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Ring opening of 2-(cyanomethyl)aziridines by acid chlorides: synthesis of novel 4-amino-2-butenenitrile derivatives through intermediate aziridinium salts

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Abstract—1-Arylmethyl-2-(cyanomethyl)aziridines were transformed into novel *N*-arylmethyl-*N*-(2-chloro-3-cyanopropyl)amides as the major reaction products upon treatment with acid chlorides in CH_2Cl_2 through the ring opening of intermediate aziridinium salts. Subsequently, *N*-arylmethyl-*N*-(2-chloro-3-cyanopropyl)amides were converted into stable *N*-arylmethyl-*N*-(3-cyano-2-propenyl)amides for the first time by means of a dehydrochlorination mediated by Et_3N in CH_2Cl_2.

The aziridine moiety represents a valuable three-membered ring system in organic chemistry, ideally suited as a building block towards a large variety of ring opened or ring expanded amines.[1] The ring opening of activated aziridines (bearing an electron-withdrawing group at nitrogen) has been studied in detail due to the high reactivity of these constrained azaheterocycles with regard to many types of nucleophiles.[2] On the other hand, the chemistry of non-activated aziridines has been evaluated to a much lesser extent, despite of the often complementary reactivity with respect to their activated counterparts. Although the ring opening of activated 2-substituted aziridines almost exclusively takes place at the unsubstituted aziridine carbon atom (except in the case of 2-aryl substitution), the regioselectivity of the ring opening of non-activated 2-substituted aziridines through intermediate aziridinium salts appears to be highly dependent on the substrate, the nucleophile and the solvent.[3] Consequently, many research efforts are devoted to this matter.

A few reports are available on the regioselective ring opening of 2-substituted aziridinium salts (different from 2-phenyl substitution) at the more hindered aziridine carbon atom.[4] This unique feature offers a useful tool in targeted organic synthesis and is considered as a important synthetic advantage of non-activated 2-substituted aziridines with regard to their activated counterparts. Recently, non-activated 2-acyl substituted aziridines have been ring opened at the substituted position upon reaction with acid chlorides.[5] In the latter report, it was erroneously stated that only 2-allyl-, 2-benzyl- and 2-acylaziridinium salts, derived from the corresponding non-activated aziridines, are known to undergo regioselective cleavage at the more hindered aziridine carbon atom. However, a large variety of 1-arylmethyl substituted 2-(bromomethyl)-, 2-(aryloxymethyl)- and 2-(alkanoyloxymethyl)aziridines have been transformed regioselectively into the corresponding *N*-(2-bromopropyl)amines upon treatment with arylmethyl bromides in acetonitrile,[6] in which the arylmethyl bromide acts both as the activator of the aziridine ring towards an aziridinium intermediate and as the provider of the nucleophile (bromide), which opens up the ring at the substituted position. In continuation of our efforts in this field, and stimulated by the recently published work on 2-acyl substituted aziridines,[5] the reactivity of a totally different type of 2-substituted aziridines, that is, 1-arylmethyl-2-(cyanomethyl)aziridines, towards acid chlorides is disclosed in the present Letter. This approach afforded a convenient route towards 4-amino-2-butenenitrile derivatives as the major reaction products, which can be considered as interesting structural

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analogues of the neurotransmitter γ-aminobutyric acid (GABA).

1-Arylmethyl-2-(cyanomethyl)aziridines **1** can be prepared in a very efficient way by the treatment of 1-arylmethyl-2-(bromomethyl)aziridines,[7] a peculiar yet promising class of β-halo amines, with 1 equiv of potassium cyanide in DMSO and heating at 60–70 °C for 3 h.[8] The combination of an aziridine moiety and a cyano group in these unexplored compounds enables the preparation of a variety of functionalized amino nitriles through the ring opening reactions of the constrained ring. Treatment of aziridines **1** with 1.05 equiv of an acid chloride (acetyl chloride or methoxyacetyl chloride) in dichloromethane under nitrogen atmosphere resulted in a mixture of β-chloro amine derivatives **3** as the major constituents (65–82%) and regioisomers **4** as the minor products (18–35%) (Scheme 1, Table 1).[9] The acid chloride reacts readily with the basic nitrogen lone pair of aziridines **1** affording highly electrophilic aziridinium intermediates **2**, which are prone to ring opening by the in situ liberated chloride anion. A distinct preferential attack of chloride at the more hindered aziridine carbon atom is observed, affording mainly *N*-(2-chloro-3-cyanopropyl)amides **3** as a new (although rather instable) class of compounds in good yields. The formation of minor regioisomers **4** is the result of the ring opening of aziridinium salts **2** at the less hindered position, and their presence in the reaction mixtures was acknowledged based on a detailed spectroscopic analysis. When acetonitrile was used as the solvent instead of dichloromethane, a similar isomeric ratio of compounds **3**/**4** was obtained. Attempts to separate β-chloroamides **3** and **4** by means of column chromatography failed due to the instability and high sensitivity towards hydrolysis of these compounds, resulting in complex mixtures.

