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Efficient synthesis of unsymmetrical 1,4-disubstituted-2,3-diketopiperazines via tandem reductive amination–cyclization

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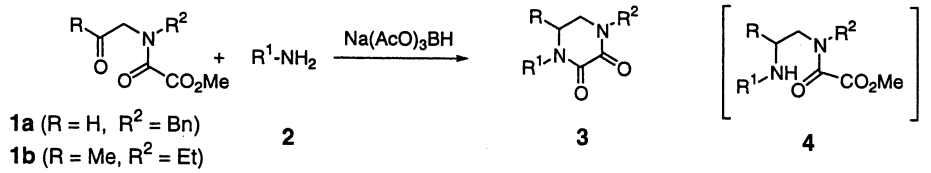
Abstract

Herein we report the efficient syntheses of 1,4-disubstituted-2,3-diketopiperazines and 1,4,5-trisubstituted-2,3-diketopiperazines, which feature a tandem reductive amination and acylation. Aliphatic and aromatic primary amines serve as viable nucleophiles under the mild reaction conditions.

Piperazine derivatives are used throughout medicinal chemistry as molecular scaffolds for biologically active compounds.[1] In the course of an ongoing drug discovery project, we required access to unsymmetrical 1,4-disubstituted-2,3-diketopiperazines. Previous syntheses of diketopiperazines have depended upon the prior construction of an ethylenediamine moiety, followed by bis-acylation with oxalic acid or its ester derivatives.[2] We have previously reported an efficient route to 1,4-disubstituted 2,3-diketopiperazines via reductive amination of a suitably substituted aldehyde with an *N*-(2-aminoethyl)oxamate ester scaffold followed by concomitant cyclization, producing diversely substituted 2,3-diketopiperazines.[3] Herein, we report a complimentary method, which introduces *N*-substitution through a primary amine. Under reductive amination conditions, **1** is combined with a primary amine **2** to produce **3** via the intermediate product **4** in a one-pot transformation (Eq. (1)). Because an array of structurally diverse amines is available, this approach to the construction of unsymmetrical 1,4-disubstituted-2,3-diketopiperazines is convenient and broadly applicable.



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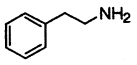
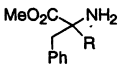
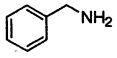
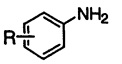
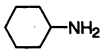
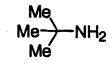
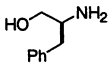
Substrate **1a**[4a] was used to explore the scope of the chemistry. Several amines were combined with **1a** under reductive amination conditions in the presence of sodium triacetoxyborohydride (Table 1).[5] Aliphatic amines produced diketopiperazines **3** in moderate to good yields (entries 1–9). Relatively unhindered amines (entries 1–3) led to moderate isolated yields of 64–75%, which was the result of a second reductive alkylation of intermediate **4** with aldehyde **1a**. The more branched amines (entries 4–9) were less prone to the aforementioned secondary pathway, thereby affording increased yields (76–88%). Improved cyclization efficiency may be a result of increased nucleophilicity of the amine from alkyl group donation and/or decreased bis-alkylation due to steric hindrance. *tert*-Butyl amine **2f** and quaternary-substituted amine **2i** underwent facile reductive amination, but cyclization was completed only after heating for 90 minutes. Aromatic amines (entries 10–14) were also successfully transformed; electron withdrawing (entries 12–13) and sterically hindered (entry 14) anilines required heating for complete cyclization.

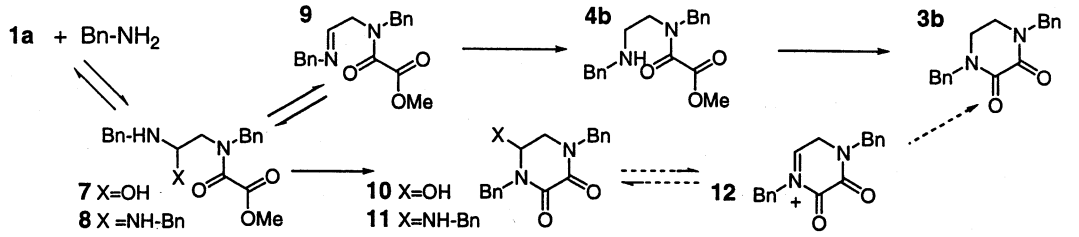
Table 1
Reductive amination of aldehyde **1a** with amines **2** to produce diketopiperazines **3** (Eq. (1))

