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A general method for the facile synthesis of optically active 2-substituted piperazines via functionalized 2,5-diketopiperazines

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ABSTRACT

Upon utilization of some common methods described in the literature for the synthesis of chiral, 2-substituted 2,5-diketopiperazines, extensive racemization was observed. Further investigation showed that heating in the presence of a mild base racemized the chiral center in the product diketopiperazines. A generalized, readily scalable route was sought and, after investigating the effect of base and temperature, conditions were identified that promoted cyclization without erosion of enantiomeric excess. An array of functionalization was tolerated and this procedure serves as a useful and reliable method for the facile synthesis of this important class of compounds.

Piperazines with substituents at the 2-position are useful intermediates in the synthesis of numerous pharmacologically active molecules (Fig. 1).[1] While there are multiple methods reported to access 2-substituted piperazines via installation of a chiral substituent at a late stage, many of these methods have drawbacks such as low enantiomeric purities or the use of chiral auxiliaries.[2]

During the course of the synthesis of AMG-1694 (**4**, Fig. 1),[3] we had to not only quickly access varied substitution of the piperazine

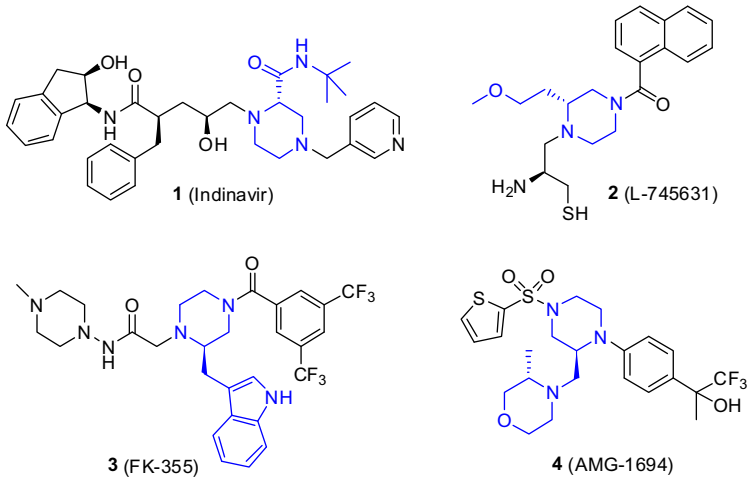

Figure 1. Representative examples of biologically active molecules containing 2-substituted piperazines.

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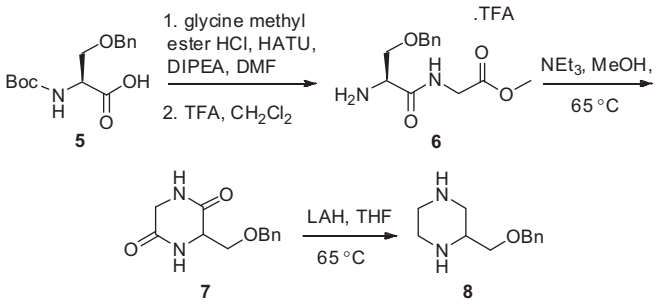


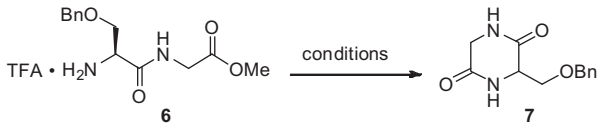
Scheme 1.

core for the purpose of rapid structure–activity relationship analysis, but we also envisaged that scale-up of these compounds would also be a requirement. We surveyed the literature in search of an appropriate synthesis of chiral 2-substituted piperazines and the initial route we examined involved the reduction of 2,5-diketopiperazine **7** to obtain a key piperazine intermediate (**8**).[4] Diketopiperazine **7** was accessed by the base-promoted cyclization of dipeptide **6**, which in turn was prepared from the commercially available protected amino acid **5** in two simple steps (Scheme 1).

Using these, literature prevalent, reaction conditions (Table 1, entry a),[5–7] the desired 2-substituted piperazine product was obtained in good yield. However, it was found to have completely racemized during the cyclization step. In attempts to eliminate this racemization we also examined several other commonly reported cyclization conditions to prepare either mono- or di-substituted diketopiperazines. In the case of di-substituted dipeptides, there are several publications that describe generalized conditions for the formation of 2,5-di-substituted diketopiperazines, where reasonable to good yields and high enantiomeric purities were obtained.[8] However, application of these methods to our system did not provide the correspondingly enantiomerically pure product. For example, heating compound **6** in water at high temperatures in the presence of triethylamine resulted in extensive hydrolysis of the ester and less than 25% cyclized product was observed (Table 1, entry b). Alternatively, no product formation was observed after heating the trifluoroacetic acid salt of compound **6** for 16 h in MeOH in the absence of a base (Table 1, entry c).

