JOC Note

Tandem Reactions of 1,3-Diacid Chlorides with 2-Methylimidazoline and 2-Methyl-1,4,5,6-tetrahydropyrimidine: One-Pot Synthesis of 1,8-Naphthyridinetetraones

Guozhong Ye,[†] Aihua Zhou,[‡] William P. Henry,[†] Yingquan Song,[†] Sabornie Chatterjee,[†] Debbie J. Beard,[†] and Charles U. Pittman, Jr.*,[†]

Department of Chemistry, Mississippi State University, Mississippi State, Mississippi 39762, and Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

cpittman@chemistry.msstate.edu

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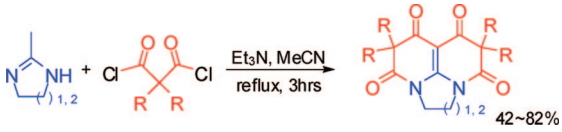
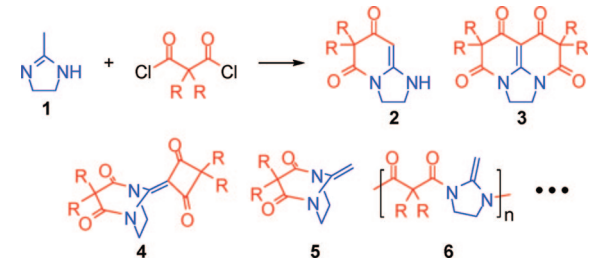


The reactions of 2-methylimidazoline and 2-methyl-1,4,5,6-tetrahydropyrimidine with 1,3-diacid chlorides, in the presence of Et_3N in refluxing MeCN give highly functionalized potentially bioactive 1,8-naphthyridinetetraones. 2-Methylimidazoline and 2-methyl-1,4,5,6-tetrahydropyrimidine can be viewed as tridentate nucleophiles which give four consecutive tandem nucleophilic attacks on electrophiles.

Secondary enamines are known to react with diacid chlorides to give nitrogen-containing heterocycles.[1a–f] Recently, 2-methylthiazolines and 2-methyloxazolines, analogues of 2-methylimidazoline, were reacted with diacid chlorides to very efficiently generate fused heterocyclic ring systems through *N*-acyl cyclic ketene-*N,O*-acetal or *N*-acyl cyclic ketene-*N,S*-acetal intermediates.[1g,h] *N,N′*-diacyl cyclic ketene-*N,N′*-acetals have been far less studied despite their potential as active carbon nucleophiles. 2-Methylimidazoline **1** was reacted with diacid chlorides because the possibility exists that *N,N′*-diacyl cyclic ketene-*N,N′*-acetals could form, similar to the generation of *N*-acyl cyclic ketene-*N,O*-acetals or *N*-acyl cyclic ketene-*N,S*-acetals.[1g,h] This might allow tandem reaction sequences to give

SCHEME 1. Possible Reactions of 1 with Diacid Chlorides



1,8-naphthyridinetetraone **3** (Scheme 1). Other products, such as **2**, **4**, **5**, and **6** are also possible.[1g–j]

We demonstrate herein the reactions of **1** with various 1,3-diacid chlorides to form the 1,8-naphthyridinetetraones **3a**−**e** as major products (Table 1). The assignment is supported by an X-ray crystallography structure determination of the THF solvate of **3c**. These reactions were successfully extended to the six-membered ring analogue, 2-methyl-1,4,5,6-tetrahydropyrimidine **7**, to form **8a**−**e**.

