

# NEW WAY OF MONO-BOC-PROTECTION OF DIAMINES

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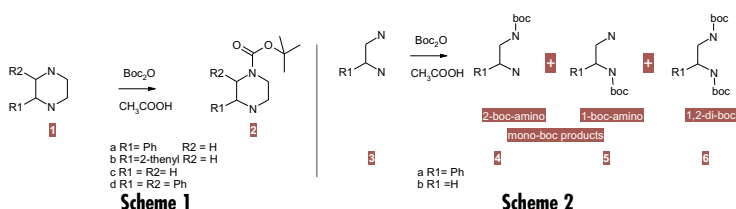
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As described in our earlier paper [1] the major objective of our research efforts was to prepare regioselectively protected unsymmetrical cyclic and aliphatic diamines. As a first result we have come up with a satisfying procedure using acetic acid medium for mono-Boc protection of 2-(hetero)aryl-piperazines (Scheme 1 **1-2a, b**)

As a „by-product” of this work we published a very simple and effective method to prepare 4-Boc-protected piperazine and 2,3-disubstituted derivatives (Scheme 1 **2-2c,d**)



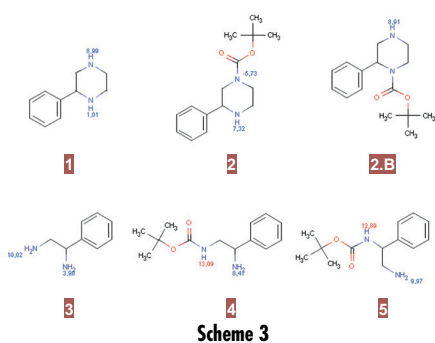
We used similar condition for the mono-Boc protection of 1-phenyl-ethylene diamines as described in case of piperazines. The yields of the mono-protected species become lower; however, the regioselectivity of the reaction remained (Table 1).

Product ratio in acetic acid medium mono-Boc-protection of ethylene diamines

diamine	3	4	5	6
a R1=Ph	30 %	40 %	0 %	30 %
b R1=H	35 %	30 %	0 %	35 %

Table 1

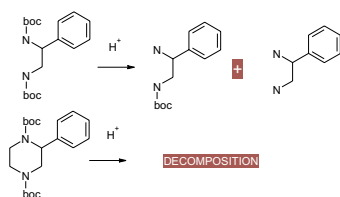
For mechanistic studies we calculated the pKa values of starting diamines and mono-Boc intermediates. We used ChemAxon's Marvin Sketch option to make the calculation. The calculated data are listed on the following scheme.



As seen on Scheme 4 the 1-Boc-amino (**4**) product has higher pKa value on the free secondary amine (**1**) than the first pKa of the piperazines derivative (**2.a**). So, in the same conditions (slightly acidic medium) the velocity of the acylation must be higher. The experimental data supported this assumption (Table 1)

In reaction 1 with Boc<sub>2</sub>O in acetic acid the yield of 2 is 60-90% depending on the purity of the starting material. No starting piperazine remains and formation of other regioisomer could not be detected.

In similar reaction of the 1-phenyl-1,2-diamino ethane (**3**) the 1-Boc-amino product (**4**) was produced at a lower yield with the formation of considerable amount of di-Boc product and remaining equivalent amount of the starting ethylene diamine. However, in neither case we could not detect the formation of the other 1-mono-Boc species (**5**). This lack of regioisomers shows that the acetic acid and the size of the di-t-butyl dicarbonate have some effect on the reaction.



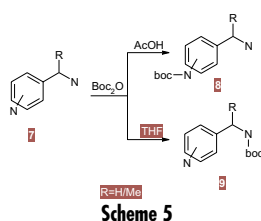
Scheme 4

We tried to study the stability of **2.B** and **5** in acidic medium, but due to the difficult synthesis we restricted our synthetic evaluation to easier models (Scheme 4).

