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Synthesis of Aziridines and Azetidines from N-(ω-Haloalkyl) Imines

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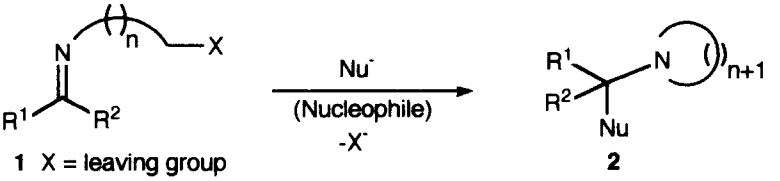
Abstract : N-(2-Haloalkyl) and N-(3-haloalkyl) imines are convenient substrates for the synthesis of aziridines and azetidines via a two-step process involving nucleophile induced addition at the imino bond followed by intramolecular nucleophilic substitution.

Imines **1**, carrying a ω-haloalkyl group as nitrogen substituent, have not been used frequently in organic synthesis because of their lability and, as a consequence, because of a lack of suitable entries.[1] However, the synthetic potential of this class of compounds, *i.e.* N-(ω-haloalkyl) imines or N-(alkylidene/arylidene)-ω-haloalkylamines, is obvious from the presence of two electrophilic centers, which allows selective elaborations, *e.g.* the synthesis of azaheterocycles **2** *via* a sequence of reactions involving nucleophilic addition and subsequent ring closure (Scheme 1). In the present article, some applications of this strategy in the direction of aziridines and azetidines are disclosed.



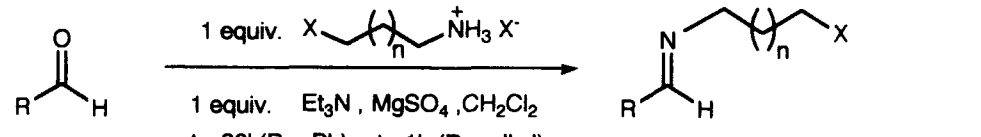
1 X = leaving group **2**

Scheme 1

N-(Alkylidene)- and N-(arylidene)-2-haloethylamines **4** (n=0) are easily accessible under mild conditions by reaction of appropriate aldehydes **3** with 2-chloroethylamine hydrochloride or 2-bromoethylamine hydrobromide in dichloromethane in the presence of triethylamine and magnesium sulfate. In similar way, the higher homologues, *i.e.* N-(alkylidene/arylidene)-3-halopropylamines **5** (n=1) were prepared from aldehydes **3** and 3-halopropylamine hydrohalides (Scheme 2).

The reaction of N-(2-ethyl-1-butylidene)-2-bromoethylamine **4c** with sodium borohydride (1 mol equiv.) in methanol afforded a mixture of 1-(2-ethylbutyl)aziridine **6** and 1,4-di(2-ethylbutyl)piperazine **7** (Scheme 3). The aziridine formation by nucleophilic addition and following intramolecular nucleophilic substitution is apparently in competition with self condensation of the intermediate β-bromoamine to afford the piperazine.[2] This reaction is concentration dependent and can be directed toward the selective formation of aziridine **6** or piperazine **7** when 2% w/v and 20% w/v starting substrate in methanol were

used respectively (Scheme 3). The flexibility of this synthetic route is an improvement as β-chloro- or β-tosyloxyethylamines only exhibit ring closure towards piperazines.[3] Aziridines **6** and piperazines **7** can



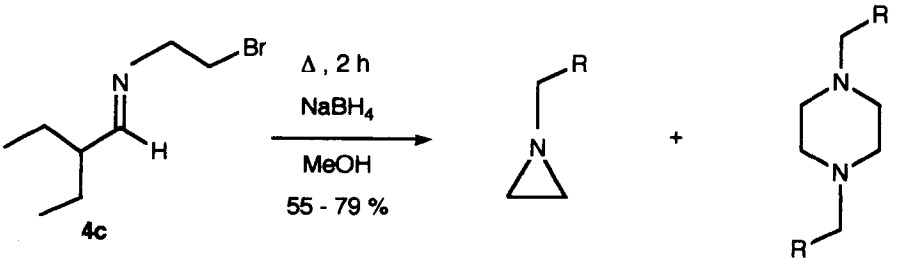
3

4a R = C_6H_5 ; X = Cl ; n = 0 (98%)
4b R = i-Pr ; X = Cl ; n = 0 (92%)
4c R = $CHEt_2$; X = Br ; n = 0 (70%)
5a R = C_6H_5 ; X = Br ; n = 1 (94%)
5b R = i-Pr ; X = Br ; n = 1 (98%)
5c R = i-Pr ; X = Cl ; n = 1 (94%)
5d R = $CHEt_2$; X = Br ; n = 1 (97%)
5e R = cHex ; X = Br ; n = 1 (98%)

Scheme 2

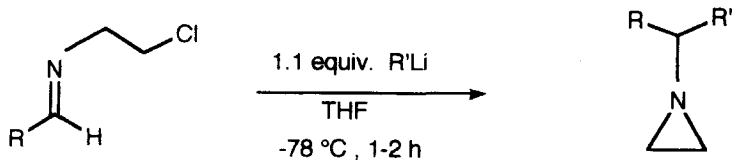
be separated by distillation, flash chromatography or preparative gas chromatography.

