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Spirocyclic Dihydropyridines by Electrophile-Induced Dearomatizing Cyclization of N-Alkenyl Pyridinecarboxamides

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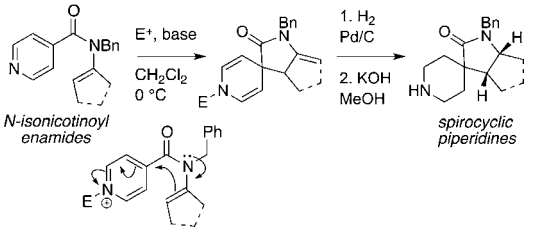
ABSTRACT



On treatment with acylating or sulfonylating agents, *N*-alkenyl pyridine carboxamides (*N*-pyridinecarbonyl enamines) undergo a dearomatizing cyclization initiated by pyridine acylation and followed by intramolecular trapping of the resulting pyridinium cation. The products are spirocyclic dihydropyridines which may be further elaborated to spirocyclic heterocycles with drug-like features.

Spiropiperidine compounds display a wide range of biological activities, and the spiropiperidine motif is considered a privileged scaffold in drug discovery.[1] The biological activity of 2,8-diazaspiro[4.5]decanes alone spans a range of therapeutic areas and has so far been associated with NOP receptor ligands,[2] NPY Y5 receptor antagonists,[3] GlyT1 receptor antagonists[4] and tryptase inhibitors (Figure 1).[5]

The synthesis of functionalized piperidines directly from corresponding pyridines by nucleophilic dearomatization is an attractive strategy.[6] While the dearomatization of neutral pyridines requires powerful, organometallic nucleophiles, more activated pyridinium cations are readily attacked by weaker, neutral nucleophiles such as silyl enol ethers.[7] *N*-Triflation with triflic anhydride promotes the attack of electron-rich arenes on the resulting pyridinium cation.[8] By tethering the nucleophile to the pyridine ring,

(1) Mullen, P.; Miel, H.; McKervey, M. A. *Tetrahedron Lett*. **2010**, *51*, 3216. Krafft, A. A.; Kurt, A.; Maier, A.; Thomas, A. W.; Zimmerli, D. *Synthesis* **2005**, 3245. DeSimone, R. W.; Currie, K. S.; Mitchell, S. A; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473. Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, P. J.; Liu, J.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 5022.

(2) Caldwell, J. P.; Matasi, J. J.; Fernandez, X.; McLeod, R. L.; Zhang, H.; Fawzi, A.; Tulshian, D. B. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 1164.

(3) Takahashi, T.; Haga, Y.; Sakamoto, T.; Moriya, M.; Okamoto, O.; Nonoshita, K.; Shibata, T.; Suga, T.; Takahashi, H.; Hirohashi, T.; Sakuraba, A.; Gomori, A.; Iwaasa, H.; Ohe, T.; Ishihara, A.; Ishii, Y.; Kanatani, A.; Fukami, T. *Bioorg. Med. Chem. Lett*. **2009**, *19*, 3511.

(4) Alberati, D.; Hainzl, D.; Jolidon, S.; Kurt, A.; Pinnard, E.; Thomas, A.; Zimmerli, D. *Bioorg. Med. Chem. Lett*. **2006**, *16*, 4321.

(5) Costanzo, M. J.; Yabut, S. C.; Zhang, H. C.; White, K. B.; De Garavilla, L.; Wang, Y.; Minor, L. K.; Tongue, B. A.; Barnakov, A. N.; Lewandowski, F.; Milligan, C.; Spurlino, J. C.; Abraham, W. M.; Boswell-Smith, V.; Page, C. P.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett*. **2008**, *18*, 2114.

(6) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev*. **2012**, *112*, 2642.

(7) Meyers, A.; Gabel, R. *J. Org. Chem*. **1982**, *47*, 2633. Comins, D. L.; Abdullah, A. H. *J. Org. Chem*. **1982**, *47*, 4315. Sperger, C. A.; Wanner, K. T. *Tetrahedron*. **2009**, *65*, 5824. Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc*. **2001**, *123*, 11829. Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett*. **2005**, *7*, 3673. Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett*. **2006**, *8*, 5325. Akiba, K.; Nishihara, Y.; Wada, M. *Tetrahedron Lett*. **1983**, *24*, 5269. Bennasar, M.-L.; Juan, C.; Bosch, J. *Tetrahedron Lett*. **2001**, *42*, 585. Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587. Katritzky, A. R.; Zhang, S.; Kurz, T.; Wang, M. *Org. Lett*. **2001**, *3*, 2807. Brice, H.; Clayden, J.; Hamilton, S. *Beilstein J. Org. Chem* **2010**, *6*, 22.

