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An efficient green synthesis of proline-based cyclic dipeptides under water-mediated catalyst-free conditions

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ABSTRACT

L-Proline-based cyclic dipeptides were synthesized from *N*-Boc-protected dipeptide methyl esters under catalyst-free condition using water as a solvent. One-pot deprotection and cyclization have been used as the key steps, providing an efficient and environmentally friendly approach. Clean reaction conditions, easy isolation, and good yields of cyclic dipeptides are the salient features of the proposed methodology.

In nature, amino acids can be found in a great variety. Their imperative role in life is indisputable. In particular, conformationally restricted amino acids have been the focus of significant interest due to their importance in drug designing. Among the amino acids, proline has attracted considerable attention in recent years due to its characteristic secondary amino group, which induces amide bonds to adopt a cis conformation favoring intramolecular cyclization of *N*-free proline-containing dipeptide methyl ester into bicyclic diketopiperazine structures. Indeed, many diketopiperazines (DKPs) with important biological implications contain the proline moiety.[1,2]

Recent reports describing research in the area of 2,5-diketopiperazines (DKPs) show that this class of compounds is useful in medicinal chemistry, combinatorial chemistry, and targeted organic synthesis.[3,4] A variety of DKPs have been found to possess interesting biological properties such as antitumor[5], antimicrobial[6], and antiviral activities.[7] Studies on their synthesis and modes of action have been reported.[8–13] Proline-based DKPs have been shown to inhibit several enzymes, as well as to recognize, modulate, and control the activity of many receptors.[14–17]

With growing interest in developing environmentally friendly reaction and atom-economic processes, the application of green solvents is considered a preferable route in organic chemistry. Compared to conventional solvents, water is preferred for organic reactions because it displays unparalleled and unique physical properties. Moreover, it is nontoxic, cheap, hazardless in handling, and environmentally benign.[18,19]

2,5-Diketopiperazines-based amino acids are head-to-tail cyclic dipeptides synthesized by the coupling of an *N*-Boc-protected α-amino acid with an α-amino acid ester, followed by *N*-Boc deprotection and intramolecular cyclization. This can generally be achieved through two steps, (1) deprotection of the *N*-Boc group with acid or base[20–22], followed by (2) intramolecular cyclization under thermal conditions.[8] On the other hand, it is worth noting that *N*-Boc deprotection can also be achieved by utilizing water without requiring any acid/base catalyst. Wang et al. recently employed this strategy to produce several *N*-Boc amino-protected derivatives.[23] Several groups[11,24,25] have reported an efficient method for the synthesis of DKPs from *N*-Boc-protected dipeptide ester using microwave conditions. Menendez and co-workers reported solvent-free conditions for cyclization of *N*-Boc-protected amino esters, and in few cases they employed 10% silica gel to enhance the conversion.[25] Tullberg et al.[11] performed a comparative study between microwave and conventional heating with various solvents at different reaction conditions for the cyclization of dipeptide methyl esters and found water to be an excellent solvent for the preparation of DKPs.

A variety of approaches have been developed to enable efficient head-to-tail water-mediated cyclization for the synthesis of 2,5-diketopiperazines in two steps. However, to the best of our knowledge, the green synthesis of L-proline-based cyclic dipeptides from *N*-Boc-protected dipeptide methyl ester in one-pot under simple and inexpensive conditions has not yet been reported. Herein, we report on a mild, catalyst-free, green procedure for one-pot synthesis of L-proline-based cyclic dipeptides from *N*-Boc-protected dipeptide ester using water as a solvent.

The synthesis of *N*-Boc-protected linear dipeptides (**3a–k**) is outlined in Table 1. The dipeptides were synthesized by the coupling of various *N*-Boc-protected amino acids[26] (**1a–k**) with L-proline methyl ester hydrochloride (**2**) in DMF solution using *N,N*-diisopropylethylamine (DIPEA) and 2-(1*H*-benzotriazol-1-yl)-1,1,3,3,-tetramethyluronium hexa-fluorophosphate (HBTU) as a coupling reagent at room temperature (Table 1, entry 1–11). In most cases, isolated yields ranged from good to excellent except for L-serine and L-aspargine (Table 1, entries 9 and 10).

