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Synthesis of vicinal (alkylamino)alkynylcyclopropanes from geminal alkynyl(chloro)cyclopropanes

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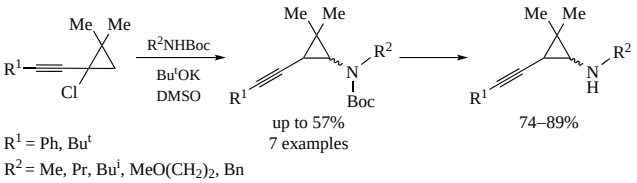
New *N*-Boc-alkyl(2-alkynylcyclopropyl)amines were synthesized from 1-alkynyl-1-chlorocyclopropanes and *N*-Boc-alkylamines under the action of Bu^{t}OK in DMSO, the intermediates having been the corresponding conjugated alkynylcyclopropenes. The Boc-derivatives can be converted into free secondary 2-alkynylcyclopropylamines, as well as β-lithiated with subsequent alkylation.



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At present, functionalized alkynylcyclopropanes are widely employed as polyfunctional building blocks.[1] They also possess important biological properties.[2] Aminocyclopropane motif is present in some biologically active natural products and drugs,[3] and is of importance for fine organic synthesis.[4] Cyclopropanes bearing both alkynyl and amino (especially primary and secondary) substituents are of significant interest. Derivatives with amino group in geminal position to the triple bond are well studied.[5] On the contrary, information on their vicinal isomers is scarce. Some derivatives of 2-ethynyl-1-aminocyclopropanecarboxylic acid were reported,[6] while 2-alkynyl-1-(dialkylamino)-cyclopropanes were obtained from alkynylchlorocyclopropanes under the action of lithium dialkylamides.[7,8] However, direct introduction of secondary amino group using similar approach was not successful[9] due to the further transformations of initially formed lithium 2-alkynylcyclopropylamides.

The use of protective groups, in particular *tert*-butoxycarbonyl (Boc), may be one of the possible ways to overcome this problem. Its easy removal, and also known ability[10] of the *tert*-butoxycarbonylamine fragment to promote α- and β-lithiations of cyclopropane ring open wide possibilities for further functionalization of the resulting 2-alkynylcyclopropylamine derivatives. This article is devoted to the study of the reactions between geminal alkynyl(chloro) cyclopropanes and Boc-derivatives of primary amines under the action of bases, and some further transformations of the formed products.

Our initial attempts to access *N*-Boc-alkyl(2-alkynylcyclopropyl)amines from readily available 1-alkynyl-1-chlorocyclopropanes using conditions, that had been successfully employed for similar syntheses of 1-alkoxy-[11] and 1-azolyl-2-alkynylcyclopropanes,[8] failed. Thus, treatment of 1-chloro-2,2-dimethyl-1-phenylethynylcyclopropane **1a** with excess of powdered KOH in DMSO at 90–100 °C in the presence of *tert*-butyl methylcarbamate led to polymeric products. According to the NMR spectra of the reaction mixture, formation of *tert*-butanol has also been detected, which points to the rapid decomposition of *tert*-butyl methylcarbamate under the action of KOH. Keeping it in mind, we hypothesized that replacement of KOH by Bu^{t}OK should prevent this process and allow one to obtain desired compounds **3**. Further experiments confirmed this proposition.

