ORGANIC LETTERS

2013
Vol. 15, No. 23
6094–6097

Modular, Gold-Catalyzed Approach to the Synthesis of Lead-like Piperazine Scaffolds†

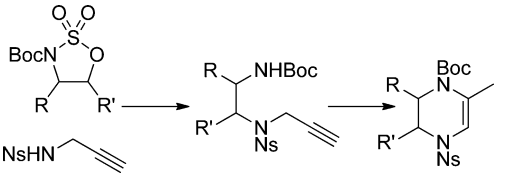
Thomas James,[§] Iain Simpson,[‡] J. Andrew Grant,[‡] Visuvanathar Sridharan,[§] and Adam Nelson*,[§]

School of Chemistry and Astbury Centre for Structural Molecular Biology, University of Leeds, LS2 9JT Leeds, U.K., and AstraZeneca, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, U.K.

a.s.nelson@leeds.ac.uk

Received October 17, 2013

ABSTRACT



Ring-opening of cyclic sulfamidates with propargylic sulfonamides yielded substrates for a gold-catalyzed cyclization to yield tetrahydropyrazines. Manipulation of the tetrahydropyrazines, by reduction or using multicomponent reactions, yielded piperazine scaffolds in which substitution of the carbon atoms was varied. Such scaffolds may have value in the synthesis of novel screening compounds with lead-like molecular properties.

Sourcing large numbers of diverse, lead-like small molecules is a major challenge in maintaining high-quality screening collections.[1,2] This challenge stems both from the poor availability of lead-like compounds[2] and the historically uneven exploration of chemical space by synthesis.[3] As an example, many commercially available screening compounds and bioactive molecules contain a piperazine ring (5.4% of the ZINC database and 7.7% of the ChEMBL database respectively; Supporting Information). Yet, in the vast majority of these compounds, the piperazine ring is isolated and is not substituted on any of its carbon atoms. Such piperazines are widely exploited in drug discovery because they allow the medicinal chemist to design molecules that may be grown in two directions while retaining basicity through appropriate substitution. As a result, many important bioactive small molecules are piperazines, including 13 of the 200 best-selling drugs in 2012.[4]

In this paper, we describe an approach to the synthesis of substituted piperazines from pairs of biconnective[5] building blocks (Scheme 1).[6] Ring-opening of a cyclic sulfamidate **1**,[7,8] prepared from the corresponding amino alcohol, with a propargylic sulfonamide **2** would yield a substrate, **3**, for a cyclization reaction. Metal-catalyzed cyclization[9,10] of the *N*-Boc- (or *N*-Cbz-)protected amine onto the alkyne would then yield a heterocyclic product **4**. This synthesis of tetrahydropyrazines **4** from the biconnective building

† Dedicated to the memory of J. Andrew Grant, a great colleague, collaborator, and scientist.

‡ AstraZeneca.

§ University of Leeds.

(1) Krier, M.; Bret, G.; Rognan, D. *J. Chem. Inf. Model.* **2006**, *46*, 512.

(2) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem., Int. Ed.* **2012**, *51*, 1114.

(3) Lipkus, A. H.; Yuan, Q.; Lucas, K. A.; Funk, S. A.; Bartelt, W. F.; Schenck, R. J.; Trippe, A. J. *J. Org. Chem.* **2008**, *73*, 4443.

(4) The structures of the top 200 selling drugs can be downloaded from: http://cbc.arizona.edu/njardarson/group: McGrath N. A.; Brichacek M.; Njardarson, J. T . *J. Chem. Educ.* 2010, *87*, 1348.

(5) MacLellan, P.; Nelson, A. *Chem. Commun.* **2013**, 2383.

(6) For a recent approach to substituted piperazines, see: Ruider, S. A.; Müller, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11908.

(7) For a review of the application of cyclic sulfamidates in heterocycle synthesis, see: Bower, J. F.; Rujirawanich, J.; Gallagher, T. *Org. Biomol. Chem.* **2010**, *8*, 1505.

(8) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811.

