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Superacid-promoted reactions of pyrazolecarboxaldehydes and the role of dicationic electrophiles

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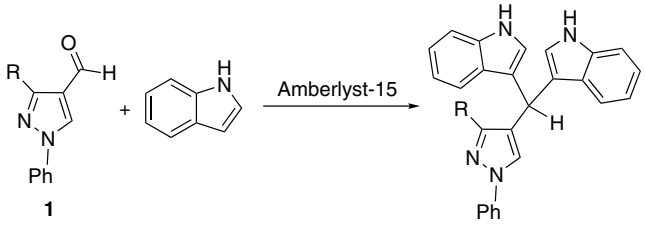
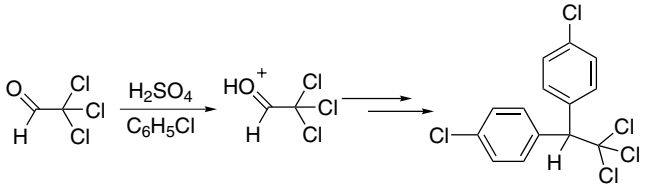
Abstract—Pyrazolecarboxaldehydes react in the Brønsted superacid triflic acid (CF_3SO_3H, TfOH) to generate electrophilic intermediates capable of reacting with benzene in condensation reactions. Appropriately substituted pyrazoles may also undergo intramolecular Friedel–Crafts-type reactions. It is proposed that the pyrazolecarboxaldehydes and related systems form diprotonated intermediates in these reactions.

In a recent report, a series of pyrazolecarboxaldehydes (**1**) were shown to condense with indole in good yields (77–96%) using a solid acid catalyst, Amberlyst 15 (Eq. 1).[1] These reactions are examples of the Friedel–Crafts-type conversion known as hydroxyalkylation.[2] Hydroxyalkylations are used in a variety of industrial synthetic methods, including the synthesis of bis-phenols resins and Bakelite polymers, in the preparation of malecite green and related colorants, and in the preparation of pharmaceuticals, like bisacodyl and diarylhydantoins. In general, the mechanism of hydroxyalkylation is thought to involve protonation of an aldehyde or ketone and subsequent attack of an arene by the carboxonium ion. Because carboxonium ions are fairly weak electrophiles, hydroxyarylation is most effective with electron-rich aromatic compounds (i.e., phenols, aryl-ethers, alkylbenzenes). With less nucleophilic arenes (i.e., benzene, halogenated benzenes, nitrobenzene), hydroxyalkylation requires the use of highly electrophilic carboxonium ions.[3] When adjacent to an electron-withdrawing group (Eq. 2) or cationic group (Eq. 3),[4a]



(1)



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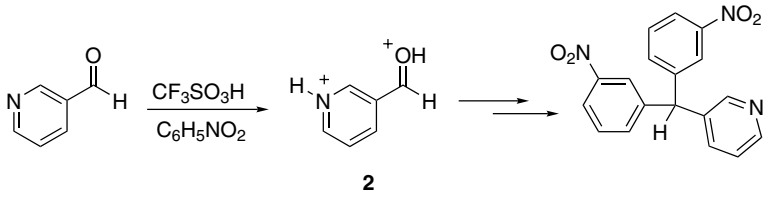

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(3)

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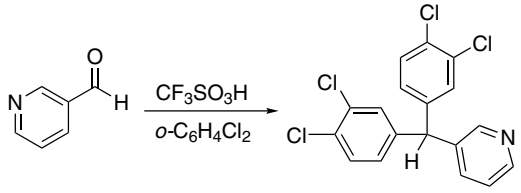
carboxonium ions can show greatly increased electrophilic reactivities and condensation is possible with deactivated arenes. Although no mechanism was proposed in the acid-catalyzed reactions of pyrazolecarboxaldehydes (Eq. 1, **1**), the condensations likely involve dicationic intermediates analogous to the diprotonated pyridinecarboxaldehyde (Eq. 3, **2**). We and others have shown in several recent reports that protonated *N*-heterocycles can be part of reactive, dicationic electrophilic systems, and that the protonated *N*-heterocycles enhance the reactivities of adjacent electrophilic centers, like carboxonium ions.[4] Pyrazoles and their derivatives are known to exhibit a variety of biological activities,[5] and consequently, new synthetic routes involving the pyrazole ring-system are widely sought after goals. In this manuscript, we report the superacid-catalyzed hydroxyalkylation reactions of benzene and a series of pyrazolecarboxaldehydes. A general mechanism involving dicationic electrophiles is proposed, and the direct observation of a diprotonated pyrazole-based electrophile is reported from experiments using low temperature ^{13}C NMR. We also report the dicationic, intramolecular cyclization of an olefinic pyrazole in superacid.

