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[a005]

Study of the ring opening of 2-(alkanoyloxymethyl)aziridinium salts by bromide and fluoride: change in regioselectivity[◆]

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The ring opening of aziridinium salts by halides constitutes a very powerful method towards the preparation of β-halo amines and, consequently, many synthetic efforts have been devoted to this matter.[1] Interestingly, the regioselectivity of these reactions often appears to be dependent on several factors such as the substrate, the nucleophile and the solvent.

1-Arylmethyl-2-(bromomethyl)aziridines and 1-arylmethyl-2-(aryloxymethyl)aziridines can be transformed regioselectively into *N*-(2-bromopropyl)amines upon treatment with a benzyl bromide in acetonitrile in a straightforward reaction.[2] Accordingly, 2-(alkanoyloxymethyl)aziridines **1a-d** were treated with allyl bromide or an arylmethyl bromide in CH_3CN and thus converted into the corresponding *N*-(2-bromo-3-alkanoyloxypropyl)amines **3a-f** in high yields and high purity after reflux for 6 hours (Scheme 1). Detailed spectral analysis confirmed the structural identity of these novel *N*-(2-bromo-3-alkanoyloxypropyl)amines **3**, excluding the formation of the corresponding regioisomers. Obviously, the intermediate aziridinium salts **2** are opened exclusively at the more hindered aziridine carbon atom by bromide in CH_3CN towards β-bromo amines **3**. This can be explained considering the weakening of the C_2-N bond upon attack by bromide, resulting in a stable transition state,[2c] followed by ring opening towards β-bromo amines **3**.

Subsequently, the latter β-bromo amines **3a-f** were treated with 1-2 equivalents of tetrabutylammonium fluoride (TBAF-$3H_2O$) in acetonitrile, affording a mixture of β-fluoro amines **4** as the major constituents (72-90%) and β-fluoro amines **5** as the minor compounds

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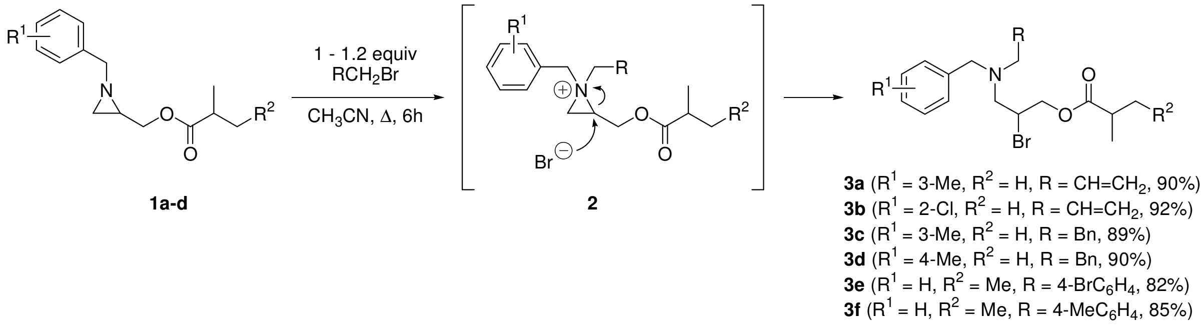
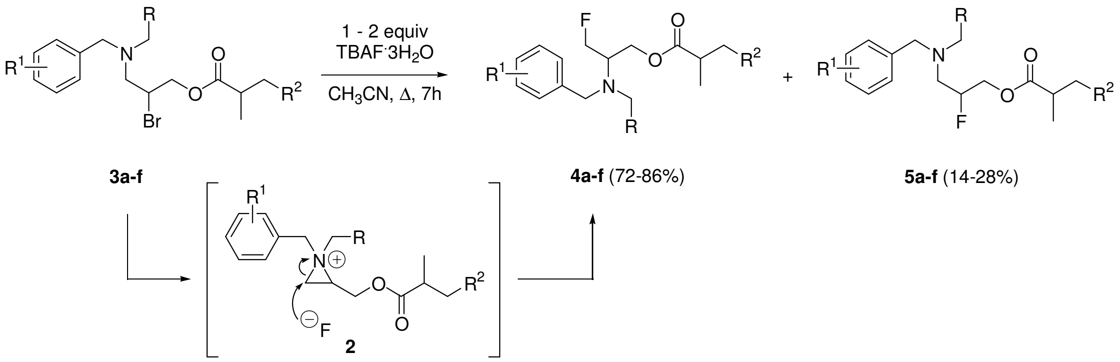
(10-28%) after reflux for 7 hours (Scheme 2). The presence of the major regioisomers **4**, in which the amino moiety has moved from the terminus of the propane skeleton towards the central carbon atom, can only be rationalized considering the formation of an intermediate aziridinium ion **2** upon heating (Scheme 2), which is then attacked by fluoride at the less hindered carbon atom of the aziridine ring. The formation of the minor isomers **5** can be the result of the attack of fluoride at the more hindered carbon atom of the aziridinium ion **2** or, alternatively, the result of an S_N2 substitution reaction at the bromomethine moiety in bromo amines **3**, although the latter is unlikely.



