Tetrahedron Letters 52 (2011) 1705–1708

Contents lists available at ScienceDirect

Tetrahedron Letters

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

A facile and rapid synthesis of *N*-benzyl-2-substituted piperazines

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ARTICLE INFO

Article history:
Received 17 November 2010
Revised 27 January 2011
Accepted 1 February 2011

Keywords:
Multicomponent reaction
UGI
Piperazines
Microwave

ABSTRACT

A facile and rapid synthetic approach of *N*-benzyl-2-substituted piperazine building-blocks via an Ugi strategy is described. This strategy is high yielding (80–92% overall yield), step-efficient and fast using microwave heating and *tert*-butylisocyanide as a convertible isocyanide. This method is useful for the obtention of key intermediates in medicinal chemistry.

The piperazine ring is a core structure present in many bioactive molecules. First, it can serve either as a linker between the groups responsible for activity or behave as a pharmacocophore like in the well known first three generations of fluoroquinolone antibiotics (i.e., levofloxacin, Fig. 1). In natural products this heterocycle is rather present in fused or oxidized forms (i.e., ergotamine, safricin B, Fig. 1). Recently published bioactive piperazines include monoamine reuptake inhibitors,[1] MAP kinase inhibitors,[2] CCK1R agonists,[3] urotensin antagonists,[4] GHSR antagonists,[5] and HIV integrase inhibitors.[6] Also, the piperazines can be used by medicinal chemists as a basic pharmacophore whose pH can be modulated by the N1 and N4 substituents,[7] thus modulating the ability to interact with the biological target. Secondly, this heterocycle is a powerful tool for the fine-tuning of pharmacokinetics of bioactive compounds. Indeed, it modulates in numerous examples the solubility, permeability, and metabolism like for imatinib (Fig. 1) or IGF-1R kinase inhibitors.[8]

The 2-substituted piperazines are of high interest for pharmacomodulation. Unfortunately, examples in the literature are limited almost exclusively to 2-methyl and 2-phenylpiperazines, because of the limited availability of suitably protected piperazines in commercial databases.[5,9,10] The 2-substituent is also a key feature of pharmacokinetic properties of piperazines as it modulates its pKa[7] and lipophilicity. As a consequence, it influences permeation, solubility, and bioavailability of the compounds. Some recent examples include the enhancement of passive membrane permeation for HIV protease inhibitors[6] or the enhancement of brain permeation in a template hopping strategy.[1] N-substituted piperazines can be metabolized to Nor-derivatives or by hydroxylation in the 2-position and subsequent ring opening (i.e., prazosin and sildenafil).[11,12] Thus, the use of a 2-substituted piperazine precursors could protect against both the metabolic processes by reducing N-dealkylation thanks to steric hindrance or by direct prevention of hydroxylation.

In that context, a convenient and rapid synthesis of *N*-benzyl-2-substituted piperazine building-blocks is of high interest for medicinal chemists (Fig. 2).

The 2-substituted piperazines can be prepared by (1) intramolecular acylation and reduction of diketopiperazines or ketopiperazines,[13] (2) alkylation and reduction of substituted pyrazines[14] or (3) lithiation and alkylation of *N*-Boc piperazines.[15] These methods often require multiple steps and the chemical diversity is limited by the commercial availability of starting materials and the harsh conditions usually required. Recently, multicomponent reaction approaches have emerged in the field of piperazine synthesis.[16,17] We have already published the use of multicomponent reactions to access biologically interesting molecules.[18] We report, in this paper, a facile and rapid method to access, in high yield and purity, diverse N-protected-2-substituted piperazines ready-to-use building-blocks.

