Tetrahedron Letters 50 (2009) 3817–3819

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Convenient synthesis of 1,3-substituted-6-phenylpiperazin-2-ones

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ARTICLE INFO

Article history:
Received 20 November 2008
Revised 3 April 2009
Accepted 6 April 2009
Available online 14 April 2009

ABSTRACT

The convenient preparation of novel 6-phenylpiperazin-2-ones from simple starting materials via a practical two-step procedure is presented. This methodology involves an initial alkylation of 2-bromoacetophenone with an amino ester followed by a one-pot reductive amination and cyclization step to furnish the desired substituted piperazinones.

The synthesis of pharmacologically interesting molecules containing a piperazinone ring has been stimulated by reports that they can be ligands for a variety of receptor sites.[1–5] The core structure of the piperazinone ring has been commonly assembled using one of two general strategies. These strategies defined by the C–N bond(s) formed during reaction (see Scheme 1).[6] The first method involves the construction of a suitable precursor that is cyclized to furnish the piperazinone nucleus (see, for example, Scheme 1A). The second strategy for ring formation is accomplished by a two-step sequence involving an initial intermolecular reaction followed by an intramolecular ring closure step (see, for example, Scheme 1B).

As part of our effort to identify novel calcitonin gene-related peptide (CGRP) receptor antagonists, we became specifically interested in the synthesis of 1,3-substituted-6-phenylpiperazin-2-ones. None of the known piperazinone syntheses allowed facile access to the compounds of interest, therefore a new and efficient route was required. We envisioned a strategy for incorporating the necessary functionality by disconnection of the piperazinone ring at the N_1–C_2 bond (Scheme 2), generating an amino-ester intermediate. Continuing the retrosynthetic analysis to the end of the sequence would then lead to α-halo ketone and amino ester starting materials. This approach should allow flexibility for installation of substituents at the N_1 and C_3 positions of the piperazinone ring and should permit rapid access to the desired compounds.

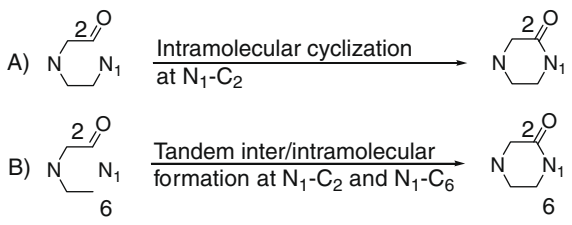
In this Letter, we report a successful and efficient synthesis of a series of novel substituted 6-phenylpiperazinones utilizing this approach.

We first investigated the alkylation of commercially available 2-bromoacetophenone (**1**) with amine hydrochloride **2a** in DMF at ambient temperature (Scheme 3).

The resulting β-ketoamine was quickly purified either by normal or by reverse phase chromatography. It should be noted that intermediate **3a** is somewhat unstable at ambient temperature and undergoes oxidative dimerization on standing. The β-ketoamine intermediate may be stored as a salt, for example, the hydrochloride salt, under argon at −20 °C for several weeks with minimal decomposition. Reductive amination of **3a** with benzylamine (**6a**) and subsequent cyclization were carried out using excess AcOH (4 equiv) and $NaBH_3CN$ (1.5 equiv) in MeOH at 50 °C, and the reaction was complete after 18 h. The major byproduct observed was reduction of the starting β-ketoamine **3a** to the corresponding alcohol. Standard workup of the reaction mixture and isolation of the product on silica gel afforded the desired piperazinone **5a** in good yield (see Table 1).

In order to investigate the importance of α-substitution in **2a**, glycine **2b** was allowed to react with **1** to give intermediate **3b** in poor yield (Table 1). Apparently, the lack of α-substitution leads to increased instability of intermediate **3b**. This intermediate was isolated by aqueous workup and, without purification, was subjected to the aforementioned reductive amination–cyclization conditions. However, only a small amount of **5b** was observed by LC/MS, and no pure product was isolated.

The potential for epimerization during the two-step synthetic method was evaluated using 3-methyl piperazinones **5c** and **5d** as a model. (*S*)-Alanine methyl ester hydrochloride (**2c**) and (*R*)-alanine methyl ester hydrochloride (**2d**) were reacted with **1** to give β-ketoamines **3c** and **3d**, respectively. Reductive amination of the β-ketoamines with **6a** and tandem cyclization produced a 1:1 mixture of diastereomeric piperazinones **5c** (*S*,*S* and *S*,*R*) and



Scheme 1. Representative examples of the C–N bond forming reactions for the generation of piperazinone rings.