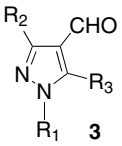
When 1,3-diphenyl-4-pyrazolecarboxaldehyde (**3a**) is reacted with the Brønsted superacid, CF_3SO_3H (triflic acid) and benzene, the condensation product is obtained in good yield (70%, Table 1). Other pyrazolecarboxaldehydes (**3b–g**) condense with benzene in high yields (74–99%) under similar conditions. In a typical procedure, 0.2 g of the pyrazolecarboxaldehyde is dissolved in 1 mL of benzene and 4 mL of CF_3SO_3H is added. After stirring several hours at 25 °C, the mixture is quenched with ice, partitioned between aqueous NaOH and $CHCl_3$, and washed with brine solution. Concentration of the resulting solution then gives product (>90% purity), which can be further purified by recrystallization (benzene:hexane). Although the procedure has not been optimized, condensation of **3f** (R_1 = Ph, R_2 = CH_3, R_3 = Cl) with benzene can be accomplished with as little as 5 equiv (0.3 mL) of triflic acid. With the use of 100% CF_3CO_2H (100 equiv), **3f** does not condense with benzene, but with 98% H_2SO_4, there is partial conversion to the condensation product **3f** (ca. 30% at 25 °C). Aldehyde **3f** is largely unreactive to *o*-dichlorobenzene in excess CF_3SO_3H at 25 °C. In contrast, 3-pyridinecarboxaldehyde gives the condensation product in greater than 87% yield under similar conditions (Eq. 4).[4a]



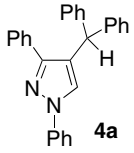
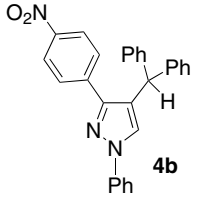
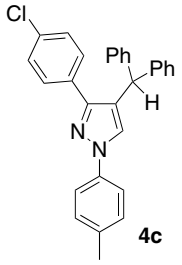
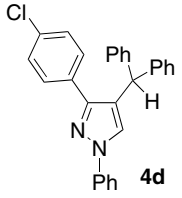
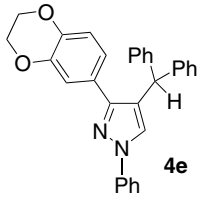
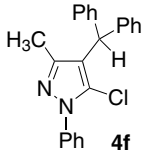
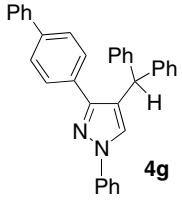
(4)

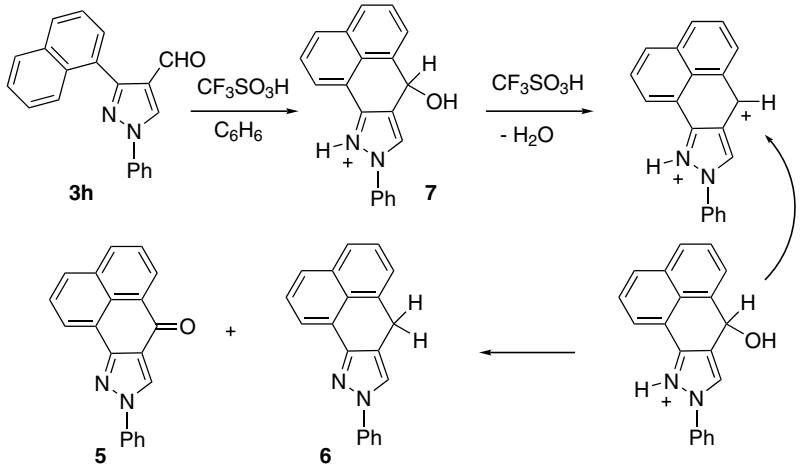
Appropriately substituted pyrazoles can also undergo intramolecular Friedel–Crafts-type reactions. For example, the naphthyl-substituted pyrazole (**3h**) gives two products (**5** and **6**) in roughly equimolar amounts (Scheme 1). These products are consistent with a cyclization reaction to form the alcohol (**7**), which disproportionates to the ketone and methylene-bridged products (**5** and **6**). Even in the presence of benzene, the intramolecular reaction occurs exclusively, and consequently, no hydroxyalkylation product is observed. Following

