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Reactions of 2-alkylimidazoles and 2-methylbenzimidazoles with 1,3-diacid chlorides. Synthesis of highly functionalized hetero-cycles under mild conditions

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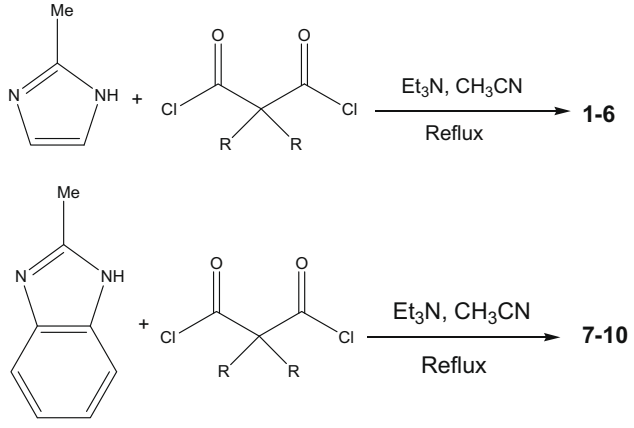
ABSTRACT

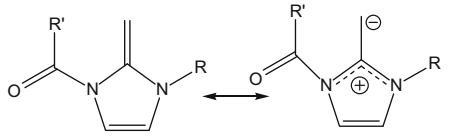
Highly functionalized heterocycles were synthesized in one-pot reactions of 2-alkylimidazoles or 2-methylbenzimidazoles with 1,3-diacid chlorides. Some of the cyclizations proceed through cyclic-*N*,*N*′-ketene acetal intermediates.

Imidazoles and benzimidazoles and their 2-alkyl derivatives react with acid chlorides.[1–13] Surprisingly, few examples of their reactions with diacid chlorides are known. Only the reports of 1H-benzoimidazol-2-yl-diphenylmethanol reacting with diethylmalonyl dichloride, ethanedioyl dichloride, and 1,2-benzenedicarbonyl dichloride to form lactones were found.[14,15] We previously reported a series of 1,3-diacid chloride reactions with both 2-methylimidazoline and 2-methyl-1,4,5,6-tetrahydro pyrimidine, where acyl cyclic ketene-*N*,*N*′-acetals were generated in situ.[16] These further reacted in a tandem pathway to give 1,8-napthyridinetetraones.[16] We thought that analogous cyclizations through cyclic ketene-*N*,*N*′-acetals might occur with 2-methylimidazole and 2-methylbenzimidazole where a C(4)–C(5) double bond is present. However, these substrates are aromatic, unlike 2-methylimidazoline. Thus, formation of a five-membered ring ketene-*N*,*N*′-acetal intermediate with 7π-electrons from 2-methylimidazole could cause the loss of a portion of the aromaticity present in the imidazole.



The two nitrogens in a cyclic ketene-*N*,*N*′-acetal donate electrons to the exocyclic double bond, and make the β-carbon extremely nucleophilic (Scheme 1). Thus, 2-alkylimidazoles or 2-alkylbenzimidazoles might function as tridentate nucleophiles that could give four consecutive attacks on electrophiles through its two nitrogens and the exocyclic β-carbon of the corresponding cyclic ketene-*N*,*N*′-acetal intermediates, if these form (analogous to those observed with 2-methylimidazoline[16]). Ultimately, this would generate highly functionalized heterocycles. Diacid chlorides are bis-electrophiles, known to cyclize with bidentate nucleophiles to give carbocycles and heterocycles.[16–20]

We have now demonstrated that analogous cyclizations can occur (Table 1). 2-Alkylimidazoles (R = methyl, ethyl, and isopropyl) and 2-methylbenzimidazole reacted with diacid chlorides in acetonitrile and triethylamine generating **1–15** whose structures depend on the 1,3-diacid chloride's structure (Tables 1–4). The structures were confirmed by ^{1}H and ^{13}C NMR and FT-IR. Six different product types were produced upon reacting 2-methylimidazole with various 2,2-disubstituted-1,3-diacid chlorides under identical conditions (Table 1). Tandem dicyclization gave **1** when the 2-alkyl substituents of the diacid chloride were ethyls, but only monocyclization to **2** occurred with methyl substituents. This monocyclization was followed by a linear dimerization to **3** over longer reaction times (or on adding more 1,3-diacid chloride). Tandem dicyclization also occurred but was followed by a ring expan-



Scheme 1. Resonance hybrids illustrating the β-carbon's polarization.

