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Electrophile-Induced Dearomatizing Spirocyclization of *N*-Arylisonicotinamides: A Route to Spirocyclic Piperidines

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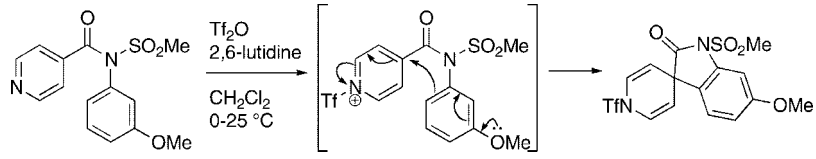
ABSTRACT



Treatment of *N*-arylisonicotinamides with trifluoromethanesulfonic anhydride triggers intramolecular nucleophilic attack of the aryl ring on the 4-position of the pyridinium intermediate. The products are spirocyclic dihydropyridines which can be converted to valuable spirocyclic piperidines related to biologically active molecules such as MK-677.

Piperidines spiro-linked with other heterocyclic rings are widespread as structural elements in numerous classes of pharmaceutically active molecules[1,2] and are considered "privileged structures" as components of G-protein coupled receptor (GPCR) ligands.[3] Functionalized piperidines may be made efficiently from pyridines, since electrophilic attack at nitrogen creates a powerfully electrophilic pyridinium cation to which nucleophiles may be added.[4] Although most work in this area has employed reactive anionic nucleophiles, Corey and Tian have shown recently that *N*-triflylpyridinium

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(1) Krafft, A. A.; Kurt, A.; Maier, A.; Thomas, A. W.; Zimmerli, D. *Synthesis* **2005**, 3245. Bignan, G. C.; Battista, K.; Connolly, P. J.; Orsini, M. J.; Liu, J.; Middleton, S. A.; Reitz, A. B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5022. DeSimone, R. W.; Currie, K. S.; Mitchell, S. A.; Darrow, J. W.; Pippin, D. A. *Comb. Chem. High Throughput Screening* **2004**, *7*, 473. Xie, J.-S.; Huang, C. Q.; Fang, Y.-Y.; Zhu, Y.-F. *Tetrahedron* **2004**, *60*, 4875. Guo, T.; Hobbs, D. W. *Assay Drug Dev. Tech.* **2003**, *1*, 579. Glennon, R. A.; Metwally, K.; Dukat, M.; Ismaiel, A. M.; De los Angeles, J.; Herndon, J.; Teitler, M.; Khorana, N. *Curr. Top. Med. Chem.* **2002**, *2*, 539. Palucki, B. L.; Feighner, S. D.; Pong, S.-S.; McKee, K. K.; Hrenick, D. L.; Tab, C.; Howard, A. D.; Van der Ploeg, L. H.; Patchett, A. A.; Nargund, R. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1955. Dhar, T. G.; Nagarathnam, R. P.; Marzabadi, M. R.; Lagu, B.; Wong, W. C.; Chiu, G.; Tyagarajan, S.; Miao, S. W.; Zhang, F.; Sun, W.; Tian, D.; Shen, Q.; Zhang, J.; Wetzle, J. M.; Firray, C.; Chang, R.; Broten, T. P.; Schorn, T. W.; Chen, T. B.; O'Malley, S.; Ransom, R.; Schneck, K.; Bendesky, R.; Harrell, C. M.; Vyas, K. P.; Zhang, K.; Gilbert, J.; Pettibone, D. J.; Patane, M. A.; Bock, M. G.; Freidinger, R. M.; Gluchowski, C. *J. Med. Chem.* **1999**, *42*, 4778. Metwally, A.; Dukat, M.; Egan, C. T.; Smith, C.; DuPre, A.; Gauthier, C. B.; Herrick-David, K.; Teitler, M; Glennon, R. A. *J. Med. Chem.* **1998**, *41*, 5084. Elliott, J. M.; Broughton, H.; Cascieri, M. A.; Chicchi, G.; Huscroft, I. T.; Kurtz, M.; MacLeod, A. M.; Sadowski, S.; Stevenson, G. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1851. Elliott, J. M.; Cascieri, M. A.; Chicchi, G.; Davies, S.; Kelleher, F. J.; Kurtz, M.; Ladduwahetty, T.; Lewis, R. T.; MacLeod, A. M.; Merchant, K. J.; Sadowski, S.; Stevenson, G. I. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1845. Efange, S. M.; Kamath, A. P.; Khare, A. B.; Kung, M.-P.; Mach, R. H.; Parsons, S. M. *J. Med. Chem.* **1997**, *40*, 3905. Chambers, M. S.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Wong, E. H. *J. Med. Chem.* **1992**, *35*, 2033. Mach, R. H.; Jackson, J. R.; Luedtke, R. R.; Ivins, K. J.; Molinoff, P. B.; Ehrenkaufer, R. L. *J. Med. Chem.* **1992**, *35*, 423.