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doi:10.1016/j.tetlet.2011.02.011

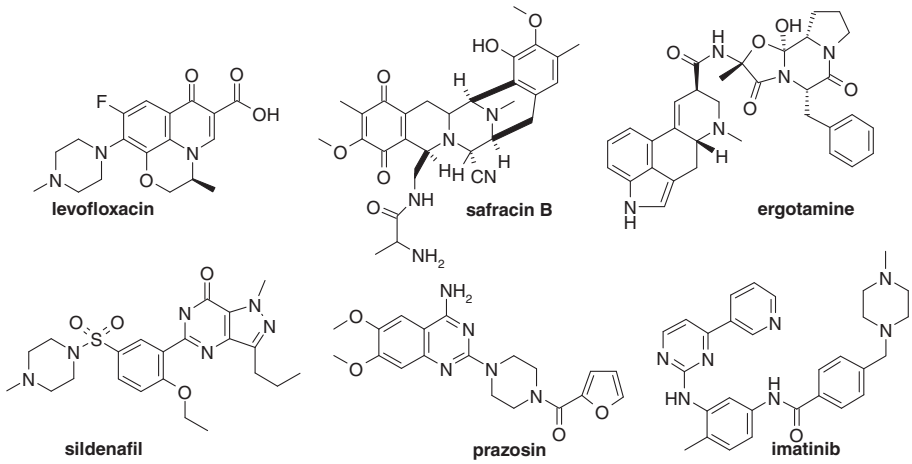


Figure 1. Examples of bioactive compounds containing a piperazine ring.

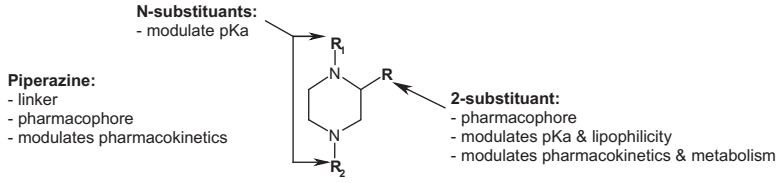


Figure 2. Roles of piperazine and 2-substituted piperazine in medicinal chemistry.

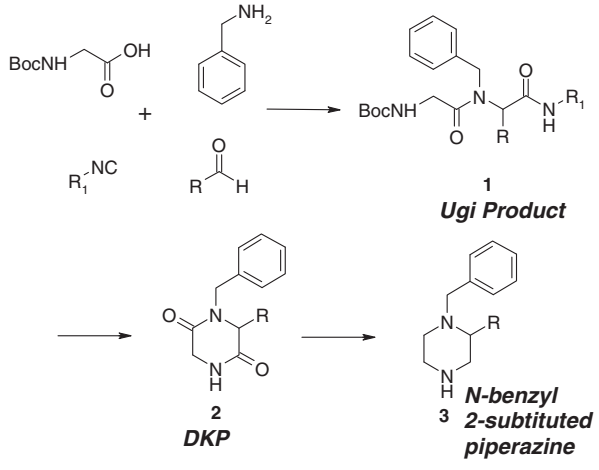
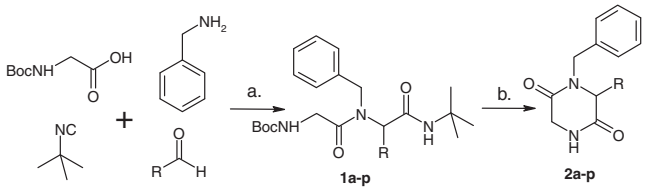


Figure 3. Synthetic strategy.

N-Protected-2-substituted piperazines of general formula **3** (Fig. 3) can be prepared by reducing the corresponding diketopiperazines **2** which are obtained via a multicomponent reaction from four cheap and readily available building-blocks: *N*-Boc-glycine, amines, aldehydes, and a convertible isocyanide (Fig. 3). In our case the benzylamine was used as a precursor of the *N*-benzyl protected piperazine. This protecting group can be selectively removed via Pd-catalyzed reduction. Yet, its presence allows the differentiation of the two nitrogen atoms in subsequent reactions. Other benzylamines can be used in the replacement of benzylamine to fine-tune the deprotection conditions.

Hulme and co-workers have reported an Ugi sequence to construct heterocyclic cores and have applied it to the synthesis of 6 keto-piperazines from glycine, Aib (α-aminoisobutyric acid), alanine, or phenylalanine.[19,20] They use either Armstrong's convertible isocyanide[19] or *n*-butylisonitrile.[20] In a strategy to minimize the cost of the reagents, we used the cheaper *t*-BuNC as a convertible isocyanide, as we have already used it for the synthesis of piperidines.[18,21,22] Moreover, the *t*-butyl amine group can be removed by intramolecular substitution using pure AcOH while *n*-butyl group requires a mixture of TFA in dichloroethane and further silica gel purification of the crude product. On the opposite, our strategy allows obtaining easily of the desired diketopiperazine (DKP) by simple precipitation of the reaction mixture in water.

