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A convenient synthesis of *N*-Boc-protected *tert*-butyl esters of phenylglycines from benzylamines

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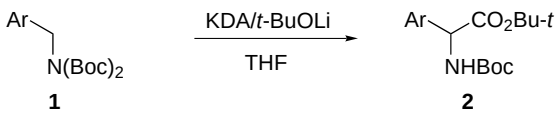
Abstract—The *N*,*N*-di-Boc-protected benzylamines undergo [1,2] Boc migration on treatment with KDA/*t*-BuOLi. By this reaction, the corresponding *N*-Boc-protected *t*-butyl esters of phenylglycines are obtained in high yields.

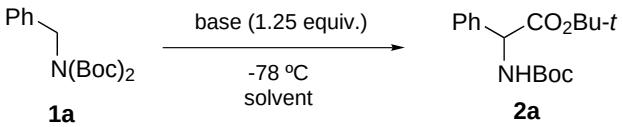
The synthesis of unnatural amino acids such as phenylglycines has received much interest for their utilization in synthetic and medicinal chemistry.[1] Recently, carboxylation of α-nitrogen carbanions derived from *N*-Boc-protected benzylamines using the BuLi·(−)-sparteine complex as a chiral base has been reported for the enantioselective synthesis of *N*-Boc-protected phenylglycines.[2] In the course of our study on the reaction of α-nitrogen carbanions with nucleophiles,[3] we found that α-nitrogen carbanions of *N*,*N*-di-Boc-protected benzylamines underwent [1,2] Boc migration. Herein, we report that the reaction of *N*,*N*-di-Boc-protected benzylamines (**1**) with KDA/*t*-BuOLi in THF at −78°C gave the [1,2] Boc migrated products, *N*-Boc-protected *t*-butyl phenylglycines (**2**), in high yields (Eq. (1)). The acid group in amino acids is usually protected as an ester, in particular a *t*-butyl ester because of its relative resistance to nucleophilic attack and its facile removal by acid-catalyzed hydrolysis.[4] The present reaction provides a convenient route for the synthesis of useful *t*-butyl esters **2** from readily available benzylamines.



1 **2** (1)

The starting **1** were prepared from the corresponding benzylamines by treatment with $(Boc)_2O$ in one-pot.[5] The [1,2] Boc migration of **1a** (Ar = Ph) was investigated using several bases and the results are summarized in Table 1. The reaction of **1a** with *n*- or *s*-BuLi in THF at −78°C gave *N*-Boc-protected benzylamine as the sole product owing to the nucleophilic reaction (runs 1 and 2). Unfortunately, the *s*-BuLi·(−)-sparteine complex in Et_2O also brought about the same result (run 3). On the other hand, LDA and lithium dicyclohexylamide (LDCA) afforded moderate yields of [1,2] Boc migrated product **2a** (runs 4 and 5). It seemed that LHMDS was not basic enough for the deprotonation of **1a** (run 6). In order to improve the yield of **2a**, the reaction with LDA was carried out in the presence of

Table 1. Reaction of **1a** with bases



1a **2a**

Run	Base	Solvent	Yield[a] (%) **2a**
1	*n*-BuLi	THF	0[b]
2	*s*-BuLi	THF	0[b]
3	*s*-BuLi/(−)-sparteine	Et_2O	0[b]
4	LDA	THF	49
5	LDCA	THF	52
6	LHMDS	THF	0[c]
7	LDA/DMPU	THF	53
8	KDA/*t*-BuOLi	THF	97
9	KDA/*t*-BuOLi	Et_2O	41
10	KDCA/*t*-BuOLi	THF	92
11	KHMDS/*t*-BuOLi	THF	0[c]

[a] Isolated yields.
[b] *N*-Boc-protected benzylamine was obtained as the sole product.
[c] The starting **1a** was recovered completely.

Keywords: phenylglycines; *t*-butyl esters; α-nitrogen carbanions; Boc migration.