(8) Corey, E. J.; Tian, Y. *Org. Lett*. **2005**, *7*, 5535. Focken, T.; Charette, A. B. *Org. Lett*. **2006**, *8*, 2985. Lemire, A.; Beaudoin, D.; Grenon, M.; Charette, A. B. *J. Org. Chem*. **2005**, *70*, 2368. Comins, D. L.; Sahn, J. J. *Org. Lett*. **2005**, *7*, 5227. Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc*. **2001**, *123*, 11829. Comins, D. L.; Zheng, X.; Goehring, R. *Org. Lett*. **2002**, *4*, 1611.

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fused or spirocyclic dihydropiperidines may be generated. We have shown that when *N*-aryl or *N*-heteroaryl pyridinecarboxamides are treated with triflic anhydride, dearomatizing cyclization reactions[9] ensue, giving spirocyclic dihydropyridines in which the second spirocyclic ring is fused with an aromatic ring.[10]

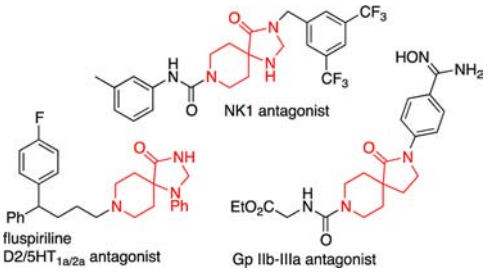


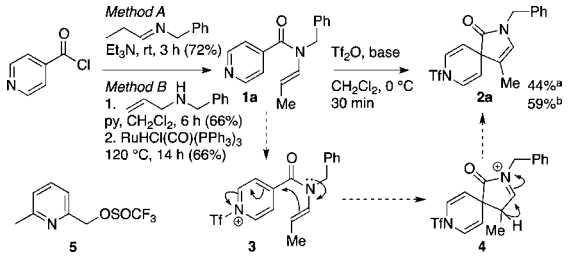
Figure 1. A selection of bioactive spirocyclic piperidines.

We now report that simple *N*-alkenyl pyridinecarboxamides also undergo dearomatizing spirocyclization and generate a versatile range of unsaturated 2,8-diazaspiro-[4.5]decanes, which are readily convertible into drug-like scaffolds.[11]

N-Alkenyl pyridinecarboxamides **1** were made by one of two methods. In method A, N-acylation of the imine formed from benzylamine and an aldehyde or ketone gave the *N*-acylenamine. Thus **1a** was formed in 72% yield by acylation with isonicotinoyl chloride condensation of *N*-benzylpropionaldimine in the presence of molecular sieves (Scheme 1). In method B, an *N*-allyl amide was isomerized to an *N*-acyl enamine by a Ru catalyst. Thus **1a** was alternatively formed in 66% yield from *N*-allyl-*N*-benzylnicotinamide.

In a preliminary experiment to establish the feasibility of cyclizing *N*-vinyl isonicotinamides, **1a** was treated with triflic anhydride in the presence of 2,6-lutidine in dichloromethane. A dearomatizing cyclization gave the spiropiperidine **2a** in 44% yield, presumably by N-triflation to yield **3**, followed by cyclization to **4** and loss of a proton to reform the enamine. The only observable side product of the reaction was the sulfinate **5**, suggesting competitive triflation and

Scheme 1. Spirocycles from *N*-Alkenyl Isonicotinamides[a]



[a] With 2,6-lutidine (1 equiv) as base. [b] With 2,6-di-*tert*-butyl-4-methylpyridine (3 equiv) as base. Tf = SO_2CF_3.

rearrangement of lutidine.[12] Switching the base to 2,6-di-*tert*-butyl-4-methylpyridine avoided this side reaction. Using just 1 equiv of this base still however led to low conversion; with 3 equiv the yield of the reaction increased to 59%.