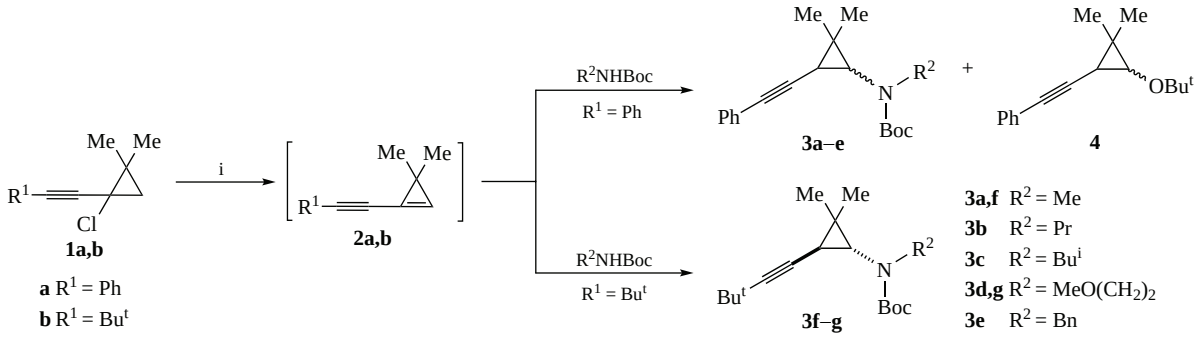
Reaction of chloro cyclopropane **1a** with *tert*-butyl methylcarbamate in the presence of Bu^{t}OK in DMSO at 60–70 °C led to full conversion of the starting material with formation of carbamate **3a** as a main product, which was isolated by column chromatography in 54% yield (Scheme 1).† Besides, 15% of *tert*-butoxycyclopropane **4** was isolated from first fractions, which obviously arose as a result of Bu^{t}OK addition to the

† *Synthesis of* tert-*butyl (2,2-dimethyl-3-alkynylcyclopropyl)alkylcarbamates* **3a**–**g** *(general procedure)*. To a solution of the corresponding *tert*-butyl alkyl carbamate (1.83 mmol) in DMSO (4 ml), Bu^{t}OK (548 mg, 4.89 mmol) was added. After vigorous stirring for 5 min, a solution of the corresponding chlorocyclopropane **1a**,**b** (1.22 mmol) in anhydrous DMSO (1 ml) was added. The mixture was stirred at 60–70 °C for 2 h, cooled to room temperature, and thereafter diluted with water (15 ml) and Et_2O (20 ml). The organic layer was separated, and the aqueous one was additionally extracted with Et_2O (2 × 10 ml). Then combined organic phases were washed with water three times, dried over anhydrous K_2CO_3, and the solvent was evaporated. The residue was subjected to column chromatography on basic Al_2O_3 (gradient 20:1→5:1 hexane–Et_2O) giving products **3a**–**g** as viscous liquids, which did not solidify on prolonged storing at 20 °C, except for compound **3c**. In case of products **3a**–**e**, the first fractions contained [(3-*tert*-butoxy-2,2-dimethylcyclopropyl)ethynyl]benzene **4** as ~3.5:1 (1*S**,3*R**/1*R**,3*R**)-diastereomer mixtures (for details, see Online Supplementary Materials and Table 1).

tert-Butyl [2,2-dimethyl-3-(phenylethynyl)cyclopropyl]methylcarbamate **3a** was prepared from cyclopropane **1a** and *tert*-butyl methylcarbamate as mixture of (1*R**,3*S**)- and (1*S**,3*S**)-isomers (4.9:1) and isolated in 54% yield. HRMS, *m*/*z*: 300.1955, 317.2222, 322.1776, 338.1510 (calc. for $C_{19}H_{25}NO_2$: *m*/*z* 300.1958 $[M + H]^+$, 317.2224 $[M + NH_4]^+$, 322.1778 $[M + Na]^+$, 338.1517 $[M + K]^+$).

(1*R**,3*S**)-**3a**: ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 3H, Me), 1.29 (s, 3H, Me), 1.43 (d, 1H, CHC≡C, ^3J 4.2 Hz), 1.50 (s, 9H, OBu^t), 2.56 (d, 1H, CHN, ^3J 4.2 Hz), 2.90 (s, 3H, NMe), 7.25–7.32 (m, 3H, *m*, *p*-H, Ph), 7.35–7.43 (m, 2H, *o*-H, Ph). ^{13}C NMR ($CDCl_3$) δ: 19.9, 21.0, 21.1 (2Me, *C*HC≡C), 28.1 (*C*Me$_2$), 28.4 [OC(*C*H$_3$)$_3$], 34.9 (br., NMe$_3$), 50.8 (CHN), 79.6 [O*C*(CH$_3$)$_3$], 79.7, 88.6 (C≡C), 123.8 (C^1, Ph), 127.5 (C^4, Ph), 128.2, 131.5 (C^2, C^3, C^5, C^6, Ph), 156.8 (C=O).

