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A new route towards *N*-(α-methoxybenzyl)aziridines

Matthias D'hooghe, Arn Hofkens and Norbert De Kimpe*

Department of Organic Chemistry, Faculty of Agricultural and Applied Biological Sciences, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

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Abstract—A new synthesis of *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines is presented. Different benzaldehydes were converted into the corresponding imines upon reaction with 2-bromo-2-methylpropylamine. Treatment of the latter imines with sodium methoxide afforded *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines in good yields.

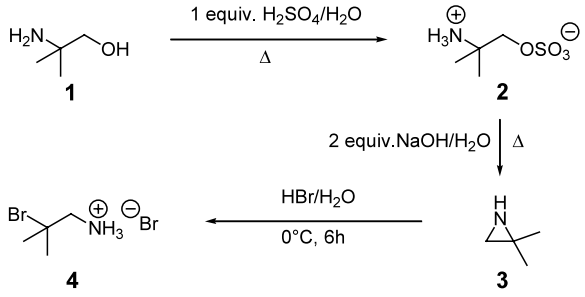
1. Introduction

Although *N*-(alkoxymethyl)aziridines are known to posses antitumor activity, as studied in mice and rats,[1] very few papers could be found concerning the synthesis of these compounds. *N*-(Ethoxymethyl)aziridine was prepared by reaction of aziridine (ethyleneimine) with ethyl halomethyl ethers in ethanol,[2a,b] while *N*-(dimethoxymethyl)aziridine was synthesized by reaction of aziridine with chloroform in the presence of sodium methoxide, the latter reaction giving rise to bis- and tris-aziridino compounds too.[2c] Since especially *N*-(α-alkoxybenzyl)aziridines seem to exhibit potential anticancer activity,[1] a new synthesis of *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines **7** is presented. Different benzaldehydes **5** were converted into the corresponding imines **6** by condensation with 2-bromo-2-methylpropylamine hydrobromide **4**, in the presence of triethylamine. Treatment of these functionalized imines with sodium methoxide afforded *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines **7** in good yields.

2. Results and discussion

The synthesis of 2-bromo-2-methylpropylamine hydrobromide **4** was performed in accordance with the literature.[3,4] 2-Amino-2-methyl-1-propanol **1** was treated with sulfuric acid, and the thus obtained ammonium sulfate **2** was further transformed into 2,2-dimethylaziridine **3**. This aziridine, which appeared to be sensitive to polymerization, was converted into 2-amino-2-methylpropylamine hydrobromide **4**, upon reaction with HBr (Scheme 1).

However, the observed regioselectivity of the ring opening of aziridine **3** was different than reported.[4] In the cited reference, 1-bromo-2-methylpropyl-2-amine hydrobromide salt was proposed as the reaction product, indicating that bromide would have attacked the less hindered carbon atom of the intermediate aziridinium salt. As known from literature data,[5–7] ring opening of aziridinium ions is nucleophile-dependent. Gmeiner and co-workers demonstrated that ring opening occurs at the more hindered position with bromide.[5,6] Based on these findings, and on the obtained spectrometric data of compound **4**, it has to be concluded that the reported structure should be corrected, as well as the articles concerning some kinetic studies of this compound.[8,9] Furthermore, some other synthetic routes towards 2-bromo-2-methylpropylamine (salts) are known.[10–13]



Scheme 1.

Keywords: aziridines; β-haloamines; aldimines.

* Corresponding author. Tel.: +00-32(9)-264-5951; fax: +00-32(9)-264-6243; e-mail: norbert.dekimpe@rug.ac.be

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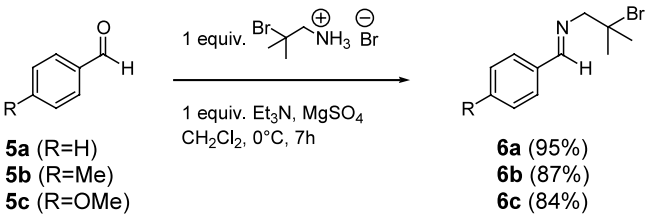


Scheme 2.

When benzaldehydes **5** were reacted with 2-bromo-2-methylpropylamine hydrobromide **4** in the presence of Et_3N and $MgSO_4$ the corresponding new imines **6** were isolated in high yields (Scheme 2). Decomposition of these thermolabile imines **6** was observed upon distillation. In the last step, imines **6** were treated with sodium methoxide in methanol, resulting in the desired *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines **7**, in good yields (Scheme 3).