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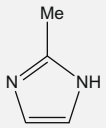
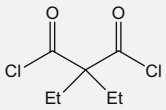
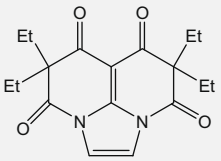
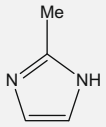
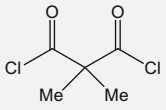
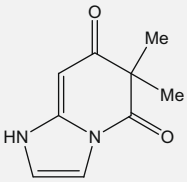
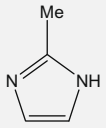
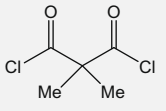
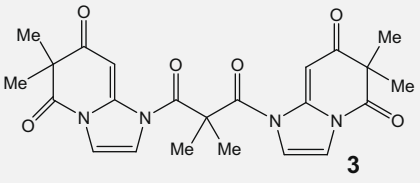
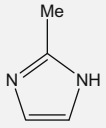
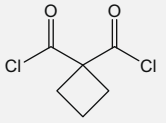
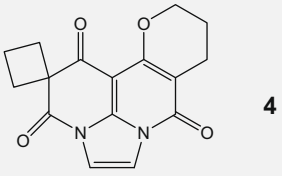
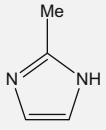
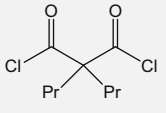
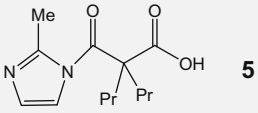
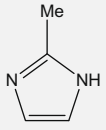
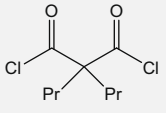
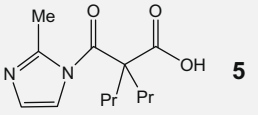
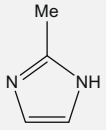
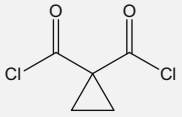
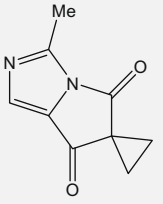
Table 1
Reactions of 2-methylimidazole with 2,2-disubstituted 1,3-diacid chlorides[a]

Substrate	1,3-Diacid chloride	Reflux time (h)	Product	Isolated yield (%)
		3	 **1**	47
		3	 **2**	39
		5	 **3**	51
		3	 **4**	54
		3	 **5**	57
		6	 **5**	70
		3	 **6**	71

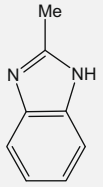
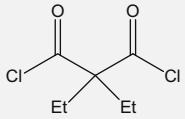
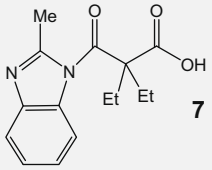
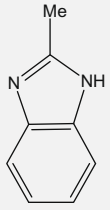
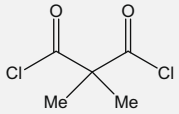
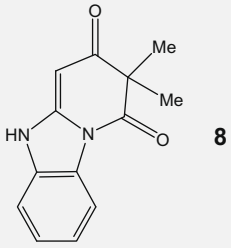
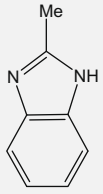
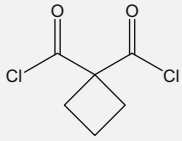
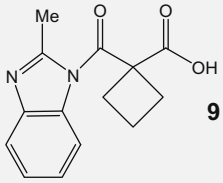
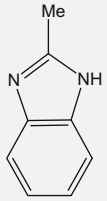
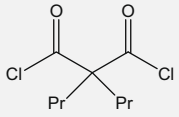
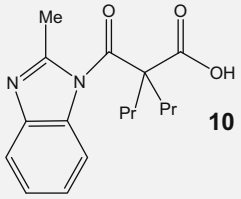
[a] The molar ratio of 2-methylimidazole/l,3-diacid chloride/Et_3N is 1/2.4/6 (2.4 mmol of 2-methylimidazole is used).