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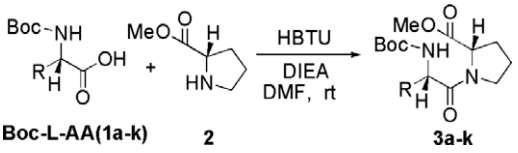
Table 1
Synthesis of linear dipeptides containing a proline



Boc-L-AA(1a-k) 2 3a-k

Entry	R (**1a–k**)	Boc-(L-amino acid)	Yield[a] (%)
1	HO–C_6H_4–CH_2–	Tyr	95
2	C_6H_5–CH_2–	Phe	92
3	CH_3–	Ala	85
4	$(CH_3)_2CH$–	Val	86
5	$(CH_3)_2CHCH_2$–	Leu	90
6	$CH_3CH_2CH(CH_3)$–	Ile	93
7	H–	Gly	82
8	–$CH_2CH_2CH_2$–	Pro	88
9	HO–CH_2–	Ser	47
10	H_2N–$COCH_2$–	Asn	45
11	$CH_3CH(OH)$–	Thr	94

[a] Isolated yield after column chromatography.

We explored the cyclization of *N*-Boc-protected Tyr-Pro methyl ester as a model substrate in water under autoclave conditions. Wang et al.[23] reported that the addition of a lesser amount of water in the deprotection step resulted in incompletion of the reaction whereas the use of excess water (>1 mL/mmol) did not significantly influence the reaction rate and product yield. The experiments were carried out with various time intervals (1–6 h), using distilled, deionized water (20 mL/mmol) at 130 °C. On the basis of these observations, we set the optimum reaction time as 4 h in order to obtain satisfactory results (Table 2).

Using these optimized reaction conditions, the efficiency of this aqueous approach was studied for the syntheses of a wide variety of amino acid (AA)-Pro cyclic dipeptides, and the results are summarized in Table 3.

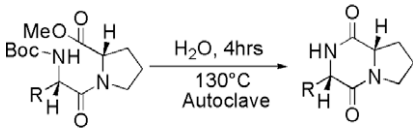
N-Boc deprotection and cyclization of **3a–k** were achieved in a single step during the synthesis of cyclic dipeptides (**4a–k**) by the use of water.[27] As can be seen from the results in Table 3, the isolated yields of **4a–k** were in a range of 70–92%. A comparative observation can be made with Cledera et al., who employed a temperature of 200 °C in an argon atmosphere for the synthesis of 2,5-DKP derivatives,[28] whereas our approach involved a temperature of only 130 °C and delivered good yields. Above all, our technique did not require an inert atmosphere, in contrast with conventional heating.[25,28] The isolated yield for the simple analog *cyclo*-L-Gly-L-Pro was 90% (Table 3, entry 7) whereas the isolated yields of *cyclo*-L-Leu-L-Pro and *cyclo*-L-Ile-L-Pro (Table 3, entry 5 and 6) were moderate. The lower isolated yields for *cyclo*-L-Leu-L-Pro and *cyclo*-L-Ile-L-Pro (70% and 73%) compared to *cyclo*-Gly-L-Pro (90%) were presumably due to the influence of the hindered bulky units present in the former (Leu, Ile). The isolated yield of *cyclo*-L-Phe-L-Pro (Table 3, entry 2) was considerably lower under the normal reaction conditions and hence slight modification was necessary to increase the yield to an acceptable level. The presence of a bulky, hydrophobic phenyl group presumably reduced the solubility of the reactants, and consequently the reaction rate under the normal reaction conditions was minimal. Hence, an enhanced yield of 88% for this reaction was realized simply by the addition of 1,4-dioxane (20%, v/v) to the reaction mixture. In this cyclization method, there was no significant epimerization at the Pro stereocenter, which was confirmed by crude NMR experiment.

Table 2
Effect of reaction time on water-mediated cyclization of L-Tyr-L-Pro linear dipeptide

Entry	Time (h)	Yield[a] (%)
1	1	72
2	2	78
3	3	79
4	4	84
5	5	85
6	6	80

[a] Isolated yield after column chromatography.

