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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 3699–3701

A simple entry to chiral non-racemic 2-piperazinone derivatives

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Received 19 January 2005; revised 16 March 2005; accepted 22 March 2005
Available online 8 April 2005

Abstract—A simple synthetic approach to chiral, non-racemic, 2-piperazinones has been developed using natural amino acids methyl esters and nitroethylene as starting materials.

In recent years, peptidomimetics have emerged as molecular targets in medicinal and combinatorial chemistry.[1] A classical approach to the preparation of peptidomimetic ligands stems from the construction of conformationally restricted peptide analogs, which could mimick the receptor-bound conformation of the natural ligands as better as possible.

The piperazinone ring has been largely used as a rigid template in the construction of new receptor ligands.[2] Furthermore, these heterocyclic compounds are of great interest since they represent the structural core of several biologically active compounds, such as Leu-Enkephalin analogs,[3] cholecystokinin receptor antagonists,[4] RGD mimetics,[5,6] and the neurokinin-2 receptor ligand.[7]

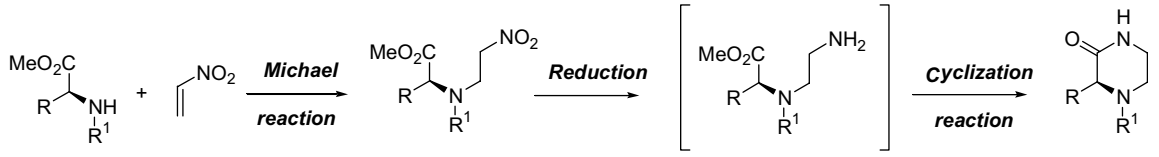
In the course of our studies directed toward the synthesis of small peptidomimetic molecules to be explored as new integrin antagonists, we envisaged a simple entry to chiral non-racemic 2- piperazinones bearing variable substituents at the C-3 position of the heterocyclic nucleus.

Our own idea entails on a synthetic sequence accounting for the use of optically active δ-nitro esters as convenient precursors of the lactam derivatives (Scheme 1).

The δ-nitro esters would be in turn obtained through an intermolecular Michael addition between nitroethylene and optically active α-amino esters. Thus, the nitro group would be used to generate an intermediate δ-amino ester in which the primary amino moiety would take part in an intramolecular cyclization reaction providing the corresponding 2-oxopiperazine nucleus.

We investigated the synthesis of chiral non-racemic 3-substituted 2-piperazinones starting from α-amino esters, whose progenitors were natural α-amino acids.

First, we used L-serine as the model compound. Thus, the amino esters **1a** and **1b** were prepared by standard chemistry,[8] involving *N*-benzylation of L-serine methyl ester and *O*-*tert*-butyldimethylsilyl (*O*-TBDMS) protected L-serine methyl ester, respectively, through



Scheme 1.

Keywords: Peptidomimetics; Piperazinones; Michael reaction; Lactamization reaction.
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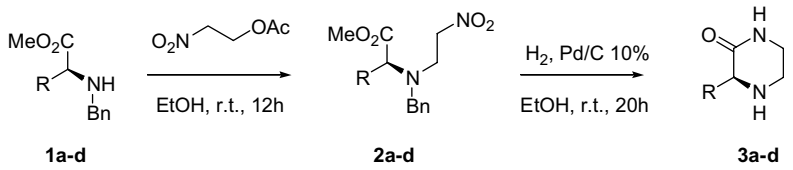
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2005.03.163



1a-d 2a-d 3a-d

Scheme 2.

$NaBH_4$ reduction of the corresponding imines with benzaldehyde.

The obtained reagents were reacted with 1 equiv of a stable precursor for nitroethylene, namely 2-acetyloxy-1-nitroethane, in absolute ethanol at room temperature, giving the expected Michael adducts **2a**,**b** in good yields after column chromatography on silica gel (Scheme 2). Upon hydrogenation (10% Pd/C, EtOH), nitro compounds **2a**,**b** were smoothly converted to piperazinones **3a**,**b** in good yields, the formation of the heterocycles being concomitant to debenzylation.

In all cases, no epimerization at the stereogenic carbon was observed, as determined by chiral HPLC analysis, using opposite enantiomer as a standard.