entry	R^1-NH_2	amine	conditions[a]	yield 3 (%)[b]	entry	R^1-NH_2	amine	conditions[a]	yield 3 (%)[b]
1		**2a**	A	64					
2		**2b**	A	66	8	R = H (*S*)	**2h**	A	88
3		**2c**	A	75	9	R = Me (±)	**2i**	B	79
4		**2d**	A	81					
5		**2e**	A	77	10	R = H	**2j**	A	80
6		**2f**	B	80	11	R = 4-OMe	**2k**	A	71
					12	R = 4-CN	**2m**	B	82
					13	R = 4-NO_2	**2n**	B	49
7		**2g**	A	50[d]	14	R = 2-Br	**2p**	B[c]	80

[a] Reactions were run on 0.7-1.5 mmol scale. (A): **1a** (1.3 equiv), **2** (1.0 equiv), AcOH (3.0 equiv), $Na(AcO)_3BH$ (1.5 equiv), 4Å MS, DCE, 0 °C-rt, 15 h. (B): same as (A), then 1.5 h reflux. [b] Isolated yields of purified diketopiperazine products **3a-p**. [c] Reaction required 15 h reflux. [d] *N,O*-acetals (*cis*-**5** and *trans*-**6**) were isolated from the reaction in 12% and 14%, respectively (see ref 8).

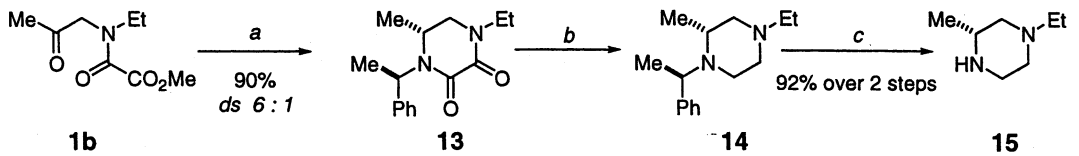
Scheme 1 is a proposed mechanistic pathway, which depicts two possible reaction manifolds that differ in the order of alkylation and cyclization events. When benzylamine and **1a** were subjected to a variety of reaction conditions,[6] we found that the proportion of isolable by-product **11** decreased with the addition of acetic acid (0, 1, 2, 3 equiv. AcOH; 52%, 18%, 6%, 0% **11**). Interestingly, when **11** was resubjected to the reaction conditions described in Table 1, it failed to produce the desired product **3b** from the putative intermediate **12**. From this, we infer that acetic acid affects the manifold by enhancing the conversion **7**/**8** to **9**, diminishing the conversion of **7**/**8** to **10**/**11** and/or enhancing the conversion of **9** to **4**. Therefore, reactions leading to the desired products described in Table 1 proceed via reductive amination, then

cyclization (**9**→**4**→**3**), rather through the *N*-acyliminium intermediate **12**.[7] Interestingly, in the case of phenyl glycinol **2g**, 3 equivalents of acetic acid were not sufficient to suppress the formation of oxazoline by-products *cis*-**5** and *trans*-**6** (Table 1, entry 7).[8,9]



Scheme 1.

Using (*R*)-α-methyl benzylamine as a chiral auxiliary, ketone **1b**[4b] was investigated for incorporation of asymmetry at C_5 in a diketopiperazine (Scheme 2). Standard conditions cleanly produced two separable diastereomers in a 6:1 ratio favoring (*R*,*R*)-**13**, the predicted major diastereomer.[10] Reduction of **13** with $LiAlH_4$[11] produced **14**, which was debenzylated with Pearlman's catalyst[12] to afford (*R*)-1-ethyl-3-methylpiperazine **15** in 92% isolated yield over two steps. The stereochemical assignment was supported by the analysis of Mosher's amides of **15**.[13,14]



Scheme 2. Reagents: (a) (*R*)-α-methyl benzyl amine (1.0 equiv.), AcOH (3 equiv.), $Na(AcO)_3BH$ (1.5 equiv.), 4 Å MS, DCE, 0°C–rt, 15 h. (*b*) $LiAlH_4$, Et_2O, 0°C–rt. (*c*) H_2, $Pd(OH)_2$, HCl, EtOH, 18 h

In summary, we have developed an alternative synthesis of unsymmetrical 1,4-substituted diketopiperazines via tandem reductive amination–cyclization. The wide availability of aliphatic and aromatic amines and the mild reaction conditions make this an attractive route for the construction of unsymmetrical substituted diketopiperazines and piperazines.

