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A facile route to 2-substituted *N*-Boc pyrrolidines†

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Abstract

Dipole stabilized carbanion **2** cyclizes to afford the key intermediate 2-benzotriazolyl-*N*-Boc-pyrrolidine **3**, which undergoes nucleophilic displacement of the benzotriazolyl group to afford various 2-substituted-*N*-Boc-pyrrolidines in good yields. © 2000 Published by Elsevier Science Ltd.

Keywords: pyrrolidine; dipole stabilization; intramolecular cyclization.

Numerous pyrrolidines are of biological importance[1a–h] and the development of versatile methods for their preparation has shown much recent activity.[1a–h,2a–g]

2-Substituted-*N*-Boc-pyrrolidines have been prepared by two general methods: (i) by direct electrophilic substitution at the 2-position of the *N*-Boc-pyrrolidine ring[3a–c] and (ii) by intramolecular cyclization of arylmethyl- or allyl-(3-chloropropyl)-*N*-Boc-amines by treatment with *s*-BuLi or *n*-BuLi.[4a,b] We now report a third approach by nucleophilic displacement of the benzotriazole moiety from *N*-Boc-pyrrolidine **3** (which is easily available from *N*-Boc-*N*-(3-halopropyl)-(benzotriazol-1-ylmethyl)amine **1**, Scheme 1): a single previous example related to the present approach utilizes 2-methoxy-*N*-Boc-pyrrolidine prepared by electromethoxylation of *N*-Boc protected pyrrolidine.[5]

Starting material **1** was prepared in two steps in 40% overall yield. Protection of 3-chloropropylamine hydrochloride with $(Boc)_2O$ in the presence of Et_3N gave *N*-Boc-3-chloropropylamine,[6] which reacted further (without purification) with benzotriazole and paraformaldehyde in the presence of *p*-TsOH in refluxing toluene with azeotropic removal of water to give *N*-Boc-*N*-(benzotriazol-1-ylmethyl)-3-chloropropylamine (**1**). The reaction conditions were optimized for the cyclization of compound **1** to compound **3**: the best solvent was toluene; others gave a complex reaction mixture (such as THF) or low yields (16% in Et_2O). The best base was *n*-BuLi which (1.5 equiv.) was preferred to *s*-BuLi and *t*-BuLi for the cyclization. Compound **3** was thus formed via intramolecular cyclization in 55% yield.

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† Dedicated to Harry Wasserman, long-time colleague and friend.

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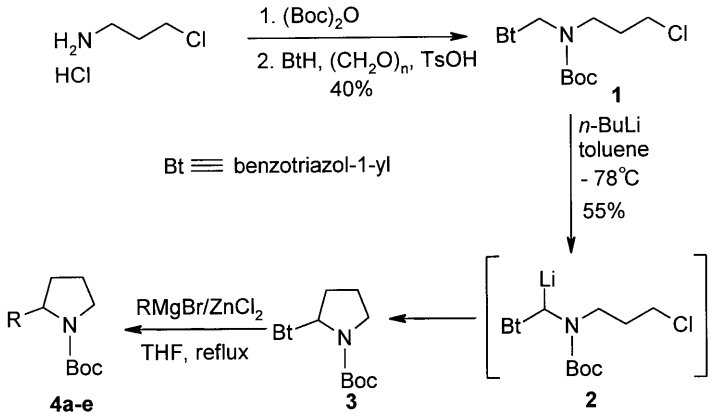

Entry	Prod.	R	Yield (%)
1	**4a**	Ph	86
2	**4b**	4-Me-C_6H_4	66
3	**4c**	4-MeO-C_6H_4	70
4	**4d**	4-Cl-C_6H_4	62
5	**4e**	Ph-C≡C	77

Scheme 1.

Treatment of the benzotriazole derivative **3** with organozinc reagents gave compounds **4** in good to excellent yields (Scheme 1). Arylzinc reagents and an alkynylzinc reagent all afforded the corresponding desired products. However, when allyltrimethylsilane or vinyloxytrimethylsilane were used as nucleophiles to carry out this reaction, no desired products were obtained.

In conclusion, a general method using *N*-Boc-*N*-(3-halopropyl)(benzotriazol-1-ylmethyl)amine as the starting material is proposed for the preparation of 2-substituted-*N*-Boc-pyrrolidines in good to excellent yields. In the cyclization step, the benzotriazole moiety assists the dipole stabilization in the formation of a carbanion intermediate to make the lithiation regiospecific.

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