After the unsuccessful application of several literature procedures it was apparent that standardized conditions to form diverse, enantioenriched 2-substituted piperazines had not been fully explored. Therefore, we examined various reaction conditions for the cyclization of compound **6**, not only to optimize the preparation of compound **7**, but also to gain a better understanding of the factors influencing the enantiomeric outcome of the reaction (Table 1). As a result of this investigation, we identified a general and simple procedure for the synthesis of 2-substituted 2,5-diketopiperazines while maintaining high stereochemical integrity.

Table 1
Effects of solvent, base, and heat on cyclization reaction times and racemization



Entry	Solvent	Base	Temp (°C)	Time[b] (h)	ee (%)
a	MeOH	Et_3N	65	10–16	0
b	H_2O	Et_3N	100	n/a	n/a
c	MeOH	—	65	n/a	n/a
d[a]	MeOH	—	65	48	98
e	MeOH	Et_3N	23	16	>99
f	MeOH	NH_3	23	4	>99
g	MeOH	NH_3	65	0.25	>99
h	MeOH	NH_3	60	0.5	97
i	MeOH	NH_3	50	1	92
j	MeOH	NH_3	40	2	91
k	MeOH	NH_3	65	1	0

[a] This reaction used the amine free base.
[b] Time to full conversion as monitored by LCMS.

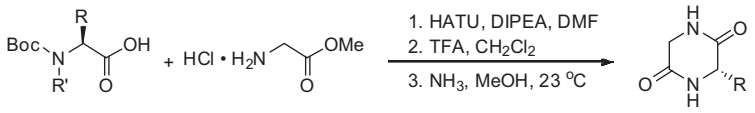
For this study we choose the benzyl protected serine glycinate **6** as the model substrate. This compound was of interest as it provided access to a key intermediate in Amgen's GKRP program,[3] and it had also proven to be a substrate that was particularly prone to racemization. The effects of varying the base and temperature on the enantiomeric excess of the product **7** are shown in Table 1.[9]

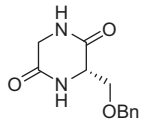
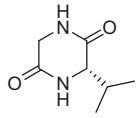
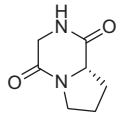
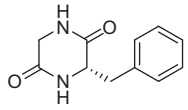
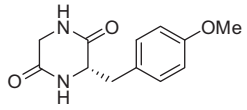
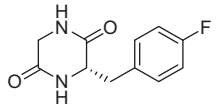
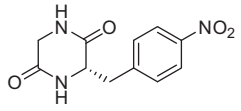
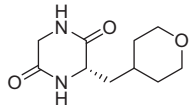
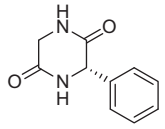
In the absence of base (entry d), the amine free base cyclized after two days at reflux temperature with minimal racemization. Although these conditions were attractive, since they provided the product in high enantiomeric purity, we wanted to eliminate the need to isolate the free amine[10] to make the protocol more amenable for large scale preparations. In addition, shorter reaction times were preferable, and therefore, additional conditions were examined. As previously noted, the use of triethylamine as a base reduced the reaction time significantly (entry a); however, it also resulted in complete erosion of the enantiomeric purity.[11] Simply running the reaction at room temperature (entry e) was sufficient to prevent racemization, however, these conditions still necessitated a long reaction time. The optimized conditions were achieved by running the reaction at room temperature and by employing ammonia (used as a 2 M solution in methanol) as the base (entry f). These conditions resulted in complete conversion in 4 h and no racemization. Continued stirring of **7** in methanolic ammonia for 24 h at room temperature resulted in a minimal loss of enantiomeric excess (1%). These conditions, occasionally referred to as the 'Fischer method',[12] have been reported to promote racemization.[13] However, this result was only highlighted in publications concerning di-substituted diketopiperazines, and it does not appear to translate to the mono-substituted diketopiperazines. The Fischer method is also reported to take several days for di-substituted diketopiperazine formation, which could contribute to the loss of optical integrity. In addition, there are several examples in the literature of methanolic ammonia being used at high temperatures to effect cyclization,[14] so we investigated the effect of heating the reaction. Brief exposure of substrate **6** in methanolic ammonia to temperatures above 60 °C resulted in very efficient cyclization (entries g and h), and the enantiomeric purity was only slightly affected when the reaction time was less than 30 min. However, running the reaction at lower temperatures required longer reaction times to go to full conversion (entries i and j), and this resulted in a deleterious effect on the enantioenrichment of the product. Entry k demonstrates further that prolonged exposure of the reaction to elevated temperatures results in rapid, complete erosion of the enantiomeric excess.[15]