Table 1. Products and yields from the reactions of pyrazolecarboxaldehydes (**3**) with CF_3SO_3H and C_6H_6

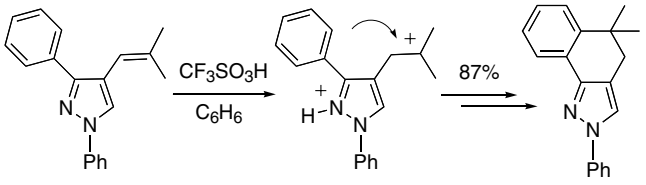


3

Products	Isolated yields (%)
 **4a**	70
 **4b**	99
 **4c**	81
 **4d**	74
 **4e**	99
 **4f**	97
 **4g**	96



Scheme 1.

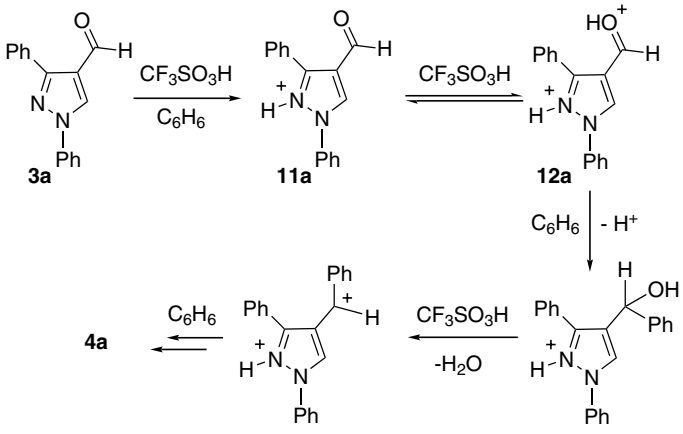


(5)

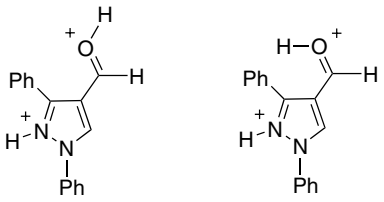
column chromatography, compound **5** is isolated in 38% yield. The olefinic pyrazole **8** gives compound **10** in good yield (Eq. 5) as the only major product upon reaction with CF_3SO_3H (even in the presence of benzene). The cyclization product likely arises from the dicationic intermediate **9**. As expected, protonation of the olefinic site occurs regioselectively to give the 3° carbocation, with the maximum possible separation of the two charge centers.

In the reactions of pyrazolecarboxaldehydes **3a**–**g**, we propose a general mechanism involving reactive, dicationic intermediates (Scheme 2). The pK_a of the pyrazole nitrogen (N-2) has been estimated to be 2.5,[6] so the chemistry begins with protonation of the nitrogen to give the monocation (**11a**). Subsequent protonation of the carbonyl group then gives the dicationic intermediate (**12a**), which is sufficiently electrophilic to react with benzene. With the reaction of a second benzene, this leads to the hydroxyalkylation product (**4a**).

