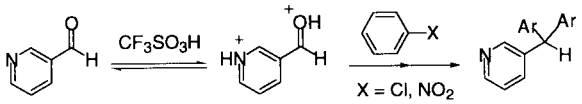
Abstract: A variety of quinolinecarboxaldehydes have been reacted with arenes in the Brönsted superacid, CF_3SO_3H (triflic acid) to give condensation products in good to excellent yields (52−99%). The quinolinecarboxaldehydes are significantly more reactive than 2-naphthalenecarboxaldehyde. It is proposed that the increased reactivity is due to the formation of dicationic, electrophilic intermediates.

Key words: heterocycles, aldehydes, electrophilic aromatic substitutions, quinolines

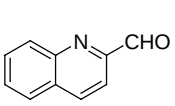
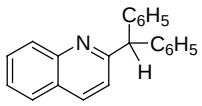
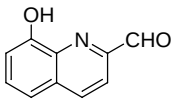
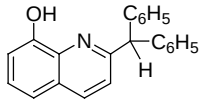
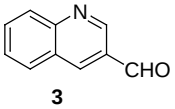
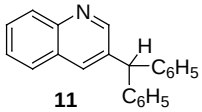
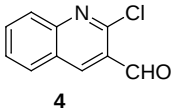
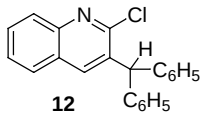
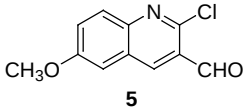
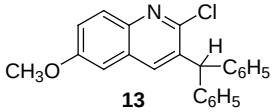
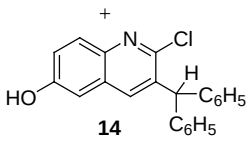
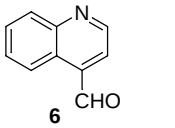
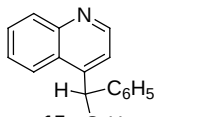
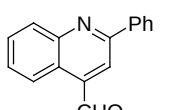
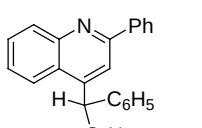
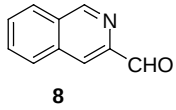
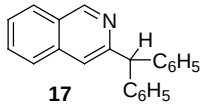
In recent years, dicationic electrophilic species have been the subject of many studies.[1] We recently described the condensation of 3-pyridinecarboxaldehyde with arenes in the Brönsted superacid CF_3SO_3H (triflic acid, TfOH) to give 3-(diarylmethyl)pyridines.[2] These studies suggested that 3-pyridinecarboxaldehyde is in equilibrium with diprotonated species in superacidic solution (Scheme 1). The pyridine ring has an easily protonated base-site, so that upon subsequent protonation of the carbonyl group, a reactive dicationic electrophile is formed. In a similar respect, quinolinecarboxaldehydes possess well-defined base-sites and should form reactive, diprotonated electrophiles in superacid. These reactive electrophiles could be useful in Friedel−Crafts type reactions to prepare substituted derivatives of quinoline. Because substituted quinolines have shown a wide array of biological activities,[3] there has been a great amount of interest in synthetic methodologies related to these heterocycles.[4] In this paper, we describe our studies of the superacid-catalyzed condensations of quinolinecarboxaldehydes with arenes and report an improved method for the preparation of (diarylmethyl)quinolines.



Scheme 1

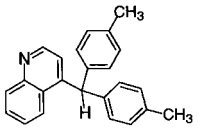
When quinolinecarboxaldehydes **1**−**7** are reacted with benzene in TfOH,[5] the condensation products **9**−**16** are formed in good to excellent yields (Table). In the case of aldehyde **5**, condensation gives the expected product **13**, but a small amount of hydroxyquinoline product **14** is also formed. Isoquinolinecarboxaldehyde (**8**) also gives the product **17** from condensation with benzene. A typical

Table Results from the reaction of Quinolinecarboxaldehydes (**1**-**7**) and Isoquinoline-carboxaldehyde (**8**) with Benzene in Triflic Acid (CF_3SO_3H)