### Isolated Diamines with Different Reactivity

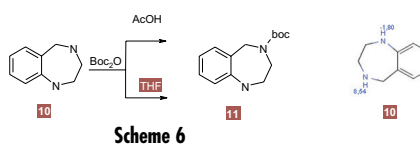
The Boc-protection of various isolated diamines such as amino-benzyl amine and (1-amino-ethyl)-phenylamine isomers smoothly followed the rule that in the presence of weak acid the less reactive amino group was protected (**8**), in neutral medium the major product was the protected aliphatic amino derivative (**9**).

This is in good correlation with the pKa calculation, which shows around 9 values for the aliphatic and 4,5 for the aromatic amino group.



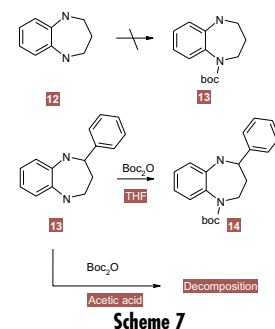
### Two Amino Groups Incorporated in Heterocyclic Systems

Unexpectedly the cyclic analog **10** showed completely different behavior in Boc-protection under neutral and acidic conditions. In both cases only the **11** type mono-protected derivative was the exclusive product.



This behavior is in good correlation with the calculated pKa value of the two ring nitrogen and also in agreement with the literature that describes the selective acetylation of the ring at position.

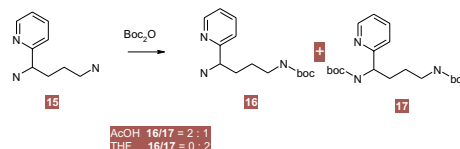
Other tetrahydro-1,4-benzodiazepine isomers shows different reactivity. The 2,3,4,5-Tetrahydro-1H-benzo[b][1,4]diazepine has practically 0 velocity in Boc-protection. 2-phenyl-2,3,4,5-tetrahydro-1H-1,5-benzodiazepine can be protected on the 5 position in neutral conditions while in acidic medium it slowly decompose to an unidentified product (scheme 7)



Ortho-phenylene diamine can also be mono-protected in a long reaction in acetic acid.

### Terminal Diamines with Longer Alkyl Chain

From the calculation of the pKa values of higher alkyl terminal diamines and their potential Boc-protected variety it is obvious that the effect of the terminal amines to each other decrease with the length of the alkyl chain. The steric hindrance of a large substituent on the terminal carbon has still a strong directive effect.



Scheme 8

### Summary

As could be seen from the above examples the calculated pKa values could serve good interpretation for the selective reaction of different diamines in acidic medium. Summarizing the basic requirement for mono protection is 5 difference between the pKa values of the two amino groups. The lower is the pKa of the free amine of the mono-Boc species (**type 4**) the higher is the yield of the mono-boc product. Isolated diamines can be reacted according to the following rule: in acidic medium the lower in neutral medium the greater pKa valued nitrogen can be protected with acceptable selectivity. Alkyl chain longer than 3 carbons reduces the favorable neighborhood effect. Over 8 pKa difference value the amines can be reacted selectively in chemical reactions.

There are certain problems which this model overlooks:

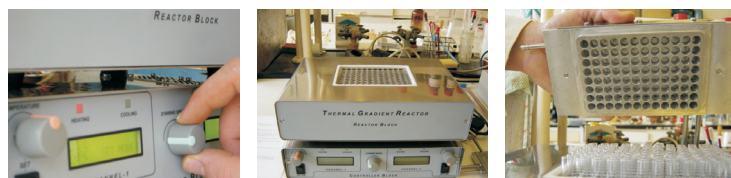
1. Stability of the protected amines vs. pH and temperature
2. Stability of the heterocyclic systems vs. pH and temperature

The bulky Boc<sub>2</sub>O is very sensitive to the steric hindrance, which is confirmed by regioselectivity of the Boc-protection and the sensitivity of the reaction velocity to the steric hindrance.

Reference: 1. Dr. László Kovács New Way of Mono-Boc-Protection of Diamines I. Balticum Organicum Synthetium, 2002 Vilnius (poster)

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