A likely mechanism is proposed in Scheme 2 using the example reaction of **1** with 2,2-dimethylmalonyl dichloride. The tandem sequence begins with nucleophilic acyl attack by the sp^2 nitrogen in **1** on a diacid chloride carbonyl carbon to form zwitterion intermediate **1a**. Loss of chloride gives ion pair **1b**. Proton removal by Et_3N generates mono-*N*-acylated 2-methylimidazoline **1c**, which nucleophilically attacks a second molecule of diacid chloride giving the zwitterion **1d**. Loss of chloride forms **1e**. A second proton removal by Et_3N occurs from the acidic methyl group in **1e** forming the cyclic *N,N′*-diacyl ketene acetal intermediate **1f**. Although the nucleophilicity of the exocyclic β-carbon is attenuated by two acyl groups, this carbon still initiates nucleophilic intramolecular attack on the acid chloride carbonyl function, forming zwitterion **1g**. Chloride loss generates **1h** with acidic β-hydrogens. Sequential proton removal by Et_3N generates intermediate **1i**, where the β-carbon is still nucleophilic. Thus, a fourth intramolecular nucleophilic attack occurs at the remaining acid chloride carbonyl carbon. This step exhibits similarities to the Baylis−Hillman reaction in which alkene derivatives activated by an EWG can react with aldehydes via amine catalysis. Following the formation of **1j** and loss of chloride to give **1k**, the fourth proton removal by Et_3N completes the tandem sequence and generates **3a**.

Other mechanistic possibilities should not be excluded at this stage. For example, the bicyclic intermediate **2** (Scheme 1) could be formed first and then undergo further cyclization with another diacid chloride to furnish **3a**.

The key to these tandem reactions is the easy formation by proton abstraction (see **1e**, **1h** in Scheme 2) and high nucleophilic activity of cyclic ketene-*N,N′*-acetal intermediates **2** (Scheme 1) or **1f** and **1i** (Scheme 2) despite the presence of adjacent electron-withdrawing carbonyls.

1,8-Naphthyridinetetraones have never been reported to our knowledge. They are of interest based on the known medicinal potential of naphthyridine and naphthyridinone systems which includes antibacterial,[2] anti-HIV,[3] antischizophrenia[4] and anti-asthma[5] activities. More than 1000 patents were located claiming synthesis and/or potential pharmaceutical applications.[6] It is

[†] Mississippi State University.
[‡] University of Kansas.

(1) (a) Ziegler, E.; Hradetzky, F.; Belegratis, K. *Monatsh. Chem.* **1965**, *96*, 1347–1351. (b) Jiang, X.; Cheng, Y.; Shi, G.; Kang, Z. *J. Org. Chem.* **2007**, *72*, 2212–2215. (c) Sheibani, H.; Mosslemin, M. H.; Behzadi, S.; Islami, M. R.; Saidi, K. *Synthesis.* **2006**, 435–438. (d) Chakrabarti, S.; Srivastava, M. C.; Ila, H.; Junjappa, H. *Synlett.* **2003**, 2369–2373. (e) Cheng, Y.; Yang, H.; Wang, M.; Williams, D. J. *Tetrahedron* **2002**, *58*, 2821–2829. (f) Chakrasali, R. T.; Ila, H.; Junjappa, H. *Synthesis* **1988**, 87–89. (g) Zhou, A.; Pittman, C. U., Jr. *Tetrahedron Lett.* **2005**, *46*, 2045–2048. (h) Zhou, A.; Pittman, C. U., Jr. *Synthesis* **2006**, 37–48. (i) Rodeschini, V.; Ahmad, N. M.; Simpkins, N. S. *Org. Lett.* **2006**, *8*, 5283–5285. (j) Nuhant, P.; David, M.; Pouplin, T.; Delpech, B.; Marazano, C. *Org. Lett.* **2007**, *9*, 287–289.

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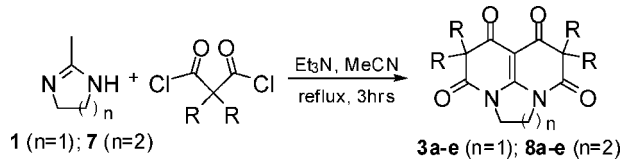
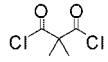
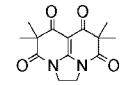
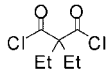
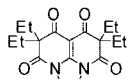
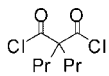
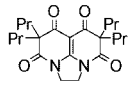
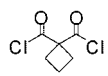
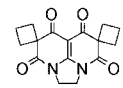
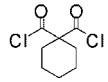
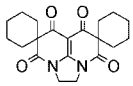
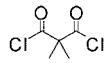
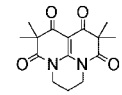
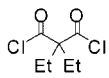
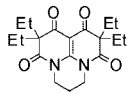
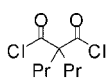
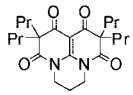
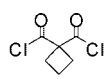
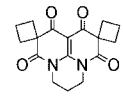
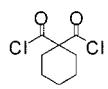
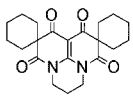
TABLE 1. Reactions of 2-Methylimidazoline and 2-Methyl-1,4,5,6-Tetrahydropyrimidine with 1,3-Diacid Chlorides[a]