In conclusion, although the cyclization of dipeptide **6** can be run at high temperatures without the erosion of the enantiomeric purity, it requires careful monitoring. In addition, temperature did not reduce the reaction time significantly when using methanolic ammonia as the base. Moreover, reaction times would likely vary for different substrates and this would make it difficult to establish generalized conditions involving heating of the reaction. Therefore, we concluded that, for a broadly applicable method, the cyclization was best conducted at room temperature in the presence of methanolic ammonia. To examine the scope of the reaction we used these general conditions to cyclize a variety of substrates (Table 2).

This method was found to be effective for both alkyl (**9** and **10**) and 4-substituted phenylalanine derivatives with varied electronic properties (**11**–**14**). In addition, the substrate with the large alkyl

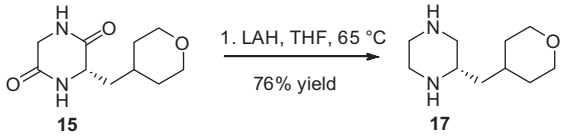
Table 2
Synthesis of varied 2-substituted diketopiperazines



Compd No.	Product	Isolated yield[a] (%)	ee[b] (%)	Time[c] (h)
7		80	>99	4
9		63	>99	3
10		60	>99	4
11		74	>99	4
12		78	>99	4
13		79	>99	4
14		79	>99	5
15		47	>99	4
16		59	>99	2

[a] Represents isolated yield over three steps.
[b] Determined by SFC analysis.
[c] Time for complete cyclization to occur as monitored by LCMS.

tetrahydropyran substituent also cyclized efficiently under the reaction conditions to give compound **15**.[16] Considering the electron-withdrawing nature of an aryl group directly attached to the piperazine ring, we were pleasantly surprised to find that the procedure was also applicable to phenylglycine derivative **16**. For all substrates, the cyclizations were complete in less than 5 h.



Scheme 2. Reduction to chiral 2-substituted piperazine **16**.

As a representative example, Scheme 2 shows that the optically pure 2,5-diketopiperazine **15** can be readily reduced by lithium aluminum hydride to access the desired 2-substituted piperazine intermediate **17** in good yield with no erosion of the enantiomeric excess.[17]

In summary, we have investigated an operationally simplistic, general method to access enantiomerically pure, 2-substituted 2,5-diketopiperazines.[18] Although variations of this protocol have been reported previously, to the best of our knowledge the current literature does not systemically investigate the instability of the chiral center with regard to base and elevated temperatures. In addition to the lowered risk of racemization, this method is appealing given that the stereochemistry is derived from readily available amino acids, no chromatography is required, and the mild

conditions and operational simplicity lend this process to large-scale preparations.[19,20]

Acknowledgment

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Supplementary data

Supplementary data (detailed conditions for each substrate shown in Table 2 and characterization data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.06.058.