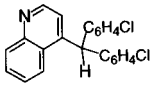
Quinoline	Product	Yield
 **1**	 **9**	96
 **2**	 **10**	94
 **3**	 **11**	95
 **4**	 **12**	78
 **5**	 **13** +  **14**	48 4
 **6**	 **15**	73
 **7**	 **16**	99
 **8**	 **17**	99

conversion can be accomplished in less than 1 hour at 25 °C. This is an improvement over earlier procedures using H_2SO_4.[6] Sulfuric acid is up to 100 times weaker an acid than TfOH.[7] Consequently, the condensation reaction of **1** with benzene in H_2SO_4 requires elevated temperatures and longer reaction times.[6]

Reaction of **6** with toluene in TfOH at 25 °C gives the condensation products in good yield, but several regioisomers are formed. If the condensation is done at a low temperature, then electrophilic attack occurs regioselectively at the *para*-position of toluene and product **18** is formed. Reaction of **6** with chlorobenzene in TfOH gave the condensation product(s) **19** in 90% overall yield with three regioisomers being produced [ratio of bis-(chlorophenyl) products: 2% *ortho,ortho*; 38% *ortho, para*; 60% *para, para*]. Despite a significant deactivation of *o*-dichlorobenzene toward electrophilic attack,[8] product **20** is formed in 75% yield by the reaction of **6** with *o*-dichlorobenzene in TfOH.



18



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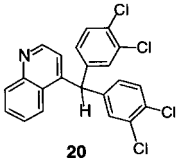
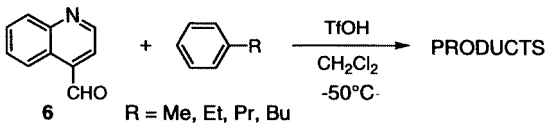


20

Since two arene molecules condense with the quinolinecarboxaldehydes, the potential exists for the preparation of molecular libraries through the use of combinatorial synthesis.[9] When **6** is reacted with toluene, ethylbenzene, propylbenzene, and butylbenzene, in TfOH at low temperature, all 10 expected products are formed and may be identified by GC/MS (Figure). The product arising from reaction with two molecules of butylbenzene is formed in relatively small quantity. This may be due to a decrease in solubility of the alkylbenzene in the acidic solution as the alkyl chain increases in size. When aldehydes **6** and **7** are reacted with the four alkylbenzenes, all 20 expected products may be observed by GC/MS.

The condensation of aldehydes or ketones with arenes is known as the hydroxyalkylation reaction.[10] In general, it has been synthetically useful only when activated arenes have been used (such as phenols), or when electron deficient aldehydes or ketones are used (such as chloral or trifluoromethyl ketones).[11] In the case of quinolinecarboxaldehydes **1**–**7** and **8**, we propose that these compounds are reactive due to their ability to form diprotonated, dicationic electrophiles. For example, **6** forms an equilibrium with **21** in strong acids and superacids, and the dicationic electrophile is sufficiently electrophilic to react with arenes like C_6H_6, C_6H_5Cl, or $C_6H_4Cl_2$ (Scheme 2). When 2-naphthaldehyde is reacted with C_6H_5Cl in TfOH, no condensation reaction occurs despite the fact that the carbonyl group is extensively protonated.[12] The protonated heterocyclic ring appears to activate the carboxonium group in species like **21**. This electrophilic activation may be the result of inductive effects like that observed with electron deficient aldehydes.



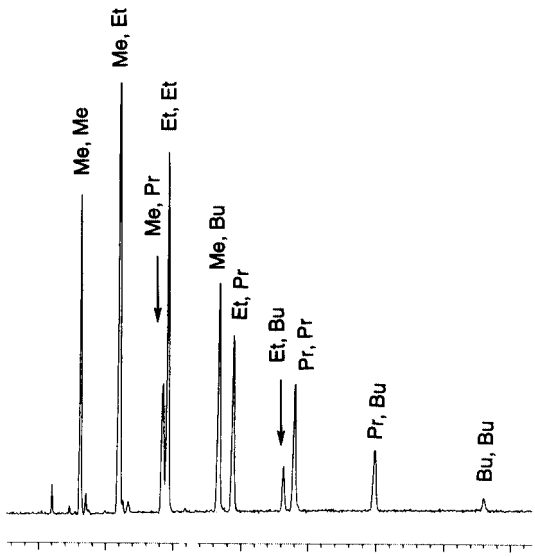
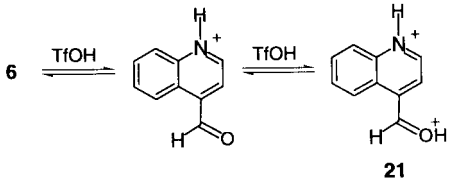