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cations are sufficiently electrophilic that they may be attacked by nucleophiles even as weak as simple arenes.[5] Dearomatizing addition of arenes to the *N*-triflyl pyridinium salts yields 4-aryl-1,4-dihydropyridines. The fact that *N*-sulfonylpyridinium cations may be trapped in situ by nucleophiles which are unreactive toward the sulfonylating agent raised the possibility that cyclization reactions of pyridines containing a tethered latent nucleophile may be successful

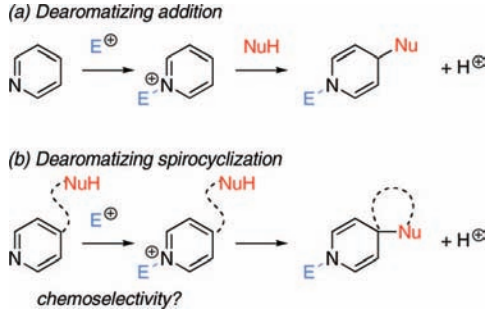
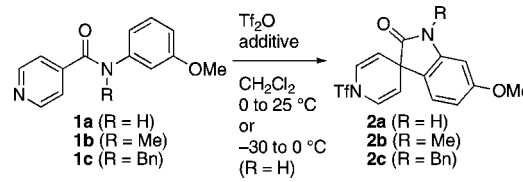


Figure 1. Dihydropyridines by dearomatizing (a) addition (ref 5) and (b) spirocyclization (this work).

(Figure 1).[6] In this paper, we show that the target spirocycles are formed when dearomatizing cyclization[7] of an *N*-arylisonicotinamide is triggered by *N*-sulfonylation in the presence of a hindered base. The reaction generates valuable benzo-fused spirocyclic dihydropyridines.

In a preliminary experiment (Scheme 1), we treated the simple anilide **1a**, formed in one step from isonicotinoyl chloride and *m*-anisidine, with triflic anhydride at −30 °C. Warming to 0 °C returned 20% of the spirocyclic dihydropyridine **2a**.

Scheme 1. Spirocyclization of an *N*-Anisylisonicotinamide



The favored conformation of secondary anilides such as **1a** places the two aryl rings trans to one another, but their tertiary analogues prefer conformations in which the two rings lie cis[8] and are therefore better orientated for cyclization. We therefore repeated the cyclization with **1a**'s *N*-methylated analogue **1b** (Table 1, entry 2). The yield of