References and notes

1. For example, the 2-piperazine motif is contained within: (a) marketed drug Indinavir, see: Dorsey, B. D.; Levin, R. B.; McDaniel, S. L.; Vacca, J. P.; Guare, J. P.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Quintero, J. C.; Lin, J. H.; Chen, I.-W.; Holloway, M. K.; Fitzgerald, P. M. D.; Axel, M. G.; Ostovic, D.; Anderson, P. S.; Huff, J. R. *J. Med. Chem.* **1994**, *37*, 3443; L-745631 (a ras farnesyltransferase inhibitor), see: (b) Leonard, D. M. *J. Med. Chem.* **1997**, *40*, 2971–2990; (c) FK-335 (neurokinin-1 [NK-1] inhibitor), see: Matsuo, M.; Hagiwara, D.; Manabe, T.; Konishi, N.; Shigenaga, S.; Murano, K.; Matsuda, H.; Miyake, H. PCT Int. Appl., to Fujisawa Pharmaceuticals, WO Patent 9637489 A1, 1996.; AMG-1694 (a GK-GKRP disruptor), see: (d) Lloyd, D. J.; St. Jean, D. J., Jr.; Kurzeja, R. J. M.; Wahl, R. C.; Michelsen, K.; Cupples, R.; Chen, M.; Wu, J.; Sivits, G.; Helmering, J.; Ashton, K. S.; Pennington, L. D.; Fotsch, C. H.; Vazir, M.; Chen, K.; Chmait, S.; Zhang, J.; Liu, L.; Norman, M. H.; Andrews, K. A.; Bartberger, M. D.; Van, G.; Galbreath, E. J.; Vonderfecht, S. L.; Wang, M.; Jordan, S. R.; Véniant, M. M.; Hale, C. *Nature* **2013**, *504*, 437.
2. (a) Anderson, H.; Banchelin, T. S.; Das, S.; Gustafsson, M.; Olsson, R.; Almqvist, F. *Org. Lett.* **2010**, *12*, 284; (b) Schanen, V.; Cherrier, M.; Sebastião, J.; Quirion, J.; Husson, H. *Synthesis* **1996**, 833; (c) Jin, S.; Liebscher, J. *Synlett* **1999**, 459; (d) Crestey, F.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *J. Org. Chem.* **2009**, *74*, 5652; (e) Gao, H.; Renslo, A. R. *J. Org. Chem.* **2007**, *72*, 8591.
3. Ashton, K. S.; Andrews, K. L.; Bryan, M. C.; Chen, J.; Chen, K.; Chen, M.; Chmait, S.; Croghan, M.; Cupples, R.; Fotsch, C.; Helmering, J.; Jordan, S. R.; Kurzeja, R. J. M.; Michelsen, K.; Pennington, L. D.; Poon, S. F.; Sivits, G.; Van, G.; Vonderfecht, S. L.; Wahl, R. C.; Zhang, J.; Lloyd, D. J.; Hale, C.; St. Jean, D. J., Jr. *J. Med. Chem.* **2014**, *57*, 309.
4. For a review on DKP syntheses, see Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, 3297.
5. A Scifinder search for 2-substituted diketopiperazines as the product of a reaction returned over 600 reactions, and triethylamine was the most common reagent used (although the use of triethylamine in the reaction sequence was not always used to effect the cyclization). Numerous examples that use triethylamine and elevated temperatures to promote the formation of a 2-substituted diketopiperazine were found, some are listed: (a) Aicher, T. D.; Chen, Z.; Chen, Y.; Faul, M. M.; Krushinski Jr., J. H.; Le Hureou, Y.; Pineiro-Nunez, M. M.; Rocco, V. P.; Ruley, K. M.; Schaus, J. M.; Thompson, D. C.; Tupper, D. E. WO Patent 2003/082877, 2003. (over 50 different diketopiperazines with various 2-substituents are listed in this reference, a single isomer is claimed as the product in each instance).; (b) Su, X.; Zhu, J.; Nie, F. PCT Appl., Nanjing University of Technology, CN201110025008, 2011.; (c) Terada, K.; Masuda, T.; Sanda, F. *Macromolecules* **2009**, *42*, 913; (d) Li, Y.; Bacon, K.; Sugimoto, H.; Fukushima, K.; Hashimoto, K.; Marumo, M.; Moriwaki, T.; Nunami, N.; Tsuno, N.; Urbahns, K.; Yoshida, N.; WO Patent 2004/084898, 2004.
6. The second most common cyclization method utilized was hydrogenation to remove the protecting group and cyclization of the free base. This procedure used a benzyl group instead of Boc on the initial amino acid. We did not pursue this method as we were using a benzyl protected serine, thus we would have had possibly encountered difficulty in removing either of the benzyl groups selectively. We also evaluated the number of commercially available Boc and benzyl protected amino acids and determined that Boc protected analogs were more widely available. In addition, the route we ultimately optimized avoids the use of H_2 gas and flammable catalyst, an advantage when dealing with large quantities of material.
7. Chiral diketopiperazines have been reported to racemize under basic conditions: Smith, G. G.; Baum, R. *J. Org. Chem.* **1987**, *52*, 2248–2255.
