Electrophilic Chemistry of Biologically Important α-Ketoacids

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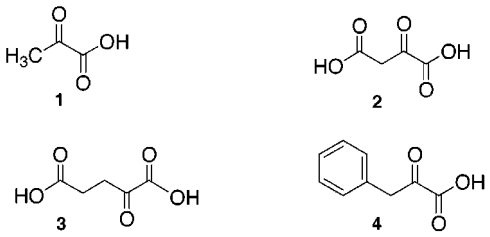
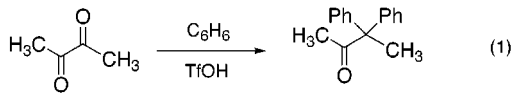
Introduction

The α-ketoacids **1**−**4** and their deprotonated anions play central roles in a number of biochemical processes.[1−4] Despite the importance of the α-ketoacids, little work has been done to evaluate these compounds in their reactivities toward weak nucleophiles such as aromatic compounds. Recently, there has been a considerable amount



of interest in the generation of strong electrophiles from 1,2-dicarbonyl systems and the ability of these electrophiles to react with aromatic compounds. Shudo and Ohwada showed that 1,2-diketones formed highly reactive, or superelectrophilic intermediates in trifluoromethanesulfonic acid (CF_3SO_3H, TfOH) which led to condensation reactions with C_6H_6 (eq 1).[5] Similar elec-

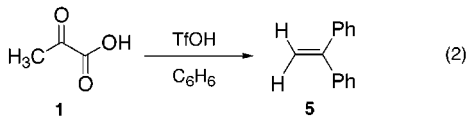


(1)

trophilic activation has been reported with the 1,2-dicarbonyl groups of isatin,[6] parabanic acid,[7] and glyoxylic acid.[8] In superacid solution, there is evidence that the 1,2-dicarbonyl groups are diprotonated and that these diprotonated intermediates exhibit superelectrophilic reactivity.[5−7] The concept of superelectrophilic activation was first proposed by Olah when an enhanced reactivity was observed with nitronium salts in superacid.[9] It was proposed that protosolvation of the nitronium cation generates the dication, which exhibits superelectrophilic chemistry.[10] Given the general reactivity of 1,2-dicarbonyl groups in superacids, it seemed plausible to us that the α-ketoacids might also exhibit superelectrophilic reactivity. In this paper, we report our studies of the electrophilic chemistry of pyruvic acid (**1**), α-ketosuccinic acid (**2**), α-ketoglutaric acid (**3**), and phenylpyruvic acid (**4**). We describe several condensation reactions involving these α-ketoacids and propose mechanisms that invoke superelectrophilic activation.

Results and Discussion

When pyruvic acid (**1**) is reacted with benzene in TfOH, 1,1-diphenylethylene (**5**) is formed as the major product (eq 2). Previous studies of 1,2-dicarbonyl compounds have

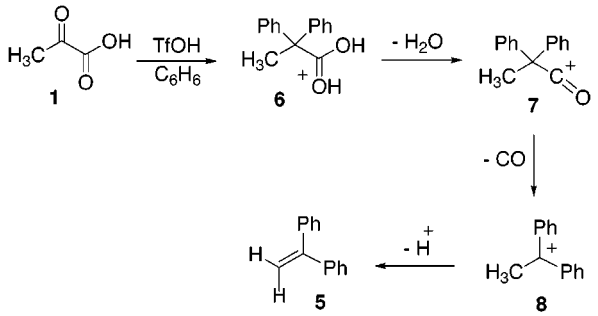


(2)

indicated that superacid-catalyzed reactions with benzene often lead to condensation reactions giving a *gem*-diphenyl group (eq 1).[5−7] The formation of **5** from pyruvic acid (**1**) suggests that a *gem*-diphenyl group is formed but that the intermediate product undergoes a dehydrative-decarbonylation.

