Superacid-Promoted Cyclodehydration Leading to the Imidazo[2,1-*a*]isoquinoline Ring System

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A series of heterocycle-substituted acetophenones were prepared and reacted with the *Brønsted* superacid CF_3SO_3H (triflic acid = trifluoromethanesulfonic acid). Cyclodehydration provided aryl-substituted imidazo[2,1-*a*]isoquinolines and related products (28–85%, seven examples). A mechanism is proposed involving dicationic intermediates.

Introduction. – Functionalized N-heterocycles are important compounds for the development of new medicinal agents. Heterocycles with bridgehead N-atoms have been of particular interest. For example, the imidazo[1,2-a]pyridine ring system has a wide spectrum of biological activity, and it is found in a number of commercial drugs [1]. These types of heterocyclic systems have also been used in various material-science applications, in particular as fluorophores [2]. The imidazo[1,2-a]pyridine and the related pyrido[1,2-a]benzimidazole ring systems have been prepared by condensations with aminopyridines [3], transition metal-catalyzed oxidative bond-formation [4], nucleophilic ring-forming reactions [5], and other routes [6]. Some of the previously reported methodologies utilize expensive or highly toxic reagents, so there is need for improved synthetic methods. In the following study, we describe an approach to azapolycyclic aromatic systems with a bridgehead N-atom, *i.e.*, imidazo[2,1-a]isoquino-lines. Our strategy involves the use of a superacid-promoted cyclodehydration reaction.

Results and Discussion. – The synthesis begins with the preparation of heterocyclic ketones suitable for cyclodehydration reactions. Thus, 2-phenyl-1*H*-imidazole (1) and 2-bromo-3',4'-dichloroacetophenone (2) provided the functionalized imidazole 3 in good yield by reaction with Ag_2CO_3 (*Scheme 1*). With the Ph substitutent, the ketone was properly situated to generate a new six-membered ring *via* cyclodehydration. A series of heterocyclic ketones, 4-9 (*Table*), were prepared using 2-bromoacetophe-



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Table. Cyclodehydration Products 10-16 from the Reactions of Ketones 3-9 with CF_3SO_3H



none or related substrates. Two analogous methods, but other reaction conditions, were used to prepare heterocyclic ketones of type **3**: halogenated ketones of type **2** and **1** were treated with K_2CO_3 in DMF or with Et_3N/Bu_4NBr in MeCN [7]. We also attempted the conversion of **1** and **2** to **3** with KOH in DMSO, and with pyridine in dioxane, respectively; however, these methods did not give the desired product.

By the reaction of compounds 3-9 in superacid, the expected imidazo[2,1a]isoquinolines 10-12 were produced (*Table*). For example, compound 3 reacted in CF₃SO₃H at 80° to give heterocycle 10 in 85% yield. Ketones 4 and 5 reacted similarly to give 11 and 12, respectively, and ketones 6-8 also provided the expected cyclodehydration products, *i.e.*, the benzimidazole derivatives 13-15. The conversion of 8 to 15 is somewhat less efficient than the other conversions. This may be the result of a modest deactivating effect involving the Cl-substituent or due to the statistical factor of having one *ortho* position blocked on the aryl group. We also prepared the pyrazole-based ketone 9 and found this to provide the cyclodehydration product, pyrazolo[5,1-*a*]isoquinoline 16.

Acid-catalyzed cyclodehydration involving aldehydes or ketones generally proceeds through the carboxonium ion intermediate formed by C=O protonation. Thus, we propose a mechanism involving diprotonated or dicationic intermediates leading to the condensation products (*Scheme 2*). The initial protonation occurs at the Nheterocyclic ring of **17**, and a second protonation gives the superelectrophilic species **18**. Cyclization occurs at the adjacent Ph substituent leading to ring formation to give **19**. Dehydration would generate the dicationic intermediate **20**, which provides the imidazo[1,2-a]pyridine **10** by deprotonation steps.



The cyclodehydration was also attempted with 1H-tetrazole derivative 21; however, only starting material was found in the product mixture. In this case, multiple protonations at the tetrazole ring may inhibit the cyclodehydration, either preventing C=O protonation or deactivating the Ph ring towards electrophilic attack. The heterocyclic amide 22 and ester 23 were also prepared. Both substances undergo bond cleavage under the reaction conditions to yield 2-phenyl-1H-imidazole. Although the respective carboxonium ions 24 are likely to be formed under the reaction conditions, cyclodehydration does not occur – presumably due to the relative low electrophilic reactivities of the carboxonium ions 24.



Conclusions. – We found that imidazo[2,1-a]isoquinolines, benzimidazo[2,1-a]isoquinolines, and a pyrazolo[5,1-a]isoquinoline may be prepared in fair-to-good yields by superacid-promoted cyclodehydration with heterocyclic ketones. A mechanism is proposed involving diprotonated, superelectrophilic intermediates leading to the aza-polycyclic aromatic compounds.