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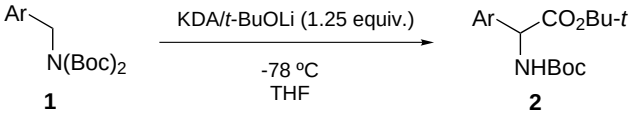
Table 2. Transformation of **1** to **2**



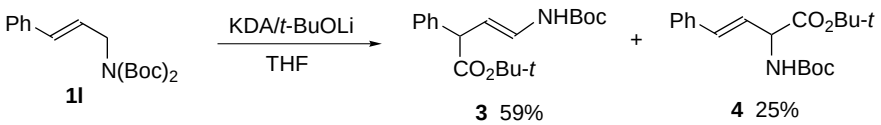
Run	1	Ar	2	Yield[a] (%) 2
1	**1b**	*p*-$CH_3C_6H_4$	**2b**	76
2	**1c**	*p*-$CH_3OC_6H_4$	**2c**	44
3	**1d**	*m*-$CH_3OC_6H_4$	**2d**	92
4	**1e**	*o*-$CH_3OC_6H_4$	**2e**	83
5	**1f**	3,4-Dimethoxyphenyl	**2f**	67
6	**1g**	*p*-ClC_6H_4	**2g**	84
7	**1h**	*o*-ClC_6H_4	**2h**	87
8	**1i**	*p*-NCC_6H_4	**2i**	78[b]
9	**1j**	1-Naphthyl	**2j**	96
10	**1k**	2-Naphthyl	**2k**	94

[a] Isolated yields. All products were identified by their spectroscopic and elemental analyses.
[b] LDA was used as a base.

an additive. DMPU was not effective as an additive (run 7), although it has been reported that the optimized yield was achieved with LDA/DMPU in the acyl migration of acyclic imides.[6] Raucher and Koolpe have reported that a non-nucleophilic and strongly basic mixture of KDA/*t*-BuOLi was readily prepared from LDA and *t*-BuOK.[7] As would be expected, the reaction of **1a** with KDA/*t*-BuOLi gave **2a** in 97% yield (run 8).[8] While KDCA/*t*-BuOLi prepared from LDCA with *t*-BuOK was also effective as a base (run 10), the starting **1a** was recovered completely by the treatment with KHMDS/*t*-BuOLi (run 11).

Table 2 shows the results of the reactions of several *N*,*N*-di-Boc-protected benzylamines **1a**–**k** with KDA/*t*-BuOLi in THF at −78°C. It can be presumed that electron-donating substituents on the phenyl group lower the acidity of the benzyl protons in **1**. In fact, electron-donating *para*-substituents, especially a methoxy group, brought about decrease of the yields of **2** (runs 1,2 and 5). In these cases, considerable amounts of *N*-Boc-protected benzylamines were produced as by-products. In other cases, the corresponding *t*-butyl esters of phenylglycines **2** were obtained in good to excellent yields. It is noted that *ortho*-methoxy substituted substrate **1e** also gave **2e** in good yield, probably due to the stabilization of the benzyl anion by intramolecular coordination of the *ortho*-methoxy group to the metal cation (run 4). In the reaction of *para*-cyano substituted one **1i**, good yield of **2i** was attained by the reaction with LDA instead of KDA/*t*-BuOLi (run 8), whereas the treatment of **1i** with KDA/*t*-BuOLi resulted in a complex mixture.

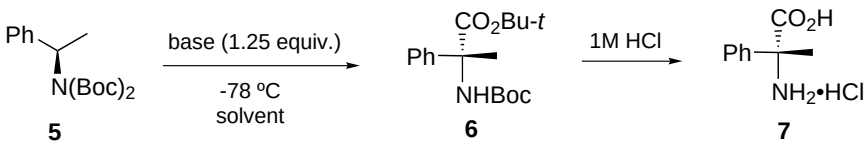
The reaction of *N*,*N*-di-Boc-protected cinnamyl amine (**1l**) with KDA/*t*-BuOLi under the same reaction conditions as above gave [1,4] Boc migrated product **3** and [1,2] Boc migrated product **4** in 59 and 25% yields, respectively (Eq. (2)).



