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Regioselective and sequential reactivity of activated 2,5-diketopiperazines

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The electrophilic reactivity of Boc-DKPs has been studied. Thanks to Boc activation, the opening ability of carbonyl lactam groups is enhanced. According to experimental conditions, this enabled the synthesis of Boc-amino acid derivatives or original dipeptides via a regioselective and sequential way. Copyright © 2009 European Peptide Society and John Wiley & Sons, Ltd.

Keywords: diketopiperazines; lactam activation; Boc group; electrophilic reactivity; amino acid

Introduction

2,5-Diketopiperazines (DKPs), head-to-tail cyclic dipeptides, have been studied widely in their relation to medicinal and synthetic chemistry [1,2]. Natural products with a DKP skeleton are quite common [3] and a variety of DKPs have been found to possess biological activity [4]. Furthermore, crystal engineering is another field where DKPs have proven useful [5,6], and this class of compounds also constitute attractive building blocks in combinatorial chemistry [2]. Finally, these heterocycles show a broad application in organic synthesis to catalyse the addition of HCN to aldehydes [7,8] and particularly as chiral auxiliaries in Diels–Alder reactions [9] and in the preparation of unnatural amino acids [10–13].

However, to the best of our knowledge, few examples of Boc-DKPs have been reported in the literature. In the synthesis of 1-amino-1-cyclopropane carboxylic acids, Bernabé *et al*. described the opening of a mono-Boc-DKP by alkaline hydrolysis [14]. Whereas, Nishiyama and co-workers were interested in the alkylidenation of a bis-Boc-DKP involving a cleavage of one of the two protecting groups [15,16]. Recently, we have published an unprecedented ring contraction by transannular rearrangement of activated lactams: under basic conditions, bis-Boc-DKPs can be easily converted into substituted pyrrolidine-2,4-diones in a highly diastereoselective manner [17–20]. Continuing our effort in the study of Boc-DKPs, we report in this article the electrophilic reactivity of such activated lactams.

Results and Discussion

Starting from DKPs **1**, Boc substituted compounds were prepared in good to excellent yields, using previously reported procedure (Table 1) [17]. A careful examination of IR spectra of DKPs **1** and corresponding Boc-DKPs **2** unambiguously showed the efficiency of the activation thanks to Boc substitution. The IR stretching vibration of the lactam group $\nu_{CO\ lactam}$ of **2** shifted to a greater frequency in comparison with the $\nu_{CO\ lactam}$ of **1**. This means that Boc group displays a role of an electron-withdrawing activator and therefore leads to an enhancement of the electrophilic reactivity of the carbonyl lactam groups over normal lactams. The $\nu_{CO\ lactam}$ of **2** are related to ν_{CO} of highly reactive carboxylic acid derivatives, such as activated esters and anhydrides.

Taking advantage of the increased reactivity, we preliminarily examined the reaction between the simplest activated DKP, bis-Boc-cyclo(Gly–Gly) **2a**, and a range of reducing reagents. The reduction of Boc amides and Boc lactams has been previously described in the literature using diisobutylaluminum hydride or BH_3 [21–23]. However, similar treatments were unsuccessful towards the bis-Boc-DKP **2a**. A more satisfactory procedure was achieved with $NaBH_4$, leading to the formation of Boc ethanolamine **3** (Scheme 1). At this stage, we assumed that this transformation occurred via a bis-lactamol intermediate that was cleaved *in situ* to give the observed product. Consequently, subjecting **2a** to the less reactive and more selective reagent $LiAlH(OtBu)_3$ enabled us to access to the mono-lactamol derivative **4** in moderate yield.

Encouraged by these results, the study was directed towards nucleophilic attacks. Only few examples of Boc lactam opening by heteronucleophiles have been published [14,24,25]. Dominguez and Ezquerra described the reaction between a pyroglutamate derivative and alcohols or amines, requiring KCN catalysis [26,27].

