Tetrahedron Letters 52 (2011) 4357–4359

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of substituted 3,9-diazaspiro[5.5]undecanes via spirocyclization of pyridine substrates

Sharavathi G. Parameswarappa, F. Christopher Pigge *

Department of Chemistry, University of Iowa, Iowa City, IA 52242, USA

ARTICLE INFO

Article history:
Received 2 May 2011
Accepted 13 June 2011
Available online 4 July 2011

Keywords:
Pyridine
Spirocyclization
Spiropiperidine
Dearomatization

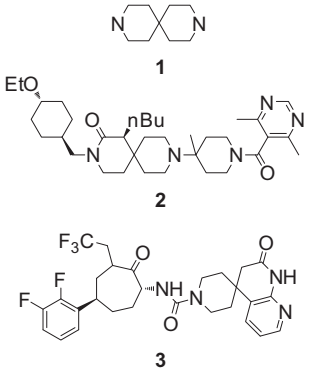
ABSTRACT

Construction of 3,9-diazaspiro[5.5]undecane derivatives can be easily achieved via intramolecular spirocyclization of 4-substituted pyridines. The reaction entails in situ activation of the pyridine ring with ethyl chloroformate followed by intramolecular addition of an attached β-dicarbonyl nucleophile in the presence of $Ti(O^iPr)_4$.

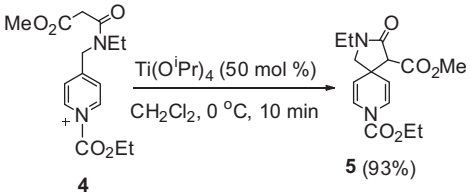
© 2011 Elsevier Ltd. All rights reserved.

Heterocyclic ring systems, particularly aza-heterocycles, are well-recognized as important structural motifs in numerous bioactive compounds. In particular, piperidine and piperazine are often encountered in medicinally active materials. More elaborate structural fragments in which the piperidine ring system has been incorporated into a spirocyclic framework have also emerged as important pharmacophore structures.[1] 3,9-Diazaspiro[5.5]undecanes represent a subset of this compound type that have proven to be especially versatile structural platforms for development of pharmacologically significant bio-active agents.

Recent applications of 3,9-diazaspiro[5.5]undecane (**1**) in medicinal chemistry include the use of N-substituted analogues as antagonists of platelet glycoprotein IIb–IIIa.[2] In addition, functionalized diazaspiroundecane **2** was found to serve as a potent antagonist of chemokine receptor CCR5, a G-protein coupled receptor that has been implicated as a viral binding site for HIV-1.[3] The spiroundecane scaffold **1** has also been utilized as the core structure in QSAR studies aimed at identifying selective CCR8 antagonists that might function as lead compounds for treatment of asthma and other allergic diseases.[4] Compound **3** has been identified as a potential anti-migraine agent by inhibiting binding of calcitonin gene-related peptide (a neuropeptide believed to be important in the pathology of migraines) to its cognate receptor at nanomolar concentration.[5] Other derivatives of **1** have been advanced as selective muscarinic M_3 antagonists with possible relevance to the treatment of chronic obstructive pulmonary disease (COPD).[6]



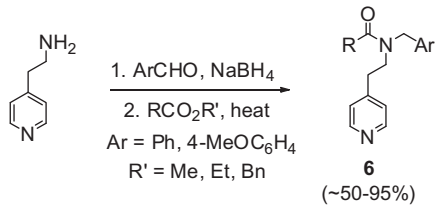
In spite of the favorable therapeutic activity and pharmacokinetic profile of 3,9-diazaspiro[5.5.]undecane derivatives in a number of settings, relatively few routes for the synthesis of these materials have been investigated.[7] In this context, we recently reported the construction of related diazaspiro[4.5]decanes via elaboration of 4-substituted pyridines.[8] Specifically, we found that



(1)

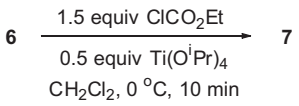
* Corresponding author.
E-mail address: chris-pigge@uiowa.edu (F.C. Pigge).