Table 3
Synthesis of cyclic dipeptides containing a proline



3a-k 4a-k

Entry	R (**3a–k**)	Products[a]	Yield[b] (%)
1	HO–C_6H_4–CH_2–	Tyr-Pro	84
2	C_6H_5–CH_2–	Phe-Pro	88[c]
3	CH_3–	Ala-Pro	76
4	$(CH_3)_2CH$–	Val-Pro	86
5	$(CH_3)_2CHCH_2$–	Leu-Pro	73
6	$CH_3CH_2CH(CH_3)$–	Ile-Pro	70
7	H–	Gly-Pro	90
8	–$CH_2CH_2CH_2$–	Pro-Pro	92
9	HO–CH_2–	Ser-Pro	91
10	H_2N–$COCH_2$–	Asn-Pro	92
11	$CH_3CH(OH)$–	Thr-Pro	75

[a] All L-cyclic dipeptides.
[b] Isolated yield after column chromatography.
[c] In this case, 1,4-dioxane (20%, v/v) was added.

This method was extended to more amino acids for broad synthetic application. The cyclization of *N*-Boc-protected L-Ala-L-Ala methyl ester, Gly-Gly methyl ester, and Gly-L-Trp methyl ester was carried out in water under the same condition. The crude reaction mixture showed almost one spot in TLC. The calculated yields of each cyclization reactions from the crude NMR analysis were 97%, 95%, and 98% respectively. Therefore, this technique can be useful for the synthesis of other 2,5-diketopiperazine.

In conclusion, we have described an efficient and green protocol for one-pot deprotection and cyclization of L-proline-based cyclic dipeptides. The notable features of the proposed technique include the use of water as a solvent medium and a feasible reaction temperature. Furthermore, the transformation proceeded well during the course of the reaction without requiring an inert atmosphere. Furthermore, the procedure offers several advantages including the absence of any catalyst, improved yields, and simple yet clean reaction conditions, making it a useful and attractive strategy in cyclic dipeptide chemistry.

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26. *Representative experimental procedure for peptide coupling*:
DIEA (0.78 g, 6.0 mmol), *N*-Boc-L-tyrosine (0.85 g, 3.0 mmol), and HBTU (1.37 g, 3.6 mmol) were added to a solution of L-proline methyl ester hydrochloride (0.5 g, 3.0 mmol) in DMF. The reaction mixture was stirred at room temperature overnight. The DMF was removed in vacuo and the residue was diluted in EtOAc, washed with $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated in vacuo. The resulting crude product was purified by column chromatography using silica gel (ethyl acetate/hexane, 1:1) affording the corresponding linear dipeptide.
27. *Representative experimental procedure for cyclization*:
N-Boc-Tyr-L-proline methyl ester held in a round-bottomed flask was dissolved in water at a ratio of 20 mL/mmol. The reaction vessel was fixed into a stainless autoclave with a pressure regulating system. The autoclave was sealed and the mixture was heated to 130 °C for 4 h. The reaction was then stopped by cooling and depressurizing the autoclave. Water was evaporated in vacuo, the remaining residue was purified by column chromatography using silica gel (MeOH/MC, 0.5:9.5).
Cyclo-L-Tyr-L-Pro: White amorphous solid; R_f 0.16 (MeOH:MC, 0.5:9.5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (2H, d), 6.77 (2H, d), 5.72 (1H, s), 4.21 (1H, dd), 4.08 (1H, t), 3.66–3.59 (1H, m), 3.56- 3.51 (1H, m), 3.44–3.39 (1H, m), 2.75 (1H, dd), 2.29 (1H, m), 2.02–1.96 (1H, m), 1.94–1.83 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.8, 165.3, 155.6, 130.5 (2C), 127.4, 116.3 (2C), 59.3, 56.4, 45.6, 36.1, 28.5, 22.7; ESI-MS (*m*/*z*): calcd for $C_{14}H_{16}N_2O_3$ $(M+H)^+$: 261.1161, found: 261.1226; $[\alpha]_D = -71.3$ (*c* 0.5, MeOH) [lit.[29] $[\alpha]_D = -72$ (*c* 0.5, MeOH)].
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