Pergamon

Tetrahedron Letters 39 (1998) 5763–5764

TETRAHEDRON LETTERS

Synthesis of 3-Substituted-4*H*-1,4-Benzoxazines

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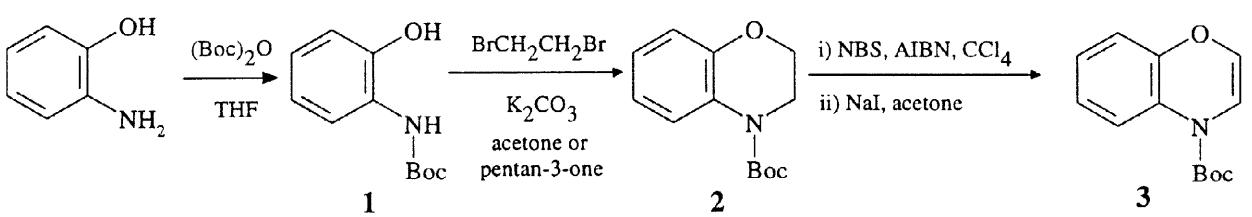
Received 15 October 1997; accepted 8 June 1998

Abstract : Various 3-substituted-4*H*-1,4-benzoxazines were prepared in good yields by lithiation-electrophilic substitution of the 4-Boc-4*H*-1,4-benzoxazine. The synthesis of this carbamic derivative, in four steps from 2-aminophenol, was described.

Some isolated examples of 2-substituted and 3-substituted-4*H*-benzoxazines have been reported[1] but the reaction sequences described are far from being generally applicable.

In the course of our investigations concerning the synthesis of biologically active derivatives containing a 1,4-benzoxazine subunit, we were interested in an easy and general procedure allowing the successive functionalizations of the 2,3 and 5 positions of this heterocyclic system.

The *tert*-butoxycarbonyl group (Boc) has been described as an excellent directing activator for both the ortho-lithiation of anilines[2] or tetrahydroquinolines[3] and the α-lithiation of the secondary amines[3,4]. We postulated that N-Boc benzoxazine **3** could be an ideal precursor for the preparation of substituted benzoxazines and, in a first time, for the synthesis of 3-substituted ones. This carbamic compound was thus prepared, in four steps from 2-aminophenol (scheme 1).



1 **2** **3**

The N-Boc derivative **1** was obtained in quantitative yield by treatment of 2-aminophenol with di-*tert*-butyl dicarbonate in dry tetrahydrofuran at room temperature. The 2,3-dihydrobenzoxazine was then prepared in 80% yield by heating **1** and 1,2-dibromoethane in refluxing acetone for 20 hours or more rapidly for 3 hours using microwaves irradiation[5] in refluxing pentan-3-one. Finally, a bromation-debromation sequence previously described[6] led to the required insaturated carbamate **3** in 86 % yield.

When **3** was reacted with LDA (1,2 eq.) at low temperature (-78°C) in dry tetrahydrofuran, deprotonation occured as expected at carbon atom 3 (α-position to nitrogen). The 3-lithioderivative obtained reacted effectively on various electrophilic reagents to give, according to the nature of the latter, 3-substituted benzoxazines **4** (table 1) or **5** (table 2) in good yields[7].

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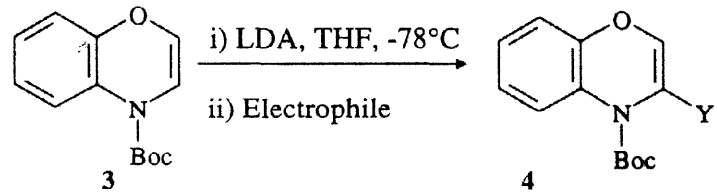
0040-4039/98/$19.00
PII: S0040-4039(98)01201-5

Table 1. Lithiation / Substitution of N-Boc benzoxazine **3**



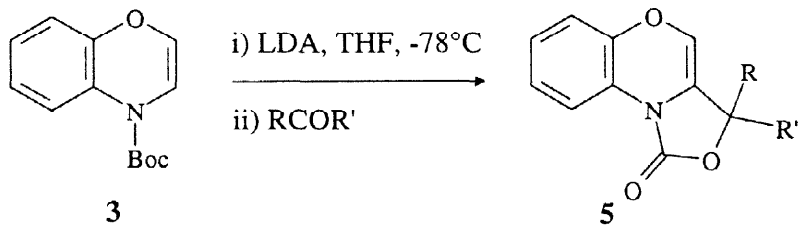
3 **4**

	Electrophile	Y	**4** Yield (%)[a]
4a	Me_3SiCl	Me_3Si	83
4b	Me_3SnCl	Me_3Sn	78
4c	I_2	I	81
4d	MeI	Me	75
4e	$ClCO_2Et$	CO_2Et	65
4f	CO_2	CO_2H	85

a/ isolated yield

Indeed, when the lithio derivative was quenched with aldehydes or ketones, the formation of intermediate alkoxide anions induced the cleavage of the carbamic moiety and the formation of compounds **5**.

Table 2 . Lithiation / Substitution of N-Boc benzoxazine **3**



3 **5**

	R	R'	**5** Yield (%)[a]
5a	Me	Me	90
5b		$-(CH_2)_5$	70
5c	Me	H	82

a/ isolated yield

In conclusion, we have developed a new, general and efficient method for the synthesis of the little known 3-substituted-4*H*-1,4-benzoxazines. The further elaboration of 2,3-disubstituted and 2,3,5-trisubstituted derivatives is currently being investigated.

References and notes

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6. Coudert, G.; Guillaumet, G.; Loubinoux, B. *Tetrahedron Lett.* **1978**, 1059-1062.
7. All compounds exhibited spectral NMR data (^1H, ^{13}C, ^{13}C-^1H correlation, COSY 90) and IR, MS data consistent with the structures.