Further evidence for the involvement of the dication intermediates (**12a**–**g**) is obtained from low temperature ^{13}C NMR studies. When pyrazolecarboxaldehyde **3a** is dissolved in a solution of FSO_3H–SbF_5–SO_2ClF (1:1:1) at −80 °C, a ^{13}C NMR spectrum is obtained which is consistent with the formation of dications **12a**-*cis* and **12a**-*trans* (Fig. 1). The ^{13}C NMR spectrum shows a mixture of two protonated species, one major component (ca. 70%) and one minor component (ca. 30%). Protonated aldehydes are known to form stereoisomeric mixtures in superacids at low temperatures.[7] The resonances at 197.0 and 195.6 are assigned to the carboxonium carbons of **12a**-*cis* and **12a**-*trans*. Although it is not presently clear which isomer is the major component of the mixture, previous studies of protonated aldehydes have found that the *trans* isomers are generally favored.[8]



Scheme 2.



^{13}C NMR Signals (125 MHz)

Major isomer:	197.0, 160.9, 140.7, 135.9, 133.5, 131.2, 130.5, 130.3, 129.3, 122.0, 118.5, 114.3
Minor isomer:	195.6, 156.8, 147.3, 135.9, 133.4,131.2, 130.6, 130.4, 129.3, 122.3, 119.2, 113.3

Figure 1. ^{13}C NMR data for compound **3a** in FSO_3–SbF_5–SO_2ClF at −80 °C, and the structures of the ionized products.

While benzaldehyde has been shown to condense with benzene in superacidic solutions, it has been proposed by two research groups that these reactions involve diprotonated, superelectrophilic intermediates arising from benzaldehyde.[8] Clear evidence was presented to show that monoprotonated benzaldehyde (the carboxonium ion) is not sufficiently electrophilic to react with benzene. However, the carboxonium ion arising from the pyrazolecarboxaldehydes (**3a**–**g**) is a strong enough electrophile to react and condense with benzene in good yields. This suggests that protonated pyrazole rings can enhance the electrophilic reactivities of adjacent electrophilic sites, like the carboxonium ion in dications **12a**–**g**. When the reactivity of pyrazole **3f** is compared to 3-pyridinecarboxaldehyde, the 3-pyridinecarboxaldehyde is found to condense with deactivated arenes while compound **3f** does not. Thus, it appears that the pyridinium ring is superior to the protonated pyrazole ring in its activation of the adjacent carboxonium ion.

In conclusion, pyrazolecarboxaldehydes are found to condense with benzene in good yields using the Brønsted superacid, CF_3SO_3H (triflic acid).[9] Appropriately substituted pyrazoles can also undergo superacid-catalyzed, cyclization reactions. It is proposed that these reactions occur via dicationic electrophilic intermediates.