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Experimental Part

General. Using oven-dried glassware, reactions were performed under Ar. Trifluoromethanesulfonic acid, CF₃SO₃H, was distilled (Ar atmosphere) prior to use. Column chromatography (CC): *ASTM* silica gel 60 (230–400 mesh) using a forced flow of 0.5–1.0 bar. NMR Spectra: *Bruker Avance III* spectrometer, at 300 or 500 (¹H), and 75 or 125 MHz (¹³C); chemical shifts rel. to the solvent peak (CDCl₃ or CD₃OD). GC/MS: *Agilent Technologies 5973N* (electron ionization; EI). HR-MS: Performed at the University of Illinois at Urbana-Champaign, Analytical Services Lab; in *m/z*.

General Procedure A: Synthesis of Heterocyclic Ketones **3**, **4**, **6**, and **8**, and Heterocyclic Amide **22**. The heterocyclic substrate (1.4 mmol), the bromo ketone or amide (1.4 mmol), and Ag_2CO_3 (382 mg, 1.5 mmol) in dry MeCN (10 ml) were heated to reflux for 12 h. The mixture was then partitioned between CHCl₃ and H₂O, and the org. extracts were subsequently washed with brine. The crude product was dried (Na₂SO₄) and concentrated by removal of solvent. CC (hexane/Et₂O) gave the pure product.

General Procedure B: Synthesis of Heterocyclic Ketone **5** and Heterocyclic Ester **23**. Adapting a published procedure [7], the heterocyclic substrate (3.47 mmol), the bromo ketone/ester (4.16 mmol), (benzyl)(triethyl)ammonium bromide (80 mg, 0.3 mmol), and Et₃N (350 mg, 3.47 mmol) in dry MeCN (10 ml) were heated to reflux for 12 h. The mixture was worked up as described above.

General Procedure C: Synthesis of Heterocyclic Ketones 7, 9, and 21. The heterocyclic substrate (2.6 mmol), the bromo ketone (2.6 mmol), and K_2CO_3 (1.4 g, 10.3 mmol) in anh. acetone (10 ml) were heated to reflux for 24 h. The mixture was worked up as described above.

General Procedure D: Cyclodehydration of 10-16. The ketone substrate (1 mmol) was dissolved in neat CF₃SO₃H (3 ml, 34 mmol), and the mixture was stirred for 12 h at 80°. The reaction was quenched by pouring the contents over several grams of ice, and the resulting mixture was then extracted twice with CHCl₃. The org. layer was then washed with H₂O and brine, dried (Na₂SO₄), and concentrated *in vacuo*. CC (hexane/AcOEt) afforded the pure product.

*1-(3,4-Dichlorophenyl)-2-(2-phenyl-1*H-*imidazol-1-yl)ethanone* (**3**). *2-Phenylimidazole* (**1**; 498 mg, 3.5 mmol) and *2-bromo-3',4'-dichloroacetophenone* (**2**; 1.3 g, 3.5 mmol) afforded **3** in 76% yield (878 mg, 2.6 mmol). Brown oil. ¹H-NMR (300 MHz, CDCl₃): 5.38 (*s*, 2 H); 7.00 (*s*, 1 H); 7.20 (*s*, 1 H); 7.41 – 7.45 (*m*, 5 H); 7.57 (*d*, J = 8.1, 1 H); 7.71 (*dd*, J = 8.4, 1.8, 1 H); 7.97(*d*, J = 1.8, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 52.8; 121.9; 126.9; 128.6; 128.8; 129.4; 129.7; 130.0; 131.2; 133.5; 134.0; 139.2; 148.4; 190.4. HR-MS: 330.0332 (C₁₇H₁₂Cl₂N₂O⁺; calc. 331.1960).

6-(3,4-Dichlorophenyl)imidazo[2,1-a]isoquinoline (10). From **3** (389 mg, 1.3 mmol). Yield: 85% (345 mg, 1.1 mmol). Dark solid. M.p. 124–125°. ¹H-NMR (300 MHz, CDCl₃): 7.31 (*dd*, J = 8.2, 2, 1 H); 7.53–7.63 (*m*, 7 H); 7.86 (*s*, 1 H); 8.70 (*d*, J = 7.9, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 114.3; 122.2; 123.6; 124.2; 125.2; 128.4; 128.5; 129.5; 130.6; 131.6; 131.9; 132.5; 132.9; 136.2; 142.6; two peaks are missing due to the magnetic *equivalence* of 300-MHz NMR. HR-MS: 312.0219 (C₁₇H₁₀Cl₂N⁺₂; calc. 312.0221).

6-Phenylimidazo[2,1-a]isoquinoline (11). Known compound; see [8].