Table 1. Optimizing the Spirocyclization

entry	starting material **1**	R =	additive	product **2**	yield (%)
1	**1a**	H		**2a**	20
2	**1b**	Me		**2b**	47
3	**1b**	Me	Et_3N	**2b**	54
4	**1b**	Me	DMAP	**2b**	70
5	**1b**	Me	pyridine	**2b**	99
6	**1c**	Bn	2,6-lutidine	**2c**	87

spirocyclic product obtained increased to 47%. Extending the reaction time led to decomposition, and reasoning that this was caused by the triflic acid generated during the reaction, we repeated the cyclization in the presence of a series of bases (Table 1, entries 3−6). Satisfyingly, with pyridine the yield of the cyclized dihydropyridine **2b** increased to 99% (Table 1, entry 5). Likewise, cyclization of the *N*-benzyl anilide **1c** in the presence of 2,6-lutidine gave **2c** in 87% yield (Table 1, entry 6).[9] The X-ray crystal structure of **2b** is illustrated in Figure 2.[10]

A range of variously substituted anilide starting materials **3**−**8** were made and treated with electrophiles under similar conditions to establish the scope of the cyclization reaction to **9**−**14** (Scheme 2 and Table 2). In general, electron-rich anilides **3**−**5** performed the most satisfactorily (Table 2,

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(5) Corey, E. J.; Tian, Y. *Org. Lett.* **2005**, *7*, 5535.

(6) For early examples of intramolecular trapping of *N*-alkyl pyridinium salts, see: Weller, D. D.; Luellen, G. R. *Tetrahedron Lett.* **1981**, *22*, 4381. Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597.

(7) For a general discussion of dearomatizing cyclization reactions, see: Ortíz, F. L.; Iglesias, M. J.; Fernández, M. J.; Sánchez, C. M. A.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580. Clayden, J. In *Strategies and Tactics in Organic Synthesis*; Harmata, M., Ed.; Academic Press: New York, 2004; Vol. 4, pp 72−96. 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. Dearomatizing cyclization onto unactivated heteroaromatic rings has been reported: see (for cyclization onto pyridines): Clayden, J.; Hamilton, S. D.; Mohammed, R. T. *Org. Lett.* **2005**, *7*, 3673. (cyclization onto pyrroles): Clayden, J.; Turnbull, R.; Pinto, I. *Org. Lett.* **2004**, *6*, 609. (cyclization onto thiophenes): Clayden, J.; Turnbull, R.; Helliwell, M.; Pinto, I. *Chem. Commun.* **2004**, 2430.

(8) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649. Azumaya, I.; Kagechika, H.; Fujiwara, Y.; Itoh, M.; Yamaguchi, K.; Shudo, K. *J. Am. Chem. Soc.* **1991**, *113*, 2833.

(9) Although pyridine gave an excellent yield of **2b**, we found 2,6-lutidine to be generally more applicable to less reactive substrates.

(10) X-ray crystal data for **2b** have been deposited with the Cambridge Crystallographic Data Centre, deposition nno. 676939.

(11) H-cubeTM manufactured by ThalesNano. See: Desai, B.; Kappe, O. *J. Comb. Chem.* **2005**, *7*, 641.

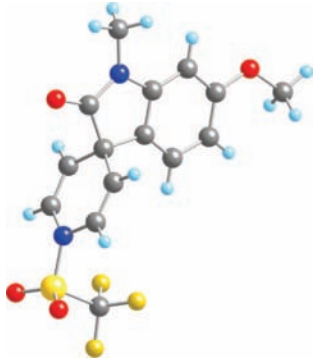
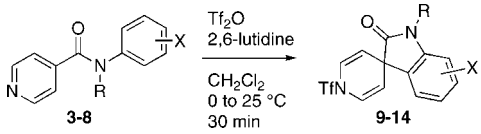


Figure 2. X-ray crystal structure of **2b**.[10]

entries 1−10). Low yields were obtained from electron-deficient anilides **7** and **8** (Table 2, entries 12, 13) Some of a regioisomeric product (**10′**, **11′**, and **14′**) was formed when the substrates were meta-substituted (Table 2, entries 7−10 and 13).