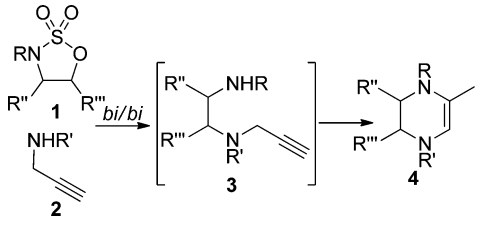
(9) For other similar cyclizations, see: (a) Nicolai, S.; Waser, J. *Org. Lett.* **2011**, *13*, 6324. (b) Han, J.; Xu, B.; Hammond, G. B. *J. Am. Chem. Soc.* **2010**, *132*, 916.

(10) For cyclizations of *N*-propargylamides to yield oxazoles, see: (a) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391. (b) Weyrauch, J. P.; Hashmi, A. S. K.; Schuster, A.; Hengst, T.; Schetter, S.; Littmann, A.; Rudolph, M.; Hamzic, M.; Visus, J.; Rominger, F.; Frey, W.; Bats, J. W. *Chem.—Eur. J.* **2010**, *16*, 956.

10.1021/ol402988s
Published on Web 11/12/2013

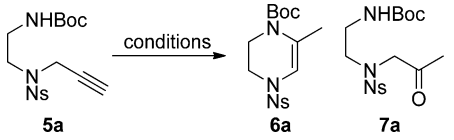
blocks **1** and **2** may be classified as a *bi*/*bi* process[5] or as an ambiphile[11] pairing reaction sequence. It was envisaged that the ene−diamine functionality might serve as a useful handle for decoration to yield small molecules with lead-like[2] properties.

Scheme 1. Overview of the Proposed Modular Synthetic Approach[a]



[a] R = Boc or Cbz; R′ = *o*- or *p*-nitrophenylsulfonyl.

Table 1. Optimization of the Synthesis of the Tetrahydropyrazine **6a**[a]



entry	conditions	yield **6a** (%)
1	5 mol % $Au(PPh_3)Cl$, 5 mol % $AgSbF_6$, dioxane, 100 °C, μw, 10 min	98
2	5 mol % $Au(PPh_3)Cl$, 5 mol % $AgSbF_6$, dioxane, 100 °C, 3 h	95
3	5 mol % $Au(PPh_3)Cl$, 5 mol % $AgSbF_6$, CH_2Cl_2, rt, 16 h[c]	83[d]
4	1 mol % Au(IPr)Cl,[b] 1 mol % $AgSbF_6$, dioxane, 100 °C, μw, 10 min	97

[a] Ns = *o*-nitrophenylsulfonyl. [b] IPr = 1,3,-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene. [c] Analysis of the crude reaction mixture by 500 MHz ^{1}H NMR spectroscopy revealed a 85:15 mixture of the tetrahydropyrazine **6a** and the ketone **7a**. [d] The ketone **7a** was also obtained in 15% yield.

Initially, the cyclization of the substrate **5a** (and subsequent double bond isomerization[10]) was investigated (Table 1).[12] With 5 mol % of $Au(PPh_3)Cl$ and 5 mol % of $AgSbF_6$[13] in dioxane at 100 °C with microwave irradiation, the tetrahydropyrazine **6a** was obtained in 98% yield after 10 min (Table 1, entry 1). With heating at 100 °C in dioxane, **6a** was obtained in 95% yield, although a longer reaction time (3 h) was required (Table 1, entry 2). At room temperature in dichloromethane, **6a** (83%) was accompanied by the ketone **7a** (15%) (Table 1, entry 3). Additional experiments demonstrated that the ketone **7a** is a kinetic product of this reaction and is a competent intermediate in the formation of the thermodynamic product, **6a**. Cyclization was also effective with 1 mol % of the *N*-heterocyclic carbene complex[14] Au(IPr)Cl and 1 mol % of $AgSbF_6$, yielding **6a** in 97% yield (Table 1, entry 4).