The same conditions converted a series of *N*-alkenylisonicotinamides **1b**–**1i** incorporating variously substituted alkenes to a range of spirocyclic dihydropyridines **2** (Table 1). Enamides **1a**–**b** derived from aldehydes gave dihydropyridines **2a**–**b** spiro-linked with pyrrolinones (entries 1 and 2), and Figure 2a shows the X-ray crystal structure of **2b**.[13] Enamides **1d**–**1i** from ketones also cyclized in generally good yields, with the alkene generated by the cyclization preferring to lie exocyclic to the new pyrrolidinone ring (entries 4–10). Enamides derived from cyclic ketones gave tricyclic products **2e**–**i**. In some cases, for example with the unsubstituted enamine **1c**, a hydrated product **6c** was isolated. While **1e** cyclized to **2e** under the standard reaction conditions, the aminal **6e** was formed when **1e** was cyclized under less basic conditions, possibly because the intermediate acyl iminium corresponding to **4** persists until aqueous workup. **6h** and **6i** were likewise formed after acid workup. Figure 2b shows the X-ray crystal structure of **6e**.[13]

Cyclization of unsymmetrically substituted isonicotinamides creates a new stereogenic center but without diastereoselectivity (entries 9–13): the chloropyridines **1h** and **1i** gave diastereoisomeric mixtures of the ring-fused spirocycles **6h** and **6i**. Cyclization onto quinolines was also successful, with **1j**–**l** yielding spirocyclic dihydroquinolines **2j**–**l** in moderate to good yield. **1l** behaved like **1e**, giving a hydrated product **6l** under less basic conditions. Formation of hydrated adducts of **6** is discussed further below (Scheme 4)

Yields from reactions promoted by triflic anhydride were moderate to excellent but were reduced with extended reaction times, presumably as a result of decomposition in the presence of the triflic acid generated in the reaction. Despite the longer reaction times required, generally higher yields of cyclized products **7**, **8**, and **9** were obtained when alternative electrophiles to triflic anhydride such as methyl chloroformate, 2,2,2-trichloroethoxycarbonyl chloride (TrocCl),

(9) Ortíz, F. L.; Iglesias, M. J.; Fernández, M. J.; Sánchez, C. M. A.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580. Clayden, J.; Knowles, F. E.; Baldwin, I. R. *J. Am. Chem. Soc.* **2005**, *127*, 2412. Ahmed, A.; Bragg, R. A.; Clayden, J.; Tchabanenko, K. *Tetrahedron Lett.* **2001**, *42*, 3407. Bragg, R. A.; Clayden, J.; Bladon, M.; Ichihara, O. *Tetrahedron Lett.* **2001**, *42*, 3411. Clayden, J.; Menet, C. J.; Mansfield, D. J. *Chem. Commun.* **2002**, 38. Ahmed, A.; Clayden, J.; Rowley, M. *Synlett.* **1999**, 1954. Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609. Clayden, J.; Turnbull, R.; Helliwell, M.; Pinto, I. *Chem. Commun.* **2004**, 2430.

(10) Arnott, G.; Brice, H.; Clayden, J.; Blaney, E. *Org. Lett.* **2008**, *10*, 3089. Brice, H.; Clayden, J. *Chem. Commun.* **2009**, 1964.

(11) For related examples, see: Sainsbury, M.; Uttley, N. I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2109. Naito, T.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Chem. Commun.* **1979**, 517. Parameswarappa, S. G.; Pigge, F. C. *J. Org. Chem.* **2012**, *77*, 8038. Parameswarappa, S. G.; Pigge, F. C. *Tetrahedron Lett.* **2011**, *52*, 4357. Parameswarappa, S. G.; Pigge, F. C. *Org. Lett.* **2010**, *12*, 3434. For a review of the chemistry of enamides, see: Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455.

(12) Binkley, R. W.; Ambrose, M. G. *J. Org. Chem.* **1983**, *48*, 1776.

(13) X-ray data for **2b** and **6e** have been deposited with the Cambridge Crystallographic Database, deposition numbers 926563 (**2b**) and 926562 (**6e**).

Table 1. Dihydropyridines by Spirocyclization with Triflic Anhydride

entry	starting material	product[a]	yield (%)
1	**1a** (R = Me)	**2a**	44[b], 59[c]
2	**1b** (R = *i*-Pr)	**2b**	49[c]
3	**1c** (R = H)	**6c**	49[c,d]
4	**1d**	**2d**	74[c]
5	**1e** (X = –)	**2e**	77[c]
6	**1e** (X = –)	**6e**[e]	76[f]
7	**1f** (X = CH_2)	**2f**	89[c]
8	**1g** (X = NBn)	**2g**	38[c]
9	**1h**	**6h**	73[b,g]
10	**1i**	**6i**	67[b,d] (2:1 dr)
11	**1j** (R = Me)	**2j**	56[b]
12	**1k** (R = *i*-Pr)	**2k**	53[b]
13	**1l**	**2l**	72[b] (3:1 dr)
14	**1l**	**6l**[e]	76[c] (3:1 dr)

[a] Conditions Tf_2O, base, CH_2Cl_2, 0 °C, 2 h. [b] With 2,6-lutidine (1 equiv) as base. [c] With 2,6-di-*tert*-butyl-4-methylpyridine (3 equiv) as base. [d] Based on 29% recovered starting material. [e] Structures of **6** below. [f] With 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv) as base. [g] After standing in $CDCl_3$.