6-[1,1'-Biphenyl-4-yl]imidazo[2,1-a]isoquinoline (12). From 5 (101 mg, 0.3 mmol). Yield: 48% (0.14 mmol). Orange oil. ¹H-NMR (300 MHz, CDCl₃): 6.60 (*dd*, J = 7.8, 1, 1 H); 6.90 (*d*, J = 0.9, 1 H); 7.01 (*d*, J = 7.6, 2 H); 7.07 (*dt*, J = 7.7, 1.2, 1 H); 7.23 (*t*, J = 7.5, 2 H); 7.29 (br. *s*, 1 H); 7.36 (*dt*, J = 7.6, 1, 1 H); 7.44 (*t*, J = 4, 2 H); 7.47 - 7.76 (*m*, 2 H); 7.81 (*d*, J = 8, 2 H); 8.24 (*d*, J = 7.6, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 119.9; 120.4; 124.2; 124.4; 125.7; 127.2; 128.1; 128.3; 128.6; 128.9; 129.0; 129.4; 136.8; 140.1; 147.7; four peaks are missing due to the magnetic *equivalence* of 300 MHz NMR. LR-MS: 320 (*M*⁺), 304, 291, 252, 160. HR-MS: 320.1321 (C₂₃H₁₆N₂⁺; calc. 320.1313).

6-Phenylbenzimidazo[2,1-a]isoquinoline (**13**). From **6** (140 mg, 0.371 mmol). Yield: 61% (132.7 mg, 0.367 mmol). Brown solid. M.p. 152–156°. ¹H-NMR (300 MHz, CDCl₃): 7.38–7.51 (*m*, 1 H); 7.51–7.80 (*m*, 10 H); 8.04 (*d*, J = 8.1, 1 H); 8.09 (*s*, 1 H); 8.94 (*d*, J = 7.5, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 109.8; 119.9; 120.3; 121.9; 123.5; 124.7; 125.3; 125.9; 128.1; 128.2; 129.0; 129.4; 129.9; 130.1; 130.3; 131.5; 136.3; 143.8; 146.9. MS: 294 (M^+), 264, 190, 147. HR-MS: 294.1153 ($C_{21}H_{14}N_2^+$; calc. 294.1157).

6-(4-Chlorophenyl)benzimidazo[2,1-a]isoquinoline (14). From 7 (329 mg, 0.95 mmol). Yield: 60% (187 mg, 0.57 mmol). Light-brown solid. M.p. 177–178°. ¹H-NMR (300 MHz, CDCl₃): 7.46–7.48 (*m*, 1 H); 7.49–7.54 (*m*, 5 H); 7.60–7.70 (*m*, 3 H); 7.78 (*d*, J = 8.1, 1 H); 8.01 (*d*, J = 8.1, 1 H); 8.01 (*s*, 1 H); 8.89 (*d*, J = 7.8, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 109.8; 119.9; 120.4; 122.0; 123.4 (*d*; J = 6.7 Hz) 124.9;

125.3; 125.6; 128.3; 129.0; 130.0; 130.1; 131.2; 131.6; 134.3; 134.7; 143.7; 146.8. MS: 330/328 (M^+), 293, 292, 190, 146. HR-MS: 328.0764 ($C_{21}H_{13}CIN_2^+$; calc. 328.0767).

10-Chloro-6-phenylbenzimidazo[2,1-a]isoquinoline (**15**). From **8** (140 mg, 0.371 mmol). Yield: 28% (132.7 mg, 0.367 mmol). Pale-yellow semisolid. ¹H-NMR (300 MHz, CDCl₃): 7.46–7.64 (*m*, 9 H); 7.80 (*dd*, *J* = 17, 7.8, 2 H); 8.18 (*m*, 2 H). ¹³C-NMR (75 MHz, CDCl₃): 109.5; 121.0; 121.3; 122.7; 124.3; 124.8 (*d*, *J* = 9.7); 128.4; 128.8; 129.16; 129.23; 130.4; 130.9; 132.8; 134.3; 136.3; 143.6; 144.7. MS: 330/328 (*M*⁺), 293, 292, 190, 146. HR-MS: 328.0764 ($C_{21}H_{13}ClN_2^+$; calc. 328.0767).

2,6-Diphenylpyrazolo[5,1-a]isoquinoline (**16**). From **9** (140 mg, 0.371 mmol). Yield: 51% (132.7 mg, 0.367 mmol). Light-brown oil. ¹H-NMR (300 MHz, CDCl₃): 7.34 (d, J = 0.6, 1 H); 7.34 – 7.48 (m, 2 H); 7.50 – 7.78 (m, 8 H); 7.76 (d, J = 7.8, 1 H); 8.06 – 8.11 (m, 2 H); 8.20 (dd, J = 8.1, 1.2, 1 H); 8.29 (s, 1 H). ¹³C-NMR (75 MHz, CDCl₃): 94.6; 112.5; 124.0; 125.3; 126.0; 126.4; 127.7; 127.9; 128.0; 128.2; 128.4; 128.7; 128.8; 128.9; 130.2; 133.2; 136.4; 139.3; 153.1. MS: 320 (M^+), 243, 216, 189, 160. HR-MS: 320.1307 ($C_{23}H_{16}N_2^+$; calc. 320.1313).

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