First, we explored the electrophilic reactivity of bis-Boc-DKP **2a** as shown in Table 2. In the presence of benzylamine, this heterocycle was converted into Boc-protected Gly residue **5a** (Table 2, entry 1). When the tested nucleophile was an alcohol, addition of TEA was necessary to achieve a complete conversion (Table 2, entries 2–3). Thus, this method appears as an interesting way to synthesise Boc-amino acid esters and Boc-amino acid amides in mild conditions. However, despite our efforts, we were unable to find an experimental procedure for effective attack by sodium thiolate (Table 2, entry 4): the lactam opening failed and we just recovered the starting material. Furthermore, it is noteworthy that we never observed any traces of product resulting from nucleophilic attack on the carbonyl Boc group [28].

In an analogous manner, we were then interested in the behaviour of mono-Boc-DKPs. For this purpose, investigations

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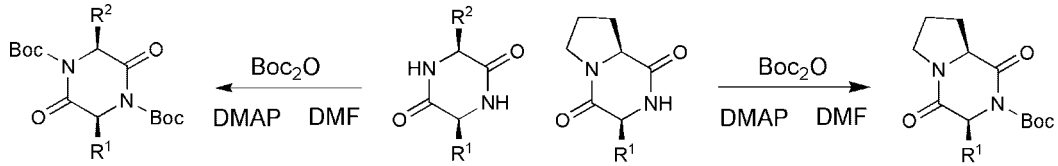
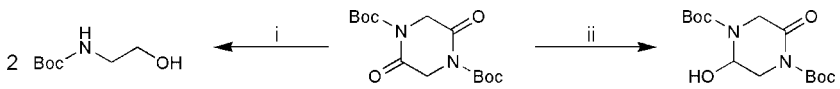
Table 1. Synthesis of Boc-DKPs



2a-c **1a-c** **1d-e** **2d-e**

Entry	1	R^1	R^2	$\nu_{CO\ lactams}$ of **1** (cm^{-1})	2	Yield (%)[a]	$\nu_{CO\ lactams}$ of **2** (cm^{-1})
1	**1a**	H	H	1637	**2a**	82	1786
2	**1b**	Bn	H	1674	**2b**	81	1790
3	**1c**	*i*Pr	H	1701	**2c**	92	1792
4	**1d**	H	–	1648, 1684	**2d**	80	1670, 1744[b]
5	**1e**	Bn	–	1664, 1692	**2e**	87	1732, 1777[b]

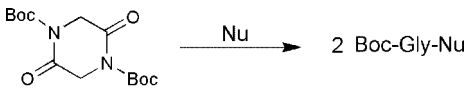
[a] Yield of product isolated by flash chromatography.
[b] Only one lactam can be activated in cyclo(Xaa–Pro).



3 (97%) **2a** **4** (56%)

Scheme 1. Reduction of bis-Boc-cyclo (Gly–Gly) **2a**. Reagents and conditions: (i) 2 equiv $NaBH_4$, THF/water (4/1), 0 °C; (ii) 1 equiv $LiAlH(OtBu)_3$, Et_2O/THF (4/1), −78 °C.

Table 2. Nucleophilic cleavage on bis-Boc-cyclo (Gly–Gly)



2a **5**

Entry	Nucleophile	Solvent	Addition of TEA[a]	5	Yield (%)[b]
1	$BnNH_2$[a]	THF	No	**5a**	69
2	MeOH	MeOH	Yes	**5b**	96
3	BnOH	BnOH	Yes	**5c**	37[c]
4	$EtS^-\ Na^+$	THF	Yes	**5d**	0

[a] Two equivalents of reagent were employed.
[b] Yield of product isolated by flash chromatography.
[c] The conversion was complete (established on the ^1H NMR crude spectrum) but it was difficult to isolate **5c** without traces of benzyl alcohol.