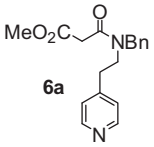
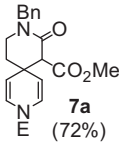
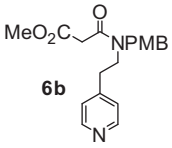
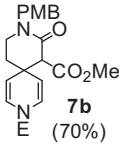
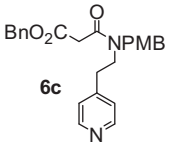
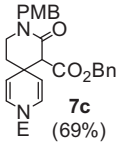
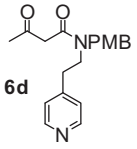
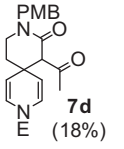
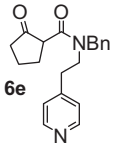
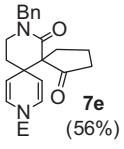
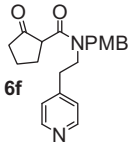
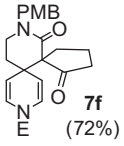
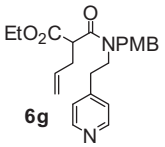
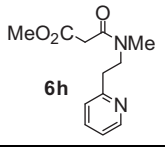
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.06.055



Scheme 1.

Table 1
Conversion of substituted pyridines **6** to 3,9-diazaspiro[undecane] derivatives **7**



Entry	Substrate	Product[a,b]
1	 **6a**	 **7a** (72%)
2	 **6b**	 **7b** (70%)
3	 **6c**	 **7c** (69%)
4	 **6d**	 **7d** (18%)
5	 **6e**	 **7e** (56%)
6	 **6f**	 **7f** (72%)
7	 **6g**	n.p.[c]
8	 **6h**	n.p.[c]

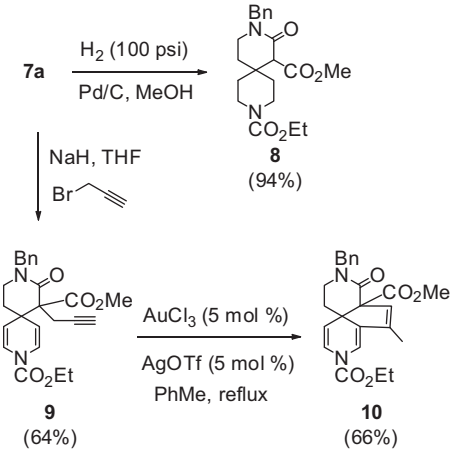
[a] E=CO_2Et.
[b] Numbers in parentheses refer to isolated yield.
[c] No product.

attachment of β-dicarbonyl pro-nucleophiles to an activated pyridine nucleus results in smooth intramolecular spirocyclization in the presence of $Ti(O^iPr)_4$ (Eq 1). Significantly, these transformations proved to be completely compatible with the acidic benzylic position of **4**, and formation of undesired anhydrobases arising from benzylic deprotonation was not observed.[9] Given the demonstrated importance of the homologous spiro(undecane) ring system, we have examined extension of this spirocyclization method to include elaboration of 4-(ethylamino)pyridines as a means for rapid construction of substituted derivatives of **1** suitable for further functionalization.

A series of substrates suitable to evaluate the efficacy of Ti-promoted spirocyclization leading to diaza(undecane) frameworks was assembled in straightforward fashion by the two-step route shown in Scheme 1. Reductive amination of commercially available 4-(aminoethyl)pyridine with either benzaldehyde or *p*-methoxybenzaldehyde afforded the corresponding secondary amine in high yield. Subsequent amidation of the secondary amines upon heating with alkyl ester derivatives gave **6** in good overall yield.