Unlike Grignard reagents, alkyllithium reagents readily add across the carbon-nitrogen double bond of N-(2-chloroethyl) imines **4a,b** at -78°C and give rise to 1-substituted aziridines **8-10**. Appropriate



4c

2 % w / v **6** ($R = CHEt_2$) 87 : 13 **7** ($R = CHEt_2$)
20 % w / v **6** ($R = CHEt_2$) 20 : 80 **7** ($R = CHEt_2$)



4a,b

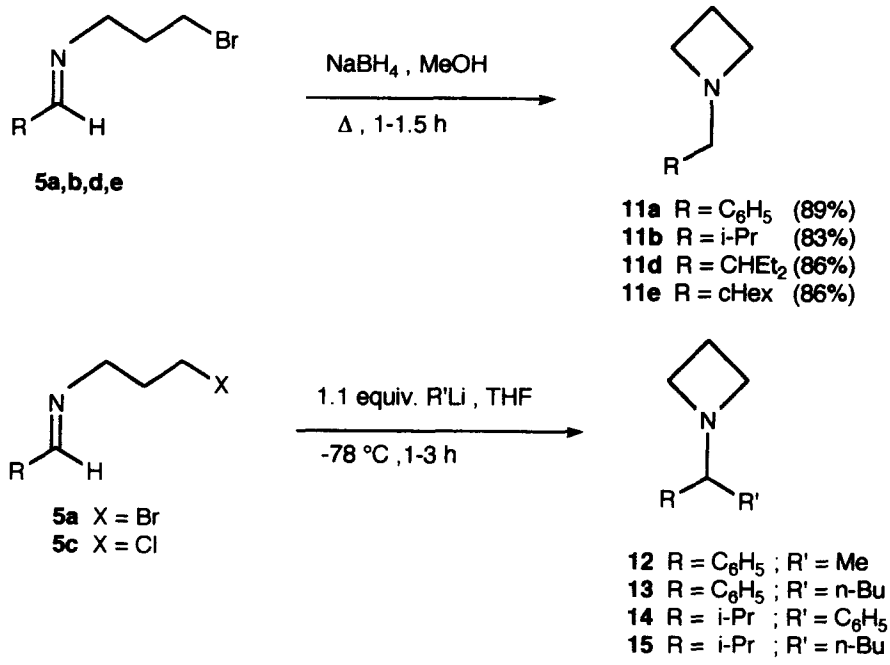
8 R = C_6H_5 ; R' = Me (58%)
9 R = C_6H_5 ; R' = n-Bu (60%)
10 R = i-Pr ; R' = n-Bu (58%)

Scheme 3

choice of the starting imine **4** and the alkyllithium reagent allow the synthesis of a whole variety of aziridines (Scheme 3) which surve as building blocks in numerous reactions.[2,4]

The reductive ring closure of N-(3-haloalkyl) imines 5 with sodium borohydride (1 mol equiv.) in methanol under reflux constitutes an excellent synthesis of 1-substituted azetidines 11 (Scheme 4). This procedure is much better, easier and more straightforward than published procedures utilizing isolated γ-bromoamines or γ-(tosyloxy)amines,[5,6] often resulting in low yields of azetidines due to competing reactions, e.g. 1,2-elimination, dimerization, fragmentation and solvolysis.[7-9] 1-Benzylazetidine **11a** has been previously prepared in 26% yield from 3-(N-benzylamino)propyl p-toluenesulfonate, and in only 5-9% via cyclization of 3-(N-benzylamino)propylsulfate.[5] These facts clearly underline the superiority of the azetidine synthesis from N-(alkylidene/arylidene)-3-bromopropylamines 5.

The addition of alkyl- and aryllithium reagents to N-(3-halopropyl) imines 5 and following ring closure in THF at -78 °C afforded 1-substituted-azetidines 12-15. Again, organomagnesium reagents did not react to give azaheterocycles. N-(Alkylidene)-3-bromopropylamines, *e.g.* **5d**, are less suitable for this azetidine synthesis because of a competitive 1,2-dehydrobromination in the side chain. The corresponding N-(alkylidene)-3-chloropropylamines *e.g.* **5c** and N-(benzylidene)-3-bromopropylamines *e.g.* **5a**, did not show this side reaction (Scheme 4).



Scheme 4

In conclusion, N-(alkylidene)- and N-(arylidene)-3-halopropylamines 5 were shown to be good sources of azetidines,[7,8] while N-(alkylidene)- and N-(arylidene)-2-haloethylamines 4 were demonstrated to be suitable starting materials for the synthesis of aziridines[2,4]. All these syntheses of small azaheterocycles concern only two-step procedures from aldehydes and constitute an improvement of known procedures.

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[1] Research Associate of the Belgian "I.W.O.N.L.".

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