Pergamon

Tetrahedron Letters 43 (2002) 865–867

TETRAHEDRON LETTERS

A facile pathway to synthesize diketopiperazine derivatives

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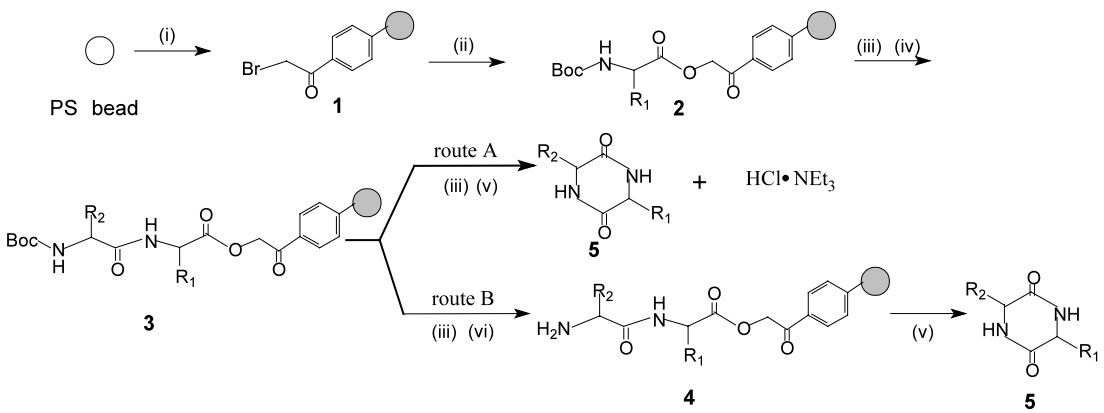
Received 3 August 2001; revised 17 September 2001; accepted 19 October 2001

Abstract—Eighteen diketopiperazines (DKPs) were synthesized in good yields by a solid-phase protocol. This synthesis reveals that the OPac linker between the peptidyl and resin support is favorable to DKP-ring formation and offers a facile and effective way to prepare diverse DKP libraries for combinatorial chemistry. © 2002 Elsevier Science Ltd. All rights reserved.

Diketopiperazine (DKP) formation during solid-phase peptide synthesis with an ester linker bond is documented in many publications as a harmful side reaction, causing peptide cleavage prematurely from the resin support. On the other hand, the DKP backbone is an important pharmacophore in medicinal chemistry, which is conformationally restrained by a six-membered ring with side chains that are orientated in a spatially defined manner.[1,2] The DKP scaffold contains two hydrogen bond accepting centers and two hydrogen donating sites which are often necessary for potential interactions between the lead compound and a targeted protein. DKPs are quite common in nature and many natural products with the DKP scaffold have been isolated encompassing a wide range of biological activities.[3–6] Moreover, in contrast to classical linear peptides, DKPs are very stable to proteolysis, one important consideration when designing potential lead structures.

In general DKP-ring formation is strongly sequence dependent. If a residue such as Pro or Gly is located at one of the two positions at the C-terminus, it is especially easy to produce a DKP-ring.[7] In the case of hindered residues like Phe, Trp, Tyr, Val, Ile, His…etc., the tendency for DKP-ring closure is quite weak. The lability to nucleophilic attack of the ester-bond linkage between the peptide and the resin is another parameter which favors DKP formation. A few reports have described the synthesis of DKP derivatives on different kinds of resin.[8–11] However, there is no report, to our knowledge, describing DKP preparation from an ester



Scheme 1. *Reagents and conditions*: (i) $BrCH_2COBr$, $AlCl_3$, nitrobenzene–DCM (1:1); (ii) Boc-AA-OH, Et_3N, DMF; (iii) 3.5N HCl/HOAc; (iv) Boc-AA-OH, HOBt, DCC, NMM, DMF; (v) 5% Et_3N/THF–H_2O (8:1); (vi) 10% DIPEA/EtOAc.

Keywords: diketopiperazine; OPac-linker; solid-phase synthesis.

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PII: S0040-4039(01)02005-6

linkage such as Pac (Phenacyl ester), which are very labile to nucleophilic attack, leading to cyclization via intramolecular aminolysis.