sion of only one of the two four-membered rings to produce **4**, when employing cyclobutane-1,1-dicarbonyl dichloride. In contrast, when the dipropylmalonyl dichloride was used, no cyclization occurred and only monoamide **5** formation was detected.

Cyclopropane-1,1-dicarbonyl dichloride was investigated in the anticipation of observing tandem dicyclization analogous to **1**, with the possibility of one or two further ring expansions, analogous to the formation of the fused dihydropyran ring in **4**. Unexpectedly, cyclization occurred instead onto the imidazole ring producing 3′-methylspiro[cyclopropane-1,6′-pyrrolo[1,2-*c*]imidazole-5′,7′-dione **6** (Table 1). The diacid chloride cyclizations observed in forming **1–4** and **6** all appear to proceed through the formation of intermediate cyclic ketene-*N*,*N*′-acetals (Schemes 2 and 3).

When the same types of reactions were explored with 2- methylbenzimidazole, monocyclization occurred only with the dimeth-

Table 2
Reactions of 2-methylbenzimidazole with 2,2-disubstituted-1,3-diacid chlorides[a]

Substrate	1,3-Diacid chloride	Reflux time (h)	Product	Isolated yield (%)
		3	 **7**	67
		3	 **8**	59
		3	 **9**	68
		3	 **10**	73

[a] The molar ratio of 2-methylbenzimidazole/l,3-diacid chloride/Et_3N is 1/2.4/6 (where 1.4 mmol of 2-methylbenzimidazole is used).

ylmalonyl dichloride giving **8** (Table 2). The other diacid chlorides did not generate products containing new rings. Only the monoamides **7**, **9,** and **10** are formed.

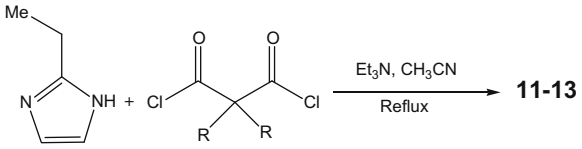
The cyclization pathway onto the imidazole ring to give **6**, exhibited by cyclopropane-1,1-dicarbonyl dichloride, becomes the predominant route when the 2-alkyl group on imidazoles is changed to ethyl or isopropyl. The 2-ethyl (Table 3) and 2-isopropyl (Table 4) imidazoles readily cyclize onto the imidazole ring, generating derivatives **11**, **13**–**15** with two fused five-membered rings.