6e (X = Y = H)
6l (X, Y = benzo)

or (−)-menthyl chloroformate were used to activate the pyridinecarboxamide, with 2,6-lutidine as base (Table 2). Spirocyclic dihydropyridines were obtained most successfully using menthyl chloroformate as an activating reagent, owing to the increased stability of *N*-menthyldihydropyridine products toward rearomatization and decomposition than comparable *N*-methyl and *N*-Troc compounds. However, no diastereoselectivity resulted from the use of (−)-menthyl chloroformate,[14] and in some cases (**7e**, **7f**) ~20% of a double bond regioisomer (**7e′**, **7f′**) was also isolated. A moderate yield of **10e** was obtained by treating **1e** with trifluoroacetic anhydride, and no cyclization resulted when the pyridine ring was alkylated, rather than acylated: isonicotinamide **1a** with methyl triflate returned the *N*-methyl pyridinium salt in 97% yield. As with triflic anhydride, cyclization of **1i** with chloroformates gave hydrated structures **11i**, **12i**.

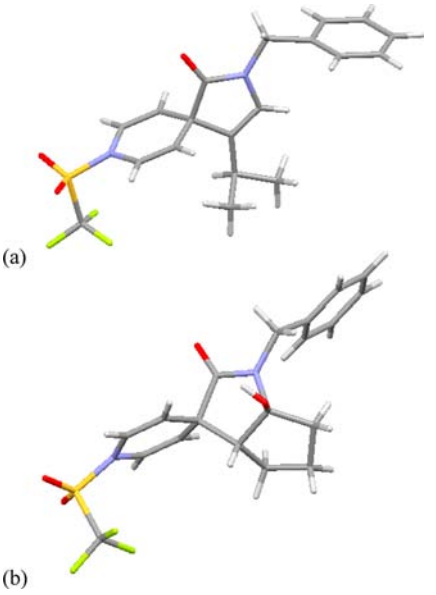


Figure 2. X-ray crystal structures of (a) **2b** and (b) **6e**.

Compounds with a spirocyclic piperidine structure isomeric with that of **2** or **7**–**9** exhibit properties that make them suitable as potential smoking cessation remedies,[15] and with these targets in mind we synthesized the *N*-alkenyl picolinamide **13** and the *N*-alkenyl pyrimidinecarboxamide **15** shown in Scheme 2. Treatment of each with activating electrophiles led to dearomatizing cyclization and the formation of spirocyclic products **14** and **16** as principally one of the two possible diastereoisomers, but these products were extremely unstable.[16]

The products of the dearomatizing spirocyclizations—**2**, **7**–**9**, **14**, and **16**—contain up to three acylenamine-like double bonds suitable for further elaboration, and in some cases this functionality made the products somewhat unstable on standing. In some instances, but especially for **16**, it was impossible to fully purify the dearomatized

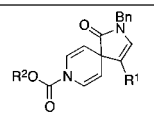
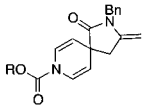
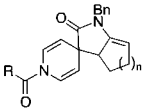
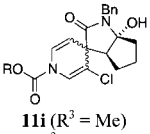
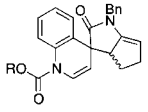
(14) Comins, D. L.; Hong, H.; Salvador, J. M. *J. Org. Chem.* **1991**, *56*, 7197.

(15) Bhatti, B. S.; Miller, C. H.; Schmitt, J. D. 2006 WO2006023630; Bhatti, B. S.; Miller, C. H.; Schmitt, J. D. 2004 WO2004005293.

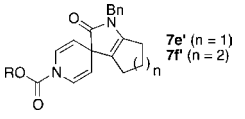
(16) Attempted cyclization of nicotinamides (3-pyridinecarboxamides) gave complex inseparable mixtures of products arising from cyclization into both the 2- and 4-positions of the pyridine.

(17) H-Cube system purchased from Thales-Nano, Záhony u. 7, H-1031 Budapest, Hungary.

