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Unexpected Debenzylation of *N*-Benzylindoles with Lithium Base. A New Method of *N*-Debenzylation[1]

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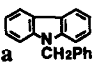
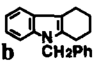
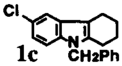
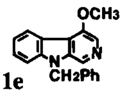
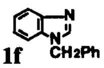
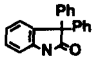
Abstract: The reaction of *N*-benzylindoles with lithium base resulted in debenzylation. The key step would be generation of benzyl carbene from the preformed *N*-benzyl anion. This reaction should serve as a new debenzylation method for indoles and related compounds.

Benzyl group should be more valuable as a protecting group for indolic NH, if easily deprotected, because it stabilizes the compound without decreasing the activity of indolic 3-position. However, only limited methods have been used for debenzylation of indoles; Birch reduction was the most effective method because catalytic hydrogenation is usually unsuccessful. We developed a new debenzylation method using $AlCl_3$ in benzene[2], but this method has not been effective for acid-sensitive and sterically hindered *N*-benzylindoles.

Recently, we unexpectedly found the debenzylation of a *N*-benzylindole derivative when it was treated with lithium base. On the basis of this finding, we have developed a new method for the debenzylation of indoles and related compounds as described in the present paper.

A solution of MeLi or LDA (5 eq.) was added to a THF solution of *N*-benzylindoles (**1**) (1 eq.) under argon atmosphere at -40°C for 1h and then allowed to stand overnight at room temperature. The results are summarized in Table 1.

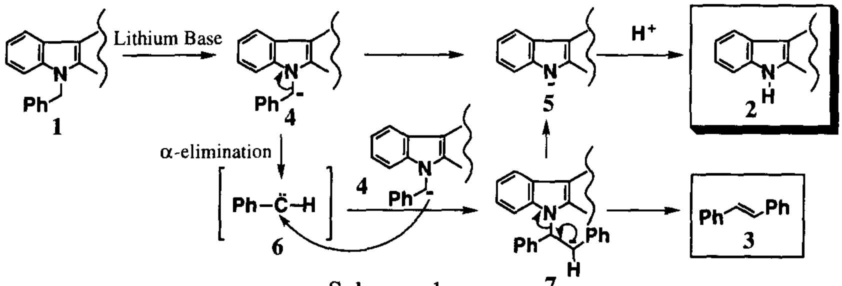
Table 1

Substrate	Lithium Base	Yield **2**	Yield **3**
 **1a**	MeLi	74%	trace
	LDA	37%	trace
 **1b**	MeLi	49%	5%
 **1c**	MeLi	64%	trace
	LDA	complex mixture	
 **1d**	MeLi[*1]	40%	trace
	LDA[*1]	40%	——
 **1e**	MeLi	55%	trace
	LDA	65%	trace
 **1f**	MeLi	35%	3%
	LDA	8%	——
 **1g**	MeLi[*2]	57%	trace

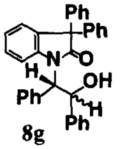
[*1] 0°C [*2]-40°, 1.5hr

The yields of resulting NH-products (**2**) were generally moderate. It is noteworthy in view of synthetic chemistry that the debenzylation of acid sensitive indole (**1b**), sterically hindered indole (**1d**), and heterocycles (**1f**, **1g**) was successful, because their debenzylation by $AlCl_3$ method[2] was unsuccessful (**1b** gave a complex mixture and others were recovered unchanged). The use of *n*-BuLi in place of MeLi and LDA gave only a mixture of unidentified products, the reason for the inconsistency being not clarified.

The mechanism of the present debenzylation is proposed in Scheme 1. The key step seems to involve the formation of the carbene (**6**) and the indole anion (**5**) from the carbanion (**4**) by α-elimination, along with the probable oxidative debenzylation by air. The carbene (**6**) reacts with **4** to yield **7**, which degrades into *trans*-stilbene (**3**) and indole anion (**5**), while we could not detect any other compound formed from **6** because of their volatility[3].



Scheme 1



8g

Some by-products were formed in several cases in addition to **3**. A typical one was **8g** (35%) formed from **1g**. It would be formed by the coupling of the carbanion (**4**) with benzaldehyde, the latter being formed by air oxidation of **4**. Williams[4] showed the debenzylation of *N*-benzylamide by treating it with *t*-BuLi, followed by oxidation with oxygen or MoOPH [Oxodiperoxymolybdenum(hexamethylphosphorictriamide)pyridine], whereas our present method[5] requires mere treatment of the *N*-benzyl compound with lithium base.

In addition to the synthetic application, our finding gives a warning that the treatment of *N*-benzyl compounds with a strong base sometimes gives rise to undesirable debenzylation.

References and Notes

1. This paper is part XXXV of "Synthetic Studies on Indoles and Related Compounds." Part XXXIV: Yokoyama, Y.; Takahashi, M.; Takashima, M.; Kohno, Y.; Kobayashi, H.; Kataoka, K.; Shidori, K.; Murakami, Y. *Chem. Pharm. Bull.* **1994**, *42*, 832-838.
2. a) Murakami, Y.; Watanabe, T.; Kobayashi, A.; Yokoyama, Y. *Synthesis* **1984**, 738-740.
   b) Watanabe, T.; Kobayashi, A.; Nishiura, M.; Takahashi, H.; Usui, T.; Kamiyama, I.; Mochizuki, N.; Noritake, K.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1152-1156.
3. Schöllkopf reported the debenzylation of *O*-benzylphenol with *n*-BuLi, and proposed the generation of carbene (**6**) from *O*-benzylcarbanion for isolation of *trans*-stilbene (**3**) and other volatile by-products formed from **6** or **3** as minor products, which support our mechanism.
   Schöllkopf, U.; Eisert, M. *Justus Liebigs Ann. Chem.* **1963**, *664*, 76-88.
4. Williams, R.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451-454.
5. Intentional exposure of the carbanion solution in the air did not accelerate the rate nor increase the yield of debenzylated products (**2**).

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