Representative procedure: 4-benzyl-1-phenyl-2,3-diketopiperazine (**3j**). To a vigorously stirring suspension of aniline **2j** (77 μL, 0.85 mmol), 4 Å powdered molecular sieves (300 mg), sodium triacetoxyborohydride (270 mg, 1.28 mmol, 1.5 equiv.) and acetic acid (145 μL, 2.55 mmol, 3 equiv.) in 8 mL of 1,2-dichloroethane at 0°C was added aldehyde **1a** (260 mg, 1.10 mmol) in 2 mL of 1,2-dichloroethane. After five minutes, the ice bath was removed and the reaction was warmed to room temperature. After 15 hours, the reaction was slowly poured into saturated aqueous $NaHCO_3$ solution, which was then extracted three times with CH_2Cl_2. The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (1/9 to 1/1: EtOAc/CH_2Cl_2) provided diketopiperazine **3j** as a white solid (191 mg, 80% yield); R_f 0.35 (50% EtOAc in CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.45 (m, 10 H), 4.75 (s, 2H), 3.89 (dd, J=7.6, 5.9 Hz, 2H), 3.57 (dd, J=7.6, 5.9 Hz, 2H); ES HRMS exact mass calculated for $C_{17}H_{17}N_2O_2$ ($M+H^+$): 281.1285, found 281.1297.

Acknowledgements

We are grateful to the following: Dr. C. W. Ross III and Dr. H. G. Ramjit for mass spectra; Dr. M. J. Bogusky and J. S. Murphy for NMR investigations; Dr. B. W. Trotter, Dr. M. A. Patane and Dr. S. L. Graham for helpful discussions; and Ms. M. A. Guttman for manuscript assistance.

