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Double Deprotonation of *N*-Boc-Aminobenzotriazole for the Preparation of Substituted Benzyne Precursors

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Abstract:- *N-Boc-aminobenzotriazole has been converted into its N,7-dilithio derivative 7 which can be trapped by a variety of electrophiles at the 7-position to give a number of new aminobenzotriazoles suitable for the generation of substituted benzynes.*
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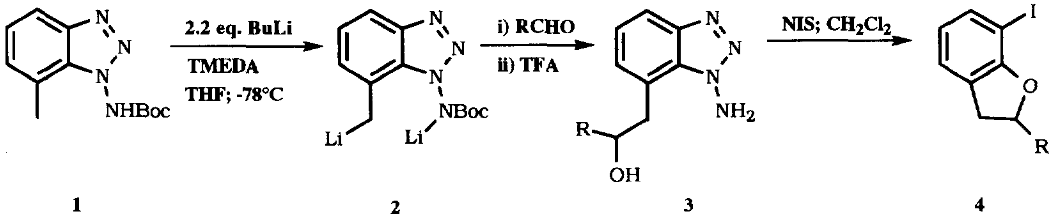
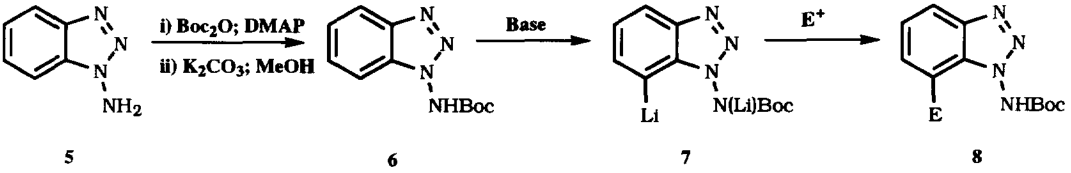
We have recently reported [Scheme 1][1] that the dianion **2** can be smoothly generated from *N*-Boc-7-methyl-1-aminobenzotriazole **1**, in a lateral lithiation reaction, presumably promoted by the ionized *N*-Boc group;[2] subsequent condensations with a variety of electrophiles, such as aldehydes, gave homologues **3**, following deprotection of the amino function. While treatment of the aminobenzotriazoles **3** with either lead(IV) acetate or *N*-bromosuccinimide using the well-established conditions of Campbell and Rees[3] gave the hoped for dihydrobenzofurans, we found that a significantly better method was to use *N*-iodosuccinimide to trigger benzyne formation, leading to excellent yields of the iodo-dihydrobenzofurans **4**.[4]



Scheme 1

In the hope of providing greater flexibility to this potentially widely applicable method for the elaboration of dihydrobenzofurans and the homologous chromans and derivatives thereof,[4] we wondered if the directing ability of the deprotonated *N*-Boc group would be sufficient to allow regioselective generation of the dianionic species **7** from the parent aminobenzotriazole **5** [Scheme 2]. This would offer the additional benefit of much easier access to the starting material, as the latter is available by direct N-amination of benzotriazole,[3] in contrast to the 7-methyl derivative **1**, which requires a six step preparation starting from 2-methyl-6-nitroaniline.[3] Furthermore, such an intermediate could permit the incorporation of a variety of heteroatomic groups [**8**; E = R_3Sn, $(RO)_2B$, I *etc*] directly attached to the 7-position of the aryl ring and hence open up further opportunities for homologation to suitable benzyne precursors using a variety of coupling reactions [*eg* Stille, Sonogashira *etc.*]. Herein, we report that it is indeed possible to generate the dianion **7**, but that significant modification of the conditions used for the homologous dianion **2** are required to secure good yields of the adducts **8**.



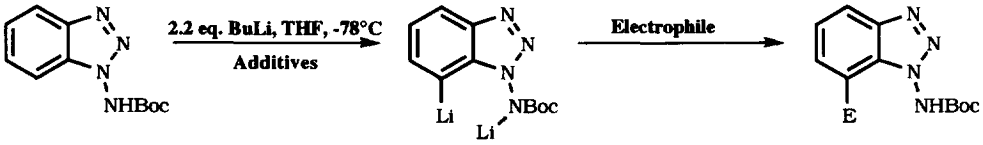
Scheme 2

Treatment of 1-aminobenzotriazole **5** with two equivalents of $(Boc)_2O$ lead to an excellent yield of the *bis*-*N*-Boc derivative; subsequent hydrolysis of one of the Boc groups was easily achieved by a basic work-up. Efforts to directly prepare the mono-Boc derivative **6** were unsuccessful, as in our previous study.[4] We began by using the same basic conditions [^nBuLi, TMEDA, THF, -78°C] which were successful for the generation of the dianion **2** with benzaldehyde as the test electrophile. However, the yields of the desired adduct **8** [E = PhCH(OH)] were never in excess of 70% with the remainder of the recovered material being starting material **6**. [Table; entry 1]. Similar yields were obtained using tributyltin chloride [entry 2] and when the solvent was changed to ether [entry 3]. Raising the temperature did not lead to a significant increase in yields and resulted in extensive decomposition of the substrate at temperatures in excess of *ca* -40°C.