Acknowledgements

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9. Analytical data for new compounds: **4a**: mp 166–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$), 5.63 (s, 1H), 7.25–7.38 (m, 14H), 7.46 (t, J = 4.8 Hz, 2H), 7.53 (s, 1H), 7.62 (dd, J = 3.0, 1.2 Hz, 2H), 7.74 (d, J = 4.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), 47.4, 118.8, 124.5, 126.2, 126.5, 127.9, 128.2, 128.4, 128.5, 128.9, 133.1, 133.2, 140.0, 144.1, 151.4; HRMS (EI^+) calcd $C_{28}H_{22}N_2$: 386.178299. Found: 386.178762. **4b**: mp 173–176 °C; ^{1}H NMR (500 MHz, $CDCl_3$), 5.62 (s, 1H), 7.20–7.62 (m, 13H), 7.72 (d, J = 5.1 Hz, 2H), 7.81 (d, J = 4.8 Hz, 2H), 7.99 (dd, J = 4.8 Hz, 2H), 8.18 (d, J = 4.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), 47.7, 126.8, 126.9, 127.7, 128.3, 128.4, 128.7, 128.8, 129.3, 129.4, 133.2, 139.7, 139.8, 143.3, 148.7; HRMS (EI^+) calcd $C_{28}H_{21}N_3O_2$: 431.163377; Found: 431.163280. **4c**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 2.40 (s, 3H), 5.55 (s, 1H), 7.22–7.35 (m, 14H), 7.44 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ, ppm: 20.9, 47.5, 118.8, 124.2, 126.6, 128.5, 128.6, 128.9, 129.4, 129.8, 131.8, 133.7, 136.2, 137.7, 143.9, 149.8. MS *m*/*z* (EI): 434.2 (M+), 357.1. HRMS (DEI): Calcd for $C_{29}H_{23}ClN_2$: 434.154977. Found: 434.154804. **4d**: mp 147–150 °C; ^{1}H NMR (500 MHz, $CDCl_3$), 5.61 (s, 1H), 7.27–7.48 (m, 15H), 7.54 (s, 1H), 7.60 (d, J = 3.3 Hz, 2H), 7.75 (d, J = 3.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$), 47.6, 118.8, 124.6, 126.4, 126.7, 128.6, 128.6, 128.9, 129.4, 131.8, 133.8; HRMS (EI^+) calcd $C_{28}H_{21}ClN_2$: 420.139110. Found: 420.139327. **4e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 4.27 (s, 4H), 5.62 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 7.19–7.49 (m, 15H), 7.72 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ, ppm: 47.4, 64.3, 64.5, 117.1, 118.7, 121.5, 124.3, 126.0, 126.5, 126.7, 127.7, 128.2, 128.5, 128.9, 129.3, 134.6, 140.0, 143.4, 143.5, 144.1. MS *m*/*z* (EI): 444.2. HRMS (DEI): Calcd for $C_{30}H_{24}N_2O_2$: 444.183778. Found: 444.183081. **4f**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 2.06 (s, 3H), 5.70 (s, 1H), 7.29–7.53 (m, 13H), 7.66 (d, J = 2.5 Hz, 2H). ^{13}C NMR($CDCl_3$, 125 MHz) δ, ppm: 14.1, 46.7, 119.4, 124.9, 125.8, 126.7, 127.9, 128.5, 129.0, 129.2, 138.6, 141.9, 149.1. MS *m*/*z* (EI): 358.86 (M+), 323, 281. **4g**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 5.77 (s, 1H), 7.31–7.37 (m, 7H), 7.39–7.45 (m, 5H), 7.47–7.54 (m, 4H), 7.61 (s, 1H), 7.71–7.73 (m, 4H), 7.80–7.83 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ, ppm: 47.6, 124.7, 126.3, 126.7, 127.1, 127.2, 127.4, 128.5, 128.6, 128.7, 128.9, 129.1, 129.5, 140.1, 140.6, 140.9, 144.26, 151.1. **10**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 1.38 (s, 6H), 2.76 (s, 1H), 7.29 (s, 1H), 7.34–7.50 (m, 5H), 7.75–7.80 (m, 3H), 8.08 (s, 1H). ^{13}C

NMR ($CDCl_3$, 125 MHz) δ, ppm: 29.3, 34.6, 35.6, 117.7, 118.7, 123.0, 124.0, 124.8, 125.8, 126.6, 128.1, 128.4, 129.4, 140.5, 145.2, 149.5. MS *m*/*z* (EI): 274 (M+), 259, 156. HRMS (DEI): Calcd for $C_{19}H_{18}N_2$: 274.146999. Found: 274.147002. **5**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 7.47 (m, 1H), 7.59 (t, J = 8.5 Hz, 2H), 7.74 (t, J = 7.3 Hz, 1H), 7.79 (t, J = 7.3 Hz, 1H), 7.92 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.0 Hz, 1H), 8.24 (d, J = 8.0 Hz, 1H), 8.63 (d, J = 7.2 Hz, 1H), 8.73 (s, 1H), 8.76 (d, J = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ, ppm: 120.1, 120.5, 123.2, 124.1, 126.3, 126.5, 127.7, 128.0, 128.6, 139.6, 129.7, 130.0, 130.5, 133.2, 135.0, 139.6, 152.3, 180.5. MS *m*/*z* (EI): 296 (M+), 282. **6**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ, ppm: 4.49 (s, 2H), 7.29–7.85 (m, 11H), 8.22 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ, ppm: 26.3, 116.5, 118.3, 119.0, 124.3, 125.7, 126.0, 126.0, 126.2, 127.8, 129.2, 129.4, 129.6, 129.6, 132.5, 134.2, 140.4, 148.3. MS *m*/*z* (EI): 282 (M+), 281.