Synthesis of Indolyldiketopiperazines with NBS

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ABSTRACT Two series of indolyldiketopiperazines were synthesized starting from methyl 1-substituted-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylate hydrochlorides via *N*-bromo-succinimide (NBS) as an important reagent. All eight compounds were characterized by nuclear magnetic resonance (NMR) and elemental analysis. Furthermore, the mechanisms of NBS-reacted rearrangements are also discussed. *Chirality 26:790–792, 2014.*

KEY WORDS: *N*-bromosuccinimide; conjugative effect; indolyldiketopiperazine; rearrangement

INTRODUCTION

Over the past decades, indolyldiketopiperazines have attracted increasing attention due to the awareness of their bioactivities such as antitumor,[1,2] antimicrobial,[3] and anti-HIV agents.[4] There are three skeletons of indolyldiketopiperazines according to their structural features: the open-ring indolyldiketopiperazines (i) in which the indolyl and diketopiperazine units were linked by a chemical bond, the close-ring ones (ii) which consist of a closed ring between the two units, and the *spiro*-ones (iii) which have *spiro*-carbons in the structures. The basic skeleton of all three structures are shown in Figure 1.

There are many methods for the synthesis of the *spiro*-compounds. For example, 1,3-cyclic addition was used to establish a *spiro*-carbon[5] and then obtain the *spiro*-indolyldiketopiperazines.[6] In addition, the *N*-bromosuccinimide (NBS) method was often found in the literature.[7] NBS, which can provide the Br+ or Br·, is a very common reagent used in many reactions such as selectrophilic substitutions[8] and radical reactions.[9] In the present work, NBS was used as the reagent of *spiro*-rearrangement and our study obtained the compounds successfully. However, a series of compounds with another skeleton were obtained in the same surroundings (Scheme 1).

EXPERIMENTAL

The substrates (methyl 1-substituted-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylate hydrochlorides **3**) were asymmetrically synthesized through a reference method.[10] All reagents were commercially available. Melting points were measured on an X-6micro-melting point apparatus and were uncorrected. The nuclear magnetic resonance (NMR) spectra were obtained on an AVANCE-400 instrument (^{1}H NMR at 400 MHz, ^{13}C NMR at 101 MHz) using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. Elemental analysis was carried out with Vario EL III elemental analyzer.

N-protected

To a mixture of one of the substrates (**3**, 1.5 mmol) and Fmoc-*L*-Pro-Cl (prepared by Fmoc-*L*-Pro, 1.8 mmol) in CH_2Cl_2 (15 mL) was added Na_2CO_3 (aq.) (15 mL) to be a double phase system and the mixture was stirred for1 h (reaction progression was monitored by thin-layer chromatography [TLC]). After the completion of the reaction, the *N*-protected compound **4** was obtained and could be used without purification.

NBS Reacted Rearrangement and Further Treatments

Compound **4** was dissolved in THF-H_2O (30 mL, 1:1, v/v) and then AcOH (5 mL) was added. After cooling the mixture to 0–5°C using an ice bath, ice-bathed NBS (3 mmol) was added dropwise. After a 5-min ice bath, it was stirred for 30 min at room temperature (reaction progression was monitored by TLC). After the completion of the reaction, it was quenched by solid Na_2SO_3, and neutralized with Na_2CO_3 (aq.). It was vacuum-filtered and distilled to wipe THF, then extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated to yield the crude product, which was also used without further purification.

Morpholine (5 mL) was added to a solution of the crude product above in CH_2Cl_2 (30 mL) and the mixture was heated to 40°C for 40 min (reaction progression was monitored by TLC), and concentrated to yield the crude product, which was further purified by column chromatography (silica gel, petroleum ether: ethyl acetate = 2:1, v/v) to give **1** or **2**.

The structures of the isolated products **1a–1d** and **2e–2h** were corroborated by ^{1}H NMR and ^{13}C NMR spectroscopy, elemental analysis, and/or ^{1}H-^{1}H NOESY.

Selected data: (2*S*,3*S*,5a*S*,10a*S*)-3-ethyl-5a,6,7,8-tetrahydro-1*H*-spiro[dipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-2,3'-indoline]-2',5,10(3*H*,10a*H*)-trione (**1a**). Yield 57.44%. White solid; mp133–134 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.59 (s, 1H), 7.36 (d, J = 7.08 Hz, 1H), 7.26 (t, J = 7.62 Hz, 1H), 6.99 (t, J = 7.48 Hz, 1H), 6.87 (d, J = 7.64 Hz, 1H), 4.81 (t, J = 8.34 Hz, 1H), 4.40 (t, J = 7.86, 1H), 3.78 (dd, J = 8.56, 3.08 Hz, 1H), 2.51 (m, 3H), 2.29-2.16 (m, 2H), 2.05-1.95 (m, 1H), 1.92-1.80 (m, 3H), 1.72-1.63 (m, 1H), 0.44 (t, J = 7.32 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 180.75, 168.34, 166.54, 142.64, 129.18, 127.81, 125.78, 122.10, 110.10, 63.66, 60.99, 58.45, 54.95 (*spiro*-C), 45.02, 34.13, 27.90, 23.70, 23.65, 11.21; NOE data: 1-Hα (1-Hβ), 1-Hβ (1-Hα, 10a-H, 3-H), 10a-H (1-Hβ, 3-H), 3-H (1-Hβ, 10a-H), 3a-H (4'-H), 4'-H (3a-H); Elemental analysis, calcd. for $C_{19}H_{21}N_3O_3$: C 67.24, H 6.24, N 12.38; found: C 67.25, H 6.25, N 12.37%.