Figure GCMS analysis of the product mix from the reaction of aldehyde **6**, alkylbenzenes, and CF_3SO_3H



21

Scheme 2

In summary, we have found that quinolinecarboxaldehydes react in good to excellent yields with arenes in CF_3SO_3H to give diarylmethylquinolines. We propose that these condensation reactions occur through dicationic intermediates. The diprotonated quinolinecarboxaldehydes are capable of reacting with moderately deactivated arenes.

Triflic acid was purchased from 3M Company and distilled under an inert atmosphere immediately prior to use. Quinolinecarboxaldehydes and the other aldehydes were purchased from commercial suppliers and used as received. Compound **2** was prepared according to a published procedure.[13] Compound **8** was prepared by the oxidation of 3-methylisoquinoline with SeO_2 in dioxane.[14] Combustion analyses were done by Galbraith Laboratories, Knoxville, Tennessee. Unless otherwise noted, recrystallizations of products were from $CHCl_3$. ^1H NMR spectra were recorded at 300 MHz and ^{13}C NMR spectra were recorded at 125 MHz.

Reaction of Quinoline and Isoquinoline Aldehydes with Arenes; General Procedure[15]

The heterocyclic aldehyde (0.2 g) was dissolved in benzene (1 mL) or the corresponding arene (1 mL, for **19** and **20**) and CF_3SO_3H (2 mL) and the mixture was stirred at r.t. for 3 h. The mixture was then poured over ice and the resulting solution was made basic by slow addition of aq 50% NaOH solution. The products were then extracted into $CHCl_3$, the organic phase was washed with H_2O then brine, dried ($MgSO_4$), and the product was isolated by removal of solvent from under vacuum.

Combinatorial Preparations

The alkylbenzenes (ca. 0.25 mL each) was combined with CF_3SO_3H and mixed with CH_2Cl_2 (2 mL). The resulting solution was then cooled to −50 °C. The heterocyclic aldehyde(s) (0.05 to 0.1 g) was dissolved in CH_2Cl_2 (2 mL) and the aldehyde solution was then added to the CF_3SO_3H/alkylbenzene solution. After stirring for 8 h, the mixture was poured over several grams of ice. The aqueous phase was extracted with hexanes to remove the excess alkylbenzenes, and then it was made basic by slow addition of aq 50% NaOH solution. The products were then extracted into $CHCl_3$, the organic phase was washed with H_2O then brine, dried ($MgSO_4$), and the product mixture was analyzed by GC/MS (DB-5 capillary column).

2-(Diphenylmethyl)quinoline (9)

Mp 105−107 °C.

^{1}H NMR ($CDCl_3$/TMS): δ = 5.91 (s, 1 H), 7.20−7.31 (m, 12 H) 7.49 (m, 1 H), 7.67 (m, 1 H), 7.75 (d, 1 H, *J* = 7.8 Hz), 8.14 (m, 1 H).

^{13}C NMR ($CDCl_3$/TMS): δ = 60.2, 122.0, 126.3, 126.7, 126.9, 127.5, 128.5, 129.4, 129.5, 132.9, 136.4, 142.7, 148.0, 162.3.

EI-MS: *m*/*z* = 295 (M^+).

Anal. calcd for $C_{22}H_{17}N$: C, 89.46, H, 5.80. Found: C, 88.72, H, 5.89.

2-(Diphenylmethyl)-8-hydroxyquinoline (10)

Mp 250−254 °C.

^{1}H NMR ($CDCl_3$/TMS):: δ = 5.85 (s, 1 H), 7.13 (m, 1 H), 7.19−7.34 (m, 12 H), 7.40 (m, 1 H), 8.06 (d, 1 H, *J* = 8.4 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 59.5, 110.0, 117.5, 123.0, 126.7, 126.9, 127.4, 128.5, 129.4, 136.5, 137.5, 142.3, 152.0, 160.8.