have been carried out on DKPs containing a Pro residue. Boc-cyclo(Gly–Pro) **2d** and Boc-cyclo(Phe–Pro) **2e** were allowed to react with a series of nucleophiles (Table 3). As expected, the attack occurred exclusively on the activated lactam, leading to the formation of *N*-terminal-protected dipeptides **6** in good to excellent yields. This regioselectivity illustrates the utility that Boc-activated lactams can possess. In addition, comparison with physical and spectoscopic data from literature for compounds **6b, 6c** and **6d** confirmed that no racemisation occurred during the ring-opening reaction whatever the nature of the nucleophile be (see the Experimental section for comparison. In addition, ^{13}C NMR spectra for **6c** and **6d** gave only one set of peaks).

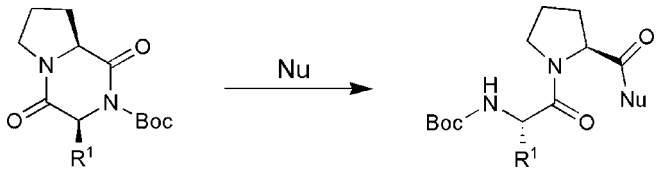
From efforts to explore a variety of heteronucleophiles, we identified an uncommon reactivity of allylic alcohol. Subjecting **2a** to an excess of allylic alcohol, we observed the opening of one lactam group, allowing us to access to dipeptide **7a** bearing a Boc group on the nitrogen in the peptidic bond (Table 4, entry 1). Similar treatment was carried out on bis-Boc-cyclo (Gly–Phe) **2b**, generating an equimolar mixture of two isomers **7b** and **8b** that were not separable by flash chromatography (Table 4, entry 2). Interestingly, starting from bis-Boc-DKP **2c**, we were delighted to find that allylic alcohol attacked exclusively on the carbonyl group of the Gly residue (Table 4, entry 3). This regioselectivity in favour of the less-hindered carbonyl group was supported unambiguously by assignment using COSY NMR. Further studies will be focused on the application that this new class of dipeptides could provide, for example, in the peptidomimetic area.

With compound **7** in hand, the cleaving ability of the remaining Boc amide was then investigated. By treatment with primary amines, an easily separable mixture containing Boc amino acid amides **9** and Boc amino acid ester **10** was furnished in good yields (Table 5). It is noteworthy that these *N*-protected amino acid derivatives were formed by a sequential process from bis-Boc-DKPs **2**.

Conclusion

In conclusion, we have described the unprecedented reactivity of Boc-DKPs towards reducing reagents and heteronucleophiles. Boc group displays a role of an electron-withdrawing activator, enhancing the electrophilicity of carbonyl lactam groups. These activated scaffolds easily afford *N*-protected amino acid derivatives and original dipeptides according to experimental conditions. Currently, we are exploring the opening ability of Boc-DKPs towards amino acid residues as an application in peptide synthesis.

Table 3. Nucleophilic cleavage on Boc-cyclo(Xaa–Pro)

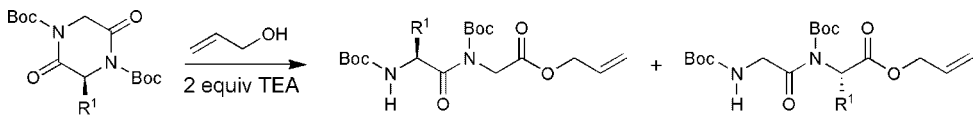


2 **6**

Entry	**2**	R^1	Nucleophile	Solvent	Addition of TEA[a]	**6**	Yield (%)[b]
1	**2d**	H	$BnNH_2$[a]	THF	No	**6a**	76
2	**2d**	H	MeOH	MeOH	Yes	**6b**	96
3	**2e**	Bn	$BnNH_2$[a]	THF	No	**6c**	68
4	**2e**	Bn	NaOH[a]	THF/H_2O	No	**6d**	82

[a] One equivalent of reagent was employed.
[b] Yield of product isolated by flash chromatography.