An effort was initiated in the present study to establish a simple procedure for the efficient synthesis of DKPs on bromoacetyl resin, as shown in Scheme 1. Functionalized resin **1** was prepared from PS (polystyrene, 1% DVB cross-linked, 100–200 mesh) beads by Friedel–Crafts acylation.[12] The yield was estimated by the weight gain of the resin. The anchorage of the first *N*-Boc-amino acid on the resin was carried out under mild conditions—mixing **1** with Boc-AA-OH and Et_3N, in DMF, at room temperature for 24 h. Ester **2** was produced in near quantitative yield based on the weight gain of the resin. The second residue was added to the resin by use of a standard DCC/HOBt coupling procedure after removal of the Boc group from **2**. The target compound **5** was obtained directly by eliminating the Boc group from **3** and then mixing with Et_3N and THF. However, the final product was inevitably contaminated with the by-product $HCl{\cdot}Et_3N$, and was very difficult to purify. It was obvious that preneutralization and washing before DKP-ring closure in a stepwise manner (route B as shown in Scheme 1) instead of route A was necessary to ensure the purity of **5**. Great care was taken to minimize premature DKP-ring closing during neutralization and washing. The use of the hindered base DIPEA (diisopropylethylamine) instead of Et_3N and shortening the washing time were imperative in our protocol.

A typical experimental procedure is as follows: A suspension of **1** (1 mmol) in DMF containing Et_3N (2.2 mmol) and Boc-AA-OH (2 mmol) was stirred at room temperature for 24 h. The liquid was drained off and the resin was washed successively with DMF (×3), 95% EtOH (×5), EtOAc (×2) and DCM (×1). Yields of **2** were evaluated from the weight gain of the resin. After the removal of the Boc group by mixing resin **2** with 3.5N HCl/HOAc for 30 min and washing with EtOAc (×5), a solution of 3 equiv. Boc-AA-OH, 3 equiv. HOBt, 3.2 equiv. DCC and 1.2 equiv. *N*-methylmorpholine in DMF was mixed with the resin for 4–6 h. Resin **3** was filtrated and washed with DMF (×3), MeOH (×5) and DCM (×2). The completeness of the second residue assemblage was monitored by ninhydrin test.[13] For the Boc deprotection, resin **3** was treated as before. Neutralization and washing were accomplished with 10% DIPEA/EtOAc (2 min), 95% EtOH (3×1 min). After draining, the resin **4** was mixed with 5% Et_3N in THF–H_2O (8:1) for 24 h. The supernatant was collected and concentrated. DKP product **5** was precipitated by mixing the residual solution with ether. Eighteen DKPs were synthesized in good yields (Table 1).

In summary, a facile and efficient method for the solid-phase synthesis of DKPs from a resin bound OPac linker has been developed. The reaction can be conveniently carried out under mild conditions, and preneutralization treatment ensured a DKP product with excellent purity. Although most of the DKP derivatives prepared in the present study consisted of at least one of the following hindered residues such as Phe, Val, Trp, Arg, Tyr(ClzB), His(Bzl), the yields were reasonable or even better. It is obvious that the lability of the OPac linkage to nucleophilic attack is suitable for the synthesis of DKPs by solid-phase methods and maybe by solution phase also. This will be amenable to the preparation of diverse DKP libraries for the study of combinatorial chemistry in the near future.

Acknowledgements

The authors would like to thank Dr. Jeper Abliz and his assistants for providing mass spectral data.

Table 1. Results of the preparation of DKPs

Entry	Compounds	Mp (°C)	Yields (%)	Mw (calcd)	FAB-MS
a	*cyclo*[Met-Phe]	140–142	79	278.4	279.1
b	*cyclo*[Trp-Phe]	>280	60	333.4	334.1
c	*cyclo*[Lys-Phe]	253–255	71	275.4	276.2
d	*cyclo*[Met(Mob)-Phe]	178–180	66	370.5	371.2
e	*cyclo*[Pro-Phe]	118–120	82	244.3	245.2
f	*cyclo*[Gln-Phe]	232–234	76	275.3	276.2
g	*cyclo*[Arg-Phe]	133–135	72	303.4	304.1
h	*cyclo*[Pro-Val]	175–178	81	196.3	197.1
i	*cyclo*[Pro-Gln]	161–163	85	225.2	226.2
j	*cyclo*[Pro-His(Bzl)]	193–195	79	324.4	325.2
k	*cyclo*[Pro-Arg]	183–185	84	253.3	254.2
l	*cyclo*[Glu(Obzl)-Trp]	170–172	72	405.4	406.2
m	*cyclo*[Glu-Tyr(ClzB)]	217–219	71	451.3	451/453
n	*cyclo*[Pro-Tyr(ClzB)]	215–217	73	419.3	419/421
o	*cyclo*[Arg-Asn]	200–202	80	270.3	271.2
p	*cyclo*[Gln-Asn]	168–170	71	242.2	243.1
q	*cyclo*[Met-Asn]	113–115	77	245.3	246.2
r	*cyclo*[Ala-Lys]	179–181	67	199.3	200.1

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