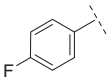
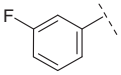
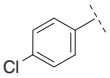
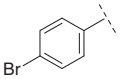
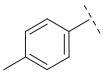
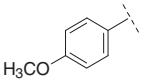
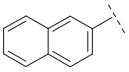
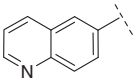
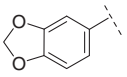
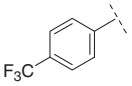
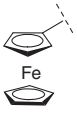


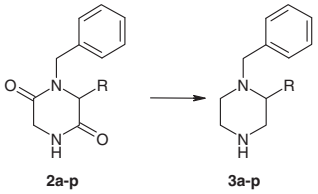
Scheme 1. Reagents and conditions: (a) MeOH, 18 h, rt; (b) glacial AcOH, microwave, 180 °C, 10 min.

The reaction proceeds as described in Scheme 1. Boc-Gly-OH, benzylamine, various aldehydes, and *t*-BuNC react in methanol at room temperature for 18 h affording the classical Ugi products (**1a–p**). For all the chosen aldehydes, either electron–withdrawing groups or electron-donor groups, yields are excellent (92–100%). Also an organometallic derivative or heteroaromatic aldehydes give good results. Then, the Ugi products are irradiated by microwaves at 180 °C for 10 min in glacial acetic acid to form the desired corresponding DKP (**2a–p**) in excellent yields (91–98%) and purities. The results are presented in the Table 1. 2-Keto-piperazines are obtained in two steps in 82–97% overall yield as compared to 44–67% using *n*-butylisonitrile.[20]

The DKPs (**2a–p**) are then reduced by using 8 equivalents of $LiAlH_4$ in THF (Scheme 2).[23] After 4 h, the corresponding 2-substituted piperazines (**3a–p**) bearing a benzyl protecting group on N1

Table 1
Synthesis of *N*-benzyl-2-substituted DKPs and *N*-benzyl-2-substituted piperazines

R-	Ugi product yield (%)		DKP yield (%)		Piperazine yield (%)	
	**1a**	100	**2a**	97	**3a**	90
	**1b**	93	**2b**	98	**3b**	86
	**1c**	96	**2c**	98	**3c**	81
	**1d**	98	**2d**	95	**3d**	77
	**1e**	94	**2e**	94	**3e**	84
	**1f**	100	**2f**	95	**3f**	80
	**1g**	93	**2g**	94	**3g**	91
	**1h**	95	**2h**	93	**3h**	83
	**1i**	97	**2i**	96	**3i**	88
	**1j**	92	**2j**	92	**3j**	80
	**1k**	90	**2k**	91	**3k**	83
	**1l**	93	**2l**	93	**3l**	87
	**1m**	92	**2m**	95	**3m**	82
	**1n**	93	**2n**	92	**3n**	78
	**1o**	100	**2o**	93	**3o**	82
	**1p**	93	**2p**	93	**3p**	79



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C then rt, 4 h.

are formed in excellent yields (77–91%) (Table 1). Slightly below average yields were observed for fluorine-containing compounds (**3c**, **3d**, and **3n**) or ferrocenic and bromine derivatives.

In conclusion, we have described a rapid and robust method to synthesize 2-substituted piperazines bearing a Bn protecting group on nitrogen atom N1 in good yields by reducing the corresponding diketopiperazines (DKPs). These latter compounds were generated in excellent yields using an Ugi reaction with a convertible isocyanide, followed by a reduction. The reported methodology appears very suitable for the synthesis of a large number of 2-substituted piperazines by simple variation of aldehyde compounds. The access to enantiomerically pure *N*-benzyl-2-substituted piperazines is currently under investigation in our laboratory.

Acknowledgments

We are grateful to the institutions that support our laboratory (Inserm, Université de Lille2, Institut Pasteur de Lille, USTL). This project was supported by Conseil Régional Nord-Pas de Calais, DRRT PRIM 2008-07 PRIM-SP.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.02.011.

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