EI-MS: *m*/*z* = 311 (M^+).

Anal. calcd for $C_{22}H_{17}NO$: C, 84.86, H, 5.50. Found: C, 83.84, H, 5.65.

3-(Diphenylmethyl)quinoline (11)

Mp 123−126 °C.

^{1}H NMR ($CDCl_3$/TMS): δ = 5.76 (s, 1 H), 7.17 (m, 4 H), 7.24−7.38 (m, 6 H), 7.51 (m, 1 H), 7.65−7.72 (m, 3 H), 8.09 (d, 1 H, *J* = 8.4 Hz), 8.79 (d, 4 H, *J* = 2.1 Hz,).

^{13}C NMR ($CDCl_3$/TMS): δ = 54.4, 126.7, 126.8, 127.7, 127.8, 128.6, 129.1, 129.2, 129.4, 135.3, 136.9, 142.5, 146.8, 152.5.

EI-MS: *m*/*z* = 295 (M^+).

Anal. calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80. Found: C, 89.58; H, 5.89.

2-Chloro-3-(diphenylmethyl)quinoline (12)

Mp 199−202 °C.

^{1}H NMR($CDCl_3$/TMS): δ = 5.76 (s, 1 H), 7.14−7.17 (m, 4 H), 7.26-7.36 (m, 6 H), 7.51 (m, 1 H), 7.66−7.71 (m, 2 H), 8.09 (d, 1 H, *J* = 8.4 Hz), 8.78 (s, 1 H).

^{13}C NMR ($CDCl_3$/TMS): δ = 54.4, 126.7, 126.8, 127.7, 127.8, 128.6, 129.0, 129.1, 129.4, 135.3, 142.5, 146.7, 152.5.

EI-MS: *m*/*z* = 329, 331 (M^+).

Anal. calcd for $C_{22}H_{16}ClN$: C, 80.10; H, 4.89. Found: C, 80.27; H, 5.02.

2-Chloro-3-(diphenylmethyl)-6-methoxyquinoline (13)

Mp 209−213 °C.

^{1}H NMR ($CDCl_3$/TMS): δ = 3.84 (s, 3 H), 5.98 (s, 1 H), 6.89 (d, 1 H, *J* = 3.0 Hz), 7.08−7.10 (m, 4 H), 7.24−7.33 (m, 7 H), 7.50 (s, 1 H), 7.88 (d, 1 H, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 53.6, 55.6, 105.0, 122.9, 126.9, 128.2, 128.6, 129.5, 129.5, 136.3, 137.8, 141.6, 142.5, 149.0, 158.1.

EI-MS: *m*/*z* = 359, 361 (M^+).

Anal. calcd for $C_{23}H_{18}ClNO$: C, 76.77; H, 5.04. Found: C, 76.36; H, 5.05.

2-Chloro-3-(diphenylmethyl)-6-hydroxyquinoline (14)

Mp 250−254 °C.

^{1}H NMR ($CDCl_3$/TMS): δ 5.76 (s, 1 H), 6.95 (d, 1 H, *J* = 3.0 Hz), 7.06−7.09 (m, 4 H), 7.25−7.34 (m, 11 H), 7.45 (s, 1 H), 7.88 (d, 1 H, *J* = 9.0 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ, 53.6, 109.0, 120.6, 122.0, 126.9, 128.3, 128.6, 129.5, 129.7, 136.5, 137.7, 141.5, 142.1, 149.2, 154.4.

EI-MS: *m*/*z* = 345, 347 (M^+).[16]

4-(Diphenylmethyl)quinoline (15)

Mp 137−141 °C.

^{1}H NMR($CDCl_3$/TMS): δ = 6.24 (s, 1 H), 6.87 (d, 1 H, *J* = 4.8 Hz), 7.08−7.12 (m, 4 H), 7.27-7.33 (m, 6 H), 7.44 (m, 1 H), 7.66 (m, 1 H), 7.96 (d, 1 H, *J* = 7.8 Hz), 8.12 (d, 1 H, *J* = 8.7 Hz), 8.80 (d, 1 H, *J* = 4.8 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 52.7, 122.1, 124.2, 126.6, 126.9, 127.2, 128.6, 128.9, 129.4, 130.2, 142.0, 148.4, 149.5, 150.1.