Table 4. Reactivity of allylic alcohol towards bis-Boc-DKPs



2 **7** **8**

Entry	**2**	R^1	Obtained product(s)	Yield (%)[a]	Ratio **7**/**8**
1	**2a**	H	**7a**	93	–
2	**2b**	Bn	**7b** + **8b**	77[b]	50/50[c]
3	**2c**	*i*Pr	**7c**	91	100/0[c]

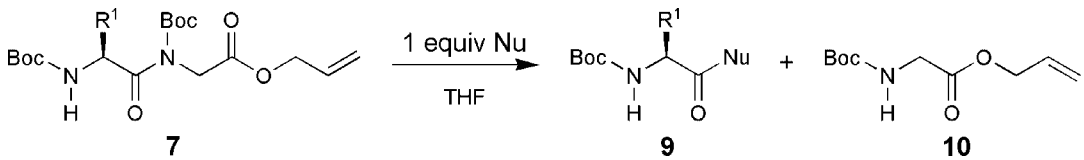
[a] Yield of product isolated by flash chromatography.
[b] Relative to the unseparable mixture **7b** + **8b**.
[c] Established on the HPLC crude analysis.

Experimental

General Procedures

All solvents were dried and freshly distilled prior to use. TLC was performed with Merck-Kieselgel 60 F_{254} plates, and spots were visualised with UV light and/or by staining with ninhydrin solution followed by heating. Flash chromatography was performed on Merck-Kieselgel 60 (230–400 mesh). Melting points were recorded on Buchi 510 melting apparatus. Optical rotations were measured with a 1 cm cell (concentration c given in g/100 ml, solvent) on a Perkin Elmer Polarimeter at 20 °C with a sodium lamp (589 nm). High-resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX-102 high-resolution magnetic sector mass spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded with Bruker 200 MHz or Bruker A DRX 400 MHz spectrometers. Chemicals shifts are reported in δ relative to an internal standard of residual chloroform

Table 5. Electrophilic reactivity of dipeptides 7 towards primary amines



7 **9** **10**

Entry	**7**	R^1	Nucleophile	**9** [Yield (%)[a]]	Yield (%)[a] of **10**
1	**7a**	H	$nPrNH_2$	**9a** [81]	74
2	**7a**	H	$BnNH_2$	**9b** [90]	81
3	**7c**	*i*Pr	$BnNH_2$	**9c** [72]	60

[a] Yield of product isolated by flash chromatography.

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(δ = 7.26 for ^{1}H NMR and 77.16 for ^{13}C NMR). The reported ^{1}H NMR signals were assigned using standard 2D NMR techniques or by direct comparison to the ^{1}H NMR spectra of corresponding starting materials. The reported ^{13}C NMR signals were assigned using DEPT-135 and HMQC techniques or by direct comparison of the ^{13}C NMR spectra of corresponding starting materials.

Typical Procedure for Activation of DKP

Compounds **2a-c**: see Ref. 17.

Compounds **2d-e**: To a solution of DKP (2.00 mmol) in dry CH_2Cl_2 (20 ml) was added triethylamine (2.00 mmol), DMAP (4.00 mmol) and di-*tert*-butyl dicarbonate Boc_2O (4.00 mmol). After stirring at room temperature under argon atmosphere for 12 h, the crude mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

Data for **2d**: mp 105 °C; $[\alpha]_D^{20}$ = +37.5 (c = 1.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.56 (s, 9H), 1.97–2.07 (m, 2H), 2.27–2.39 (m, 2H), 3.56–3.63 (dd, 2H, J = 8.2 Hz, J = 5.9 Hz), 4.07–4.16 (dd, 1H, J_{AB} = 16.5 Hz, J_{CH-CH} = 0.7 Hz), 4.15–4.22 (t, 1H, J = 8.0 Hz), 4.65–4.73 (d, 1H, J_{AB} = 16.5 Hz); HRMS (FAB+) m/z calcd for $C_{12}H_{19}N_2O_4$ [M + H$^+$] 255.1267, found 255.1264.