Reasoning that a more effective base combination might provide an improvement, we added 2.2 equivalents of 12-crown-4 to the reaction mixture prior to addition of the electrophile [Bu_3SnCl] and were pleased to secure a 92% isolated yield of the expected stannyl derivative [entry 4]. However, for reasons of cost and toxicity, this was hardly a practical solution and, unfortunately, use of a catalytic quantity of the crown ether led to much reduced yields [*eg* entry 5]. This led us to try what is effectively the open-chain form of 12-c-4, tetraglyme,[5] and we found that this restored the excellent yield obtained using 2.2 equivalents of the crown ether [entry 6]; a marginally better result was obtained using 5.5 equivalents of tetraglyme [entry 7]. Under these conditions, excellent yields were also obtained when D_2O, *p*-methoxybenzaldehyde and DMF were employed as electrophiles [entries 8~10].

Unfortunately, these conditions led to poor yields with enolizable aldehydes such as *n*-hexanal [entry 11]; presumably, the dianion **7** is sufficiently basic to deprotonate such electrophiles. A recently established method which can overcome such a drawback and render an anionic species more nucleophilic and less basic, is conversion into the corresponding organocerium species.[6] We were delighted to find that, when one equivalent of anhydrous ceric chloride was added followed by *n*-hexanal, the desired adduct was isolated in 79% yield [entry 12]. Similarly, this combination using $CeCl_3$ also significantly improved the returns when *p*-methoxybenzaldehyde and DMF were used as electrophiles [entries 13 and 14]. The relative hardness of the dianion **7** was indicated by its ability to add in a [1.2]-fashion to 2-hexenal [entry 15]. Finally, the dianion **7** was also found to add efficiently to trimethyl borate to give the expected adduct in 71% isolated yield [entry 16].

Table : Generation and Trapping of Dianion 7 derived from *N*-Boc-1-aminobenzotriazole

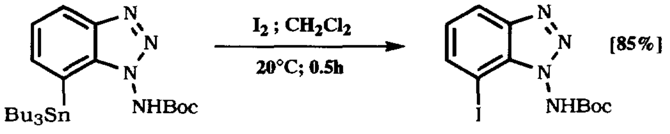


6 **7** **8**

Entry	Additive(s)	Electrophile	E	% Isolated yield
1	2.2 eq. TMEDA	PhCHO	PhCH(OH)	65*
2	2.2 eq. TMEDA	Bu_3SnCl	Bu_3Sn	64*
3	2.2 eq. TMEDA [Ether as solvent]	Bu_3SnCl	Bu_3Sn	71*
4	2.2 eq. 12-c-4	Bu_3SnCl	Bu_3Sn	92
5	0.2 eq. 12-c-4	Bu_3SnCl	Bu_3Sn	22*
6	2.2 eq tetraglyme	Bu_3SnCl	Bu_3Sn	89*
7	5.5 eq tetraglyme	Bu_3SnCl	Bu_3Sn	94
8	5.5 eq tetraglyme	D_2O	D	89
9	5.5 eq tetraglyme	*p*-$MeOC_6H_4CHO$	*p*-$MeOC_6H_4CH(OH)$	79
10	5.5 eq tetraglyme	DMF	CHO	67*
11	5.5 eq tetraglyme	*n*-$C_5H_{11}CHO$	*n*-$C_5H_{11}CH(OH)$	20*
12	5.5 eq tetraglyme; 1 eq. $CeCl_3$	*n*-$C_5H_{11}CHO$	*n*-$C_5H_{11}CH(OH)$	79
13	5.5 eq tetraglyme; 1 eq. $CeCl_3$	*p*-$MeOC_6H_4CHO$	*p*-$MeOC_6H_4CH(OH)$	95
14	5.5 eq tetraglyme; 1 eq. $CeCl_3$	DMF	CHO	95
15	5.5 eq tetraglyme	$^nPrCH:CHCHO$	$^nPrCH:CHCH(OH)$	75
16	5.5 eq tetraglyme	$(MeO)_3B$	$(MeO)_2B$	71

* The balance of material was recovered *N*-Boc-aminobenzotriazole **6**

Under the optimized conditions using tetraglyme and cerium(III) chloride, essentially no adduct was obtained using 1,2-epoxyhexane as the electrophile; evidently, an even greater degree of nucleophilicity will have to be obtained to enable epoxides to be successfully used as electrophiles with dianion **7**. In contrast, variable yields of the iodide **10** were obtained when the dianion **7** was treated with a number of iodonium sources, the best being 55% using iodo-perfluorohexane. Alternatively, the expected facile tin-iodine exchange occurred when the stannyl derivative **9** was treated with a solution of iodine in dichloromethane [Scheme 3] allowing for an efficient access to the iodo derivative **10**.



9 **10**

Scheme 3

In summary, we have found that the dianion **7** is a viable intermediate, under the appropriate conditions, for the generation of a variety of substituted benzyne precursors **8**. In addition, the efficient incorporation of formyl, tin, iodine and boron at the 7-position opens up many possibilities for the incorporation of a wide range of substituents by using the plethora of both old and new coupling reactions now available. Our efforts are now aimed in this direction and will be reported in due course.

Acknowledgements

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