On the basis of these considerations, a mechanism is proposed for the conversion of **1** to **5** in TfOH (Scheme 1). The first step involves a condensation reaction to

Scheme 1



produce **6**. Like other 1,2-dicarbonyl systems, both carbonyl groups in **1** may be protonated to initiate the electrophilic attack on benzene. Decarbonylation[11] proceeds through the acyl cation **7,** and loss of carbon monoxide is facile due to the stability of cation **8**. Product

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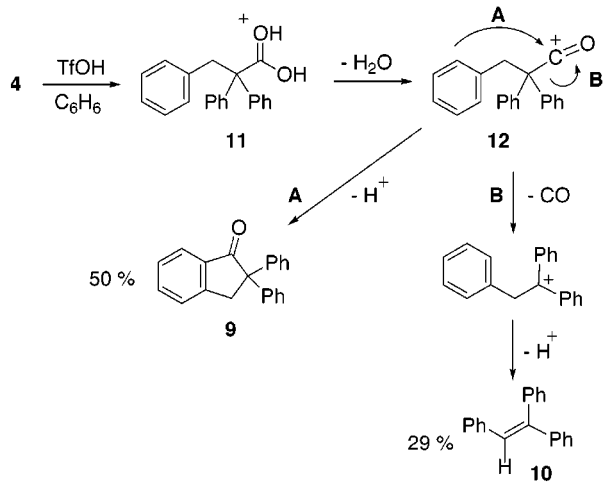
5 is formed upon aqueous workup of the reaction. A small amount of 1,1-diphenylethanol can also be detected in the product mix by GCMS. In accord with the proposed mechanism, 2,2-diphenylpropionic acid also reacts with TfOH and C_6H_6 to give **5** as the only major product.

Phenylpyruvic acid (**4**) reacts with benzene in TfOH to give the condensation products **9** and **10** in 50% and 29% yields, respectively. As described in Scheme 2, **4**

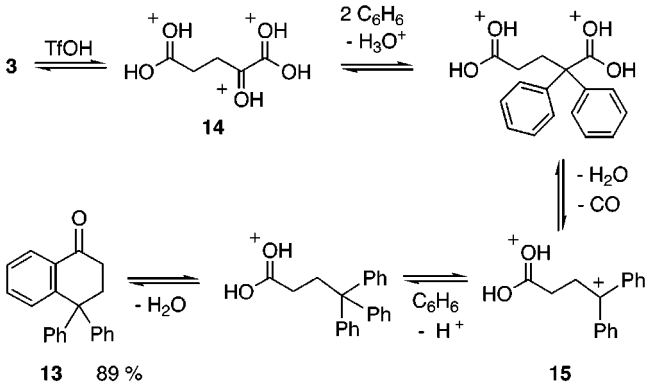
Scheme 2



condenses with two benzenes as an initial reaction step to give **11**, and this is followed by loss of water to generate the acyl cation **12**. Cation **12** may then react according to pathway **A** to give **9** or react by pathway **B** to lose CO and give **10**. Compound **9** is formed as the major product, which indicates that the cyclization occurs more rapidly than loss of CO. Like other 1,2-dicarbonyl systems, phenylpyruvic acid (**4**) generates strong electrophilic intermediates upon solvation in superacid.

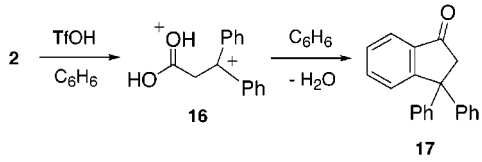
When α-ketoglutaric acid (**3**) is reacted with C_6H_6 in TfOH, tetralone derivative **13** is formed in 89% yield as the only major product (Scheme 3). The structure of **13**

Scheme 3



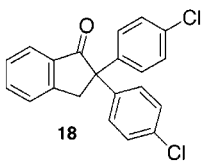
was established by NMR analysis and confirmed by the X-ray crystal structure.[12] The condensation with benzene is consistent with the formation of a diprotonated or triprotonated (**14**) superelectrophilic intermediate. Based in part on an earlier study of the Friedel−Crafts chemistry of β-phenylcinnamic acid,[13] it is proposed that a dehydrative-decarbonylation gives the resonance-stabilized dication (**15**) and reaction with a third benzene is followed by cyclization to give product **13**.