(3*S*,8a*S*)-3-((2-(4-Methoxybenzoyl)-1*H*-indol-3-yl)methyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (**2e**). Yield 55.24%. Faint yellow solid; mp181–183 °C;

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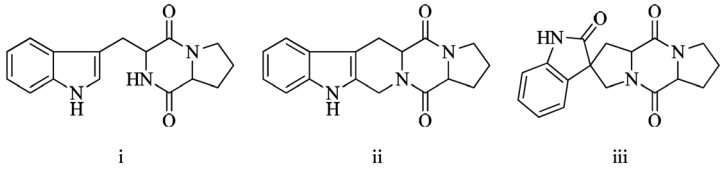

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Fig. 1. Basic structures of three indolyl diketopiperazines.

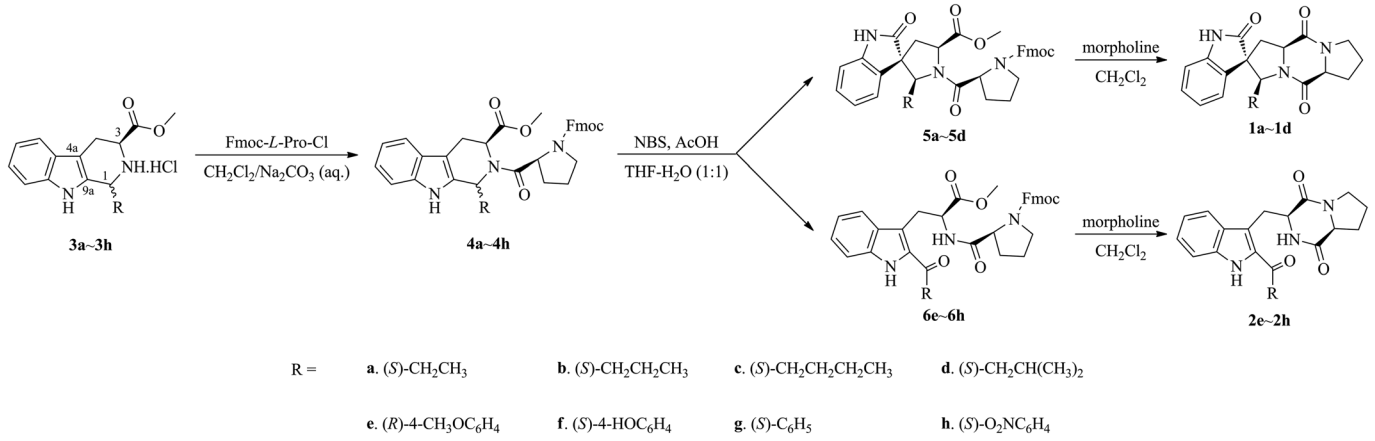
^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.22 (s, 1H, indole-NH), 8.15 (s, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.3 Hz, 2H), 7.51 (d, J = 8.3 Hz, 1H), 7.47-7.38 (m, 1H), 7.27-7.21 (m, 1H), 6.93 (d, J = 8.8 Hz, 2H), 4.30 (dd, J = 8.3, 2.9 Hz, 1H), 3.96 (t, J = 7.5 Hz, 1H), 3.89 (s, 3H), 3.72 (d, J = 5.3 Hz, 2H), 3.58 (dd, J = 8.3, 5.3 Hz, 2H), 3.44 (dd, J = 14.5, 8.6 Hz, 1H), 2.26 (ddd, J = 12.2, 10.5, 7.7 Hz, 1H), 2.01-1.84 (m, 3H);^{13}C NMR (101 MHz, $CDCl_3$) δ: 187.58, 169.79, 165.93, 163.63, 136.49, 132.91, 132.40, 130.31, 127.50, 126.30, 121.15, 121.04, 119.56, 113.96, 112.44, 59.07, 56.55, 55.61, 45.38, 27.94, 24.83, 22.79; Elemental analysis, calcd. for $C_{24}H_{23}N_3O_4$: C 69.05, H 5.55, N 10.07; found: C 69.07, H 5.52, N 10.06%.

Characterization data of other compounds (**1b–1d**, **2f–2h**) are shown in the Supporting Information.