Scheme 2. Scope of the Spirocyclization



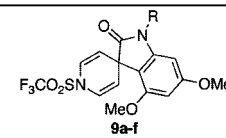
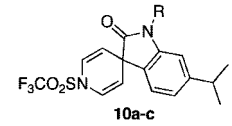
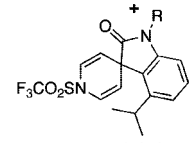
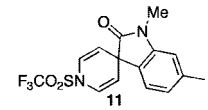
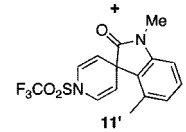
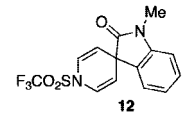
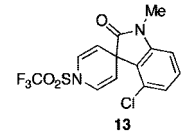
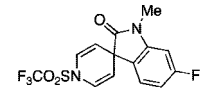
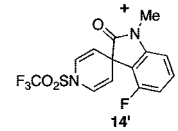
The generally high-yielding cyclizations of the electron-rich substrates prompted us to try cyclizations of similar compounds to give challenging but also more versatile products. Some success was obtained—for example, while an electron-withdrawing *N*-protecting group (Boc or $MeSO_2$) slowed down the cyclization, 3,5-dimethoxy-substituted **3d** and **3e** still gave good yields of cyclized products **9d** and **9e** (Table 2, entries 4 and 5). Triflic anhydride activation was required for all but the most reactive substrates, but the electron-rich anilide **3b** also cyclized to **9f** in excellent yield on treatment with an excess of methyl chloroformate (Table 2, entry 6).

Compounds related to the isonicotinamides were also studied (Scheme 3). Isonicotinic esters cyclized slowly, but the lower degree of activation and the less favorable s-cis conformation of these molecules conspired to make these cyclizations significantly less efficient. Nonetheless, **16** was obtained in yields of 30−43% when the cyclization of **15** was performed in refluxing dichloromethane or dichloroethane.

The isomeric nicotinamide **17** yielded principally the rearomatized pyridine **18** arising from nucleophilic attack of the aryl ring on the 4-position of the pyridine and elimination of trifluoromethylsulfinate, while cyclization of the picolinamide **19** was followed by ring-opening of the resulting 1,2-dihydropyridine to form the dienal **20**.

All of the valuable spirocyclic targets related to the products contain a fully saturated piperidine ring. We

Table 2. Scope of the Spirocyclization

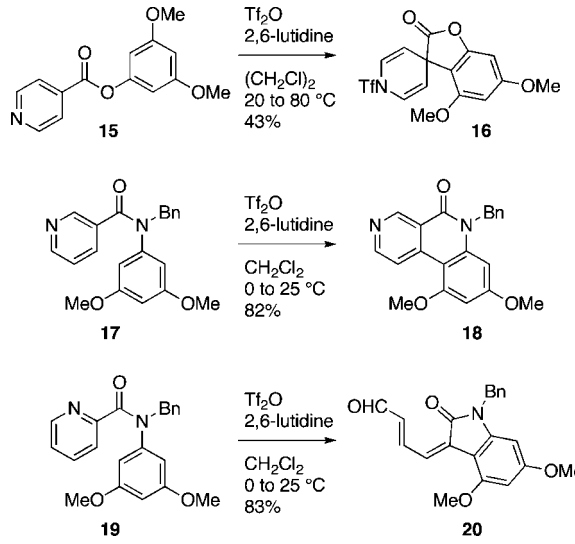
entry	starting material	X =	R =	product(s)	yield (%)
1	**3a**	3,5-di-MeO	Me	 **9a-f**	**9a** 92
2	**3b**		Bn		**9b** 88
3	**3c**		PMB		**9c** 88
4	**3d**		SO_2Me		**9d** 77
5	**3e**		Boc		**9e** 48
6	**3b**		Bn[a]		**9f** 98[a]
7	**4a**	3-*i*-Pr	Me	 **10a-c** +  **10a'-c'**	**10a, 10a'** 48 + 11
8	**4b**		Bn		**10b, 10b'** 50 + 15
9	**4c**		PMB		**10c, 10c'** 43 + 14
10	**5**	3-Me	Me	 **11** +  **11'**	**11, 11'** 43 + 28[b]
11	**6**	H	Me	 **12**	**12** 24[c]
12	**7**	3-Cl	Me	 **13**	**13** 6
13	**8**	3-F	Me	 **14** +  **14'**	**14, 14'** 12 + 17