For NMR spectra of (1*R**,3*R**)-**3a** and characteristics of **3b**–**g**, **4**, see Online Supplementary Materials.



Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, DMSO, 60–70 °C, 2 h.

Table 1 Reactions of chlorocyclopropanes **1a**,**b** with *tert*-butyl carbamates.

Entry	Reactant	R^2	*N*-Boc derivatives **3a**–**g** (yield, %; 1*R**,3*S**/1*R**,3*R** ratio)	Yield (%) of by-product **4**
1	**1a**	Me	**3a** (54; 4.9 : 1)	15
2	**1a**	Pr	**3b** (57; 7.4 : 1)	17
3	**1a**	Bu^i	**3c** (52; 6.5 : 1)	13
4	**1a**	$MeO(CH_2)_2$	**3d** (48; 6.5 : 1)	15
5	**1a**	Bn	**3e** (32; 5.5 : 1)	22
6	**1a**	Pr^i	none	36
7	**1a**	Ph	none	38
8	**1b**	Me	**3f** (36; > 20 : 1)	–
9	**1b**	$MeO(CH_2)_2$	**3g** (19; > 20 : 1)	–

double bond of intermediate conjugated cyclopropene **2a** formed from starting compound upon dehydrochlorination. Similar results were obtained using *tert*-butyl carbamates with *n*-propyl, 2-methoxyethyl, isobutyl and benzyl groups at nitrogen atom when all of them gave the corresponding products **3b**–**e** in moderate yields with some formation of ether **4** (see Scheme 1, Table 1).

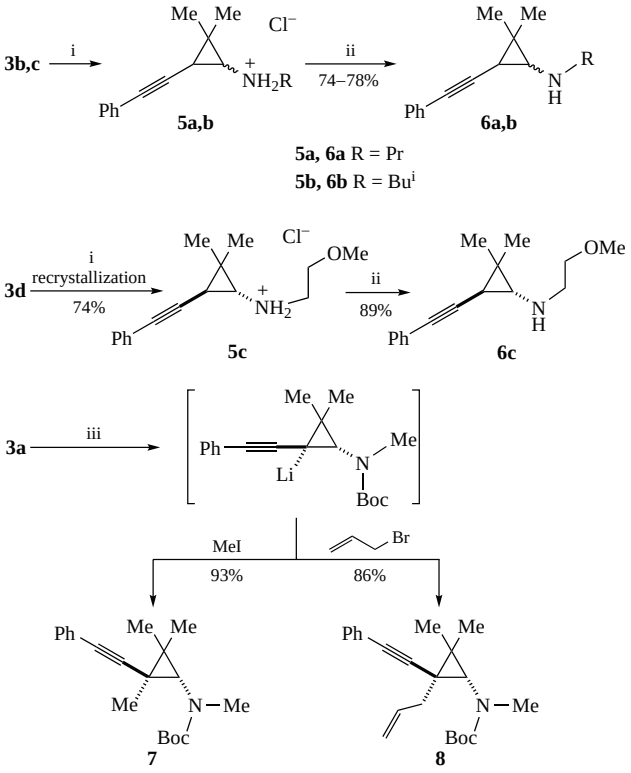
However, the attempted reactions with Boc-protected isopropylamine and aniline (see Table 1, entries 6, 7) did not give the desired aminocyclopropane products, which was probably due to steric factors in the corresponding N-anions. As it could be expected, in both cases the yield of ether **4** was higher (36–38%) compared to the reactions with less hindered *tert*-butyl carbamates (15–22%, entries 1–5).