Uneventfully, the results observed are consistent with the formation of an intermediate primary amine, which could not be isolated, since it cyclized spontaneously to form the lactam nucleus.

Same results were observed when optically active α-amino esters **1c**[9] and **1d**,[10] derived from L-aspartic acid and L-glutamic acid, respectively, were used as the starting materials. Sequential conjugate addition to nitroethylene and catalytic reduction of the intermediate Michael adducts paved the way to the synthesis of chiral, non-racemic, 2-oxopiperazines **3c**,**d** (Table 1).[11]

The chiral piperazinones **3a**–**d** represent very interesting templates for the synthesis of peptidomimetics, through functionalization either on the ring nitrogen atoms or through transformation of the side chains introduced in the cycle.

To this end, we first tried to bind the N-4 nitrogen atom with amino- or hydroxy-substituted chains, to be presently used for the introduction of the most common basic integrin binding motifs. Unfortunately, a direct functionalization of the N-4 nitrogen atom through standard chemistry gave low yields of the expected products after tedious chromatography.

Table 1. Synthesis of piperazinone derivatives **3a**–**d**

Amino ester	R	Compound **2** (% yield)[a]	Compound **3** (% yield)[a]
1a	CH_2OH	60	50
1b	$CH_2OTBDMS$	70	50
1c	CH_2CO_2Me	60	60
1d	$CH_2CH_2CO_2Me$	80	30[b]

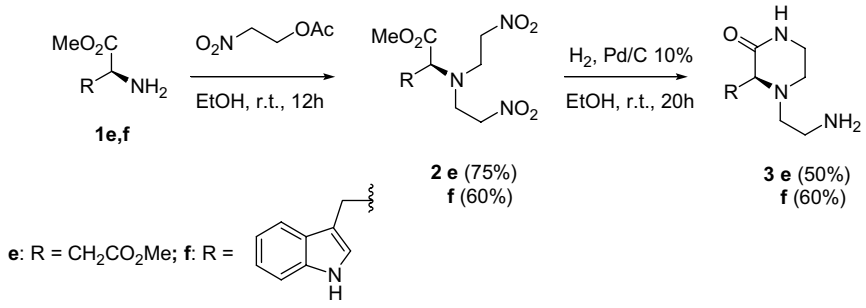
[a] Isolated yield after flash chromatography.

[b] The observed low yield is caused by concomitant formation of the tetrahydro-pyrrolo[1,2-*a*]pyrazine-1,6-dione deriving from intramolecular cyclization of the secondary amino function, which is released during the reductive process.

Thus, we extended our attention to the preparation of the heterocyclic scaffolds already endowed with appropriate functionalities at the N-4 nitrogen atom.

Preliminary studies showed the possibility to obtain chiral piperazinones bearing hydroxy- and amino-substituted side chains, representing versatile appendages for the conjugation with the integrin binding motifs.

Thus, reaction between optically active α-amino esters **1e**,**f** and 2-acetyloxy-1-nitroethane (2 equiv) proceeded uneventfully to afford the expected Michael adducts **2e**,**f**, which were submitted to catalytic hydrogenation allowing the piperazinone derivatives **3e**,**f** in good yields (Scheme 3). Similarly, reductive amination of **1e**,**f** with suitably protected 4-hydroxy-butanal, reaction of the released secondary amines with 2-acetyloxy-1-nitroethane and reduction of the intermediate Michael adducts **4e**,**f**, paved the way to compounds **5e**,**f** in good yields.

