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[A001]

Deprotection of *N*-Pivaloylindoles, Carbazoles and beta-Carbolines with a Lithium Base

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Abstract.- *Treatment of a variety of pivaloylindoles, carbazoles and with LDA at 40-45 °C led to their fast and efficient deprotection.*

Introduction

N-Protection is a very important aspect of indole chemistry because of the poor stability of indole under a variety of conditions, specially acidic ones, and also because *N*-protection allows, and often directs, the lithiation of the heterocyclic nucleus. Due to the high basicity and nucleophilicity of the indole five-membered ring, protection of the C2-3 bond can also be sometimes desirable. The most commonly employed indole N-protecting groups are arylsufonyl derivatives (*e.g.* tosyl), carbamates (*e.g.* BOC), trialkylsilyl groups (*e.g.* triisopropylsilyl), N,O-acetals (*e.g.* SEM) and some alkyl groups (*e.g.* benzyl) [1]. Protecting groups for the indole C2-3 bond are currently very scarce, and based on the use of expensive starting materials [2].

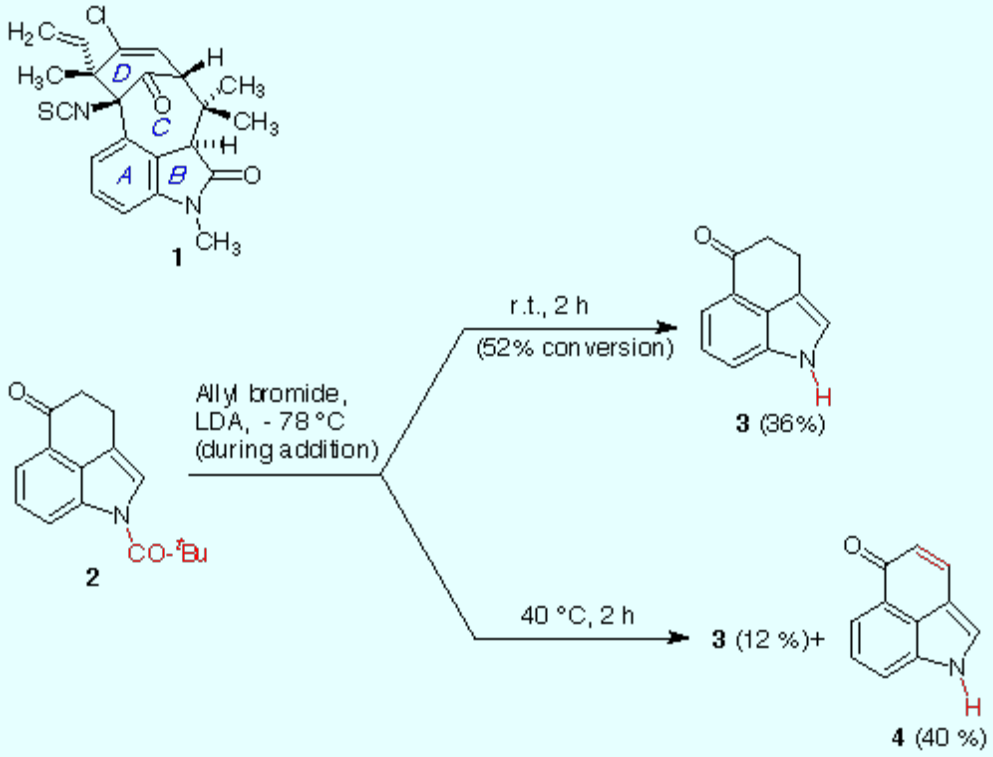
Pivaloyl would be a very interesting protecting group for indole because, due to steric reasons, it protects both the N-1 and C-2 indole positions. For instance, it has been used to direct intramolecular Friedel-

Crafts acylations of indole-3-propionic acid derivatives to C-4 rather than to the electronically more favourable C-2 [3]. However, pivaloyl is notoriuosly difficult to remove. Although deprotection of pivaloylindoles has occasionally been achieved by use of alkoxides, the generality of this method has not been established because it has been studied only in a few specific cases, and the yields found are variable and sometimes very poor. For instance, sodium methoxide gave only 19% yield in the deprotection of a *N*-pivaloylcyclohepta[*cd*]indole derivative [4], although it had worked very well on a closely related cyclohexa[*cd*]indole system [5].

Due to the potential advantages of pivaloyl as a protecting group for indole, a general deprotection method of pivalolyindoles is desirable. Is this context, we report here our findings the use of LDA to achieve this transformation.