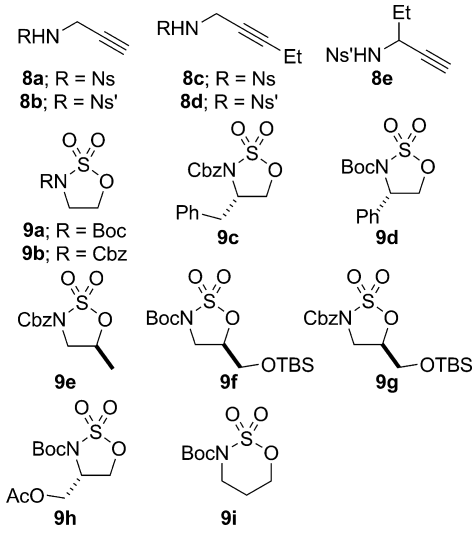


Figure 1. Structures of building blocks. Ns = *o*-nitrophenylsulfonyl; Ns′ = *p*-nitrophenylsulfonyl.

A range of building blocks (Figure 1) was prepared to allow the investigation of the scope and limitations of the cyclization reaction. The potential substrates **5** were prepared by treatment of a propargylic sulfonamide **8** with sodium hydride in DMF and reaction with a cyclic sulfamidate **9** (Table 2).

The cyclization substrates **5b**−**i** were treated with 5 mol % of $Au(PPh_3)Cl$ and 5 mol % of $AgSbF_6$ in dioxane at 100 °C (Table 2 and Figure 2). Under these conditions, the substrates **5b**−**e** and **5g**−**i** cyclized smoothly to give the corresponding tetrahydropyrazines in 79−98% yield. This study demonstrated that either a Boc- or a Cbz-protected amine is a competent nucleophile in the cyclization. However, **5f** possesses two potential nucleophiles, a Boc-protected amine and an alcohol, positioned at the same distance from the alkyne: at 100 °C in dioxane, the two possible products, **6f** and **10**,[15] were obtained in 36% and 48% yield, respectively. The outcome was controlled at room temperature, and the dihydrooxacine **10** (81%) was the only product observed.

(11) Rolfe, A.; Samarakoon, T. B.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 1216.

(12) (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Ito, H.; Harada, T.; Ohmiya, H.; Sawamura, M. *Beilstein J. Org. Chem.* **2011**, *7*, 951. (c) Zhang, Y.; Donahue, J. P.; Li, C.-J. *Org. Lett.* **2007**, *9*, 627. (d) Kang, J.-E.; Kim, H.-B.; Lee, J.-W.; Shin, S. *Org. Lett.* **2006**, *8*, 3537. (e) Müller, T. E.; Grosche, M.; Herdtweck, E.; Pleier, A.-K.; Walter, E.; Yan, Y.-K *Organometallics* **2000**, *19*, 170.

(13) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.

(14) Marion, N.; Ramón, R. S.; Nolan, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 448.

(15) For a base-catalyzed cyclization to give 1,4-oxazines, see: Vandavasi, J. K.; Hu, W.-P.; Chen, H.-Y.; Senadi, G. C.; Chen, C.-Y.; Wang, J.-J. *Org. Lett.* **2012**, *14*, 3134.

(16) In contrast, the reactions of **5j**−**m**, catalyzed by 5 mol% of $Au(PPh_3)Cl$ and 5 mol% of $AgSbF_6$ in dioxane at 100 °C, were not clean.

Table 2. Synthesis and Gold-Catalyzed Reactions of Alkyne Substrates (See Figure *2*)

entry	building blocks	substrate[a] (method[b], yield (%))	product[a] (method[b], yield (%))
1	**8a**, **9b**	**5b** (A1, 95)	**6b** (B1, 98)
2	**8a**, **9c**	**5c** (A1, 72)	**6c** (B1, 90)
3	**8b**, **9d**	**5d** (A1, 70)	**6d** (B1, 96)
4	**8a**, **9e**	**5e** (A1, 94)	**6e** (B1, 96)
5	**8b**, **9f**	**5f** (A1, 68)	**6f** (B1, 36)[c]
6		**5f**	**10** (B2, 81)
7	**8b**, **9f**	**5g** (A2, 74)	**6g** (B1, 79)
8	**8b**, **9g**	**5h** (A2, 67)	**6h** (B1, 85)
9	**8b**, **9h**	**5i** (A1, 89)	**6i** (B1, 92)
10	**8c**, **9a**	**5j** (A1, >98)	**7b** (B3, 68)
11	**8d**, **9b**	**5k** (A1, 91)	**7c** (B3, 85)
12	**8e**, **9b**	**5l** (A1, 90)	**7d** (B3, 46)
13	**8c**, **9i**	**5m** (A1, 83)	**7e** (B3, 61)