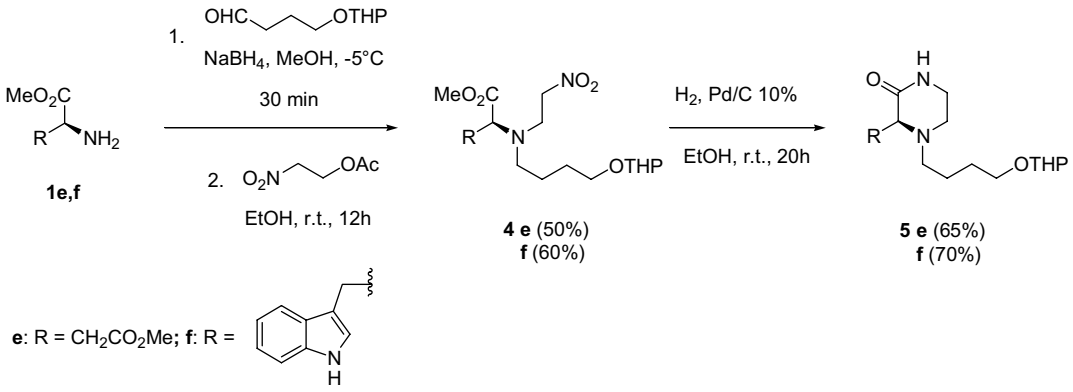


1e,f

2 e (75%)
f (60%)

3 e (50%)
f (60%)

Scheme 3.



Scheme 4.

Also in these cases, no epimerization has carried out, as observed by chiral HPLC analysis (Scheme 4).

In summary, we have developed a very simple protocol that allows the preparation of chiral non-racemic 2-piperazinone derivatives starting from cheap and readily available starting materials. The reported methodology appears very suitable for the synthesis of a large number of piperazinone-based peptidomimetic molecules to be explored as new integrin antagonists. Indeed, a wide range of optically active α-amino esters and aldehydes may be used to produce differently functionalized δ-nitro esters precursors of the piperazinone scaffold.

Acknowledgments

The authors are grateful to MIUR (PRIN 2004) for financial support.

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11. Representative procedure: (3-Oxo-piperazin-2-yl)-acetic acid methyl ester (**3c**): A solution of 2-acetyloxy-1-nitroethane (1 equiv) in absolute EtOH (5–10 mL) was added dropwise to a solution of α-amino ester **1c** (10 mmol) in absolute EtOH (10 mL). The reaction mixture was stirred at room temperature for 12 h and the solvent was evaporated. The residual oil was dissolved in ether (10 mL), washed with $NaHCO_3$ solution (2 × 20 mL, satd. aq) and brine (2 × 20 mL). The dried organic extracts were concentrated and the residue purified by flash chromatography to give the Michael adduct **2c** (60%): oil, $[\alpha]_D^{20}$ −78 (*c* 1.67, $CHCl_3$). IR (film): 1731, 1555, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.59 (dd, 1H, part of a AB system, J = 7.6 and 16 Hz), 2.85 (1H, dd, part of a AB system, J = 7.2 and 16 Hz), 3.20–3.40 (m, 2H), 3.66 (d, 1H, part of a AB system, J = 14 Hz), 3.67 (s, 3H), 3.76 (s, 3H), 3.84 (d, 1H, part of a AB system, J = 14 Hz), 3.91 (t, 1H, J = 7.6 Hz), 4.20 (dt, 1H, J = 5.6 and 13.2 Hz), 4.33 (ddd, 1H, J = 5.6, 8, 13.2 Hz), 7.20–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.54, 49.44, 51.98, 56.19, 60.33, 74.42, 127.75, 128.57, 128.83, 137.92, 171.21, 171.75. A solution of **2c** (5 mmol) in EtOH (50 mL) was hydrogenated at 70 psi with Pd/C 10% in a Parr apparatus for 20 h. The reaction mixture was filtered through Celite and the solvent evaporated to give the 2-oxopiperazine derivative **3c** as an orange solid, mp 78–83 °C; $[\alpha]_D^{20}$ −18.5 (*c* 1.1, MeOH). IR (KBr): 3365, 1731, 1651, 1265 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 2.72 (dd, part of a AB system, 1H, J = 7.6 and 16.8 Hz), 2.87 (dd, part of a AB system, 1H, J = 4.4 and 16.8 Hz), 3.08 (ddd, 1H, J = 4.4, 10, 13.2 Hz); 3.21 (ddd, 1H, J = 2.8, 4.8, 13.2 Hz); 3.50–3.58 (m, 1H), 3.64–3.76 (m, 1H), 3.69 (s, 3H), 3.81 (dd, 1H, J = 4.4 and 7.6 Hz); ^{13}C NMR (100 MHz, CD_3OD): 20.93, 41.64, 51.23, 51.75, 56.12, 166.43, 172.36.