The results of spirocyclization studies are shown in Table 1. The pyridine substrates **6** were subjected to reaction conditions previously developed for the preparation of spirodecane derivatives **5** (Eq 1). Specifically, pyridines **6** were exposed to a slight excess of ethyl chloroformate in order to generate an activated acyl pyridinium salt in situ. In the presence of sub-stoichiometric amounts of $Ti(O^iPr)_4$ intramolecular nucleophilic addition was found to occur rapidly, and the desired spiro(dihydropyridine) products **7** were easily isolated and purified by column chromatography.[10] Pyridine derivatives **6** possessing an amide-ester β-dicarbonyl side chain proved to be the best substrates for cyclization and dihydropyridines **7a–c** were obtained in good yield. An acyclic β-keto amide side chain gave the reaction in significantly lower yield; however, incorporation of the ketone into a cyclopentanone fragment provided tricyclic dihydropyridines **7e** and **7f** reasonably efficiently. Interestingly, incorporation of an alkyl substituent on the activated methylene group in an acyclic β-ester amide side chain appeared to shut down the spirocyclization reaction manifold (Table 1, entry 7). Attempted spirocyclization of a 2-substituted pyridine reactant also failed, presumably a consequence of steric interference with formation of the acyl pyridinium intermediate (Table 1, entry 8).

The results depicted in Table 1 illustrate the facility with which functionalized diazaspiroundecane ring systems can be assembled starting from readily available pyridine precursors. The dearomatized dihydropyridine products **7** are also well-suited for additional synthetic elaboration. For example, hydrogenation of **7a** in the



Scheme 2.

presence of Pd/C catalyst afforded the N-protected spiro-bis(piperidine) **8** via selective reduction of the dihydropyridine ring in excellent yield (Scheme 2). Additionally, **7a** is also amenable to alkylation with carbon electrophiles, as shown in the reaction with propargyl bromide to give **9**. Subsequent gold-catalyzed cycloisomerization of **9** was found to proceed smoothly to provide the novel tricyclic compound **10**.[8,11]

In conclusion, intramolecular spirocyclization of 4-aminoethyl substituted pyridines offers a viable route for accessing 3,9-diazaspiro[5.5]undecane derivatives. Moreover, products of this cyclization manifold (**7**) are susceptible to further synthetic manipulation and so may serve as valuable medicinal chemistry building blocks.

Acknowledgments

We thank the Roy J. Carver Charitable Trust for generous financial support (Grant No. 09-3279). FCP thanks the University of Iowa College of Liberal Arts & Sciences and the Obermann Center for Advanced Studies for sponsorship of a Career Development Award.

Supplementary data

Supplementary data (compound characterization data for **6**–**10**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.055.