3a (R^1 = 3-Me, R^2 = H, R = $CH=CH_2$, 90%)
3b (R^1 = 2-Cl, R^2 = H, R = $CH=CH_2$, 92%)
3c (R^1 = 3-Me, R^2 = H, R = Bn, 89%)
3d (R^1 = 4-Me, R^2 = H, R = Bn, 90%)
3e (R^1 = H, R^2 = Me, R = 4-BrC_6H_4, 82%)
3f (R^1 = H, R^2 = Me, R = 4-MeC_6H_4, 85%)

Scheme 1



Scheme 2

In this project, the same aziridinium salts **2** have been studied as intermediates in ring opening reactions with halides (Scheme 1 and 2), and surprisingly a different regioselectivity upon ring opening by bromide and fluoride has been observed. Apparently, these aziridinium salts are opened exclusively at the more hindered aziridine carbon atom by bromide and mainly at the less hindered aziridine carbon atom by fluoride, both in acetonitrile. The difference in polarizability between bromide and fluoride can account for this behavior, since the high polarizability of bromide enables the formation of a favorable transition state, stabilized by acetonitrile, upon attack at the substituted aziridine carbon atom, whereas the low polarizability of fluoride impede such a stabilizing interaction, hence the preferential attack at the unsubstituted carbon atom of the intermediate aziridinium salt. The favorable transition state upon attack of bromide has been acknowledged previously by means of high level *ab initio* calculations for an analogous substrate.[2c] The peculiar behaviour of ring opening reactions of aziridinium salts by fluoride has also been noted before by others, although in these cases ring opening of *N*-H or *N*-activated aziridines by fluoride (upon treatment with HF or Olah's reagent) usually occurred at the more hindered aziridine carbon atom instead of at the less hindered carbon atom.[3]

Experimental part

As a representative example, the synthesis of 3-[allyl-(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate **3a** is described. To a solution of 1-(3-methylbenzyl)aziridin-2-ylmethyl 2-methylpropanoate **1a** (2.47 g, 10 mmol) in acetonitrile (50 mL) was added allyl bromide (1.45 g, 1.2 equiv) under stirring, and the resulting mixture was heated for 6 hours under reflux. Evaporation of the solvent afforded 3-[allyl-(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate **3a**, which was purified by means of column chromatography (hexane/ethyl acetate 49/1) on silica gel in order to obtain an analytically pure sample. 3-[Allyl-(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate **3a**. Colorless liquid. Yield 90%. $R_f = 0.04$ (Hexane/Ethyl acetate 49/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (6H, d, J=7.2 Hz, $(CH_3)_2CH$); 2.34 (3H, s, CH_3Ar); 2.54 (1H, sept, J=7.0 Hz, $(CH_3)_2)CH$); 2.84 en 2.93 (2H, 2×d×d, J=13.7, 8.8, 5.9 Hz, N(*HCH*)CHBr); 3.06 en 3.17 (2H, 2×d×d, J=14.0, 6.9, 6.1 Hz, N(*HCH*)$CH=CH_2$); 3.53 en 3.67 (2H, 2×d, J=13.5 Hz, N(HCH)Ar); 4.07-4.16 (1H, m, CHBr); 4.27 en 4.50 (2H, 2×d×d, J=11.9, 6.3, 3.7 Hz, (HCH)O); 5.15-5.22 (2H, m, $CH=CH_2$); 5.79-5.92 (1H, m, $CH=CH_2$); 7.05-7.26 (4H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.87 and 18.96 ($((CH_3)_2)CH$); 21.41 (CH_3Ar); 33.94 ($(CH_3)_2CH$); 48.77 (CHBr); 57.50, 57.67 and 59.12 ($3\times CH_2N$); 65.70 (CH_2O); 118.07 ($CH=CH_2$); 125.93, 127.95, 128.25 and 129.61 (HC_{arom}); 135.23 ($CH=CH_2$); 137.90 and 138.70 ($2\times C_{arom,quat}$); 176.48 (CO). IR (NaCl): $\nu_{C=O} = 1736$ cm^{-1}. MS (70 eV): m/z (%): 368/70 (M^++1, 23); 288 (M^+-Br, 100). Anal. Calcd for $C_{18}H_{26}BrNO_2$: C 58.70, H 7.12, N 3.80. Found: C 58.91, H 7.31, N 3.66.