Data for **2e**: mp 113 °C; $[\alpha]_D^{20}$ = +11.7 (c = 0.96, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (s, 9H), 1.62–2.19 (m, 4H), 2.75–2.83 (dd, 1H, J = 9.3 Hz, J = 6.8 Hz), 3.25 (d, 2H, J = 5.3 Hz), 3.38–3.65 (m, 2H), 5.05 (t, 1H, J = 5.3 Hz), 7.19 (m, 2H), 7.31 (m, 3H)); HRMS (FAB+) m/z calcd for $C_{19}H_{25}N_2O_4$ [M + H$^+$] 345.1736, found 345.1740.

Synthesis of Compound 3

To a solution of 1,4-di(Boc)piperazine-2,5-dione **2a** (0.050 g, 0.16 mmol) in 5 ml THF/H_2O (4/1) was added $NaBH_4$ (0.012 g, 0.32 mmol) at 0 °C under stirring. The reaction was allowed to stir for 4 h at room temperature. Then, AcOEt (10 ml) was added. The organic layer was washed with 0.1 N HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (CH_2Cl_2/AcOEt (100/0 → 60/40)). The desired compound was obtained (0.035 g, 69% yield) as a colourless oil. Physical and spectoscopic data were consistent with the literature [29].

Synthesis of Compound 4

To a solution of 1,4-di(Boc)piperazine-2,5-dione **2a** (0.482 g, 1.53 mmol) in 15 ml Et_2O/THF (4/1) was added LiAlH(O*t*Bu)$_3$ (0.391 g, 1.53 mmol) at −78 °C under stirring and argon atmosphere. The reaction was allowed to stir for 1 h at −78 °C and then for 12 h at room temperature. The mixture was then filtered on celite and AcOEt (30 ml) was added. The organic layer was washed with 0.1 N HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (CH_2Cl_2/AcOEt (100/0 → 95/5)). The desired compound was obtained (0.274 g, 56% yield) as white crystals. mp 96 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.35 (s, 9H), 1.42 (s, 9H), 3.34–4.20 (m, 4H), 4.78 (br s, 1H), 5.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.2, 43.3, 45.2, 80.0, 82.3, 88.5, 151.7, 155.6, 169.6; HRMS (FAB+) m/z calcd for $C_{14}H_{25}N_2O_6$ [M + H$^+$] 317.1713, found 317.1705.

Typical Procedure for Nucleophilic Attack Using Benzylamine

To a solution of activated DKP **2** (0.35 mmol) in THF (5 ml) was added benzylamine at room temperature under stirring and argon atmosphere. The reaction was allowed to stir for 2 h. Then, the crude mixture was concentrated *in vacuo* and purified by silica gel column chromatography.

Data for **5a**: Physical and spectoscopic data were consistent with the literature [30].

Data for **6a**: $[\alpha]_D^{20}$ = +9.1 (c = 1.35, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.46 (s, 9H), 1.88–2.46 (m, 4H), 3.40–3.59 (m, 2H), 3.95 (d, 2H, J = 4.5 Hz), 4.31–4.56 (m, 2H), 4.60–4.65 (m, 1H), 5.39 (m, 1H), 7.30 (m, 6H); HRMS (FAB+) m/z calcd for $C_{19}H_{28}N_3O_4$ [M + H$^+$] 362.2008, found 362.2007.

Data for **6c**: Physical and spectoscopic data were consistent with the literature [31].

Typical Procedure for Nucleophilic Attack Using an Alcohol

To a solution of activated DKP **2** (0.35 mmol) in alcohol (2 ml) was added TEA (0.70 mmol). After stirring at room temperature under argon atmosphere for 2 h, the solution was diluted with AcOEt (5 ml) and then washed with 0.1 N aqueous solution of HCl (5 ml). After drying on $MgSO_4$, the solvent was removed *in vacuo* providing the desired compound.