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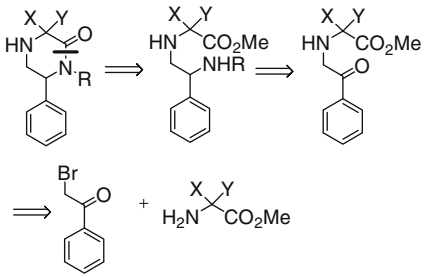
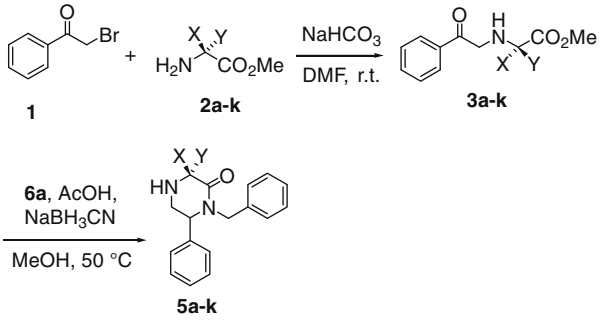
doi:10.1016/j.tetlet.2009.04.036



Scheme 2. Retrosynthetic analysis of 6-phenyl-piperazin-2-ones.



Scheme 3. Synthesis of 1-benzyl-6-phenylpiperazin-2-ones.

5d (*R*,*R* and *R*,*S*) in excellent yield. Chiral purity determination of the diastereomeric mixtures of **5c** and **5d** by chiral HPLC revealed that there was no observable epimerization of the 3-position stereocenter.[7]

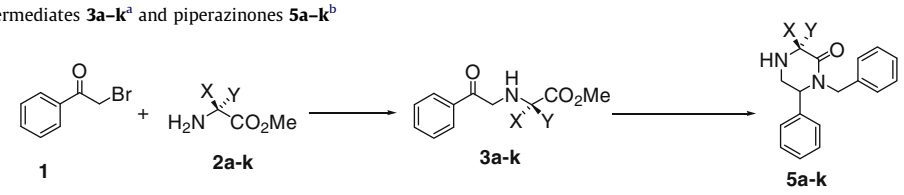
In order to investigate the scope of this method, a variety of amino ester hydrochlorides (**2e–k**) were allowed to react with **1** to give the corresponding intermediates **3e–k** as shown in Table 1. Treatment of these intermediates with **6a** as described above gave piperazinones **5e–k** in good to excellent yields. The yield for piperazinone **5e** was low compared to other entries in Table 1 due to incomplete cyclization to the desired product.

Compounds **7b–l** presented in Table 2 were generated by reductive amination of **3a** with amines **6b–l** to show an extension of this method (Scheme 4). The isolated yields after silica gel purification were modest to good. Although reductive alkylation of **6j** with intermediate **3a** was observed, subsequent cyclization to the desired compound **7j** did not occur.

In conclusion, we have developed a novel synthesis for the preparation of 1,3-substituted-6-phenylpiperazin-2-ones in which diverse functionality can be readily incorporated into the 1 and 3 positions of the ring system. Beginning with simple starting materials, this straightforward synthesis avoids protecting groups and allows for the generation of elaborate ring systems without the loss of stereochemical integrity.

Representative procedure: 1-benzyl-3,3-dimethyl-6-phenylpiperazin-2-one (**5a**). Methyl α-aminoisobutyrate hydrochloride (**2a**) (400 mg, 2.60 mmol), 2-bromoacetophenone **1** (570 mg, 2.86 mmol), and $NaHCO_3$ (547 mg, 6.51 mmol) were combined in anhydrous DMF (15 mL) and stirred for 18 h at ambient temperature. The reaction mixture was quenched with HCl (1 N, 10 mL) and extracted with EtOAc (25 mL). The aqueous layer was made alkaline with saturated aqueous $NaHCO_3$ and extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography on silica gel, eluting with a gradient of hexane:EtOAc/100:0 to 20:80, provided **3a** as a white solid (328 mg, 54% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, J = 8.4, 1.1 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.46 (t, J = 6.9 Hz, 2H), 4.10 (s, 2H), 3.68 (s, 3H), 1.42 (s, 6H); MS: m/z = 236 (M+1). β-Ketoamine **3a** (100 mg, 0.286 mmol, TFA salt), amine **6a** (47.0 μl, 0.429 mmol), and AcOH (82.0 μL, 1.43 mmol) were dissolved in MeOH (1.0 mL) and stirred for 5 min. $NaBH_3CN$ (27 mg. 0.429 mmol) was added and the resulting solution heated to 50 °C for 18 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), H_2O (3 mL) was added, and the product was extracted into EtOAc (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography on silica gel, eluting with a gradient of hexane:EtOAc/100:0 to 0:100, provided **5a** as a white solid (53 mg, 63% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.26–7.37 (m, 4H), 7.17 (d, J = 7.1 Hz, 2H), 7.15 (d, J = 7.0 Hz, 2H), 5.61 (d, J = 14.6 Hz, 1H) 4.39

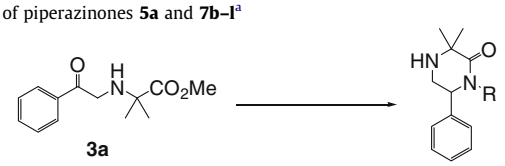
Table 1
Synthesis of β-ketoamine intermediates **3a–k**[a] and piperazinones **5a–k**[b]