Compound **1b** bearing *tert*-butyl group at the triple bond upon reaction with Boc-derivatives of methylamine and 2-methoxyethylamine gave expected products **3f** and **3g**, respectively (entries 8, 9), in somewhat lower yields (19–36%) than those of products **3a**,**d** with close structure. Most likely, this is due to difference in electron-donating/withdrawing properties between *tert*-butylethynyl and phenylethynyl groups, which results in less pronounced polarization of the double bond in cyclopropene **2b**, making the latter less reactive toward nucleophiles. Unlike compounds **3a**–**e** formed as mixtures of two stereoisomers, carbamates **3f**,**g** were obtained as single diastereomers with *trans*-arrangement of alkynyl and *tert*-butoxycarbonylamino substituents. Their configuration was established from values of vicinal spin coupling constant between cyclopropane protons of ~4 Hz (for *cis*-isomers, this value approaches 7 Hz). Such stereoselectivity coincides with our previous results[8,11] concerning the reactions of alkynylchlorocyclopropanes with alcohols and azoles in the KOH/DMSO system.

It is of note that the presence of *tert*-butoxy group in the used carbamates plays an important role in the successful outcome of the reactions, apparently due to its inductive effect that increases the nucleophilicity of the corresponding N-anions. This is indicated, for example, by the fact that the reaction of cyclopropane **1a** with methyl propylcarbamate, according to the NMR spectra of the reaction mixture, affords the required (methoxycabonylamino)cyclopropane derivative only in trace amounts along with ether **4** in yield about 40%.

Having *N*-Boc-protected amines **3** in hand, we studied some of their chemical transformations. Under the action of HCl, compounds **3b**–**d** cleanly underwent Boc-deprotection (Scheme 2) resulting in novel amines **6a**–**c** in high yields. The initially formed salts **5a**,**c** could be also isolated in an individual state in 74–93% yields. Recrystallization from diethyl ether made it possible to isolate individual (1*R**,3*S**)-isomer of hydrochloride **5c**, which upon treatment with aqueous K_2CO_3 gave the corresponding single isomer of amine **6c**.

The ability of cyclopropane carbamates of type **3** to undergo lithiation-substitution processes was tested on the representative example **3a**. Its reaction with a small excess of *n*-BuLi in THF at 60–70 °C followed by quenching with iodomethane provided methylation product **7** in 93% yield (see Scheme 2) while similar processing with allyl bromide afforded the corresponding allylcyclopropane **8 (**for experimental details and characteristics of



Scheme 2 *Reagents and conditions*: i, HCl (9 M in Pr^{i}OH), 20 °C; ii, K_2CO_3, H_2O; iii, BuLi, THF, –65 to –70 °C, 1 h.

compounds **5a**,**c**, **6a**–**c**, **7** and **8**, see Online Supplementary Materials). In both cases, full conversion of both isomers of the starting compound **3a** and formation of products as single isomers with *cis*-arrangement between introduced substituent and the $BocNHCH_2$ group were observed. Such good selectivity is probably the result of the effect of alkynyl substituent promoting β-lithiation combined with the directing effect of the $BocNHCH_2$ fragment which would stabilize neighboring organolithium site *via* complexation. This result is in a good agreement with the data on previously studied lithiation-substitution processes in 1-(*N*-Boc-alkyl)-2-phenylcyclopropylamines[10] and opens up good opportunities for further selective modifications of compounds **3** to obtain a variety of highly functionalized 2-alkynylcyclopropylamines.

In summary, an original synthesis of previously unknown *N*-Boc-alkyl(2-alkynylcyclopropyl)amines from 1-alkynyl-1-chlorocyclopropanes has been developed. An ability of these compounds to undergo β-lithiation with subsequent regio- and stereoselective introduction of substituents has been demonstrated.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.09.020.

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