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Preparation of Substituted Piperazinones via Tandem Reductive Amination–(*N*,*N*′-Acyl Transfer)–Cyclization

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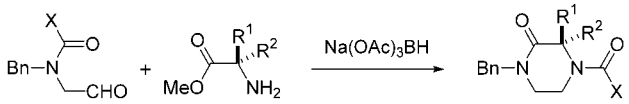
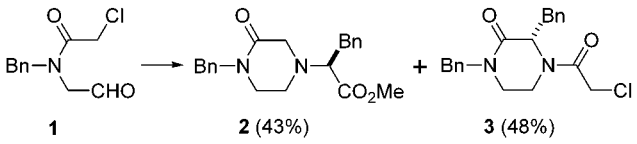
ABSTRACT



A one-pot, tandem reductive amination–transamidation–cyclization reaction was employed to produce substituted piperazin-2-ones in good yields. Various amino acid methyl esters and transferable acyl groups were examined to establish the reaction's scope.

Piperazinone rings have been used often in medicinal chemistry because of their structural similarity to constrained peptides, and numerous methods of ring assembly have been developed with the introduction of substitution at varying positions.[1a] There are many examples of multiple bond-forming reactions between primary amines and doubly activated substrates to produce piperazinone products.[1,2] In a previous report (Scheme 1),[2] reductive amination of

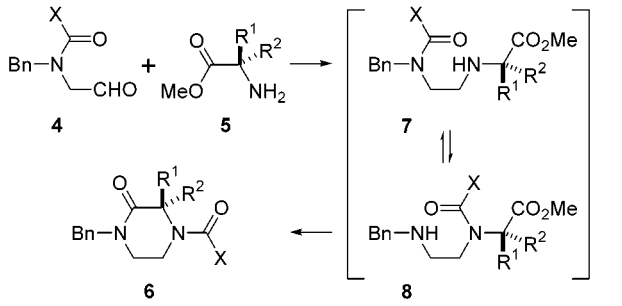
Scheme 1



1 **2** (43%) **3** (48%)

2-chloro-*N*-(2-oxoethyl)acetamide **1** with L-phenylanaline methyl ester resulted in the expected product **2**, as well as the unanticipated piperazinone **3**.

Scheme 2



4 **5** **7** **6** **8**

The reaction pathway outlined in Scheme 2 accounts for the conversion of **1** to **3** and describes the basis for a novel approach to the synthesis of piperazinones. An *N*-(2-oxoethyl)amide **4**, when treated with an α-amino ester **5** under reductive amination conditions, produces *N*-acylpiperazinone **6** through the intermediacy of **7** and **8**, which presumably interconvert via an intramolecular *N*,*N*′-acyl transfer. An attractive feature of this synthetic scheme is that the incorporation of piperazinone C3-substitution is facilitated

(1) (a) Review: Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proced. Int.* **2002**, *34*, in press. (b) Goff, D. A. *Tetrahedron Lett.* **1998**, *39*, 1473. (c) Yahiro, N.; Ito, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 321. (d) Valls, N.; Segarra, V. M.; Bosch, J. *Heterocycles* **1986**, *24*, 943. (e) Askew, B. C.; McIntyre, C. J.; Hunt, C. A.; Claremon, D. A.; Gould, R. J.; Lynch, R. J.; Armstrong, D. J. *J. Bioorg. Med. Chem. Lett.* **1995**, *5*, 475.

(2) Dinsmore, C. J.; Zartman, C. B. *Tetrahedron Lett.* **2000**, *41*, 6309.

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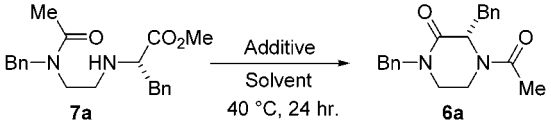
by the wide availability of natural and unnatural α-amino acids.

In an effort to explore this new method of piperazinone synthesis, we replaced the α-chloroacetyl group of **1** with various acyl groups to determine substrate compatibility. Initial attempts to effect the transformation were focused on the reductive amination[3] of *N*-(2-oxoethyl)acetamide (**4a**, X = Me, Scheme 2) with L-phenylalanine methyl ester in the presence of sodium triacetoxyborohydride and 4 Å molecular sieves in 1,2-dichloroethane (DCE). After initial formation of intermediate **7a** (X = Me, R^1 = H, R^2 = Bn), refluxing the reaction for two weeks afforded only 80% conversion to the desired piperazinone product **6a**.