[a] Ns = *o*-nitrophenylsulfonyl; Ns′ = *p*-nitrophenylsulfonyl. [b] Methods: (A1) **8**, NaH (1.1 equiv), DMF then **9** then 5 M HCl; (A2) **8**, NaH (1.1 equiv), DMF then **9** then 1 M citric acid solution; (B1) 5 mol % $Au(PPh_3)Cl$, 5 mol % $AgSbF_6$, dioxane, 100 °C; (B2) 5 mol % $Au(PPh_3)Cl$, 5 mol % $AgSbF_6$, $CDCl_3$, rt; B3: 1 mol % Au(IPr)Cl, 1 mol % $AgSbF_6$, 2:1 dioxane−H_2O, 120 °C, sealed tube (IPr = 1,3,-Bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene). [c] **10** was also obtained in 48% yield.

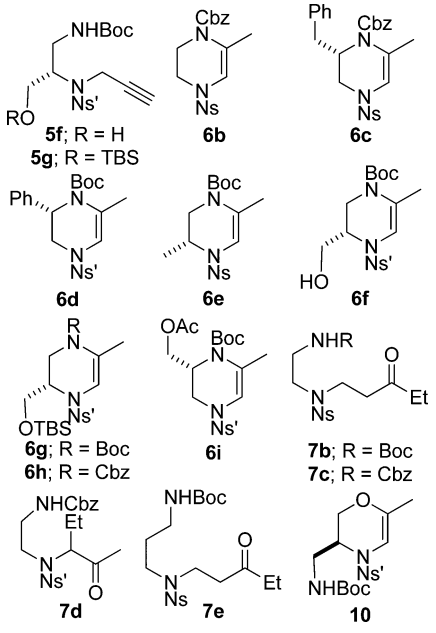


Figure 2. Structures of the substrates **5f**,**g** and the products of gold-catalyzed reactions. [a]Ns = *o*-nitrophenylsulfonyl; Ns′ = *p*-nitrophenylsulfonyl.

The reactions of **5j**−**m** could be controlled by using 1 mol % of Au(IPr)Cl and 1 mol % of $AgSbF_6$ in 2:1 dioxane−H_2O at 120 °C in a sealed tube (entries 10−13, Table 2); under these conditions, highly regioselective hydration of the alkyne was observed.[16,17] With the 1,2-disubstituted alkynes **5j**, **5k**, and **5m**, hydration occurred distal to the N-sulfonyl group, which might be explained by the intermediacy of a chelated intermediate (Figure 3).[18,19]

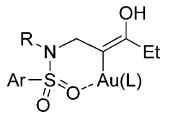


Figure 3. Proposed intermediate in the highly regioselective hydration of the 1,2-disubstituted alkynes **5j**, **5k**, and **5m**.

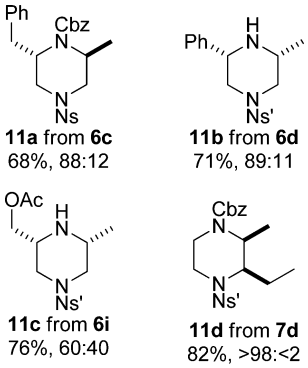


Figure 4. Products of the reductions of the tetrahydropyrazines **6** and the ketone **7d**. Where appropriate, the major diastereomeric product is drawn. Method: TFA (10 equiv), Et_3SiH (6 equiv), CH_2Cl_2, 0 °C → rt.