8. (a) Suzuki, K.; Sasaki, Y.; Endo, N.; Mihara, Y. *Chem. Pharm. Bull.* **1981**, *29*, 233; (b) Ueda, T.; Saito, M.; Kato, T.; Izumiya, N. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 568; (c) Tullberg, M.; Grotli, M.; Luthman, K. *Tetrahedron* **2006**, *62*, 7484; (d) Perez-Picaso, L.; Escalante, J.; Olivo, H. F.; Rios, M. Y. *Molecules* **2009**, *14*, 2836. This method (heating the Boc-precursor at 200 °C in water in a sealed tube) was not attempted on our system, as the previous reference suggested that it was substrate limited.
9. The SFC method used was as follows: Chiralpak® ADH column (4.6 × 150 mm) using 25% ethanol in supercritical CO_2 (total flow was 4 mL/min).
10. Free basing the substrate prior to cyclization required an aqueous work-up, something we wanted to avoid on large scale.
11. These conditions were also used in the cyclization of material derived from Boc-phenylglycine and resulted in complete racemization.
12. Fischer, E. *Chem. Ber.* **1906**, *39*, 2893.
13. Nitecki, D. E.; Halpern, B.; Westley, J. W. *J. Org. Chem.* **1968**, *33*, 864. This Letter highlights the issue of long reaction times which they infer leads to racemization when using base to facilitate the cyclization. However, these examples only examined di-substituted diketopiperazines. We have shown that the conditions for di-substituted do not necessarily translate to the formation of mono-substituted diketopiperazines, and that the mono-substituted diketopiperazines are generally formed in under 5 h.
14. (a) Harrison, B. A.; Kimball, S. D.; Mabon, R.; Rawlins, D. B.; Rice, D. S.; Voronkov, M. V. WO Patent 2009/021169, 2009. (b) Sebti, S. M.; Hamilton, A. D.; WO Patent 2008/079945, 2008. (c) Aicher, T. D.; Chen, Z.; Le Huerou, Y.; Martin, F. M.; Pineiro-Nunez, M. M.; Rocco, V. P.; Ruley, K. M.; Schaus, J. M.; Spinazze, P. G.; Tupper, D. E. WO Patent 2004/014895, 2004.
15. Subjection of a single enantiomer of the diketopiperazine **7** to the reaction conditions led to erosion of ee with continued heating.
16. The slightly lower yield obtained in this reaction can be attributed to the fact that the diketopiperazine product was partially soluble in the solvent used to remove the salt by-products. Due to the ease of procedure however, this purification method was deemed superior to column chromatography, even with the slight loss of yield.
17. For a detailed procedure see: Ashton, K.; Bartberger, M. D.; Bo, Y.; Bryan, M. C.; Croghan, M.; Fotsch, C. H.; Hale, C. H.; Kunz, R. K.; Liu, L.; Nishimura, N.; Norman, M. H.; Pennington, L. D.; Poon, S. F.; Stec, M. M.; St. Jean, D. J., Jr.; Tamayo, N. A.; Tegley, C. M.; Yang, K. WO Patent 2012/027261, 2012.
18. A 250-mL round-bottomed flask was charged with the *N*-Boc amino acid (10.0 mmol, 1.00 equiv), glycine methyl ester hydrochloride (1.256 g, 10.0 mmol, 1.00 equiv), DMF (50 mL), and DIPEA (3.50 mL, 20.5 mmol, 2.05 equiv) and the reaction mixture cooled to 0 °C. HATU (3.802 g, 10.0 mmol, 1 equiv) was added and the reaction stirred for 3 h while warming to room temperature. EtOAc (150 mL) was added and the organic layer was washed with 75 mL each of 0.5 N hydrochloric acid, saturated aqueous sodium bicarbonate, water, and brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The crude material was dissolved in CH_2Cl_2 (33 mL) and TFA (17 mL) and stirred for 2 h at room temperature. The mixture was then concentrated and water removed by the formation of an azeotrope with toluene (2 × 40 mL). To this crude material was added 2 N NH_3 in methanol (40 mL). The reaction time and workup procedure for the cyclization are specified for each compound in the Supplementary material section.
19. The reaction to synthesize product **7** has been performed on 0.5 mol scale. The procedure was run as described by the general method; the cyclization took 4 h and the yield over the three steps was 61%.
20. (a) St. Jean, D. J., Jr.; Ashton, K. S.; Bartberger, M. D.; Chen, J.; Chmait, S.; Cupples, R.; Galbreath, E.; Helmering, J.; Hong, F.-T.; Jordan, S. R.; Liu, L.; Kunz, R. K.; Michelsen, K.; Nishimura, N.; Pennington, L. D.; Poon, S. F.; Reid, D.; Sivits, G.; Stec, M. M.; Tadesse, S.; Tamayo, N.; Van, G.; Yang, K. C.; Zhang, J.; Norman, M. H.; Fotsch, C.; Lloyd, D. J.; Hale, C. *J. Med. Chem.* **2014**, *57*, 325; (b) Bourbeau, M. P.; Ashton, K. S.; Yan, J.; St. Jean, D. J., Jr. *J. Org. Chem.* **2014**, *79*, 3684.