It was immediately apparent that *N*,*N*′-acyl transfer (**7**→**8**) was the rate-determining step.[4] Transamidation has been well studied in the context of peptide segment coupling[5] and has been applied to medium- and large-ring syntheses via a ring-expanding "Zip" reaction.[6] To optimize the conversion of **7** to **8**, the reductive amination product **7a** was synthesized and subjected to various solvents and additives to examine their effect on the transamidation−cyclization reaction rate (Table 1). This study revealed that the only additive to efficiently promote piperazinone formation over 24 h was acetic acid with maximal conversion in acetonitrile.

Table 1. Optimization of Transamidation−Cyclization Sequence: Conversion of **7a** to Piperazinone **6a**[a]

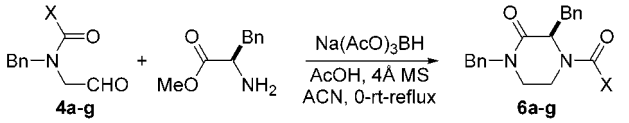


	additive (% conversion)					
solvent	none	aq HCl	TFA	AcOH	MsOH	Et_3N
DCE	0	0[b]	0	50	0	0
THF	0	0[b]	1−5	40	0	0
DMSO	0	0	0	10	0	0
ACN	0	0[b]	0	55	0	0

[a] Reactions were run in 1 mL of the desired solvent at 1.0 M substrate and 1.0 M additive concentrations for 24 h at 40 °C in a thermocontrolled LC sample tray. Aliquots were analyzed by HPLC every 2 h. Values denote the percent conversion of **7a** to product **6a** after 24 h. [b] Hydrolysis of the acetamide **7a** was observed.

To explore the transferability of various acyl groups (X in **4**), we subjected several aldehydes (**4a**−**g**) to the optimized reaction conditions (Table 2).[7] When alkyl substituents were employed, both the reaction time and extent of racemization increased dramatically as the size of the alkyl

Table 2. Reductive Amination of Aldehydes **4a**−**g** with D-Phe-OMe to Provide Piperazinones **6a**−**g**



entry	aldehyde	X	reflux time (h)	product	% yield[a]	% ee[b]
1	**4a**	Me	7	**6a**	69	95
2	**4b**	Et	190	**6b**	76	65
3	**4c**	*i*-Pr	96[c]	**6c**	78	15
4	**4d**	*t*-Bu	48[c]	**6d**	92	27
5	**4e**	Ph	4	**6e**	86	>99
6	**4f**	CF_3	0[d]	**6f**	87	>99
7	**4g**	OBn	72[c]	**6g**	81	44

[a] Yields of isolated **6a**−**g**. [b] Determined by chiral HPLC analysis, using authentic opposite enantiomer as a standard. [c] Reaction was performed in a sealed tube. Upon completion of the reductive amination, the vessel was heated at 120 °C for the specified time. [d] Reaction was complete after 18 h at room temperature.

group increased (**4a**−**d**, entries 1−4). Presumably, this was due to increased steric demand imposed upon the transition state for the rate-limiting transacylation step (vide infra). With the more reactive amides **4e** and **4f** (entries 5 and 6, respectively), the reaction time decreased and no racemization was detected. When benzyl carbamate **4g** was employed (entry 7), the reaction proceeded smoothly, albeit slowly and in low enantiomeric excess. However, treatment of *N*-(2-oxoethyl)sulfonamides to the reaction conditions provided only the corresponding reductive amination products with no detectable piperazinones after prolonged heating (data not shown).[8]

To explore the effect of the amino acid side chain on the reaction rate, various amino acid methyl esters were treated with aldehyde **4a** to produce piperazinones **6h**−**n** in moderate to good yields (Table 3). Substitution of the amino acid extended the reaction time considerably (entry 1 vs 2−8). Furthermore, the degree of substitution at the β-carbon of the amino ester influenced the reaction rate. Monosubstitution to the β-carbon slowed the reaction slightly (entry 2 vs 3−6), while disubstitution slowed the reaction even further (entry 2 vs 7−8).

(3) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

(4) In each example studied, rapid accumulation of **7** was followed by gradual formation of piperazinone **6**, as assessed by LC/MS analysis. None of **8** was observed.

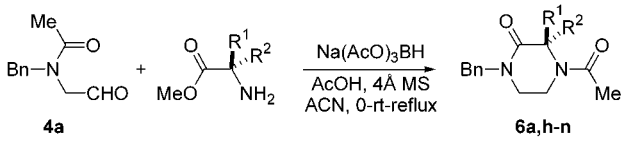
(5) For a review, see: Coltart, D. M. *Tetrahedron* **2000**, *56*, 3449.