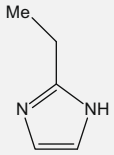
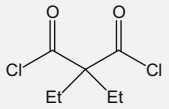
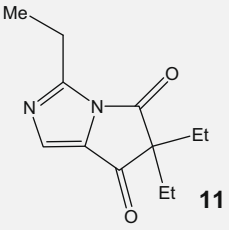
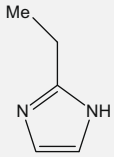
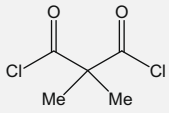
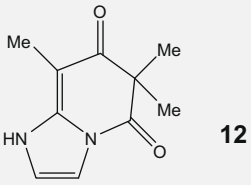
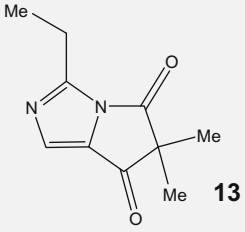
Likely mechanisms for the formation of products **1–4** (Table 1) and **8** (Table 2) are shown in Scheme 2. Initial nucleophilic acyl attack by nitrogen of 2-methylimidazole on a diacid chloride carbonyl carbon generates zwitterionic intermediate **16a**. Ion pair **16b** is formed by the loss of chloride. Reversible proton removal from either the methyl group or nitrogen could occur to give **16c** or its tautomer, respectively. Proton removal by Et_3N from the methyl group generates *N*-acyl cyclic ketene-*N*,*N*′-acetal **16c,** where an intramolecular acyl nucleophilic attack of the exocyclic β-carbon results in another zwitterionic intermediate **16d**. Loss of chloride and subsequent proton removal by Et_3N from **16e** give the monocyclic product **16f** (**2,** where R = CH_3). Proton removal by Et_3N generates ambident anion **16g** which then reacts with an acid chloride to form **16h**. **16h** cyclizes by nucleophilic attack of the exocyclic ketene *N*,*N*′-acetal's carbon. Loss of chloride from **16i** and deprotonation of **16j** finally forms the highly functionalized tricylic product **16k** (**1**, where R = Me). When two molecules of **16g** react with one diacid chloride, **16l** (**3**, where R = Me) is formed.

The cyclizations to form imidazopyrrollodiones are illustrated in Scheme 3. The generation of two fused five-membered rings may be activated by the generation of anion **17c** (Scheme 3). Placement of one or two methyl groups on the exocyclic methylene of the ketene-*N*,*N*′-acetal intermediate **17a** favors cyclization onto the imidazole ring. The variability of these 2-alkylimidazole and 2-methylbenzimidazole reactions with diacid chlorides forming highly functionalized imidazonapthyridinetetraone (**1**), imidazopyridinediones (**2, 8, and 12**) and imidazopyrrolodiones (**6, 11, 13, 14, and 15**) at identical conditions is remarkable. Tandem or single cyclizations at the exocyclic methylene and cyclization onto the imidazole ring are all observed and all occur through cyclic ketene-*N*,*N*′-acetal intermediates. Unlike 2-methylimidazoline[16], some reactions gave no cyclic product.

The formation of these different products probably arises through small differences in the activation barriers of these routes.

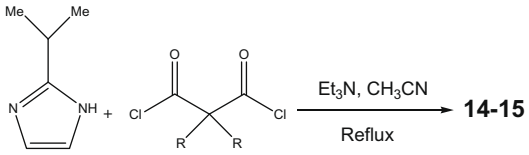
Table 3
Reactions of 2-ethylimidazole with 2,2-disubstituted-1,3-diacid chlorides[a]

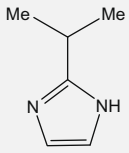
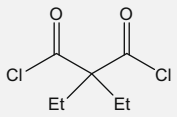
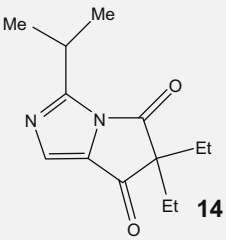
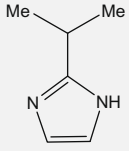
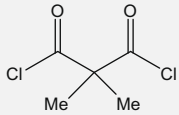
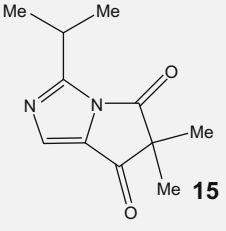


Substrate	1,3-diacid chloride	Reflux time (h)	Product	Isolated yield (%)
		3	 **11**	71
		3	 **12**	28
			+  **13**	58