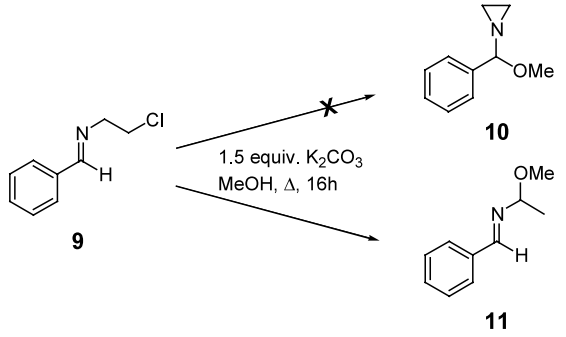
The synthesis of aziridines **7** can be rationalized considering a nucleophilic addition of methoxide across the imino bond, followed by an intramolecular nucleophilic substitution. Alternatively, compounds **6** might undergo first intramolecular substitution by the imino nitrogen after which the iminium ion is trapped by methoxide to give the final products **7**. The elimination products **8**, i.e. 2-azadienes, which by the way could not be formed when 1-bromo-2-methylpropyl-2-amine was used instead of 2-bromo-2-methylpropylamine (see correction of the literature above), were isolated in small quantities (2–3%). Purification of the title compounds was performed by a distillation process (Table 1). A similar procedure was evaluated for the synthesis of *N*-(α-methoxybenzyl)aziridine **10**, starting from *N*-(2-chloroethyl)imine **9**, but instead an elimination of HCl, followed by addition of MeOH, resulted in the formation of *N*-(benzylidene)-1-methoxyethylamine **11** (Scheme 4). Imine **9** was synthesized from benzaldehyde and 2-chloroethylamine hydrochloride in the presence of triethylamine.[14]

Spectrometric data of *N*-(α-methoxybenzyl)-2,2-dimethylaziridine **7a**: ^{1}H NMR ($CDCl_3$, 270 MHz): δ 0.90–1.50 (7H, m, 2×Me and (HCH)N), 1.64 (1H, s, (HCH)N), 3.27 (3H, s, OMe), 4.29 (1H, s, NCHO), 7.20–7.50 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$, 67 MHz): δ 18.0 (2×Me), 26.42 (CMe_2), 38.45 (CH_2N), 53.73 (OMe), 95.54 and 96.62 (NCHO), 127.49 and 128.26 (2×$C_{ortho,arom.}$ and 2×$C_{meta,arom.}$), 128.35 ($C_{para,arom.}$), 137.57 ($C_{quat.,arom.}$); IR (NaCl, cm^{-1}): ν = 1446, 1373, 1337, 1162, 1075; MS (70 eV): *m*/*z* (%): no M$^+$, 160 (6), 159 (16), 158 (10), 122 (10), 121 (100), 104 (10), 91 (14), 82 (10), 77 (16), 70 (43), 55 (11). Spectrometric data of 2-bromo-2-methylpropylamine hydrobromide **4**: ^{1}H NMR (D_2O, 60 MHz): δ 1.41 (6H, s, 2×Me), 3.61 (2H, s, CH_2); ^{13}C NMR (D_2O, 67 MHz): δ 24.85 (2×Me), 40.80 (CH_2), 55.11 (CBr).

Table 1. Synthesis of *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines **7**

Entry	Ratio **7**:**8**[a]	Compound	Bp	Yield (%)
1	94:6	**7a**	50–55°C/ 0.010 mmHg	51
2	97:3	**7b**	52–56°C/ 0.020 mmHg	85
3	95:5	**7c**	70–73°C/ 0.015 mmHg	54

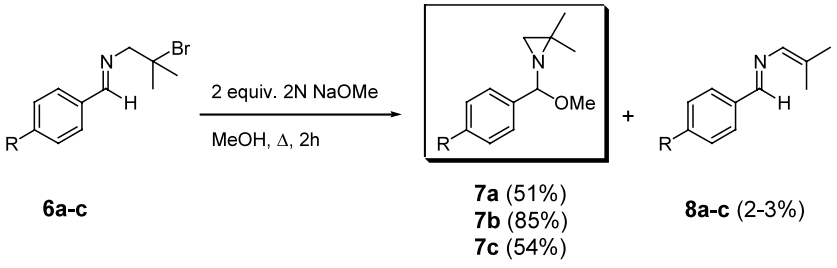
[a] The ratio was derived from the ^{1}H NMR spectrum of the reaction mixture and from GC analysis



Scheme 4.

3. Conclusions

A new and efficient procedure for the preparation of *N*-(α-methoxyarylmethyl)-2,2-dimethylaziridines, compounds with potential anticancer activity, was developed. Furthermore, it was shown that the synthesis of 2-bromo-2-methylpropylamine hydrobromide from 2,2-dimethylaziridine **3** has to be corrected in the literature.



Scheme 3.

Acknowledgements

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