(6) (a) Kramer, U.; Guggisberg, A.; Hesse, M.; Schmid, H. *Angew. Chem.* **1977**, *89*, 899. (b) Doll, M. K.-H.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta* **1996**, *79*, 541.

(7) **Representative Procedure: (3*R*)-4-Benzoyl-1,3-dibenzylpiperazin-2-one (6e).** To a 0 °C stirring suspension of D-Phe-OMe hydrochloride (100 mg, 0.464 mmol, 1.0 equiv), 4 Å molecular sieves (200 mg), AcOH (79 μL, 1.4 mmol, 3 equiv), and $Na(AcO)_3BH$ (147 mg, 0.693 mmol, 1.5 equiv) in 5 mL of ACN was added dropwise over 5 min a 2.5 mL ACN solution of aldehyde **4e** (129 mg, 0.675 mmol, 1.1 equiv). After the reaction mixture was stirred for 90 min, the ice bath was removed and the reaction mixture was warmed to ambient temperature and stirred for 18 h. The reaction mixture was heated to reflux for 4 h, cooled, and poured into aqueous saturated $NaHCO_3$ solution, which was then extracted three times with DCM. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (0 to 50% EtOAc in DCM) provided piperazinone **6e** as a colorless oil (153 mg, 86% yield). For full characterization of compounds described herein, see Supporting Information.

(8) Both the methanesulfonamide and toluenesulfonamide versions of amide **4** were prepared and subjected to the reaction conditions. After 120 h at 80 °C, the only detectable product (LC/MS analysis) was the corresponding reductive amination product.

Table 3. Reductive Amination of Aldehyde **4a** with α-Amino Esters to Provide Piperazinones **6a**,**h**−**n**



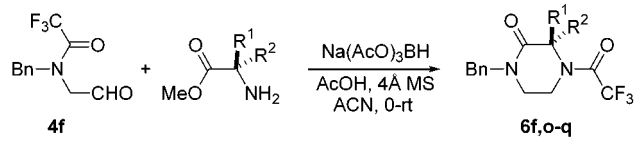
entry	R^1	R^2	reflux time (h)	product	% yield[a]	% ee[b]
1	H	H	1	**6h**	53	
2	H	Me	3	**6i**	80	99
3	H	CH_2Ph	7	**6a**	69	95
4	H	*i*-Bu	10	**6j**	76	92
5	H	CH_2OH	10	**6k**	30	>99
6	H	CH_2CO_2Me	10	**6l**	54	82
7	H	*i*-Pr	24	**6m**	58	86
8	H	Ph	16	**6n**	84	17
9	H	$(CH_2)_2CO_2Me$	0	**9**[c]	40	nd
10	Me	Me	72[d]	**10**[e]	75	

[a,b] See corresponding footnotes in Table 2. [c] Product **9** is the methyl pyroglutamate, derived from direct cyclization of intermediate **7**. [d] See footnote c in Table 2. [e] Product **10** is the 2,3-dihydro-1-pyrrolo[1,2-*a*]imidazol-6-one illustrated in ref 9c.

Some α-amino esters failed to produce piperazinone products. Not surprisingly, reductive amination with glutamic acid dimethyl ester (Table 3, entry 9) was followed by premature lactamization of the amino group in intermediate **7** onto the R^2 side chain ester to afford pyroglutamate **9** (not shown) as the sole product. The use of an α,α-disubstituted amino ester (entry 10) resulted in the exclusive formation of fused bicyle **10**[9a,b] by a novel process involving dehydration and intramolecular Claisen-type reaction.[9c]

The trifluoroacetamide **4f** is the most versatile synthon for the synthesis of piperazinones, not only because the products are easily deprotected for further functionalization but also because reaction times are short and optical purities are high (Table 4). Unlike the other amide derivatives studied, reactions of **4f** with α-amino esters proceeded at

Table 4. Reductive Amination of Aldehyde **4f** with α-Amino Esters to Provide Piperazinones **6f**,**o**−**q**



entry	R^1	R^2	time at room temp (h)	product	% yield[a]	% ee[b]
1	CH_2Ph	H	18	**6f**	87	>99
2	*i*-Pr	H	40	**6o**	79	100
3	Ph	H	40	**6p**	81	95
4	Me	Me	168[c]	**6q**	10[d]	

[a,b] See corresponding footnotes in Table 2. [c] Heated at reflux. [d] Percent conversion by LC-MS detection. Product **6q** was not isolated.

room temperature. In comparison to the same reactions with acetamide **4a** (see Table 3), racemization was reduced significantly in the case of **6f** and **6o** (Table 4, entries 1 and 2, respectively) and dramatically in the case of phenylglycine-derived **6p** (entry 3). Furthermore, the yields were uniformly good. Unfortunately, the use of an α,α-disubstituted amino ester (entry 4) remained problematic; the reaction to give **6q** proceeded with low conversion even at higher temperatures and prolonged reaction times.