The ring opening of aziridinium salts by halides constitutes a very powerful method for the preparation of synthetically interesting β-halo amines and, consequently, many synthetic efforts have been reported in this field.[3,10]

The presence of a β-chloro nitrile moiety in amides **3** facilitated a dehydrochlorination reaction towards the corresponding α,β-unsaturated nitrile derivatives. In this way, novel 4-amino-2-butenenitrile derivatives **5** were prepared as mixtures of *E*/*Z*-isomers by a simple basic treatment of 3-chlorobutanenitriles **3** with 1.5 equiv of Et_3N in CH_2Cl_2 for 21 h at room temperature (Scheme 2, Table 2).[11] The stable butenenitriles **5** could be purified easily from the reaction mixtures by means of column chromatography on silica gel, affording pure samples for analytical purposes, although the *E*/*Z*-isomers could not be separated from each other.

Table 1. Synthesis of *N*-arylmethyl-*N*-(2-chloro-3-cyanopropyl)amides **3** from 1-arylmethyl-2-(cyanomethyl)aziridines **1**

Entry	Starting aziridine	R^1	R^2	**3**/**4**[a] (Ratio)	Isolated yield (%)
1	**1a**	H	Me	**3a**/**4a** (68/32)	95
2	**1b**	4-Cl	Me	**3b**/**4b** (70/30)	98
3	**1b**	4-Cl	CH_2OMe	**3c**/**4c** (65/35)	100
4	**1c**	4-Me	CH_2OMe	**3d**/**4d** (70/30)	86
5	**1d**	4-OMe	Me	**3e**/**4e** (82/18)	100
6	**1d**	4-OMe	CH_2OMe	**3f**/**4f** (75/25)	93
7	**1e**	3-OMe	Me	**3g**/**4g** (68/32)	97
8	**1e**	3-OMe	CH_2OMe	**3h**/**4h** (80/20)	100

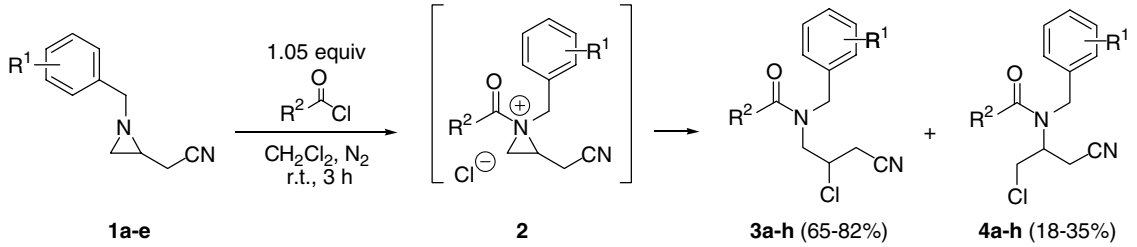
[a] Determined by means of ^1H NMR.

The minor constituents **4**, present in the reaction mixtures obtained from the treatment of 2-(cyanomethyl)aziridines **1** with an acid chloride, did not undergo an elimination reaction, but instead hydrolysis of an in situ formed intermediate 4,5-dihydrooxazolinium salt **7** took place during an aqueous workup, affording 4-(alkanoyloxy)butanenitriles **6** (Scheme 2). The latter compounds were isolated by column chromatography allowing full spectroscopic characterization.