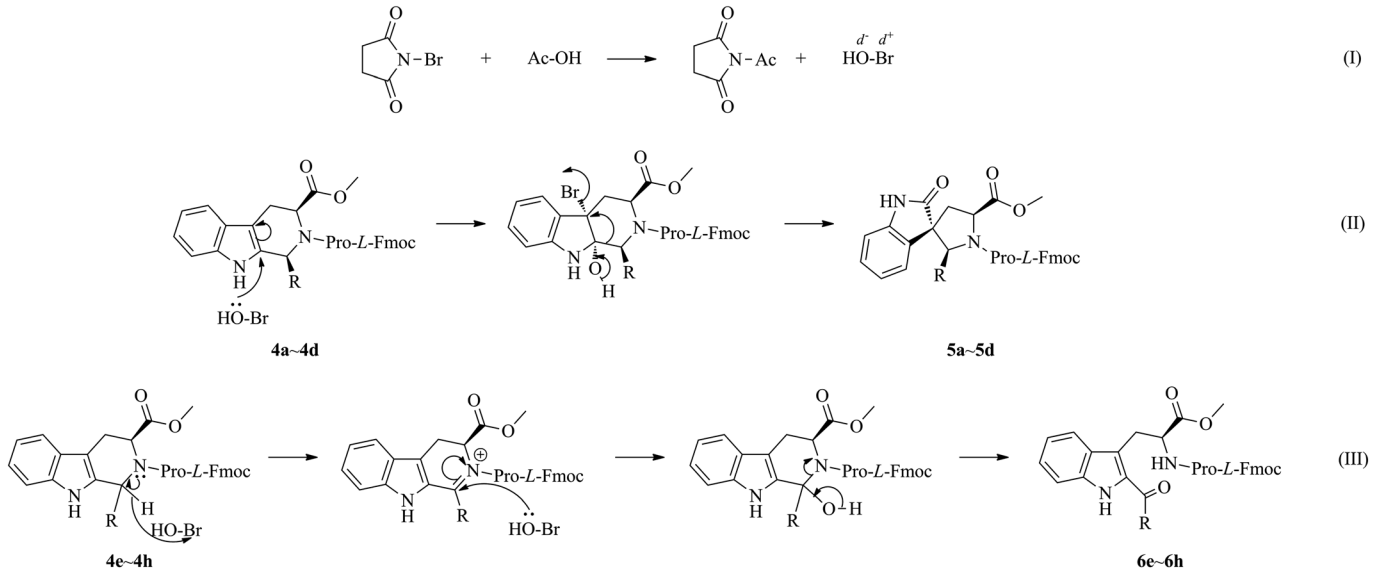
RESULTS AND DISCUSSION

As shown in Scheme 1, the R- of the starting material appeared to be the important influencing factor whether the endproducts were spiro-cyclic or open-cyclic compounds. While the R was aliphatic, the spiro-product would be given; while aromatic, it would be an open-cyclic compound.

It is possible that there were two paths for the reaction of NBS according to the effects between conjunctive and electrophile: one was the 1-C in **4**, the other was the 4a,9a-double bond, which was on the unit of indolyl. First, HO-Br, which deviated the OH part, was given by NBS and AcOH



Scheme 1. Synthesis of two series of indolyl diketopiperazines through three-step procedures including NBS rearrangements.



Scheme 2. Plausible mechanisms of NBS rearrangements.

(see Scheme 2(I)). When the R was an aromatic group,1-C was neighbored by three conjugated units (an indolyl group, a phenyl or its diverse, and an amido group), which made the carbon easy to change from the hybridization sp^3 to sp^2 and obtain a $C=N^+$, the conjunctive effect showing the main effect. H-1 was dropped with a HO-Br and the 1-C was made a double-bond with N, and then the carbon was attacked by OH duplet. After electron transfers, the open-cyclic structure was obtained (see Scheme 2(III)). When the R was an aliphatic group, 1-C was neighbored by two conjugated units (an indolyl group and an amido group), and a more electrophile effect was obtained. It was more possible that the 4a,9a-double bond would be more active for reacting than the 1-C. The 4a,9a-double bond was attacked by HO-Br to give a *trans*-4a-bromo-9a-hydroxy intermediate, and then rearranged like a pinacol-rearrangement to get the spiro- compound (see Scheme 2 (II)). Otherwise, the compounds with 1- aromatic group also had a stronger steric hindrance for rearrangement to be a spiro-structure, which evinced more difficulty. Moreover, during the rearrangement, the configuration of C-1 of **4** worked as an important character for the stereochemistry of **5**, which made the 4a,9a- bond turn to the opposite orientation.

During the NBS-related step, AcOH showed an acidic system and afforded OH to make HO-Br. What's more, an acidic system was necessary, and the starting temperature should not be too high, around 0°C was better, and after reacting, it could be at room temperature. The reaction time was not a consideration at present.

CONCLUSION

In conclusion, we synthesized two series of indolyldiketopiperazines starting from methyl 1-substituted-1,2,3,4-tetrahydro-*β*-carboline-3-carboxylate hydrochlorides via NBS as the reagent. Two plausible mechanisms of NBS-reacted rearrangements were discussed theoretically.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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