[a] Eith MeOCOCl (5 equiv). **9f** carries a NCO_2Me substituent. [b] Isolated as an inseparable mixture. [c] Using Et_3N as base.

therefore explored the hydrogenation of the dihydropyridines **9** to yield piperidines **21**. High pressures of hydrogen were required for complete reduction of the dihydropyridines, which was carried out efficiently using a commercial H-cube hydrogenation flow apparatus.[11] After reduction, it proved feasible to deprotect the *N*-benzyl-substituted lactam **21b** by oxidation,[12] yielding **21c**, and the triflyl group by dissolving metal reduction, yielding **21e**.

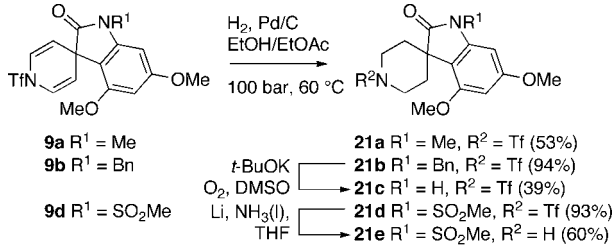
(12) Gigg, R.; Conant, R. *J. Chem. Soc., Chem. Commun.* **1983**, 465.

Scheme 3. Related Cyclizations



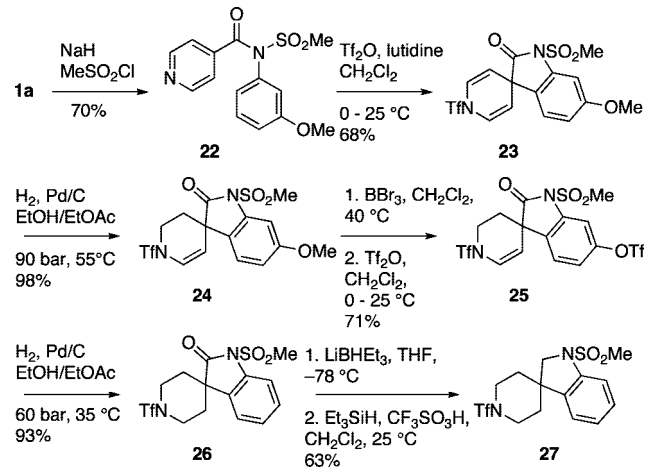
MK-677 is a growth hormone receptor 1a secretagogue containing the otherwise unfunctionalised benzo-fused spirocyclic piperidine core of **27**.[2] Although simple phenyl

Scheme 4. Spiropiperidines by Hydrogenation



substituents had failed to cyclize in good yield (Table 2, entry 11), we succeeded in synthesizing compounds in this class by a reduction strategy exemplified in Scheme 5. Treatment

Scheme 5. Synthesis of a Spirocyclic Piperidine



of the *N*-sulfonylamide **22** (which was made from **1a**) with triflic anhydride and 2,6-lutidine returned the cyclized dihydropyridine **23** in 68% yield. Reduction of this product to the spirocycle **27** was achieved by partial hydrogenation to **24**, demethylation with boron tribromide, and formation of the triflate ester **25**. Further hydrogenation gave the spiropiperidine−oxindole **26**. A final reduction of the lactam ring with superhydride followed by triethylsilane yielded the benzo-fused spirocycle **27**.

Acknowledgment. We acknowledge the support of GlaxoSmithKline, the EPSRC, and the National Science Foundation of South Africa. We thank Mr. James Clayton for synthetic assistance and Dr. Madeleine Helliwell for determining the X-ray crystal structure of **2b**.

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

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