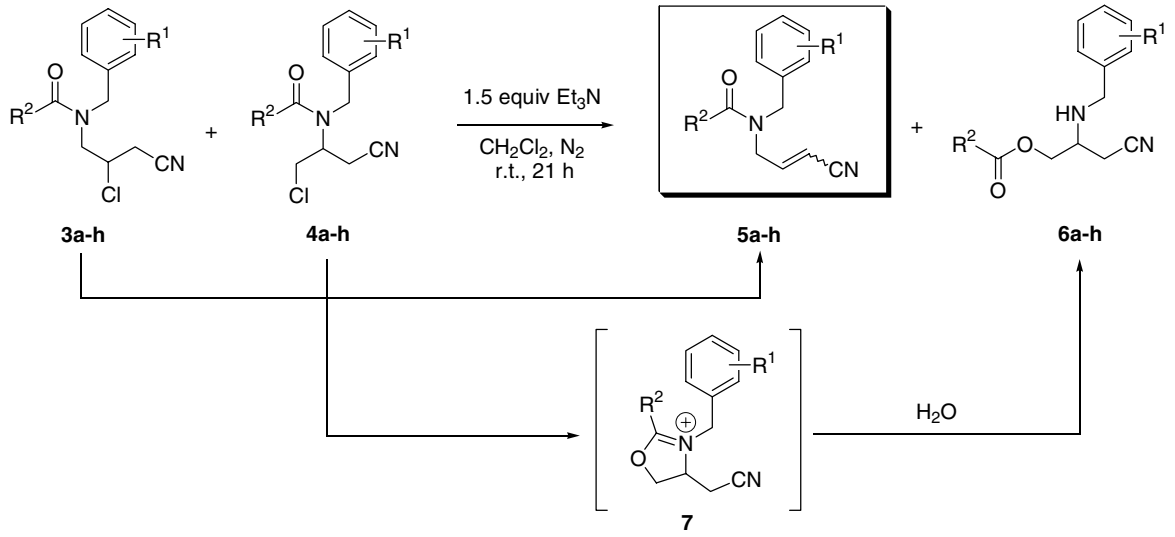
The reaction mixtures contained a third unidentified side product in small quantities (<10%), which could not be isolated by means of column chromatography. Probably, it concerns an isomeric form of 2-butenenitriles **5** in which the double bond has migrated towards the 3-position (based on ^1H NMR).

The reaction of 2-(cyanomethyl)aziridines **1** with benzoyl chloride, however, resulted in rather complex reaction mixtures in which the desired β-chloro amines were present based on ^1H NMR. Treatment of these reaction mixtures with Et_3N afforded the corresponding butenenitrile derivatives, although the complexity of the mixtures thus obtained did not allow isolation by means of column chromatography.

The search for new pathways towards amino nitriles as precursors of the corresponding amino acids is an important challenge in organic synthesis, and to date many efforts are devoted to the development of new entries towards a variety of amino nitrile derivatives.[12] The general interest in structural (in casu unsaturated) analogues of the neurotransmitter γ-aminobutyric acid (GABA), as well as the manifold efforts reported in



Scheme 1.



Scheme 2.

Table 2. Synthesis of *N*-arylmethyl-*N*-(3-cyano-2-propenyl)amides **5** from *N*-arylmethyl-*N*-(2-chloro-3-cyanopropyl)amides **3**

Entry	R^1	R^2	Product **5** (Yield[a], *E*/*Z*[b])	**5**/**6**[b] (Ratio)
1	H	Me	**5a** (44%, 70/30)	**5a/6a** (81/19)
2	4-Cl	Me	**5b** (39%, 70/30)	**5b/6b** (73/27)
3	4-Cl	CH_2OMe	**5c** (32%, 65/35)	**5c/6c** (80/20)
4	4-Me	CH_2OMe	**5d** (24%, 70/30)	**5d/6d** (84/16)
5	4-OMe	Me	**5e** (36%, 73/27)	**5e/6e** (75/25)
6	4-OMe	CH_2OMe	**5f** (35%, 65/35)	**5f/6f** (79/21)
7	3-OMe	Me	**5g** (47%, 75/25)	**5g/6g** (65/35)
8	3-OMe	CH_2OMe	**5h** (38%, 70/30)	**5h/6h** (75/25)

[a] After column chromatography.
[b] Determined by means of ^1H NMR.

the literature for the production of L-carnitine from crotonobetaine illustrate the relevance of 4-amino-2-butenenitrile derivatives **5** in organic chemistry.[13]

In conclusion, the reactivity of 2-(cyanomethyl)aziridines towards acid chlorides has been evaluated for the first time, pointing to a useful transformation of the former into new *N*-arylmethyl-*N*-(2-chloro-3-cyanopropyl)amides through the ring opening of intermediate aziridinium salts with a preferential attack of chloride at the more hindered aziridine carbon atom. These findings broaden the present knowledge on 2-substituted aziridinium salts and their applicability in organic synthesis. *N*-Arylmethyl-*N*-(2-chloro-3-cyanopropyl)amides were subsequently converted into novel *N*-arylmethyl-*N*-(3-cyano-2-propenyl)amides by means of a dehydrochlorination reaction mediated by Et_3N in CH_2Cl_2.