(2)

Next, the [1,2] Boc migration of *N*,*N*-di-Boc-protected (*R*)-1-phenylethylamine (**5**) was attempted with KDA/*t*-BuOLi or KDCA/*t*-BuOLi. As shown in Table 3, the

Table 3. Transformation of **5** to **6**

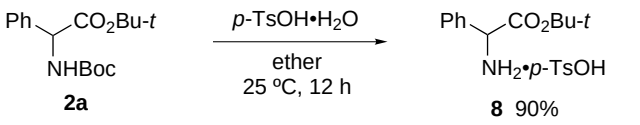


Run	Base	Solvent	Yield[a] (%) 6	% ee of 7 (config.)[b]
1	KDA/*t*-BuOLi	THF	95	~0
2	KDCA/*t*-BuOLi	THF	84	~0
3	KDA/*t*-BuOLi	Et_2O	66	33 (*R*)[c]
4	KDA/*t*-BuOLi	Toluene	43	35 (*R*)[d]
5	KDCA/*t*-BuOLi	Toluene	20	38 (*R*)[e]
6	KDA/*t*-BuOLi	Hexane	22	33 (*R*)[f]

[a] Isolated yields.
[b] The ee values and absolute configurations of the obtained **6** were determined by their conversion to **7**. See text.
[c] $[\alpha]_D^{23}$ −28.2 (*c* 3.95, 1 M HCl).
[d] $[\alpha]_D^{23}$ −30.0 (*c* 4.15, 1 M HCl).
[e] $[\alpha]_D^{23}$ −32.3 (*c* 2.25, 1 M HCl).
[f] $[\alpha]_D^{23}$ −28.3 (*c* 3.25, 1 M HCl).

reactions in THF gave completely racemic [1,2] migrated product **6** in high yields (runs 1 and 2). Using less polar Et_2O, toluene, or hexane as a solvent, **(*R*)-6** (retention) was produced in 33–38% ee, although the yields were decreased (runs 3–6). The ee values of the obtained **6** were determined by their acid hydrolysis to α-methylphenylglycine (**7**) which specific rotations were compared with reported data; **(*R*)-7**: lit.[9] $[\alpha]_D^{23}$ −85.5 (*c* 1.0, 1 M HCl).

Several methods have been reported for the selective deprotection of the *N*-Boc group in *N*-Boc-protected *t*-butyl esters of α-aminoacids.[10] Actually, the treatment of **2a** with 1 equiv. of *p*-TsOH in ether afforded *p*-TsOH salt of phenylglycine *t*-butyl ester (**8**) selectively (Eq. (3)).



(3)

In summary, we have demonstrated that [1,2] Boc migration was effected by the treatment of *N*,*N*-di-Boc-protected benzylamines with KDA/*t*-BuOLi. This reaction provides a useful method for the synthesis of *t*-butyl esters of phenylglycines from benzylamines.

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5. Preparation of **1a**: To an ice-cooled solution of benzylamine (1.07 g, 10 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of $(Boc)_2O$ (2.18 g, 10 mmol) in CH_2Cl_2 (10 mL). After the mixture was stirred at room temperature for 30 min, the solvent was removed in vacuo. To the crude *N*-Boc–protected benzylamine, $(Boc)_2O$ (3.27 g, 15 mmol) and DMAP (0.2 g) were added and the mixture was stirred at 80°C for 2 h. The product **1a** was purified by column chromatography on silica gel (98% yield): ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 18 H), 4.76 (s, 2 H), 7.28 (brs, 5 H); ^{13}C NMR ($CDCl_3$): δ 27.9 (q), 49.4 (t), 82.3 (s), 126.8 (d), 127.0 (d), 128.1 (d), 138.3 (s), 152.3 (s).
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8. Typical procedure is as follows. To a suspension of *t*-BuOK (0.14 g, 1.25 mmol) and diisopropylamine (0.175 mL, 1.25 mmol) in THF (5 mL) was added 1.6 M *n*-BuLi in hexane (0.78 mL, 1.25 mmol) at −78°C and the mixture was stirred for 15 min. To the mixture, a solution of **1a** (0.307 g, 1 mmol) in THF (5 mL) was added dropwise and additional stirring was continued for 30 min at this temperature. The reaction mixture was diluted with 1 M HCl (20 mL) and the mixture was extracted with ether (10 mL×3). The product **2a** was isolated by column chromatography on silica gel (97% yield): ^{1}H NMR ($CDCl_3$): δ 1.38 (s, 9H), 1.43 (s, 9H), 5.20 (d, 1H, J=7.6 Hz), 5.57 (d, 1H, J=7.6 Hz), 7.27–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 27.6 (q), 28.2 (q), 57.9 (d), 79.5 (s), 81.9 (s), 126.6 (d), 127.7 (d), 128.3 (d), 137.4 (s), 154.5 (s), 169.8 (s).
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