As a representative example, the synthesis of 2-[allyl-(3-methylbenzyl)amino]-3-fluoropropyl 2-methylpropanoate **4a** and 3-[allyl-(3-methylbenzyl)amino]-2-fluoropropyl 2-methylpropanoate **5a** is described. To a solution of 3-[allyl-(3-methylbenzyl)amino]-2-bromopropyl 2-methylpropanoate **3a** (3.68 g, 10 mmol) in acetonitrile (50 mL) was added TBAF-$3H_2O$ (4.73 g, 1.5 equiv) under stirring and the resulting mixture was heated for 7 hours under reflux. Extraction with water (40 mL) and Et_2O (3×30 mL), Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 2-[allyl-(3-methylbenzyl)amino]-3-fluoropropyl 2-methylpropanoate **4a** (72%) and 3-[allyl-(3-methylbenzyl)amino]-2-fluoropropyl 2-methylpropanoate **5a** (28%). Both isomers were separated by means of column chromatography (hexane/ethyl acetate 34/1) in order to obtain analytically pure samples. 2-[Allyl-(3-methylbenzyl)amino]-3-fluoropropyl 2-methylpropanoate **4a.** Colorless liquid. $R_f = 0.16$ (Hexane/Ethyl acetate 34/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 and 1.19 (6H, 2×d, J=6.9 Hz, $(C\mathit{H}_3)_2CH$); 2.34 (3H, s, CH_3Ar); 2.57 (1H, sept, J=7.0 Hz, $(CH_3)_2)C\mathit{H}$); 3.20-3.35 (3H, m, CHN and $NC\mathit{H}_2CH=CH_2$); 3.73 en 3.76 (2H, 2×d, J=14.3 Hz, N(HCH)Ar); 4.20 (1H, d×d, J=11.4, 6.5 Hz, $(\mathit{H}CH)O$); 4.30 (1H, d×d×d, J=11.4, 6.5, 1.2 Hz, $(HC\mathit{H})O$); 4.50 and 4.66 (2H, d×d, J=47.5, 5.1 Hz, CH_2F); 5.09-5.24 (2H, m, $CH=C\mathit{H}_2$); 5.73-5.86 (1H, m, $C\mathit{H}=CH_2$); 7.04-7.32 (4H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.06 ($(\mathit{C}H_3)_2)CH$); 21.52 (CH_3Ar); 34.12 ($(CH_3)_2\mathit{C}H$); 54.06 and 54.81 ($2×CH_2N$); 56.85 (d, J=18.5 Hz, CHN); 61.55 (d, J=5.8 Hz, CH_2O); 82.34 (d, J=171.9 Hz, CH_2F); 117.28 ($CH=\mathit{C}H_2$); 125.57, 127.82, 128.26 and 129.22 (HC_{arom}); 136.84 ($\mathit{C}H=CH_2$); 137.94 and 139.87 ($2×C_{arom,quat}$); 176.92 (CO). ^{19}F (CCl_3F): δ –227.42 (t×d, J=46.0, 22.4 Hz, CH_2F). IR (NaCl): $\nu_{C=O} = 1738\ cm^{-1}$. MS (70 eV): m/z (%): 307 (M^+, 1); 274 (M^+-CH_2F, 5); 206 (45); 174 (40); 105 (100). Anal. Calcd for $C_{18}H_{26}FNO_2$: C 70.33, H 8.53, N 4.56. Found: C 70.50, H 8.70, N 4.41. 3-[Allyl-(3-methylbenzyl)amino]-2-fluoropropyl 2-methylpropanoate **5a.** Colorless liquid. $R_f = 0.09$ (Hexane/Ethyl acetate 34/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.16 (6H, d, J=7.2 Hz, $(C\mathit{H}_3)_2CH$); 2.34 (3H, s, CH_3Ar); 2.55 (1H, sept, J=7.0 Hz, $(CH_3)_2)C\mathit{H}$); 2.74 (2H, d×d, J=19.8, 5.5 Hz, $NC\mathit{H}_2CHF$); 3.15 (2H, d, J=6.3 Hz, $NC\mathit{H}_2CH=CH_2$); 3.62 (2H, s, NCH_2Ar); 4.11-4.34 (2H, m, CH_2O); 4.76 (1H, d×d×d×d, J=48.8, 11.7, 5.8, 3.0 Hz, CHF); 5.14-5.23 (2H, m, $CH=C\mathit{H}_2$); 5.85-5.93 (1H, m, $C\mathit{H}=CH_2$); 7.04-7.25 (4H, m, CH_{arom}). ^{13}C NMR (68 MHz, $CDCl_3$): δ 18.92 ($(\mathit{C}H_3)_2)CH$); 21.42 (CH_3Ar); 33.88 ($(CH_3)_2\mathit{C}H$); 53.39 (d, J=23.1 Hz, $N\mathit{C}H_2CHF$); 57.82 ($N\mathit{C}H_2CH=CH_2$); 59.13 (NCH_2Ar); 64.42 (d, J=21.9 Hz, CH_2O); 90.33 (d, J=173.1 Hz, CHF); 117.96 ($CH=\mathit{C}H_2$); 125.95, 127.89, 128.22 and 129.61 (HC_{arom}); 135.43 ($\mathit{C}H=CH_2$); 137.90 and 138.83

($2\times C_{arom,quat}$); 176.80 (CO). ^{19}F (CCl_3F): δ (–189.50)-(–189.34) (m, CHF). IR (NaCl): $\nu_{C=O}$ = 1736 cm^{-1}. MS (70 eV): m/z (%): 307 (M^+, 3); 174 (99); 105 (100). Anal. Calcd for $C_{18}H_{26}FNO_2$: C 70.33, H 8.53, N 4.56. Found: C 70.54, H 8.72, N 4.32.

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