Data for **5b**: Physical and spectoscopic data were consistent with the literature [32].

Data for **6b**: $[\alpha]_D^{20}$ = −70.4 (c = 1.31, $CHCl_3$) [lit., −69 (c = 1.16, $CHCl_3$)]. Physical and spectoscopic data were consistent with the literature [33,34].

Data for **7a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.38 (s, 9H), 1.44 (s, 9H), 4.43 (br s, 4H), 4.57 (m, 2H), 5.14–5.29 (m, 3H), 5.79–5.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.9, 28.4, 45.3, 46.9, 65.9, 79.7, 84.9, 118.9, 131.5, 151.5, 155.8, 168.3, 172.4; HRMS (FAB+) m/z calcd for $C_{17}H_{29}N_2O_7$ [M + H$^+$] 373.1975, found 373.1989.

Data for **7c**: $[\alpha]_D^{20}$ = +30.1 (c = 1.46, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.72 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz), 1.35 (s, 9H), 1.44 (s, 9H), 2.03–2.13 (m, 1H), 4.23 (d, 1H, J = 17.2 Hz), 4.54–4.61 (m, 3H), 5.14–5.28 (m, 3H), 5.52–5.56 (m, 1H), 5.78–5.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.7, 19.8, 27.9, 28.3, 31.2, 43.4, 58.5, 65.8, 79.4, 84.6, 118.5, 131.5, 151.3, 155.7, 169.5, 175.3; HRMS (FAB+) m/z calcd for $C_{20}H_{35}N_2O_7$ [M + H$^+$] 415.2444, found 415.2452.

Synthesis of Compound 6d

To a solution of activated DKP **2e** (0.139 g, 0.41 mmol) in THF (2 ml) was added NaOH (0.017 g, 0.43 mmol) in H_2O (2 ml) at room temperature. The reaction was allowed to stir for 3 h. Then, AcOEt (5 ml) was added and the organic layer was washed with 0.1 N HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The desired compound was obtained (0.120 g, 82% yield) as a white solid. $[\alpha]_D^{20}$ = −32.9 (c = 1.12, EtOH) [lit., −32.0 (c = 1.00, EtOH)]. Physical and spectoscopic data were consistent with the literature [35,36].

Typical Procedure for Nucleophilic Cleavage on Dipeptides 7

To a solution of dipeptides **7** (0.40 mmol) in THF (5 ml) was added amine (0.40 mmol) at 50 °C under stirring and argon atmosphere. After 10 h, AcOEt (10 ml) was added. The organic layer was washed with 0.1N HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography.

Data for **9a**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (t, 3H, J = 7.4 Hz), 1.27 (s, 9H), 1.56 (q, 2H, J = 7.4 Hz), 3.22 (q, 2H, J = 13.5 Hz), 5.74 (d, 2H, J = 5.7 Hz), 5.50 (br t, 1H), 6.55 (br s, 1H); HRMS (FAB+) m/z calcd for $C_{10}H_{21}N_2O_3$ [M + H$^+$] 217.1475, found 217.1475.

Data for **9b**: Physical and spectoscopic data were consistent with the literature [30].

Data for **9c**: $[\alpha]_D^{20} = -3.7$ ($c = 1.41, CH_2Cl_2$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.95 (d, 3H, $J = 6.9$ Hz), 0.99 (d, 3H, $J = 6.9$ Hz), 1.45 (s, 9H), 2.15–2.25 (m, 1H), 3.90–3.98 (dd, 1H, $J = 9.8$, $J = 6.3$ Hz), 4.47 (d, 2H, $J = 5.8$ Hz), 5.07 (br t, 1H, $J = 5.6$ Hz), 6.39 (br s, 1H), 7.27–7.36 (m, 5H); HRMS (FAB+) *m/z* calcd for $C_{17}H_{27}N_2O_3[M+H^+]$ 307.1938, found 307.1737.

Data for **10**: Physical and spectoscopic data were consistent with the literature [37].

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