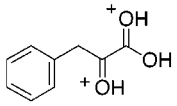
The electrophilic chemistry of α-ketosuccinic acid (**2**) was also examined. When **2** is reacted with C_6H_6 in TfOH, **17** is formed as the major product in 90% yield (eq 3).



Similar to the conversion of **3** to **13**, condensation at the ketone group of **2** is followed by a dehydrative-decarbonylation to give the dication **16**, and reaction of **16** with a third benzene is followed by a cyclization to provide **17**.[13]

Compounds **1**−**4** were also reacted with benzene in H_2SO_4, and none of the products (**5**, **9** and **10**, **13**, and **17**, respectively) were formed. Reactions of **1**−**4** with H_2SO_4 and benzene gave complex product mixtures. The contrasting chemistry in superacid (TfOH) and strong acid (H_2SO_4) is seen in the reaction of **4** with chlorobenzene. Phenylpyruvic acid (**4**) does not react with chlorobenzene in H_2SO_4; however, **4** gives the expected product (**18**) in TfOH. Since TfOH is up to 10^2 times stronger acid than H_2SO_4,[14] and carboxylate groups are extensively protonated in H_2SO_4,[15] these results suggest that an equilibrium is established in TfOH between the mono- and diprotonated phenylpyruvic acid (**19**).





In the work described above, the α-ketoacids **1**−**4** are reacted with benzene in superacidic TfOH and two characteristic types of reaction steps are observed. In all cases, the electrophilic condensations occur at the ketone to give products or intermediates having the *gem*-diphenyl group. Carbonyl condensation with benzene has often been an indication of dicationic intermediates.[16] The other characteristic reaction step involves the dehydrative-decarbonylations of the acid groups from the condensation products. Although it is not certain if dications are involved in the dehydrative-decarbonylations, solvation of the product water molecule may be an important driving force.

(12) Crystal data for **13**: $C_{22}H_{18}O$, MW 298.36, colorless irregular trapezoid, triclinic, space group *P*-1 (No. 2), a = 9.2401(10) Å, b = 9.4511(10) Å, c = 11.247(12) Å, α = 86.117(2)°, β = 69.114(2)°, γ = 61.266(2)°, U 798.19(15) Å^3, Z = 2, D_c = 1.241 g/cm^3, F(000) 316, μ (Mo Kα) 0.075 mm^{-1}, graphite-monochromated Mo Kα λ =0.710 73 Å, T = 293(2) K. Final discrepance factors: $R1$ = 0.0443 and $wR2$ = 0.0734 for 2545 reflections with $F_o > 4\sigma_F$.

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Experimental Section

^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz. High-resolution mass spectra were recorded at the Southern California Mass Spectrometry Facility, University of California, Riverside. Triflic acid was obtained from 3M and distilled prior to use. Benzene was dried over Na. Pyruvic acid, phenylpyruvic acid, 2,2-diphenylpropionic acid, and α-ketoglutaric acid were purchased from Aldrich; α-succinic acid was purchased from Lancaster. Reactions were done under a dry, N_2 atmosphere.

Reaction of Pyruvic Acid (1). In a vented flask, 0.325 g (3.7 mmol) of pyruvic acid (**1**) was suspended in 1 mL of C_6H_6, and 4 mL of TfOH was added. The mixture was stirred for 12 h at 25 °C and then poured over ca. 20 g of ice. The resulting solution was extracted with $CHCl_3$, and the organic extracts were washed with H_2O followed by brine and dried over $MgSO_4$. Concentration in vacuo gave a white solid (**1,1-diphenylethene**, **5**) that was further purfied by flash chromatography (9:1 hexanes/ether) to give 0.353 g (2.0 mmol, 60%).