1 (n=1); **7** (n=2) — **3a-e** (n=1); **8a-e** (n=2)

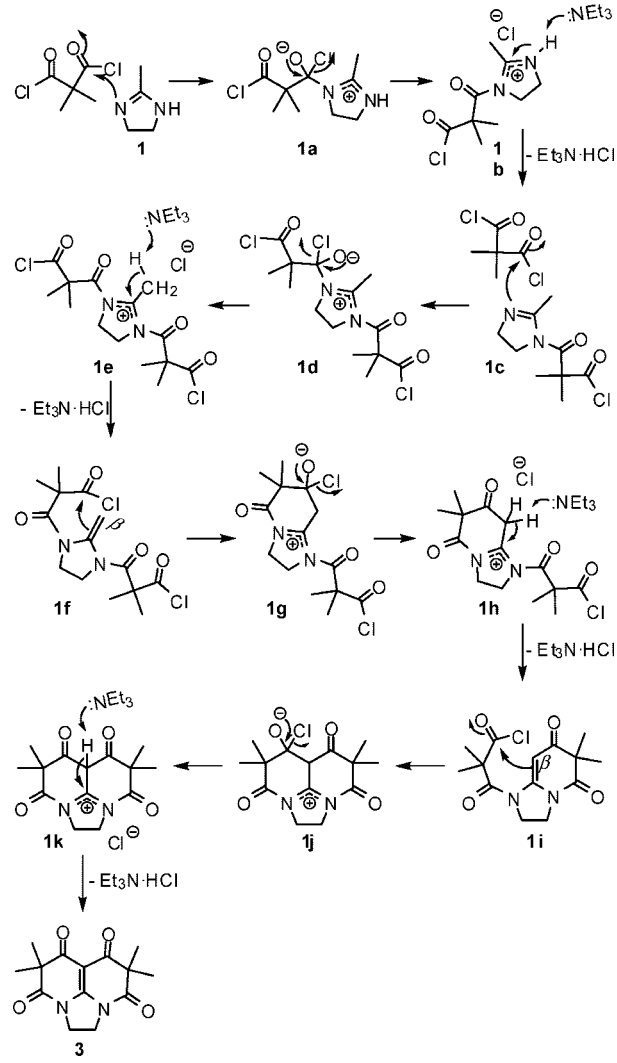
substrate	diacid chloride	product & number		yield(%)[b]
			**3a**	72
			**3b**	49
			**3c**	61
			**3d**	82
			**3e**	63
			**8a**	73
			**8b**	52
			**8c**	65
			**8d**	42
			**8e**	65

[a] The molar ratio of **1** (or **7**)/diacid chloride/Et_3N = 1:2.5:8. [b] Isolated yield.

worth noting that 1,8-naphthyridine systems (but not 1,8-naphthyridinetetraones) can be conventionally synthesized by treating 2-aminopyridine or 2,6-diaminopyridine with malonates.[7]

In conclusion, 2-methylimidazoline and 2-methyl-1,4,5,6-tetrahydropyrimidine undergo facile tandem reactions with 1,3-diacid chlorides to give highly functionalized 1,8-naphthyridinetetraones. 2-Methylimidazoline and 2-methyl-1,4,5,6-tetrahydropyrimidine and their derivatives, which were insufficiently examined due to their limited availability in the past, warrant further study based on their distinctive reactivities. Reactions of amidines **1** (n = 1, 2) with the diacid chlorides of oxalic or phthalic acids or with phosgene did not produce tricyclic analogues of **3**. Current efforts are focused on expansion of the scope of this reaction, such as using 2,2-diarylmalonyl dichlorides, chiral, and larger amidine ring systems (i.e., $n > 2$) to achieve different types of fused-ring systems.