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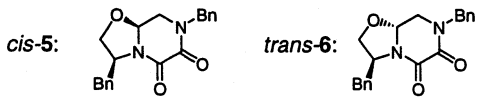
4. (a) Synthesis of **1a**: (i) benzylamine, $ClCOCO_2Me$, Et_3N, CH_2Cl_2, 0°C, 1 h. (ii) NaH, allyl bromide, DMF, 0°C–rt, 4 h, 54% over two steps. (iii) OsO_4, $NaIO_4$, acetone:H_2O (1:1), rt, 2 h, crude product used without further purification. (b) Synthesis of **1b**: (i) *N*-ethyl-2-methylallylamine, $ClCOCO_2Me$, Et_3N, EtOAc, 0°C, 1 h, 100%. (ii) OsO_4, $NaIO_4$, acetone:H_2O (1:1), rt, 3 h, 58%.
5. Selected data for compounds: **1a**: ^1H NMR (400 MHz, $CDCl_3$) 66:34 mixture of amide rotamers: major δ 9.35 (s, 1 H), 7.19–7.35 (m, 5 H), 4.50 (s, 2 H), 4.01 (s, 2 H), 3.85 (s, 3 H); minor: δ 9.37 (s, 1 H), 7.19–7.35 (m, 5 H), 4.64 (s, 2 H), 4.12 (s, 2 H), 3.78 (s, 3 H); $C_{12}H_{14}NO_4$: *m/z* (ES^+) 236.2 (MH^+). **3a**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.15–7.38 (m, 10H), 4.64 (s, 2H), 3.70 (t, $J=7.1$ Hz, 2H), 3.21–3.53 (m, 4H), 2.94 (t, $J=7.1$ Hz, 2H); HRMS (ES) exact mass calcd for $C_{19}H_{21}N_2O_2$ ($M+H^+$): 309.1598; found 309.1585. **3b**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.36 (m, 10H), 4.67 (s, 4H), 3.33 (s, 4H); HRMS (ES) exact mass calcd for $C_{18}H_{19}N_2O_2$ ($M+H^+$): 295.1441; found 295.1431. **3c**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.36 (m, 5H), 4.66 (s, 2H), 3.42–3.45 (m, 2H), 3.37–3.40 (m, 2H), 2.85 (tt, $J=4.0$, 4 Hz, 1H). 0.89 (m, 2H), 0.71 (m, 2H); HRMS (ES) exact mass calcd for $C_{14}H_{17}N_2O_2$ ($M+H^+$): 245.1285; found 245.1269. **3d**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.37 (m, 5H), 4.84 (sept, $J=6.8$ Hz, 1H), 4.68 (s, 2H), 3.36–3.39 (m, 2H), 3.32–3.35 (m, 2H), 1.14 (d, $J=6.8$ Hz, 6H); HRMS (ES) exact mass calcd for $C_{14}H_{19}N_2O_2$ ($M+H^+$): 247.1441; found 247.1425. **3e**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.38 (m, 5H), 4.68 (s, 2H), 4.43 (tt, $J=3.8$, 11.9 Hz, 1H), 3.36 (s, 4H), 1.65–1.85 (m, 5H), 1.25–1.46 (m, 4H), 1.09 (dtt, $J=13$, 13, 3.7 Hz, 1H); HRMS (ES) exact mass calcd for $C_{17}H_{23}N_2O_2$ ($M+H^+$): 287.1754; found 287.1744. **3f**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.36 (m, 5H), 4.66 (s, 2H), 3.46–3.50 (m, 2H), 3.32–35 (m, 2H), 1.46 (s, 9H); HRMS (ES) exact mass calcd for $C_{15}H_{21}N_2O_2$ ($M+H^+$): 261.1598; found 261.1585. **3g**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.19–7.34 (m, 10H), 4.66 (d, $J=14.6$ Hz, 1H), 4.54 (d, $J=14.6$ Hz, 1H), 4.44 (m, 1H), 3.84–3.88 (m, 2H), 3.32 (m, 1H), 3.21 (m, 1H), 3.05–3.09 (m, 2H), 3.01 (m, 1H), 2.95 (dd, $J=14.1$, 6.6 Hz, 1H), 2.84 (br s, 1H); HRMS (ES) exact mass calcd for $C_{20}H_{23}N_2O_3$ ($M+H^+$): 339.1703; found 339.1703. *cis*-**5**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.04–7.38 (m, 10H), 4.98 (dd, $J=10.2$, 3.7 Hz, 1H), 4.74 (d, $J=14.5$ Hz, 1H), 4.59 (d, $J=14.5$ Hz, 1H), 4.37 (m. 1H), 4.15 (br d, $J=9.3$ Hz, 1H), 3.86 (m, 1H), 3.44 (br d, $J=13.5$ Hz, 1H), 3.40 (dd, $J=11.8$, 3.8 Hz, 1H), 3.03 (dd, $J=11$, 11 Hz, 1H), 2.85 (dd, $J=13.5$, 9.1 Hz, 1H); HRMS (ES) exact mass calcd for $C_{20}H_{21}N_2O_3$ ($M+H^+$): 337.1547; found 337.1548. *trans*-**6**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.37 (m, 10H), 4.90 (dd, $J=9.9$, 4.6 Hz, 1H), 4.74 (d, $J=14.6$ Hz, 1H), 4.58 (d, $J=14.6$ Hz, 1H), 4.57 (m. 1H), 4.11 (dd, $J=9.2$, 7.0 Hz, 1H), 3.80 (dd, $J=9.2$, 6.8 Hz, 1H), 3.42 (dd, $J=12.4$, 4.8 Hz, 1H), 3.30–3.36 (m, 2H), 2.88 (dd, $J=13.6$, 9.2 Hz, 1H); HRMS (ES) exact mass calcd for $C_{20}H_{21}N_2O_3$ ($M+H^+$): 337.1547; found 337.1548. **3h**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.40 (m, 10H), 5.35 (dd, $J=11.0$, 5.6 Hz, 1H), 4.67 (d, $J=14.7$ Hz, 1H), 4.52 (d, $J=14.7$ Hz, 1H), 3.74 (s, 3H), 3.42 (dd, $J=14.9$, 5.6 Hz, 1H), 3.25–3.36 (m, 2H), 3.22 (dd, $J=7.3$, 4.4 Hz, 1H), 3.05 (dd, $J=14.8$, 10.9 Hz, 1H), 2.98–3.05 (m, 1H); HRMS (ES) exact mass calcd for $C_{21}H_{23}N_2O_4$ ($M+H^+$): 367.1652; found 377.1646. **3i**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.28–7.37 (m, 3H), 7.21–7.27 (m, 5H), 7.10–7.13 (m, 2H), 4.69 (d, $J=14.6$ Hz, 1H), 4.58 (d, $J=14.6$ Hz, 1H), 3.82 (d, $J=13.7$ Hz, 1H), 3.76 (s, 3H), 3.29 (ddd, $J=12.8$, 9.0, 3.9 Hz, 1H), 3.10 (ddd, $J=12.8$, 6.1, 3.9 Hz, 1H), 2.98 (d, $J=13.7$ Hz, 1H), 2.90 (ddd, $J=12.9$, 9.0, 3.9 Hz, 1H), 2.50 (ddd, $J=12.7$, 6.2, 3.9 Hz, 1H), 1.45 (s, 3H); HRMS (ES) exact mass calcd for $C_{22}H_{25}N_2O_4$