Reaction of Phenylpyruvic Acid (4). Using a procedure similar to that of pyruvic acid, 0.146 g (0.88 mmol) of phenylpyruvic acid was reacted with 4 mL of TfOH and 2 mL of C_6H_6. Isolation of the crude product mixture was followed by column chromatography (4:1 hexanes/ether), which gave **1,2,2-triphenylethene** (**10**) 0.066 g (0.26 mmol, 29%) and **2,2-diphenyl-1-indanone** (**9**): 0.125 g (0.44 mmol, 50%); mp 92−94 °C (lit.[17] mp 96−97 °C); ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 2H), 7.14 (m, 1H), 7.25−7.44 (m, 10H), 7.53 (d, J = 7.2 Hz, 1H), 7.65 (t, J = 7.2 Hz, 1H), 7.85 (d, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.6, 62.6, 125.0, 125.7, 126.6, 127.1, 127.8, 128.0, 128.3, 135.2, 143.3, 151.9, 205.1; GCMS (M^+), 284; HRMS $C_{21}H_{16}O$ m/z calcd 284.1201, found 284.1203.

Using 0.335 g (2.0 mmol) of phenylpyruvic acid, 4 mL of TfOH, and 2 mL of C_6H_5Cl, **2,2-bis(4-chlorophenyl)-1-indanone** (**18**) was isolated (0.25 g, 0.71 mmol, 35%; 4:1 hexane/ether); mp 117−120 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 2H), 7.16 (d, J = 8.7 Hz, 4H), 7.23 (d, J = 8.8 Hz, 4H), 7.41 (m, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.66 (m, 1H), 7.78 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 44.4, 61.7, 125.3, 125.9, 128.2, 128.6, 129.4, 132.9, 135.2, 135.7, 141.5, 151.4, 204.4; GCMS (M+) 352; HRMS $C_{21}H_{14}OCl_2$ m/z calcd 352.0422, found 352.0439.

Reaction of α-Ketoglutaric Acid (3). Using a procedure similar to that for pyruvic acid, 0.72 g (4.9 mmol) of α-ketoglutaric acid was combined with 15 mL of TfOH and 2 mL of C_6H_6. Isolation of 1.41 g (4.3 mmol, 89%) of the crude product was followed by recrystallization from C_6H_6 to give 0.67 g (2.2 mmol, 46%) of **4,4-diphenyl-1-tetralone** (**13**): mp 188−189 °C (lit.[18] mp 189−190 °C); ^{1}H NMR ($CDCl_3$) δ 2.31 (t, J = 6.3 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H), 6.53 (m, 1H), 6.81 (m, 4H), 7.04−7.11 (m, 6H), 7.18 (m, 2H), 7.93 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 35.7, 36.9, 53.2, 126.8, 127.2, 127.5, 128.2, 129.2, 130.9, 132.8, 133.1, 145.7, 149.6, 197.8. GCMS (M^+), 298; HRMS $C_{22}H_{18}O$ m/z calcd 298.1358, found 298.1357.

Reaction of α-Ketosuccinic Acid (2). Using a procedure similar to that for pyruvic acid, 1.01 g (7.6 mmol) of α-ketosuccinic acid was combined with 10 mL of TfOH and 2 mL of C_6H_6. Isolation of 2.10 g (6.8 mmol, 90%) of the crude product was followed by column chromatography (4:1 hexane/ether) to give 1.07 g (3.88 mmol, 51%) of **3,3-diphenyl-1-indanone** (**17**): mp 128−130 °C (lit.[19] mp 130−131 °C); ^{1}H NMR ($CDCl_3$) δ 3.55 (s, 2H), 7.21−7.37 (m, 10H), 7.42−7.50 (m, 2H), 7.64 (dt, J = 1.2, 7.5 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 56.0, 65.8, 123.6, 126.5, 127.9, 128.0, 128.4, 134.7, 135.7, 146.7, 159.8, 204.9; GCMS (M+), 284. HRMS $C_{21}H_{16}O$ m/z calcd 284.1201, found 284.1203.

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Supporting Information Available: NMR spectra for compounds **9**, **13**, **17**, and **18**; X-ray structure and data of compound **13** including a list of atomic coordinates, bond lengths, and bond angles. This material is available free of charge via the Internet at http:pubs.acs.org.

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