EI-MS: *m*/*z* = 295 (M^+).

Anal. calcd for $C_{22}H_{17}N$: C, 89.46; H, 5.80. Found: C, 89.58; H, 5.89.

4-(Diphenylmethyl)-3-phenylquinoline (16)

Mp 148-151 °C.

^{1}H NMR ($CDCl_3$/TMS): δ = 6.31 (s, 1 H), 7.16−7.52 (m, 16 H), 6.73 (m, 1 H), 7.98 (m, 2 H), 8.22 (d, 1 H, *J* = 8.7 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 52.9, 119.9, 120.0, 124.0, 126.2, 126.3, 126.9, 127.4, 127.6, 128.6, 129.2, 129.5, 130.4, 139.7, 142.1, 148.6, 150.1, 156.8.

EI-MS: *m*/*z* = 371 (M^+).

Anal. calcd for $C_{28}H_{21}N$: C, 90.53, H, 5.70. Found: C, 91.00, H, 5.76.

3-(Diphenylmethyl)isoquinoline (17)

Mp 146−149 °C.

^{1}H NMR ($CDCl_3$/TMS): δ = 5.85 (s, 1 H), 7.17−7.31 (m, 11 H), 7.52 (m, 1 H), 7.61 (m, 1 H), 7.65 (m, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 9.22 (s, 1 H).

^{13}C NMR ($CDCl_3$/TMS): δ = 59.0, 119.6, 126.5, 126.5, 126.8, 127.1, 127.4, 128.4, 129.5, 130.3, 136.2, 142.9, 152.4, 156.8.

EI-MS: *m*/*z* = 295 (M^+).

Anal. Calcd. for $C_{22}H_{17}N$: C, 89.46%, H, 5.80%. Found: C, 88.97%, H, 5.87%.

4-[(Bis-4-tolyl)]methylquinoline (18)

^{1}H NMR ($CDCl_3$/TMS): δ = 2.33 (s, 6 H), 6.18 (s, 1 H), 6.90 (d, 1 H, *J* = 4.8 Hz), 6.99 (d, 4 H, *J* = 8.1 Hz), 7.11 (d, 4 H, *J* = 8.1 Hz), 7.44 (m, 1 H), 7.65 (m, 1 H), 7.98 (d, 1 H, *J* = 8.7 Hz), 8.13 (d, 1 H, *J* = 8.4 Hz), 8.80 (d, 1 H, *J* = 4.2 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 21.3, 52.2, 122.0, 122.6, 126.7, 129.3, 129.8, 130.4, 136.6, 139.6, 148.6, 150.2, 150.3, 150.6.

EI-MS: *m*/*z* = 323 (M^+).

Anal. calcd for $C_{24}H_{21}N$: C, 89.12; H, 6.54. Found: C, 88.48; H, 6.86.

4-[Bis(3,4-dichlorophenyl)]methylquinoline (20)
Viscous oil.

^{1}H NMR ($CDCl_3$/TMS): δ = 6.11 (s, 1 H), 6.80 (d, 1 H, *J* = 4.8 Hz), 6.88 (dd, 2 H, *J* = 2.1, 8.4 Hz), 7.15 (d, 2 H, *J* = 2.1 Hz), 7.37 (d, 2 H, *J* = 8.4 Hz), 7.47 (m, 1 H), 7.69 (m, 1 H), 7.79 (d, 1 H, *J* = 8.7 Hz), 8.14 (d, 1 H, *J* = 8.4 Hz), 8.82 (d, 1 H, *J* = 4.5 Hz).

^{13}C NMR ($CDCl_3$/TMS): δ = 50.83, 121.8, 123.4, 126.5, 127.2, 128.6, 129.5, 130.5, 130.8, 131.1, 131.7, 133.2, 141.1, 146.9, 148.5, 150.1.

EI-MS: *m*/*z* = 433 (M^+).

Anal. calcd for $C_{22}H_{13}Cl_4N$: C, 61.00; H, 3.03. Found: C, 63.44; H, 4.05.

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(16) Insufficient quantities were obtained for elemental analysis.

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