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Can functionalized *N*-acyloxy aziridines be easily deprotected?

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Abstract

Nitrogen deprotection of polyfunctionalized *N*-acyloxy aziridines was studied considering the compatibility of reaction conditions with the different functional groups on the aziridine ring. ***To cite this article: S. Fioravanti et al., C. R. Chimie 8 (2005)***.

Résumé

La déprotection de l'azote de *N*-acyloxy aziridines fonctionnalisées a été étudiée en considérant la compatibilité des conditions de réaction avec les différents groupes fonctionnels sur l'anneau des aziridines. ***Pour citer cet article : S. Fioravanti et al., C. R. Chimie 8 (2005)***.

Keywords: Carbamates; Aziridines; Protecting groups

Mots clés : Carbamates ; Aziridines ; Groupes protecteurs

1. Introduction

Carboxylate groups are among the protecting groups most commonly used for blocking amino functions. Several methods to introduce a wide variety of these groups were proposed [1]. The use of different sulfonyloxycarbamates ($ArSO_3NHCO_2R$) in the amination reactions gives directly several *N*-acyloxy protected nitrogen-containing compounds [2].

In the course of our study, we reported an aza-Michael initiated ring closure (MIRC) [3] route to efficiently obtain a large number of different functionalized aziridines [4]. The increasing complexity of the synthesized aziridines due to substituents of the ring carbon atoms seems to play a fundamental role in the transformation reactions of the aziriridine ring, first of all the nitrogen deprotection reaction. Protecting groups must be easily removed in order to obtain corresponding unblocked aziridines, thus obtaining an additional site for further synthetic transformations. Considering the value of aziridines like versatile building blocks [5] for the synthesis of a large number of nitrogen-

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containing compounds, it is very important the choice of the sulfonyloxycarbamate employed in the direct aziridination of functionalized olefins.

Recently we synthesized and tested several nosyloxycarbamates ($NsONHCO_2R$, Ns = 4-nitrophenylsulfonyl) bearing different R groups as efficient aza-MIRC reactants [6].

In this communication, we report the first results about the role of substituents on the ring carbon atoms in the deprotection reaction of different functionalized aziridines. These latter were obtained by the aziridination of the corresponding olefins with four different carbamates, namely ethyl, *tert*-butyl, benzyl and 9-fluorenylmethyl nosyloxycarbamates.

2. Results and discussion

The carbamates **1a–d** were synthesized according to a procedure reported in Ref. [7]. We considered different olefins bearing electron-withdrawing groups. The aza-MIRC reactions were performed in the presence of CaO in CH_2Cl_2 at room temperature and gave the expected *N*-protected aziridines **2–6** in very high yields (Fig. 1).

Compounds **2–6** were treated under the usual deprotection conditions for each considered protecting group [1]. Reaction conditions and results are depicted in the Table 1.

As reported in Table 1, the cleavage of the ethoxycarbonyl group (entry 1) failed for **2** and gave the undesired transesterification reaction of the carbamate function, while in the other considered cases only GC traces of unprotected aziridines were observed. With *tert*-butoxycarbonyl (Boc) group as the protecting group (entry 2), a partial deprotection was obtained with aziridines **3b** and **4b**. **5b** gave a complex mixture of unidentified decomposition products. Aziridines **2b** and **6b** cannot be obtained using *tert*-butyl nosyloxycarbamate.

Carbobenzoxy (Cbz) group (entry 3) was successfully removed from substrates **5c** and **6c**, but the reductive deprotection procedure was not compatible with the functional groups carried by aziridines **2c–4c**.

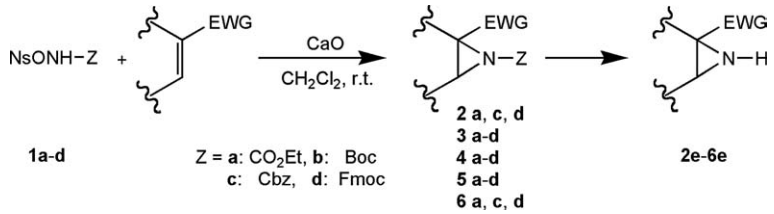
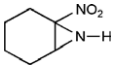
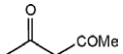
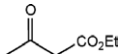
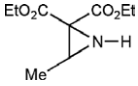
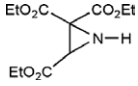


Fig. 1. Synthesis and deprotection of *N*-acyloxy aziridines.

Table 1
Deprotection of *N*-acyloxy aziridines

Entry	*Z*	Deprotection procedure	 **2e**	 **3e**	 **4e**	 **5e**	 **6e**
1	CO_2Et	NaOH/MeOH [a]	– [b]	Traces	–	–	–
2	Boc	$BF_3{\cdot}Et_2O$ [c]	– [d]	36% [e]	30% [e]	–	– [d]
3	Cbz	Pd/C 10% HCO_2NH_4 MeOH [f]	–	Traces	Traces	Quant. conv.	Quant. conv.
4	Fmoc	20% Piperidine CH_2Cl_2		Quant. conv.	Quant. conv.	Quant. conv.	Quant. conv.

[a] 1 mmol of aziridine and 0.15 mmol of NaOH in 5 ml of MeOH at room temperature for 24 h.
[b] 56% of methyl 1-nitro-7-azabicyclo[4.1.0]heptane-7-carboxylate was obtained.
[c] 1 mmol of both aziridine and BF_3 in 2 ml of anhydrous Et_2O at room temperature for 24 h.
[d] *tert*-butyl nosyloxycarbamate did not react with the considered olefin.
[e] *N*-protected aziridine was partially recovered (up to 20%).
[f] 1 mmol of aziridine and 8 mmol of HCO_2NH_4 in the presence of 0.3% of catalyst in 20 ml of MeOH at 40 °C for **4**.

Free aziridines were efficiently obtained from compounds **3d**–**6d** by using a 20% piperidine solution in dichloromethane to remove 9-fluorenylmethyloxycarbonyl (Fmoc) group (entry 4). A typical procedure to remove the Fmoc group [8] is reported as follows for **5e**: *N*-protected aziridine **5d** (0.42 g, 1 mmol) was dissolved in 3 ml of a 20% piperidine solution in dichloromethane and stirred at room temperature for 15 min. After solvent removal, cold MeOH was added and the mixture was filtered. By evaporation, **5e** was obtained in quantitative yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ = 1.18–1.31 (m, 9H), 2.53 (s, broad, 1H), 2.63 (q, 1H, J = 5.5 Hz), 4.15–4.30 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ = 14.0, 14.1, 15.2, 39.7, 45.6, 61.7, 62.5, 166.1, 168.6 ppm; GC–MS: *m*/*z* (%): 201 (M^+, <1), 156 (11), 155 (28), 128 (14), 127 (81), 110 (25), 100 (17), 82 (24), 56 (19), 55 (100), 54 (30), 45 (37); ES-MS Q-TOF *m*/*z* Calc. for $C_9H_{16}NO_4$ (MH^+) 202.1079. Found 202.1073.

Drastic deprotection conditions showed that a reasonable compatibility could not be achieved with the considered polyfunctionalized aziridines. EWG groups, like nitro or carbonyl, seem to strongly interfere with the reaction outcome, while the mild basic deprotection conditions are the most versatile, both for the stability of the aziridine ring and for the different functional groups. An easy and generally compatible method for the deprotection of aziridines is a goal of valuable importance [9] for the design and construction of aziridine combinatorial libraries [10] directed towards particular pharmacological targets.

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