SCHEME 2. Mechanism Proposed for the Formation of 3a



Experimental Section

General Procedure. Triethylamine (8 mmol) was added dropwise under nitrogen at room temperature to a stirred solution of diacid chloride (2.5 mmol) in 15 mL of MeCN. 2-Methylimidazoline **1** or 2-methyl-1,4,5,6-tetrahydropyrimidine **7** (1 mmol) was

(2) (a) Seefeld, M. A.; Miller, W. H.; Newlander, K. A.; Burgess, W. J.; DeWolf, W. E., Jr.; Elkins, P. A.; Head, M. S.; Jakas, D. R.; Janson, C. A.; Keller, P. M.; Manley, P. J.; Moore, T. D.; Payne, D. J.; Pearson, S.; Polizzi, B. J.; Qiu, X.; Rittenhouse, S. F.; Uzinskas, I. N.; Wallis, N. G.; Huffman, W. F. *J. Med. Chem.* **2003**, *46*, 1627–1635. (b) Davies, D. T.; Jones, G. E.; Pearson, N. D. WO 006 648, 2008.

(3) Dress, K. R.; Johnson, T. W.; Plewe, M. B.; Tanis, S. P.; Zhu, H. WO 042 883, 2007; *Chem. Abstr.* **2006**, *146*, 441772.

(4) Favor, D. A.; Johnson, D. S.; Repine, J. T.; White, A. D. WO 090 272, 2006; *Chem. Abstr.* **2006**, *145*, 293102.

(5) Guay, D.; Girard, M.; Hamel, P.; Laliberte, S.; Friesen, R. WO 018 579, 2003; *Chem. Abstr.* **2003**, *138*, 205042.

(6) For more examples, see: (a) Ren, P.; Zhang, G.; You, S.; Sim, T.; Gray, N.; Xie, Y.; Wang, X.; He, Y. WO 136 465, 2007; *Chem. Abstr.* **2007**, *148*, 33755. (b) Cosford, N. D. P.; Layton, M. E.; Liang, J.; Lindsley, C. W.; Sanderson, P. E.; Zhao, Z. WO 091 395, 2006; *Chem. Abstr.* **2006**, *145*, 293099. (c) Wang, Y.; Mull, E. S. WO 101 988, 2003; *Chem. Abstr.* **2006**, *140*, 16716. (d) Shimamoto, T.; Inoue, H.; Hayashi, Y. WO 07 704, 1999; *Chem. Abstr.* **1999**, *130*, 196577. (e) Leach, C. A.; Smith, S. A. WO 086 400, 2003; *Chem. Abstr.* **2003**, *139*, 337978.

(7) Allen, C. F. H. *Chem. Rev.* **1950**, *47*, 275–305.

dissolved in 10 mL of MeCN and then added dropwise into the above solution at room temperature. The reaction system was then refluxed for 3 h, and the solvent was removed by rotary evaporation. Acetone (15 mL) was added to the residue to give a solid/liquid mixture. The mixture was filtered and thoroughly washed with acetone (3 × 15 mL). The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography.

Example characterization data for **3a**: $R_f = 0.37$ (ethyl acetate); white solid; mp = 258−260 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.24 (s, 4H), 1.48 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.1, 173.6, 158.8, 92.9, 53.3, 42.2, 24.3; IR (KBr, cm^{-1}): 1715, 1679, 1602, 1510, 1466, 1383, 1351, 1272, 1210, 1063, 1042; HRMS (ESI-TOF, $[M + Na]^+$): calcd for $C_{14}H_{16}N_2NaO_4$, 299.1008; found, 299.0982.

Supporting Information Available: Synthetic procedures; characterization data, and copies of ^{1}H and ^{13}C NMR spectra of all new compounds; CIF file and thermal ellipsoid drawings of THF solvate of **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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