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# Synthesis of 1-Arylmethyl-2-(2-cyanoethyl)aziridines and Their Rearrangement into Novel 2-(Aminomethyl)cyclopropanecarbonitriles

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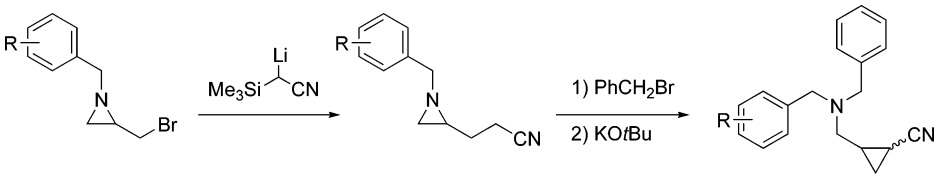


1-Arylmethyl-2-(bromomethyl)aziridines were transformed into novel 2-(2-cyanoethyl)aziridines upon treatment with α-lithiated trimethylsilylacetonitrile in THF in an efficient and straightforward approach. The latter aziridines underwent ring opening by reaction with benzyl bromide in acetonitrile, affording 5-amino-4-bromopentanenitriles through a regiospecific ring opening of intermediate aziridinium salts by bromide. Further elaboration of these γ-bromonitriles resulted in the synthesis of novel 2-[*N*,*N*-bis-(arylmethyl)aminomethyl]cyclopropanecarbonitriles in high yields by means of a 1,3-cyclization protocol upon treatment with KO*t*Bu in THF.

## Introduction

In recent years, many efforts have been devoted to the development of new methods for the biocatalytic conversion of aminonitriles into the corresponding amino acids.[1] Consequently, the search for novel types of functionalized aminonitrile derivatives has gained much interest and has become an important challenge in organic synthesis.[2] Furthermore, conformationally constrained amino acids have attracted special attention because of their potential usefulness in medicinal chemistry,[3] although synthetic approaches toward these compounds or their precursors are rather scarce. In continuation of our interest in the preparation of 2-aminocyclopropanecarboxylates (β-ACC's)[4] and 2-aminocyclopropanecarbonitriles,[5] the synthesis of 2-(aminomethyl)cyclopropanecarbonitriles was envisaged as constrained analogues of the neurotransmitter γ-aminobutyric acid (GABA). 2-(Aminomethyl)cyclopropanecarboxylates **1** are considered to be valuable compounds in medicinal chemistry with a broad applicability, ranging from $GABA_C$ (ant)agonists[6] to a potential use in the treatment of diabetes II,[7] cancer,[8] and hepatitis C.[9] Also in peptide chemistry, interesting applications of analogous compounds have been reported, such as the recent discovery of a parallel sheet structure

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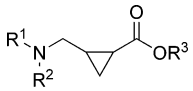
in cyclopropane γ-peptides.[10] Despite their biological relevance, very few synthetic approaches toward 2-(aminomethyl)cyclopropanecarboxylic acid derivatives are available in the literature. These methods comprise the cyclopropanation of allylic amines by means of diazoacetates,[11] the reaction of allylsulfonamides with phenyl(alkynyl)iodonium salts,[12] and the ring opening of 3-azabicyclo[3.1.0]hexan-2-one derivatives.[13]