(M+H$^+$): 381.1809; found 381.1804. **3k**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.41 (m, 5H), 7.23 (d, J=9.0 Hz, 2H), 6.91 (d, J=9.0 Hz, 2H), 4.75 (s, 2H), 3.81–3.87 (m, 2H), 3.80 (s, 3H), 3.53–3.58 (m, 2H); HRMS (ES) exact mass calcd for $C_{18}H_{19}N_2O_3$ (M+H$^+$): 311.1390; found 311.1381. **3m**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64 (d, J=8.5 Hz, 2H), 7.45 (d, J=8.8 Hz, 2H), 7.24–7.34 (m, 5H), 4.69 (s, 2H), 3.88 (m, 2H), 3.53 (m, 2H). HRMS (ES) exact mass calcd for $C_{18}H_{16}N_3O_2$ (M+H$^+$): 306.1237; found 306.1222. **3n**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J=9.0 Hz, 2H), 7.51 (d, J=9.3 Hz, 2H), 7.25–7.36 (m, 5H), 4.70 (s, 2H), 3.90 (m, 2H), 3.55 (m, 2H). HRMS (ES) exact mass calcd for $C_{17}H_{16}N_3O_4$ (M+H$^+$): 326.1133; found 326.1138. **3p**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, J=8.0, 1.2 Hz, 1H), 7.31–7.41 (m, 6H), 7.30 (dd, J=7.9, 1.6 Hz, 1H), 7.24 (dd, J=7.6, 1.5 Hz, 1H), 4.89 (d, J=14.7 Hz, 1H), 4.65 (d, J=14.6 Hz, 1H), 3.83 (m, 1H), 3.76 (m, 2H), 3.50 (m, 1H); HRMS (ES) exact mass calcd for $C_{17}H_{16}BrN_2O_2$ (M+H$^+$): 359.0390; found 359.0412.

6. Analogous results were obtained when aniline was used rather than benzylamine.
7. (a) While the generation of *N*-acyliminium ions (e.g. **12**) from intermediates comparable to **10** and **11** using Brønsted or Lewis acid conditions is well precedented (Ref. 7b), it is unlikely that **12** is formed under the comparatively mild reaction conditions described herein. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon Press: New York, 1991; Vol. 2, pp. 1047–1082.
8. Structures of *cis*-**5** and *trans*-**6**, which were isolated from the reaction in 12 and 14%, respectively:



9. As a further control experiment, *trans*-**6** was resubjected to the reaction conditions described in Table 1. After 6 hours, no detectable amount of **3g** was formed. This supports our assertion that the generation of an *N*-acyliminium ion (e.g. **12**) from an *N*,*O*-acetal (e.g. **10** or *trans*-**6**) is unlikely to be a major contributor to the formation a diketopiperazine under these conditions.
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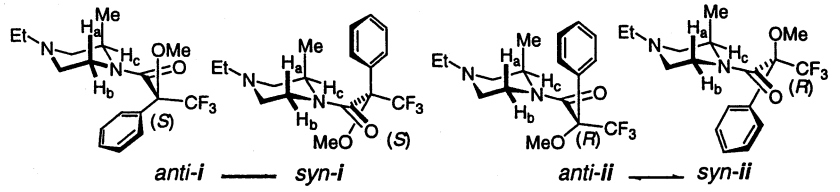
13. The absolute configuration was determined using the NMR-based method of Hoye and Renner for cyclic secondary amines (Ref. 14c). Thus, compound **15** was converted to the corresponding (*S*)- and (*R*)-MTPA amides ***i*** and ***ii*** (1.2 equiv. MTPA-Cl, 3.3 equiv. Et_3N, CH_2Cl_2). Dominant conformations are illustrated below for ***i*** (amide rotamer ratio 72:28) and ***ii*** (77:23). Selected ^{1}H NMR spectral data ($CDCl_3$) indicate chemical shift differences are consistent with (*R*)-stereochemistry at C_5 of **13**.



H	δ ***i*** (ppm) *anti / syn*	δ ***ii*** (ppm) *anti / syn*
H_a	3.22 / 2.98	2.40 / 3.10
H_b	3.66 / 4.46	3.67 / 4.57
H_c	4.94 / 4.30	4.74 / 4.02
Me	1.34 / 0.40	1.25 / 1.33

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