References and notes

1. (a) Wang, J.; Cady, S. D.; Balannik, V.; Pinto, L. H.; DeGrado, W. F.; Hong, M. *J. Am. Chem. Soc.* **2009**, *131*, 8066; (b) Methot, J. L.; Hamblett, C. L.; Mamprien, D. M.; Jong, J.; Harsch, A.; Szewczak, A. A.; Dahlberg, W. K.; Middleton, R. E.; Hughes, B.; Fleming, J. C.; Wang, H.; Kral, A. M.; Ozerova, N.; Cruz, J. C.; Haines, B.; Chenard, M.; Kenific, C. M.; Secrist, J. P.; Miller, T. A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6104; (c) Xiao, D.; Palani, A.; Aslanian, R.; McKittrick, B. A.; McPhail, A. T.; Correll, C. C.; Phelps, P. T.; Anthes, J. C.; Rindgen, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 783; (d) Oberdorf, C.; Schepmann, D.; Vela, J. M.; Diaz, J. L.; Holenz, J.; Wünsch, B. *J. Med. Chem.* **2008**, *51*, 6531; (e) Bienaymé, H.; Chêne, L.; Grisoni, S.; Grondin, A.; Kaloun, E.-B.; Poigny, S.; Rahali, H.; Tam, E. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4830; (f) Bondensgaard, K.; Ankersen, M.; Thøgersen, H.; Hansen, B. S.; Wulff, B. S.; Bywater, R. P. *J. Med. Chem.* **2004**, *47*, 888; (g) Kazmierski, W. M.; Furfine, E.; Spaltenstein, A.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3431.
2. Smyth, M. S.; Rose, J.; Mehrotra, M. M.; Heath, J.; Ruhter, G.; Schotten, T.; Seroogy, J.; Volkots, D.; Pandey, A.; Scarborough, R. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1289.
3. Yang, H.; Lin, X.-F.; Padilla, F.; Gabriel, S. D.; Heilek, G.; Ji, C.; Sankuratri, S.; de Rosier, A.; Berry, P.; Rotstein, D. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 209.
4. Shamovsky, I.; de Graaf, C.; Alderin, L.; Bengtsson, M.; Bladh, H.; Börjesson, L.; Connolly, S.; Dyke, H. J.; van den Heuvel, M.; Johansson, H.; Josefsson, B.-G.; Kristoffersson, A.; Linnanen, T.; Lisius, A.; Männikkö, R.; Nordén, B.; Price, S.; Ripa, L.; Rognan, D.; Rosendahl, A.; Skrinjar, M.; Urbahns, K. *J. Med. Chem.* **2009**, *52*, 7706.
5. (a) Burgey, C. S.; Potteiger, C. M.; Deng, J. Z.; Mosser, S. D.; Salvatore, C. A.; Yu, S.; Roller, S.; Kane, S. A.; Vacca, J. P.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6368; See also: (b) Degnan, A. P.; Conway, C. M.; Dalterio, R. A.; Macci, R.; Mercer, S. E.; Schartman, R.; Xu, C.; Dubowchik, G. M.; Macor, J. E. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3555.
6. Stocks, M. J.; Alcaraz, L.; Bailey, A.; Bowers, K.; Donald, D.; Edwards, H.; Hunt, F.; Kindon, N.; Pairaudeau, G.; Theaker, J.; Warner, D. J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7458.
7. (a) Yang, H.; Lin, X.-F.; Padilla, F.; Rotstein, D. M. *Tetrahedron Lett.* **2008**, *49*, 6371. and references cited.; (b) Macleod, C.; Martinez-Teipel, B. I.; Barker, W. M.; Dolle, R. E. *J. Comb. Chem.* **2006**, *8*, 132.
8. Parameswarappa, S. G.; Pigge, F. C. *Org. Lett.* **2010**, *12*, 3434.
9. For other examples of intramolecular nucleophilic additions to pyridines leading to spiro-dihydropyridine products, see: (a) Brice, H.; Clayden, J. *Chem. Commun.* **2009**, 1964; (b) Arnott, G.; Brice, H.; Clayden, J.; Blaney, E. *Org. Lett.* **2008**, *10*, 3089; (c) Arnott, G.; Clayden, J.; Hamilton, S. D. *Org. Lett.* **2006**, *8*, 5325; (d) Goldmann, S.; Born, L.; Kazda, S.; Pittel, B.; Schramm, M. *J. Med. Chem.* **1990**, *33*, 1413; (e) Weller, D. D.; Stirchak, E. P.; Weller, D. L. *J. Org. Chem.* **1983**, *48*, 4597.
10. The preparation of **7a** is representative. Under Ar, a solution of **6a** (0.50 g, 1.6 mmol) in dichloromethane (10 mL) was cooled to 0 °C. Titanium isopropoxide (0.24 mL, 0.8 mmol) was added and the reaction was stirred for 2 min. Ethyl chloroformate (1.52 mL, 2.4 mmol) was then added and the reaction stirred an additional 5–7 min. The reaction mixture was then loaded directly onto a silica gel column and purified using 75% EtOAc in hexanes as the eluent to afford **7a** as a yellow gummy oil (0.44 g, 72%). ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 7.37–7.26 (m, 5H), 6.94–6.83 (m, 2H), 4.84–4.66 (m, 4H), 4.25 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.44 (s, 1H), 3.37–3.18 (m, 2H), 2.11–2.00 (m, 1H), 1.76–1.67 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 169.2, 164.6, 151.1, 136.7, 128.8, 128.1, 127.7, 123.3, 109.6, 109.1, 107.7, 107.1, 63.0, 60.9, 52.3, 50.3, 41.6, 36.9, 35.1, 14.5. IR (thin film) ν (cm^{-1}) 1722, 1686, 1646. HRMS (ESI): calculated for $C_{21}H_{24}N_2O_5Na$ [M+Na]$^+$, 407.1583; found 407.1593.
11. Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326.