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 aza-polycyclic aromatic systems with a bridgehead N-atom, *i.e.*, imidazo[2,1-*a*]isoquinolines. 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-

Scheme 1

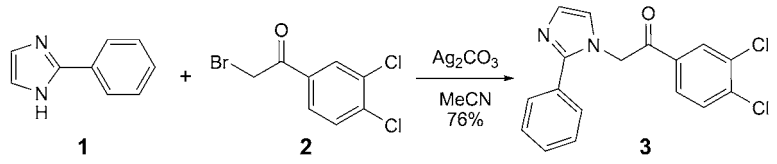
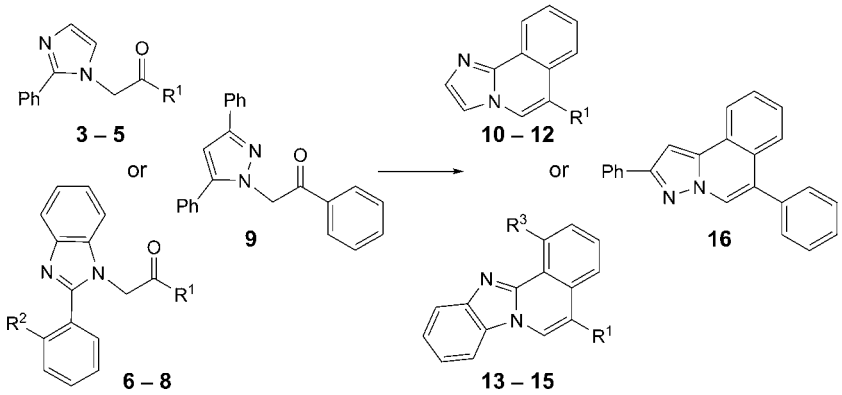


Table. *Cyclodehydration Products* **10**–**16** *from the Reactions of Ketones* **3**–**9** *with* CF_3SO_3H



Starting material	R^1	R^2	Product	Yield [%][a])
3	3,4-Cl_2–C_6H_3		**10**	85
4	Ph		**11**	60
5	C_6H_5–C_6H_4		**12**	48
6	Ph	H	**13**	61
7	4-Cl–C_6H_4	H	**14**	60
8	Ph	Cl	**15**	28
9			**16**	51

[a]) Yield of purified product.

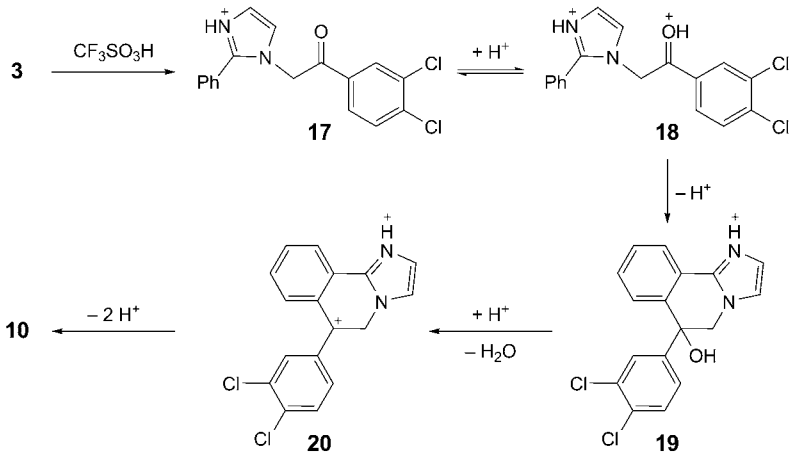
none or related substrates. Two analogous methods, but other reaction conditions, were used to prepare heterocyclic ketones of type **3**: halogenated ketones of type **2** and **1** were treated with K_2CO_3 in DMF or with Et_3N/Bu_4NBr in MeCN [7]. We also attempted the conversion of **1** and **2** 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[2,1-*a*]isoquinolines **10**–**12** were produced (*Table*). For example, compound **3** reacted in CF_3SO_3H 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**.

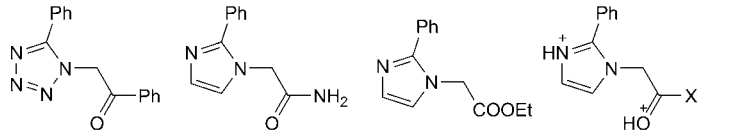
Acid-catalyzed cyclodehydration involving aldehydes or ketones generally proceeds through the carboxonium ion intermediate formed by C=O protonation. Thus, we propose a mechanism involving diprotonated or dicationic intermediates leading to the condensation products (*Scheme 2*). The initial protonation occurs at the N-heterocyclic 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.

Scheme 2



The cyclodehydration was also attempted with 1*H*-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-1*H*-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, CF_3SO_3H, 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 (^{1}H), and 75 or 125 MHz (^{13}C); chemical shifts rel. to the solvent peak ($CDCl_3$ or CD_3OD). 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 $CHCl_3$ and H_2O, and the org. extracts were subsequently washed with brine. The crude product was dried (Na_2SO_4) and concentrated by removal of solvent. CC (hexane/Et_2O) 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 Et_3N (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 CF_3SO_3H (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 $CHCl_3$. The org. layer was then washed with H_2O and brine, dried (Na_2SO_4), 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 ($C_{17}H_{12}Cl_2N_2O^+$; 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°. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 ($C_{17}H_{10}Cl_2N_2^+$; 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 ($C_{23}H_{16}N_2^+$; 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°. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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°. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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 ($C_{21}H_{13}ClN_2^+$; 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.46–7.64 (*m*, 9 H); 7.80 (*dd*, *J* = 17, 7.8, 2 H); 8.18 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 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. ^{1}H-NMR (300 MHz, $CDCl_3$): 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). ^{13}C-NMR (75 MHz, $CDCl_3$): 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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