Results and Discussion

During the course of our studies on the synthesis of compounds related to the natural multi-drug resistance inhibitor *N*-methylwelwitindolinone C isothiocyanate (welwistatin, compound **1**) [6,7] we examined the alkylation of tricyclic ketone **2** [3,5] with allyl bromide in the presence of LDA as a base at - 78 °C, followed by 2 h qat room temperature. The only observed product (together with unreacted starting material) was compound **3**, from depivaloylation of **2**. Harsher conditions (2 h at 40 °C) led to a mixture of **3** and **4**, presumably arising from hydroxylation of the anion derived from **3** by traces of oxygen, followed by elimination.



Scheme 1

The observations summarized in Scheme 1 led us to consider the possibility of employing LDA for the deprotection of pivaloylindoles. After some experimentation, we found that treatment of pivaloylindole itself with 2 equivalents of LDA in THF at 40-45 °C led to its quantitative deprotection. In order to verify the generality of the method, several variously substituted pivaloylindole derivatives **5** were prepared by treatment of the corresponding indoles with sodium hydride followed by addition of the suitable alkyl halide. The results obtained in the reaction of these compounds with LDA to give the unprotected indoles **6** are summarized in Scheme 2 and Table 1.

The reactions carried out on a number of indoles substituted at the 3, 4, 5 and 7 positions (entries 2-7) proceeded in excellent yields. A variety of functional groups like aldehyde (entry 3), ester (entries 6 and 7) and ether (entry 8) were tolerated without any noticeable decomposition, and a carboxylic group in a side chain at C-3 caused only a slight decrease in yield (entry 9), in spite of its reactivity towards LDA. On the other hand, and because of steric interference, 2-substituted and 7-substituted indoles were less reactive and thus the reactions starting from 7-methyl-1-pivaloylindole (entries 4 and 5) and 2-phenyl-1-pivaolylindole (entries 10 and 11) required 40 h and 90 h to achieve completion, respectively, although the yields were again excellent.

Scheme 2

Table 1

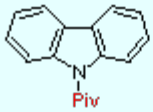
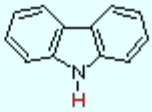
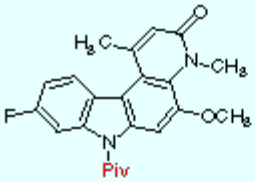
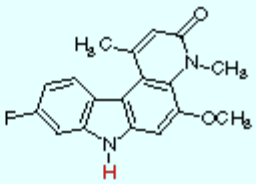
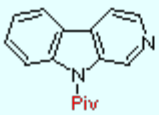
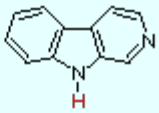
Entry	R^2	R^3	R^4	R^5	R^7	Reaction time, h	Product	Yield, %
1	H	H	H	H	H	2	4a	100
2	H	CH_3	H	H	H	2	4b	99
3	H	CHO	H	H	H	2	4c	99
4	H	H	H	H	CH_3	2	4d	55
5	H	H	H	H	CH_3	40	4d	93
6	H	H	$CO_2C_2H_5$	H	H	2	4e	89
7	H	H	H	$CO_2C_2H_5$	H	2	4f	93
8	H	H	H	OCH_3	H	2	4g	92
9	H	$CH_2CH_2CO_2H$	H	H	H	2	4g	78
10	C_6H_5	H	H	H	H	2	4h	45
11	C_6H_5	H	H	H	H	90	4h	92
12	CH_3	H	H	H	H	2	4i	33

The reaction starting from 2-methyl-1-pivaloylindole, together with the expected compound **6i**, gave **8** as

the major product, presumably by assisted metallation to **7** followed by intramolecular transfer of the pivaloyl group. Intermolecular pivaloyl transfer seems to be excluded by the very different yields obtained for **6i** and **8**.

Scheme 3

We also studied the deprotection of several more complex heterocyclic systems containing *N*-pivaloylated indole subunits, including carbazole **9**, a pyridocarbazole derivative **11** and beta-carboline **13**. As shown in Scheme 4, these reactions also proceeded in good to excellent yields.

Entry	Starting compound	Product	Yield, %
1	 7	 8	93
2	 9	 10	79
3	 11	 12	80

Scheme 4

In conclusion, we have developed an efficient protocol that allows the deprotection of a wide variety of *N*-pivaloylindoles and can also be extended to *N*-pivaloylcarbazoles and *N*-pivaloyl-beta-carbolines, generally in high to excellent yields. This finding should facilitate the future use of pivaloyl as a protecting group in indole chemistry, taking advantage of the possibility that this group offers of simultaneously protecting the N1 and C2 positions of indole.

Acknowledgment

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