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# Use of Polyanions for Alkylation of Hydrazine Derivatives

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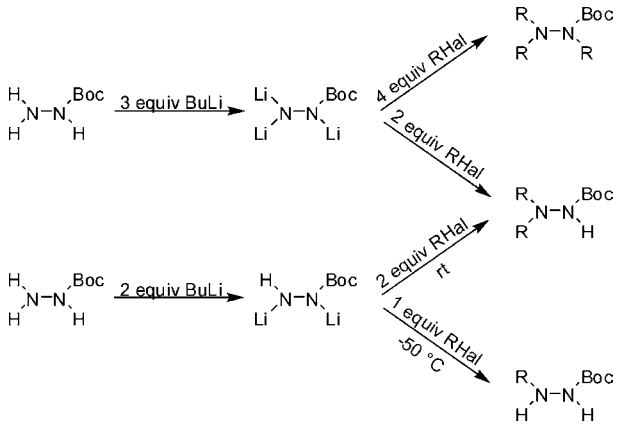
## ABSTRACT




**Alkylation of hydrazine and its derivatives still remains a quite complicated task. The novel method utilizing the polyanion strategy is reported. Formation and use of trianion for alkylation of hydrazine derivatives is first reported. Described method provides fast and convenient access to multialkylated derivatives. Scope and limitations of new method are also investigated.**

Hydrazine derivatives are long known and widely used compounds. Recently, some interesting biological properties of such compounds have been discovered.[1] Therefore, interest for methods of synthesis of compounds containing hydrazine moiety is continuously growing.[2] Nevertheless, alkylation of hydrazine and its derivatives remains a quite complicated task.

A number of systematic methods for obtaining hydrazine derivatives were recently developed,[3] although these methods have several limitations, like multiplicity of steps and lability of protecting groups in harsh conditions. Thus, efforts were made to reduce the number of required protecting groups in systematic methods of hydrazine derivatization.[4] A new method utilizing dianion strategy and virtually one protecting group for alkylation of hydrazine derivatives was recently published.[5] The methodology we wish to report here gives an approach to alkylation of hydrazine derivatives using only one protecting group.

We began with *tert*-butyl hydrazinecarboxylate. Despite the known instability of carbamate-type protecting groups

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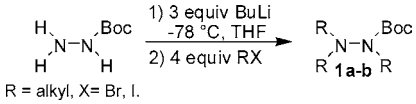
against organolithium reagents,[6] our previous work has shown that it may be sufficiently stable.[5]

On the other hand, attempts to use the Cbz protecting group in the presence of BuLi were unsuccessful and produced a mixture of products. This was caused by metalation of benzylic $CH_2$ in the Cbz group, followed by its decomposition or alkylation. Alkylation products of benzylic $CH_2$ were separated and determined by NMR spectroscopy.

$BocNHNH_2$ has three reactive NH groups with different acidities. The difference between amine and amide reaction centers can be roughly estimated as 10 p$K_a$ units.[7] The reactivity of corresponding anions is also different. Thus, this difference can be used for selective alkylation as was very recently shown.[5]

Three equivalents of BuLi were used for metalation of *tert*-butyl hydrazinecarboxylate to produce the trianion. To the best of our knowledge, this is the first report of the existence and use of trianion for an alkylation of hydrazine. This trianion can be alkylated using 4 equiv of alkyl halide to form the corresponding trialkyl derivative (Scheme 1).

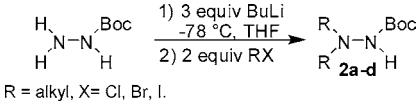
**Scheme 1.** Alkylation of Trianion with 4 equiv of Alkyl Halide




Methyl iodide and allyl bromide reacted as expected. Surprisingly, the benzyl bromide was unable to give the corresponding tribenzyl derivative even with excess benzyl halide, affording only 2,2-dibenzyl-Boc-hydrazine,[8c] probably due to steric hindrance.

Use of 2 equiv of alkyl halide gives the corresponding 2,2-dialkyl derivative **2a**−**d** (Scheme 2). Again, the reaction

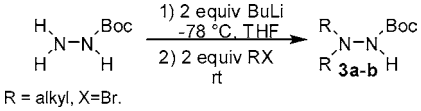
**Scheme 2.** Alkylation of Trianion with 2 equiv of Alkyl Halide




goes selectively because of the low reactivity of Boc-connected nitrogen. Using 1-bromo-4-clorobuthane as alkylating agent yielded the *tert*-butyl pyrrolidin-1-ylcarbamate (**2d**). This method provides easy access to such kind of heterocycles.

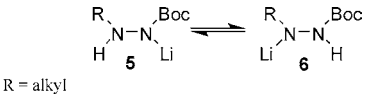
Treating $BocNHNH_2$ with 2 equiv of BuLi should give 1,2-dianion because the first equivalent reacts with the most acidic BocNH group and the second reacts with the amine NH group. Consequently, treating this dianion with 2 equiv of alkyl halide should give the corresponding 1,2-dialkyl derivative, but alkylation of 1,2-dianion unexpectedly gave 2,2-dialkyl derivatives **3a**,**b** (Scheme 3).