Table 2. Dihydropyridines by Spirocyclization with Chloroformates

entry	starting material	product[a]	yield (%)
			
1	**1a**	**7a** (R^1 = R^2 = Me)	69
2		**8a** (R^1 = Me, R^2 = Cl_3CCH_2)	69
3		**9a** (R^1 = Me, R^2 = menthyl)	38[b]
4	**1b**	**8b** (R^1 = *i*-Pr, R^2 = Cl_3CCH_2)	44
5		**9b** (R^1 = *i*-Pr, R^2 = menthyl)	58[b]
			
6	**1d**	**8d** (R = Cl_3CCH_2)	73
7		**9d** (R = menthyl)	73[b]
			
8	**1e**	**7e** (n = 1, R = OMe)	67 + 17[c]
9		**8e** (n = 1, R = Cl_3CCH_2O)	73
10		**9e** (n = 1, R = O-menthyl)	92[b], 82[b,d]
11		**10e** (n = 1, R = CF_3)[e]	45
12	**1f**	**7f** (n = 2, R = OMe)	72 + 19[c]
13		**8f** (n = 2, R = Cl_3CCH_2O)	79
			
14	**1i**	**11i** (R^3 = Me)	64[b]
15		**12i** (R^3 = menthyl)	66 (1:1:1:1 dr)
			
16	**1l**	**7l** (R = Me)	79 (2:1 dr)

[a] With trichloroethyl, methyl, or (−)-menthyl chloroformate as electrophile: conditions ROCOCl, 2,6-lutidine, CH_2Cl_2, 0 °C−rt, 2 h. [b] 1:1 dr. [c] Yield of regioisomer **7e′** or **7f′** (structure below). [d] Carried out on a 2 g scale. [k] With trifluoroacetic anhydride as electrophile.

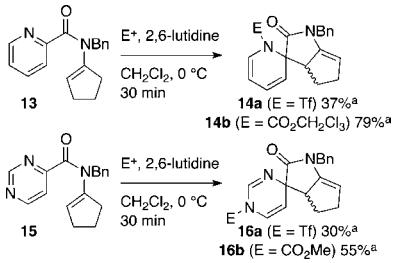


spirocycles from their decomposition products. However, hydrogenation of selected dihydropyridines **2**, **7**, and **9** using a flow hydrogenation apparatus (H-Cube)[17] gave stable spirocyclic piperidines **20**, **24**, and **25** (at higher pressures) or dihydropiperidines **19**, **22**, and **23** (at lower pressures, where only the double bond in the five-membered ring was hydrogenated) as shown in Scheme 3. **20** and **25** were readily deprotected by methanolysis of the carbamate. The alkenes in **2a** could also be functionalized by bromoetherification to give first **17** and then, with greater quantities of NBS, **18**.

As an alternative strategy for stabilizing the unsaturated products, inclusion of an alcohol in the reaction mixture during the dearomatizing cyclization allowed the spirocycles to be trapped as aminals **27**, as shown in Scheme 4.

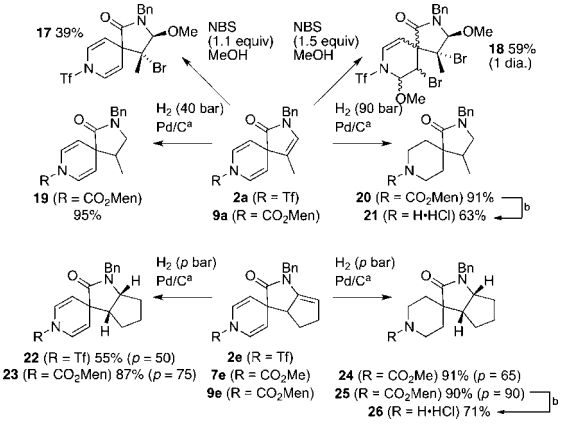
In conclusion, we report that *N*-alkenyl isonicotinamides and their congeners undergo spirocyclizing dearomatization

Scheme 2. Dearomatizing Cyclization of Pyrimidinecarboxamides and Picolinamides[a]



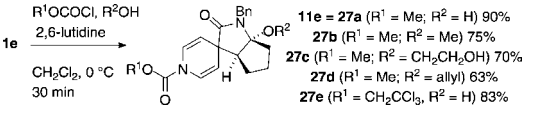
[a] 5−9:1 mixture of diastereoisomers.

Scheme 3. Reduction and Deprotection; Men = (−)-Menthyl (all as 1:1 mixtures of diastereoisomers)[a]



[a] H_2, *p* bar, Pd/C, EtOH, EtOAc, H-cube. [b] (1) KOH, MeOH, 120 °C, 16 h; (2) HCl, MeOH.

Scheme 4. Nucleophilic Trapping of the Intermediate



to yield partially saturated heterocyclic products on treatment with sulfonating or acylating agents.

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Supporting Information Available. Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.