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Facile one-step synthesis of 2,5-diketopiperazines

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ABSTRACT

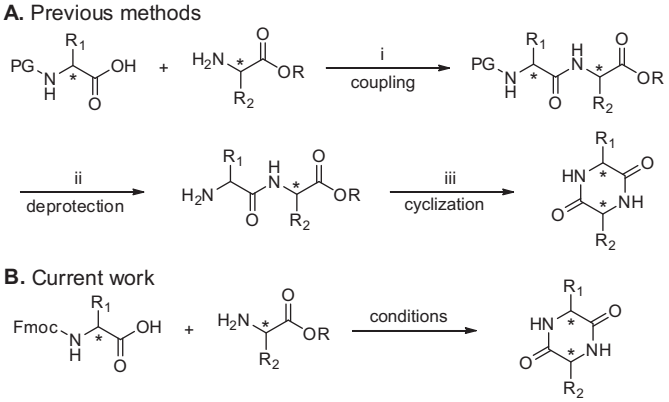
We report a one-step protocol for the general synthesis of 2,5-diketopiperazines from an Fmoc-protected amino acid and an amino acid ester. The application of the method is highlighted by rapid and efficient preparation of various 2,5-diketopiperazines.

2,5-Diketopiperazine (DKP) is a privileged scaffold for numerous bioactive molecules.[1] DKPs have been used as a key structural fragment for anticancer agents by different mechanisms such as cell-cycle inhibitors,[2] breast cancer resistance protein inhibitors,[3] plasminogen activator inhibitors,[4] and DNA binders.[5] Substituted DKPs have also been used in the development of anti-infective therapeutics including antiviral,[6] antibacterial,[7] and antifungal agents.[8] Moreover, DKPs have found application as inhibitors of phosphodiesterase-5 for the treatment of erectile dysfunction,[9] and antagonists of oxytocin for the treatment of preterm labor.[10] Recently, experimental evidence has highlighted the intriguing neuroprotective properties of DKPs in various cellular and animal models.[1c,11]

Many methods are known for the preparation of DKPs.[1a] A common route includes a three-step process: (i) coupling of an *N*-protected amino acid to an amino acid ester, (ii) deprotection of the *N*-protecting group (e.g., Boc, Fmoc, and Cbz), and (iii) base-assisted cyclization of the dipeptide ester (Scheme 1A). Despite the tremendous utility of this method in producing DKPs, it requires multiple-step synthesis with tedious purification processes. To date, one-pot procedure for the synthesis of DKPs is limited.[12] In the course of our research in developing multifunctional neuroprotective agents, we performed a series of reactions intended to synthesize tryptophan/tyrosine-containing DKPs as potential neuroprotective agents for the treatment of traumatic brain injury (TBI).

Tertiary amines such as TEA and DIPEA are ubiquitous catalysts used for the amide bond formation.[13] They are also known to slowly remove the Fmoc group from an amino group.[14] Moreover, tertiary amines are among the common choices of bases to assist the formation of DKPs for the cyclization of the dipeptide esters.[15] Therefore, we hypothesized that a one-pot synthesis of DKPs may be achieved using Fmoc-protected amino acid and amino acid ester in the presence of a tertiary amine, which may provide a rapid and efficient synthetic method for DKPs (Scheme 1B).

To implement this method, a solution of Fmoc-Trp(Boc)-OH (**1a**) and H_2N-Ala-OEt·HCl (**2a**) in DMF was treated with HBTU in



Scheme 1. Synthetic methods to DKPs. (A) classical method and (B) current work.

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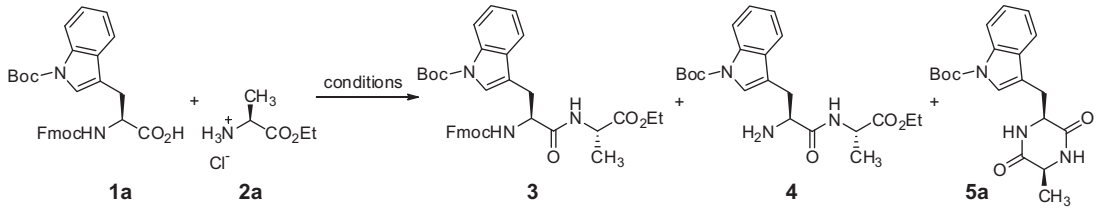
Table 1
Optimization of reaction conditions for the generation of DKP **5a**[a]