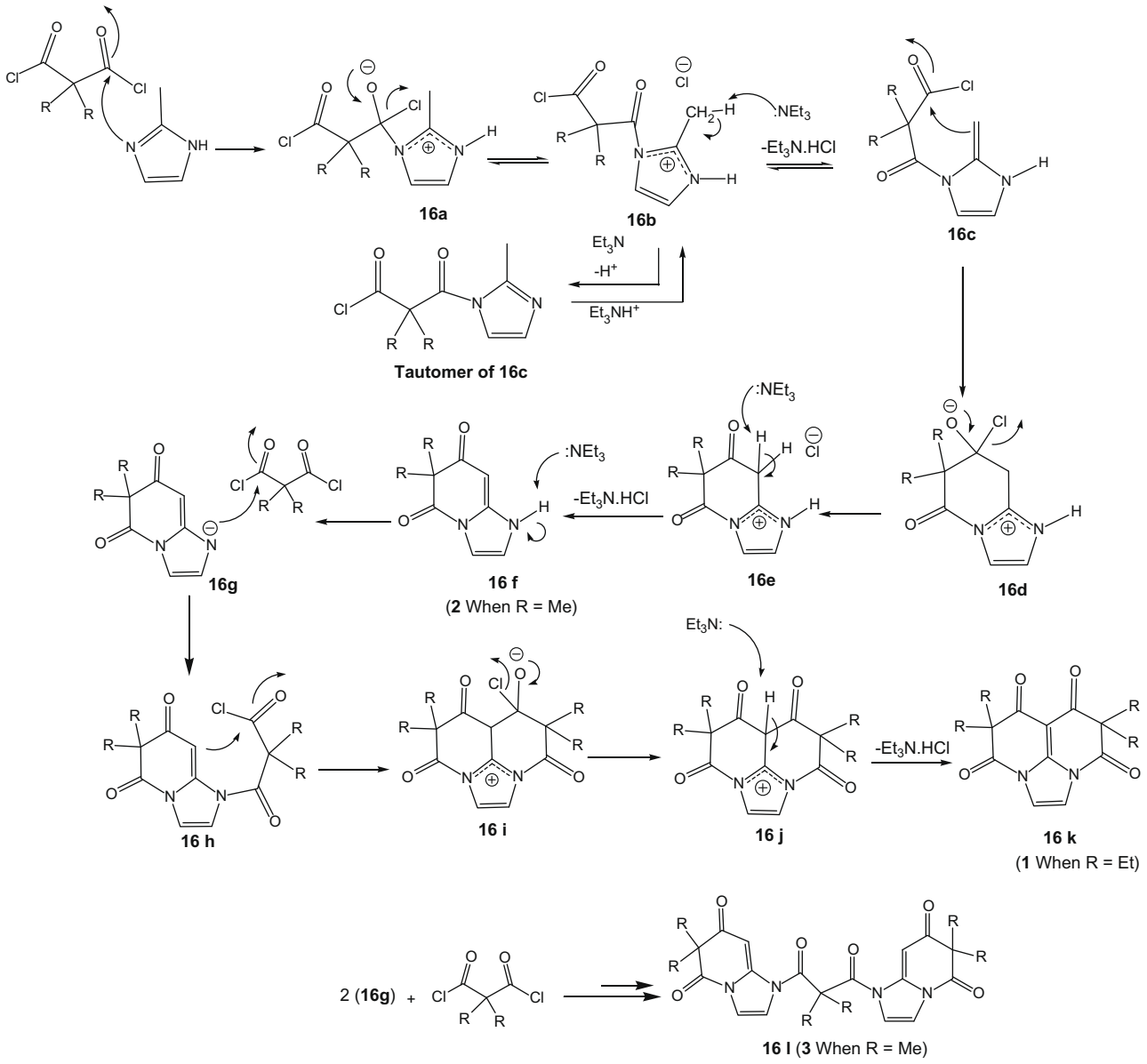
[a] The molar ratio of 2-ethylimidazole/l,3-diacid-chloride/Et_3N is 1/2.4/6 (2.0 mmol of 2-methylimidazole is used).