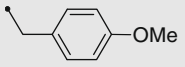
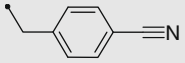
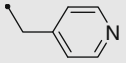
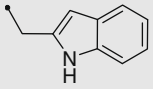
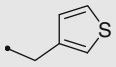
X	Y	Amino-ester	Intermediate	Yield of intermediate **3**[c] (%)	Product	Yield of product **5**[c] (%)
Me	Me	**2a**	**3a**	54	**5a**	63
H	H	**2b**	**3b**	7[d]	**5b**	0[e]
Me	H	**2c**	**3c**	46	**5c**	73
H	Me	**2d**	**3d**	47	**5d**	74
Cyclohexyl	H	**2e**	**3e**	74	**5e**	39[f]
$-(CH_2)_2-$		**2f**	**3f**	83	**5f**	67
$-(CH_2)_5-$		**2g**	**3g**	59	**5g**	59
Benzyl	H	**2h**	**3h**	74	**5h**	60
CH_2NHCO_2t-Bu	H	**2i**	**3i**	49	**5i**	94
CH_2CO_2t-Bu	H	**2j**	**3j**	30	**5j**	60
4-Nitrobenzyl	H	**2k**	**3k**	74	**5k**	67

[a] Reaction conditions: 1–3 mmol amino ester **2a–k**; 1.1 equiv 2-bromoacetophenone (**1**); 2.5 equiv $NaHCO_3$; DMF, ambient temperature.
[b] Reaction conditions: 0.25–0.40 mmol ketone **3a–k**; 1.5 equiv amine; 4.0 equiv AcOH; 1.5 equiv $NaBH_3CN$; MeOH, 50 °C.
[c] Yields of isolated intermediates and products.
[d] Intermediate was not purified. Yield estimated by LC/MS.
[e] Small amount of desired **5b** observed by LC/MS, but no pure product was obtained.
[f] Only 39% conversion to piperazinone **5e**, but recovered 25% of uncyclized intermediate.

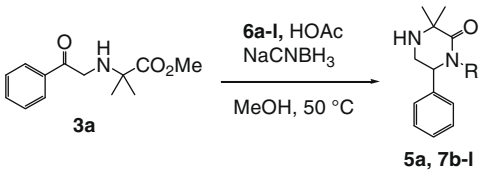
Table 2
Synthesis of piperazinones **5a** and **7b–l**[a]



3a **5a, 7b-l**

Amine	R	Product	Yield[b] (%)
Benzylamine (**6a**)	CH_2Ph	**5a**	63
Aniline (**6b**)	Ph	**7b**	32
Phenethylamine (**6c**)	CH_2CH_2Ph	**7c**	65
4-Methoxybenzylamine (**6d**)		**7d**	71
4-Cyanobenzylamine (**6e**)		**7e**	31
4-Pyridylmethylamine (**6f**)		**7f**	88
(1*H*-indol-2-ylmethyl)amine (**6g**)		**7g**	43
3-Thienylmethylamine (**6h**)		**7h**	41
Methylamine (**6i**)	Me	**7i**	53
Cyclopentylamine (**6j**)	Cyclopentyl	**7j**	0[c]
β-Alanine *tert*-butyl ester (**6k**)	$CH_2CH_2CO_2t$-Bu	**7k**	31
Ammonia (**6l**)	H	**7l**	48

[a] Reaction conditions: 0.25–0.40 mmol amines **6a–l**; 1.5 equiv ketone 3a; 4.0 equiv AcOH; 1.5 equiv $NaBH_3CN$; MeOH, 50 °C.
[b] Yields of isolated products.
[c] Only intermediate formed and no cyclization to desired **7j**.



3a **5a, 7b-l**

Scheme 4. Synthesis of 3,3-dimethyl-6-phenylpiperazin-2-ones.

(t, *J* = 3.5 Hz, 1H), 3.41 (dd, *J* = 14.0, 4.2 Hz,1H) 3.35 (d, *J* = 14.9 Hz, 1H) 2.87 (dd, *J* = 13.9, 2.9 Hz,1H) 1.62 (bs, 1H), 1.51 (s, 3H) 1.50 (s, 3H); HRMS: *m/z* = 295.1811; calcd *m/z* = 295.1805 for $C_{19}H_{22}N_2O$.

Acknowledgments

The authors wish to thank Jim Perkins for assistance in chiral HPLC analysis of diastereomers; the MRL West Point mass spectroscopy and NMR spectroscopy groups for spectroscopic data; and Dan Paone, Donnette Staas, Mike Wood, and Blair Zartman for helpful suggestions.

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7. Chiral HPLC conditions—column: Chiracel OJ; eluent: EtOH; <1% of other diastereomer detected.