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9. As a representative example, the synthesis of *N*-benzyl-*N*-(2-chloro-3-cyanopropyl)acetamide **3a** is described here. To an ice-cooled solution of 1-benzyl-2-(cyanomethyl)aziridine **1a** (0.68 g, 4 mmol) in dichloromethane (10 mL) was added a solution of acetyl chloride (0.33 g, 1.05 equiv) in dichloromethane (4 mL) under nitrogen atmosphere via a syringe, and the resulting solution was stirred for 3 h at room temperature. Evaporation of the solvent afforded a mixture of *N*-benzyl-*N*-(2-chloro-3-cyanopropyl)acetamide **3a** and regioisomer **4a** in a 68/32 ratio. Acetamide **3a**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (3H, s, CH_3); 2.82 and 2.90 (2H, 2 × d × d, J = 17.3, 6.5, 5.0 Hz, (HCH)CN); 3.43 and 3.91 (2H, 2 × d × d, J = 14.1, 7.4, 5.6 Hz, N(*HCH*)CH); 4.43–4.51 (1H, m, CHCl); 4.67 and 4.75 (2H, 2 × d, J = 17.2 Hz, N(HCH)Ar); 7.14–7.41 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.78 (CH_3); 25.54 (*C*H_2CN); 52.13, 53.33 and 54.07 (2 × CH_2N and CHCl); 116.25 (CN); 126.34, 128.06 and 129.23 (HC_{arom}); 136.05 ($C_{arom,quat}$); 172.40 (C=O). IR (NaCl, cm^{-1}): ν_{CN} = 2252, $\nu_{C=O}$ = 1646. MS (70 eV): *m*/*z* (%): 251/3 (M^++1, 40).

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11. As a representative example, the synthesis of *N*-benzyl-*N*-(3-cyano-2-propenyl)acetamide **5a** is described here. To a mixture of *N*-benzyl-*N*-(2-chloro-3-cyanopropyl)acetamide **3a** and regioisomer **4a** (0.75 g) in dichloromethane (10 mL) was added a solution of triethylamine (0.30 g, 1.5 equiv) in dichloromethane (2 mL) under nitrogen atmosphere via a syringe, and the resulting solution was stirred for 21 h at room temperature. The reaction mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (3 × 15 mL). Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded *N*-benzyl-*N*-(3-cyano-2-propenyl)acetamide **5a** as a mixture of *E*/*Z*-isomers (*E*/*Z* 70/30), which were purified by means of column chromatography on silica gel. Acetamide **5a**. Yield 44%. R_f = 0.19 (Hexane/EtOAc 9/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 and 2.21 (6H, 2 × s, 2 × CH_3); 4.17 (2H, d × d, J_Z = 6.5, 1.5 Hz, NC*H*$_2$CH=CH); 4.27 (2H, d × d, J_E = 6.1, 1.4 Hz, NC*H*$_2$CH=CH); 4.56 and 4.61 (4H, 2 × s, 2 × $NCH_2C_{arom,quat}$); 5.39 (1H, d × t, J_E = 11.1, 1.7 Hz, CH=C*H*CN); 5.46 (1H, d × t, J_Z = 11.0, 1.7 Hz, CH=C*H*CN); 6.27 (1H, d × t, J_Z = 11.0, 6.5 Hz, CH_2C*H*=CH); 6.46 (1H, d × t, J_E = 11.1, 6.1 Hz, CH_2C*H*=CH); 7.15–7.41 (10H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref = $CDCl_3$): δ 21.51 and 21.80 (2 × CH_3); 46.50 and 48.35 (2 × N*C*H$_2$CH=CH); 49.31 and 52.93 (2 × N*C*H$_2$C$_6$H$_5$); 100.73 and 102.03 (2 × CH=*C*HCN); 114.75 and 115.34 (2 × CN); 126.72, 128.14, 128.52, 128.90, 129.18 (HC_{arom}); 135.99 and 136.83 (2 × C_{quat}); 148.95 and 149.57 (2 × *C*H=CHCN); 170.52 and 171.41 (2 × C=O). IR (NaCl, cm^{-1}): ν_{CN} = 2220, $\nu_{C=O}$ = 1649. MS (70 eV): *m*/*z* (%): 215 (M^++1,100).

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