**Scheme 3.** Alkylation of Dianion with 2 equiv of Alkyl Halide




The one explanation could be the relatively fast intramolecular equilibrium between anions **5** and **6** in the reaction mixture.(Scheme 4). The anion **6** is rapidly consumed by

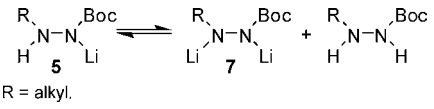
**Scheme 4.** Equilibrium of Anions




reaction with alkyl halide bringing the reaction toward the formation of product **3**.

The other possible way is the equilibrious lithiation of anion **5** by itself (Scheme 5) or any other anion producing. dianion **7**.

**Scheme 5.** Selflithiation of Anion **5**




Taking into account the difference in acidities of amine and amide centers (or basicities of corresponding anions) it can be assumed that equilibrium is strongly shifted toward anion **5**, but the reactivity of formed dianion **7** is much greater, so it reacts rapidly and is continually consumed.

Once dianion **7** formed, it reacts with alkyl halide producing anion **8**. This equilibriously metalates anion **5** yielding product **3** and again dianion **7** (Scheme 6). Thus anions **5**, **7**, and **8** are acting like catalytic cycle.

Other equilibriums are also possible, but those discussed above are in better accordance with experimental data. First, we suppose that the initial alkylation goes fast. Therefore, after shot time most of the anions in the reaction mixture

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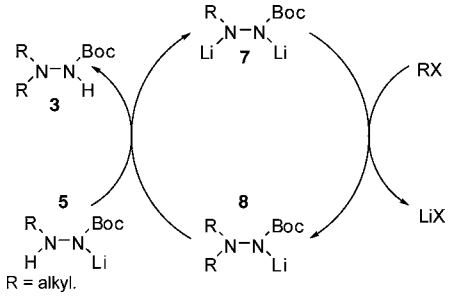
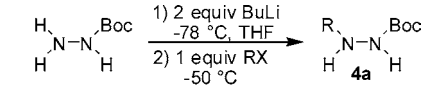
**Scheme 6.** Equilibrium of Anions




are represented by anion **5**. Second, if one of the equilibrium components continuously consumed, it becomes irreversible and can be presented as disproportionation. Thus, any eqilibrium with retention of lithium at amide nitrogen would give large amount of starting material or monoalkylated product and yield lower than 50%. In our case, reaction proceeded cleanly with yield more than 50%. However, if addition of alkyl halide was made at room temperature some amount of mono- and trialkylated products could be observed.

The formation of the 2-allyl-Boc-hydrazine[4a] was achieved only by freezing down the equilibrium at −50 °C and using 1 equiv of allyl bromide (Scheme 7). Nevertheless use of

**Scheme 7.** Alkylation of Dianion with 1 equiv of Alkyl Halide



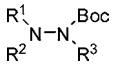

other alkylating agents at the same conditions gave mixture of products.

All attempts to use 1 equiv of BuLi for an alkylation gave mixture of products. 2,2-Dialkylated products also have been separated from the mixture. Mechanism of its formation should also be related to anion equilibrium discussed. It seems that anion equilibrium is quite general feature of hydrazine anions. Some other reports on formation of unexpected product isomers from hydrazine anions (probably due to the interanion equilibrium) were previously described in literature.[5,9]

Boc protecting group can be removed from all of reported compounds and then they can be derivatized by common methods.

Several new methods for the selective hydrazine alkylation were developed. Use of a trianion for this purpose is reported for the first time. Scope and limitations of applicability of this new method were demonstrated (Table 1). Formation of unexpected products is reported. The first generalization and explanation for this and similar effects previously reported in literature was made. In summary, this method can be easily applied in the systematic synthesis of hydrazine derivatives and heterocycles.

**Table 1.** Alkylation Products




| | $R^1$ | $R^2$ | $R^3$ | conditions | yield, % |
|---|---|---|---|---|---|
| **1a**[a] | Me | Me | Me | 4 equiv of MeI, 1 d, rt | 89 |
| **1b** | All | All | All | 4 equiv of AllBr, 1 d, rt | 68 |
| **2a**[a] | Me | Me | H | 2 equiv of MeI, 3 h, rt | 74 |
| **2b** | All | All | H | 2 equiv of AllBr, 3 h, rt | 77 |
| **2c** | Bn | Bn | H | 2 equiv of BnBr, 3 h, rt | 72 |
| **2d** | $-(CH_2)_4-$ | | H | 1 equiv of $Br(CH_2)_4Cl$, 2 h, rt | 65 |
| **3a** | All | All | H | 2 equiv of AllBr, 2 h, rt | 67 |
| **3b** | Bn | Bn | H | 2 equiv of BnBr,3 h, rt | 62 |
| **4a** | All | H | H | 1 equiv of AllBr, 2 h, −50 °C | 50 |

[a] See ref 8a for compond **1a** and ref 8b for compond **2a**.

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**Supporting Information Available:** Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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