Table 4
Reactions of 2-isopropylimidazole with 2,2-disubstituted-1,3-diacid chlorides[a]



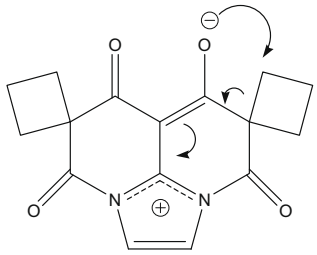
Substrate	1,3-Diacid chloride	Reflux time (h)	Product	Isolated yield (%)
		3	 **14**	76
		3	 **15**	71

[a] The molar ratio of 2-isopropylimictazole/l,3-diacid chloride/Et_3N is 1/2.4/6 (where 1.7 mmol of 2-isopropylimidazole is used).



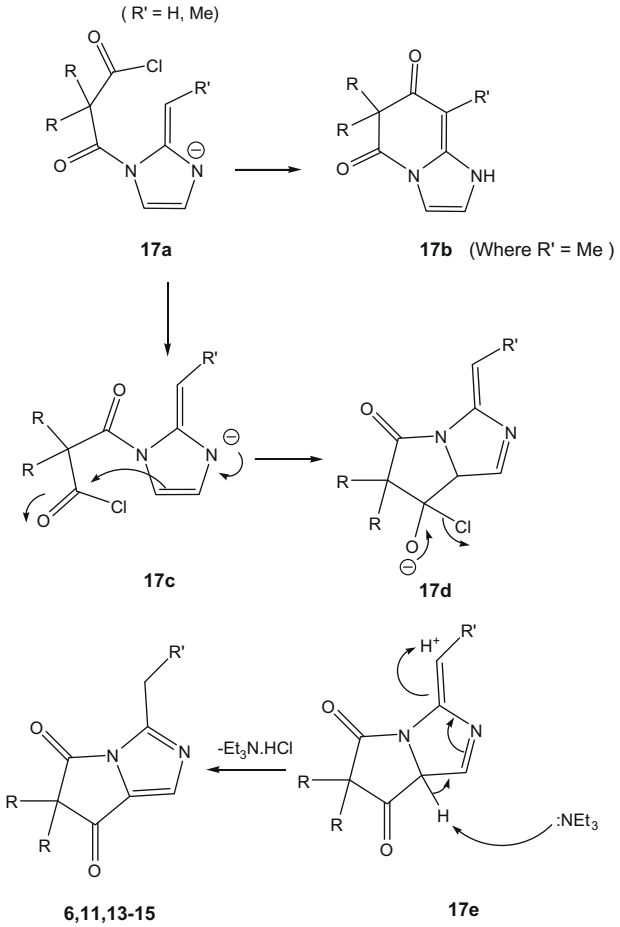
Scheme 2. Mechanisms proposed for cyclizations through cyclic ketene-*N*,*N*′-acetals.

Thus, subtle steric and electronic factors and solvation differences favor alternative pathways. For example, reactions conducted, where enhanced steric crowding was introduced at 2-position, favored cyclization at the imidazole ring in all cases (Tables 3 and 4). Steric effects reduced the nucleophilicity of the β-carbon, enhancing cyclization via Scheme 3 relative to Scheme 2. Opening of one of the four-membered rings during the formation of **4** is likely the result of the significant negative charge build up on oxygen of the highly dipolar push–pull precursor (**18**). In related ketene-*N*,*N*′-acetals with two carbonyl functions bound to the β-carbon, long bond lengths, and lower bond orders were found between the ring carbon and β-carbon.[21] This is indicative of a strong contribution from a zwitterion-like dipolar structure. When the single four- to six-membered ring expansion forms **4**, the amount of dipolar contribution decreases going from **18** to **4**. This reduces the propensity of the second four-membered ring to open. Other similar four-membered ring expansions to carbonyl oxygens have been reported.[22,23]



18

All reactions in Tables 1–4 proceed under relatively mild conditions, forming highly functionalized products. These reactions have potential for library syntheses via combinatorial pathways. They generate highly functionalized heterocyclic systems. Currently, investigations are underway to understand how to specifically control each pathway.



Scheme 3. Mechanism for cyclization onto the five-membered ring when the β-carbon is substituted.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.116.

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