The tetrahydropyrazines **6c**−**d** and **6i**, and the ketone **7d**, were reduced to the corresponding piperazines by treatment with triethylsilane and trifluoroacetic acid (Figure 4). The sense of diastereoselectivity depended on the identity of the carbamate protecting group. With the Cbz-protected substrate **6c**, the 2,6-*trans*-disubstituted piperazine **11a** was obtained predominantly, presumably as a result of axial attack of the reducing agent on the conformation of the intermediate iminium ion in which 1,3-strain[20] is minimized. The Boc-protected substrates **6d** and **6i** yielded predominantly the 2,6-*cis*-disubstituted piperazines **11b** and **11c**; here, Boc deprotection may precede reduction via an alternative reactive conformation. Finally, reductive amination of the NHCbz-substituted ketone **7d** yielded highly selectively the 2,3-*cis*-disubstituted piperazine **11d**.

Multicomponent reactions of the tetrahydropyrazines **6a** and **6i** and the NHBoc-substituted ketone **7b** were also

(17) See also: Hashmi, A. S. K.; Molinari, L.; Rominger, F.; Oeser, T. *Eur. J. Org. Chem.* **2011**, 2256.

(18) Tsukano, C.; Yokouchi, S.; Girard, A.-L.; Kuribayashi, T.; Sakamoto, S.; Enomoto, T.; Takemoto, Y. *Org. Biomol. Chem.* **2012**, *10*, 6074.

(19) For a related directing effect, see: Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, S. K. A. *Angew Chem. Int. Ed.* **2013**, *52*, 2593.

(20) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

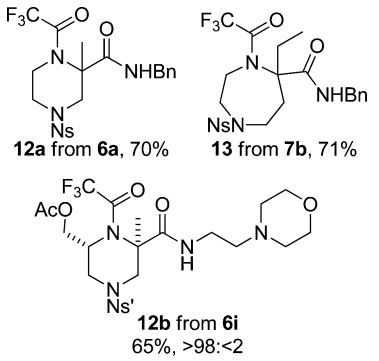


Figure 5. Products of the multicomponent reactions of the tetrahydropyrazines **6** and the ketone **7b**. Where appropriate, the major diastereomeric product is drawn. Method: (1) TFA, CH_2Cl_2 then evaporate; (2) benzylisontrile or 2-morpholinoethylisonitrile, EtOH, 0 °C.

investigated (Figure 5). In each case, the substrate was treated with TFA in dichloromethane, evaporated, and treated with an isonitrile in ethanol. The tetrahydropyrazines **6a** and **6i** yielded the differentially protected piperazine carboxylic acid derivatives **12a**,**b**.[21] The reaction of **6i** was highly (> 98: < 2) diastereoselective; the sense of diastereoselectivity may stem from minimization of steric interactions in the product-determining transition state of

(21) Bowers, M. M.; Carroll, P.; Joullié, M. M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 857.

(22) El Kaim, L.; Grimaud, L. *Tetrahedron* **2009**, *65*, 2153.

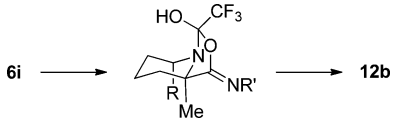


Figure 6. Rationalization of stereochemical outcome of the multicomponent reaction of **6i**.

the Mumm rearrangement (Figure 6).[22] Finally, the ketone **7b** was converted into the 1,4-diazepane **13** in 71% yield.

In summary, we have developed a modular approach to the synthesis of lead-like piperazine scaffolds. The approach involves reaction between cyclic sulfamidate and propargylic sulfonamide building blocks to yield substrates for a gold-catalyzed cyclization reaction. Crucially, by variation of the specific building blocks used, it was possible to be vary the substitution and relative configuration of the piperazine scaffolds obtained. It is envisaged that the approach may be exploited in the synthesis of libraries of substitutionally diverse piperazines with lead-like molecular properties.

Acknowledgment. We thank AstraZeneca and EPSRC for funding.

Supporting Information Available. General experimental procedures and spectra of key transformations. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.