Examination of molecular models for the tetrahedral intermediate[10] mediating the rate-limiting interconversion of **7** and **8** reveals the nature of the interactions responsible for slowing the reaction time. The calculated lowest energy structure[11] of the intermediate leading to piperazinone **6b** (Figure 1) shows one of several orientations that may be

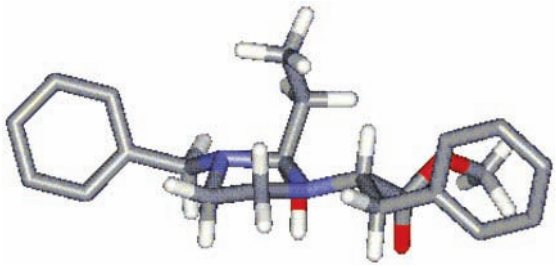
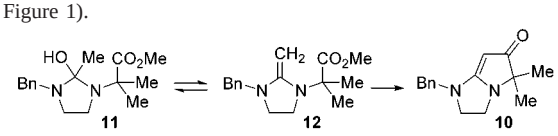


Figure 1. Calculated lowest energy conformation of tetrahedral intermediate leading to acyl-group transfer for piperazinone **6b**.

relevant. Clearly, branching at the α-carbon of the transferring acyl group and at the α- or *β*-carbon of the amino ester moiety results in an increased number of gauche and syn-pentane-like interactions, presumably raising the overall energy required for *N*,*N*′-acyl transfer to occur.

The methodology described herein was used to synthesize a conformationally restricted inhibitor of the posttranslational protein processing enzyme farnesyltransferase (FTase). Inhibitors of FTase (FTIs) are promising antitumor agents, and several are currently being evaluated in human clinical trials.[12] During our investigations of piperazinone FTIs, we discovered that they adopt a folded conformation when bound

(9) (a) Wang, L.-B.; Yu, C.-Y.; Huang, Z.-T. *Synthesis* **1994**, *12*, 1441. (b) Armati, A.; De Ruggieri, P.; Rossi, E.; Stradi, R. *Synthesis* **1986**, *7*, 573. (c) Formation of **10** was thought to arise from facile dehydration of **11** (from **7**, X = R^1 = R^2 = Me) to give **12**, followed by cyclization. Dehydration of **11** presumably relieves severe syn-pentane-like interactions (cf. Figure 1).



(10) (a) Kemp, D. S.; Choong, S.-L. H.; Pekaar, J. *J. Org. Chem.* **1974**, *39*, 3841.

(11) (a) Molecular modelling: conformations were generated using metric matrix distance geometry algorithm JG (S. Kearsley, Merck & Co., Inc., unpublished). Structures were subjected to energy minimization within the Macromodel program (ref 11b) using MMFF force field. (b) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

to the enzyme and that a macrocyclic constraint (e.g., **13**, Figure 2) enhances their potency by preorganizing the bound

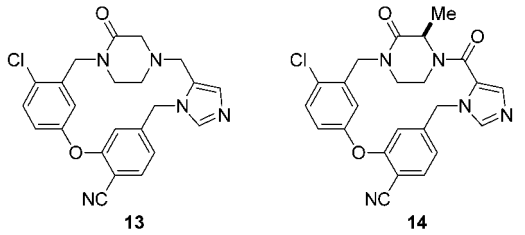


Figure 2. Piperazinone farnesyltransferase inhibitors **13** and **14**.

conformation.[13] In the interest of altering the metabolic fate of **13** by blocking key positions, the (*R*)-3-methyl-2-piperazinone analogue **14** was prepared.

Protection of 4-chloro-3-methylphenol (Scheme 3) as the corresponding *tert*-butyldiphenylsilyl ether followed by benzylic bromination provided compound **15**. Displacement of the bromide with ethanolamine provided the amino alcohol **16**, which underwent EDC-mediated acylation with acid **18**, derived from oxidation of the previously reported aldehyde **17**.[13a] The resulting alcohol was subjected to Swern oxidation conditions to provide the key aldehyde **19**.