1a **2a** **3** **4** **5a**

Entry	Reagent[b]	Base, equiv[c]	Solvent[d]	Time (h)	*T* (°C)	**5a**[e] (%)
1	HBTU	DIPEA (3.0)	DMF	24	rt	0
2	HBTU	TEA (3.0)	DMF	24	rt	Trace[f]
3	HBTU	TEA (3.0)	DMA	24	rt	Trace[f]
4	HBTU	TEA (3.0)	DCM	24	rt	0
5	HBTU	TEA (3.0)	CH_3CN	24	rt	0
6	HBTU	TEA (3.0)	THF	24	rt	0
7	HBTU	TEA (3.0)	Dioxane	24	rt	0
8	HBTU	TEA (2.0)	DMF	24	rt	0
9	HBTU	TEA (3.0)	DMF	24	rt	Trace[f]
10	HBTU	TEA (4.0)	DMF	24	rt	Trace[f]
11	HBTU	TEA (5.0)	DMF	24	rt	Trace[f]
12	HBTU	TEA (6.0)	DMF	24	rt	Trace[f]
13	HBTU	TEA (10)	DMF	24	rt	Trace[f]
14	HBTU	TEA (2.0)	DMF	24	50	0
15	HBTU	TEA (3.0)	DMF	24	50	73
16	HBTU	TEA (4.0)	DMF	24	50	74
17	HBTU	TEA (5.0)	DMF	24	50	75
18	HBTU	TEA (6.0)	DMF	24	50	75
19	HBTU	TEA (10)	DMF	24	50	75
20	EDC	TEA (5.0)	DMF	24	50	12
21	DIC	TEA (5.0)	DMF	24	50	0
22	HATU	TEA (5.0)	DMF	24	50	37
23	**TSTU**	**TEA (5.0)**	**DMF**	**24**	**50**	**82**
24	HOBt	TEA (5.0)	DMF	24	50	0
25	TSTU	DIPEA (5.0)	DMF	24	50	0
26	TSTU	NMM (5.0)	DMF	24	50	6
27	TSTU	DMAP (5.0)	DMF	24	50	24
28	TSTU	Lutidine (5.0)	DMF	24	50	0

The significance of bold values mentioned in optimal conditions.
[a] The reaction was carried out with 1.0 mmol of **1a**, 1.0 mmol of **2a**, and 1.0 mmol of coupling reagent in 5.0 mL of solvent.
[b] HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, TSTU = *N*,*N*,*N*′,*N*′-tetramethyl-*O*-(*N*-succinimidyl)uroniumtetrafluoro borate, DIC = *N*,*N*′-diisopropylcarbodiimide, HOBt = 1-hydroxybenzotriazole hydrate, EDC = *N*-(3-dimethylamino propyl)-*N*′-ethylcarbodiimide hydrochloride, HATU = 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluoro-phosphate.
[c] TEA = triethylamine, DIPEA = diisopropyl ethylamine, NMM = 4-methylmorpholine, DMAP = 4-(dimethylamino)pyridine.
[d] DMF = *N*,*N*-dimethyl formamide, DMA = *N*,*N*-dimethylacetamide.
[e] Isolated yields.
[f] <5%.

the presence of 3 equiv of either DIPEA or TEA at room temperature for 24 h (Table 1, entries 1 and 2). When DIPEA was used, dipeptide **3** was isolated as the only product in almost quantitative yields. However in the presence of TEA, the reaction generated not only **3** (52%), but also the deprotected dipeptide **4** (44%), and a small amount of DKP **5a** (<5%). Accordingly, TEA was chosen for further investigation in different solvents (entries 3–7). We found that the reaction performed in DMA proceeded similarly to that in DMF, while in other tested solvents dipeptide **3** was the only isolated product. After a short screening of the equiv of TEA and reaction temperature (entries 8–19), 5 equiv of TEA at 50 °C was identified as the best combination, giving 75% isolated yields of **5a** with no detectable racemization based on ^{1}H NMR studies (entry 17). We subsequently screened other possible coupling reagents (entries 20–24), and found that TSTU was the most effective (82%, entry 23). It was noted that common coupling reagents, such as DIC (entry 21) and HOBt (entry 24), did not lead to the formation of DKP **5a** in detectable amounts, while EDC (entry 20) and HATU (entry 22) generated **5a** in limited yields. Finally, various bases were screened (entries 25–28). We found that TEA was superior to other tested bases including DIPEA, NMM, DMAP, and lutidine. It is interesting to note that the reaction using tertiary amine DIPEA gave no detectable formation of DKP **5a**.

Next, we explored the utility of this protocol for the preparation of DKPs using the optimized reaction conditions, 5 equiv of TEA, and TSTU as the coupling reagent in DMF (Table 2). When H_2N-Ala-OEt (**2a**) was used, all four selected Fmoc-protected amino acids (Fmoc-Trp(Boc)-OH, Fmoc-Tyr(*t*Bu)-OH, Fmoc-Phe-OH, and Fmoc-Ile-OH) reacted smoothly to generate DKPs **5a**–**d** in good to excellent yields (entries 1–4). Similarly, good yields of DKPs were obtained when H_2N-Leu-OEt (**2b**) was used (entries 5, 6 and 8), with the exception of Fmoc-Phe-OH, which generated DKP **5g** in modest yields along with significant amount of uncyclized dipeptide ester H_2N-Phe-Leu-OEt. Reactions employing H_2N-Val-OEt (**2c**) resulted in good yields for Fmoc-Ile-OH (entry 12), modest yields for Fmoc-Trp(Boc)-OH and Fmoc-Tyr(*t*Bu)-OH (entries 9 and 10), and trace amount of DKP for Fmoc-Phe-OH (entry 11). Generally decreased yields of these reactions were likely due to the increased steric hindrance of the isopropyl group of the valine side chain. These results