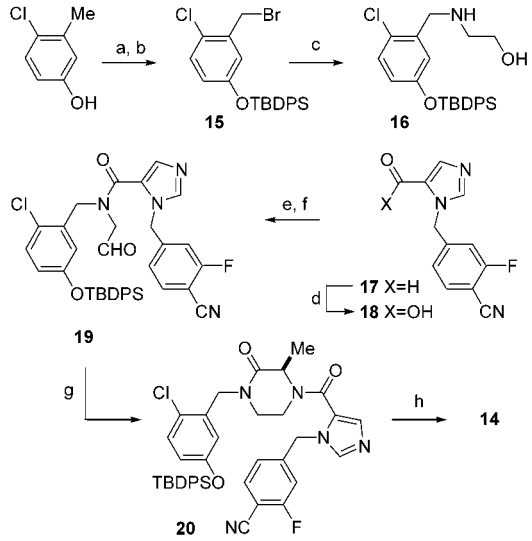
Compound **19** was subjected to reductive amination conditions in the presence of D-Ala-OMe, and after 3 h of reflux, the piperazinone **20** was isolated in 72% yield. Tandem deprotection−macrocyclization was accomplished in the presence of KF on alumina in refluxing acetonitrile to provide the FTI **14** in good yield. The FTase inhibitory activity of **14** (IC_{50} = 4 nM) was 6-fold less potent than that of **13** (IC_{50} 0.7 nM), which may be attributed to the presence of the carbonyl group between the imidazole and piperazinone rings.[14]

(12) (a) Karp, J. E.; Kaufmann, S. H.; Adjei, A. A.; Lancet, J. E.; Wright, J. J.; End, D. W. *Curr. Opin. Oncol.* **2001**, *13*, 470. (b) Gibbs, J. B. *J. Clin. Invest.* **2000**, *105*, 9. (c) Bell, I. M. *Exp. Opin. Ther. Patents* **2000**, *10*, 1813.

(13) (a) Dinsmore, C. J.; Bogusky, M. J.; Culberson, J. C.; Bergman, J. M.; Homnick, C. F.; Zartman, C. B.; Mosser, S. D.; Schaber, M. D.; Robinson, R. G.; Koblan, K. S.; Huber, H. E.; Graham, S. L.; Hartman, G. D.; Huff, J. R.; Williams, T. M. *J. Am. Chem. Soc.* **2001**, *123*, 2107. (b) Dinsmore, C. J.; Bergman, J. M.; Bogusky, M. J.; Culberson, J. C.; Hamilton, K. A. Graham, S. L. *Org. Lett.* **2001**, *3*, 865.

(14) Dinsmore, C. J.; Bergman, J. M.; Wei, D. D.; Zartman, C. B.; Davide, J. P.; Greenberg, I. B.; Liu, D.; O'Neill, T. J.; Gibbs, J. B.; Koblan, K. S.; Kohl, N. E.; Lobell, R. B.; Chen, I.-W.; McLoughlin, D. A.; Olah, T. V.; Graham, S. L.; Hartman, G. D.; Williams, T. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 537.

Scheme 3. Synthesis of Farnesyltransferase Inhibitor **14**[a]



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 100%; (b) NBS, AIBN, CCl_4, 80 °C, 53%; (c) $HOCH_2CH_2NH_2$, $NaHCO_3$, EtOAc/H_2O, 100%; (d) $NaClO_2$, NaH_2PO_4, *t*-BuOH/2-methyl-2-butene/H_2O, 46%; (e) **18**, EDC, HOBt, **16**, DIEA, DMF, 74%; (f) $(ClCO)_2$, DMSO, Et_3N, DCM, from −78 °C to rt, 100%; (g) D-Ala-OMe, $Na(AcO)_3BH$, 4 Å molecular sieves, AcOH, ACN, from 0 °C to rt to 80 °C, 72%; (h) KF·AlO_3, ACN, 80 °C, 82%.

We have developed a one-pot synthesis of substituted *N*-acylpiperazinones from *N*-(2-oxoethyl)amides and α-amino esters by a novel tandem reductive amination−transamidation−cyclization process. The rate of the reaction is governed largely by the character of the transferring acyl group and by steric congestion at the α- and *β*-carbons of the amino ester. *N*-(2-Oxoethyl)trifluoroacetamides (e.g., **4f**) undergo the most efficient transformation to piperazinones, with minimal racemization. The new method was applied effectively to a convergent synthesis of the conformationally constrained FTase inhibitor **14**.

Acknowledgment. We thank J. Christopher Culberson for providing Figure 1 and Carl F. Homnick for generously providing chiral HPLC analyses.

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

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