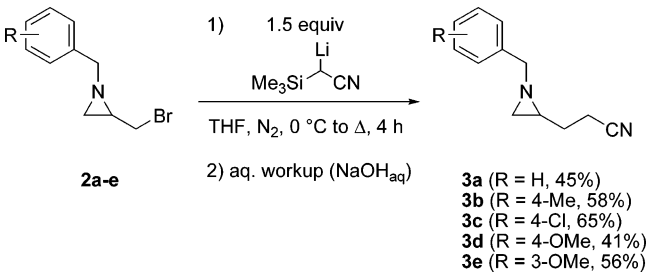
**1**

In the present report, the synthesis of 2-(2-cyanoethyl)-aziridines is disclosed as a new and versatile class of building blocks in organic chemistry. Whereas the chemistry of 2-(cyanomethyl)aziridines has been studied previously for the preparation of different types of aminonitriles,[5,14] the synthesis and reactivity of their higher homologues 2-(2-cyanoethyl)aziridines comprises an unexplored field of research, as only one similar compound has been reported so far, i.e., 1-butyl-2-(2-cyanoethyl)aziridine-2-carbonitrile obtained via cycloaddition of butyl azide with the appropriate olefin.[15] In this paper, 1-arylmethyl-2-(2-cyanoethyl)aziridines were subsequently transformed into novel 2-[*N*,*N*-bis(arylmethyl)aminomethyl]cyclopropanecarbonitriles in an efficient and straightforward approach by means of an intramolecular 1,3-cyclization protocol of intermediate 5-amino-4-bromopentanenitriles, obtained through ring opening with benzyl bromide. This is the first report of the use of γ-halo-δ-aminopentanenitriles as substrates for a 3-*exo*-*tet* cyclization toward 2-(aminomethyl)cyclopropanecarbonitriles.

## Results and Discussion

1-Arylmethyl-2-(bromomethyl)aziridines **2**, prepared from the corresponding benzaldehydes in a three-step procedure,[16] are suitable synthetic equivalents for the aziridinylmethyl cation, providing an easy access to 2-substituted 1-(arylmethyl)aziridines upon treatment with carbon-centered as well as heteroatom-centered nucleophiles.[17] Further elaboration of this approach resulted in the synthesis of 1-arylmethyl-2-(2-cyanoethyl)aziridines **3** as a novel class of compounds upon treatment of 2-(bromomethyl)aziridines **2** with 1.5 equiv of α-lithiated trimethylsilylacetonitrile (prepared by treatment of trimethylsilylacetonitrile with an equimolar amount of *n*-BuLi in THF at 0 °C) in THF after reflux for 4 h (Scheme 1). Only by utilizing 1.5 equiv of α-lithiated trimethylsilylacetonitrile and heating under reflux for 4 h could the reaction be driven to completion. If fewer equivalents were used or shorter reaction times were applied, the reaction mixture contained a certain amount of starting material. The trimethylsilyl group was cleaved off from the initially formed silylated aziridine intermediate during workup by means of an aqueous NaOH solution (1 N). 1-Arylmethyl-2-(2-cyanoethyl)aziridines **3** were obtained in high purity by means of column chromatography on silica gel. The reactive nature of the constrained aziridine ring in 2-(2-cyanoethyl)aziridines **3** enables the preparation of a variety of new aminonitrile derivatives, complementary to the synthetic usefulness of 1-arylmethyl-2-(cyanomethyl)aziridines.

**SCHEME 1**




It should be noted that the use of methyl or ethyl trimethylsilyl acetate instead of trimethylsilylacetonitrile, applying either exactly the same reaction conditions or slightly modified conditions according to a literature procedure,[18] did not result in any reaction, and the starting material was recovered completely each time. In the literature, only very few isolated examples of 2-(2-alkoxycarbonylethyl)aziridines have been reported, and no general approach is available toward these azaheterocycles.[19]

Treatment of 2-(2-cyanoethyl)aziridines **3** with 1 equiv of benzyl bromide in acetonitrile afforded novel 5-amino-4-bromopentanenenitriles **5** in excellent yields after reflux for 5 h (Scheme 2). These δ-aminonitriles were purified by means of column chromatography on silica gel (hexane/EtOAc 9/1) in order to obtain analytically pure samples. In this transformation, benzyl bromide is responsible for both the activation of the aziridine ring toward an aziridinium intermediate **4** and the delivery of the nucleophilic bromide anion which induces ring opening of the aziridinium ion.

In accordance with the previously observed reactivity of 2-(bromomethyl)-, 2-(aryloxymethyl)-, 2-(alkanoyloxymethyl)-, and 2-(cyanomethyl)aziridines toward arylmethyl bromides in acetonitrile,[14b,20] a regiospecific ring opening of the intermediate 2-(2-cyanoethyl)aziridinium salts **4** by bromide occurred at the

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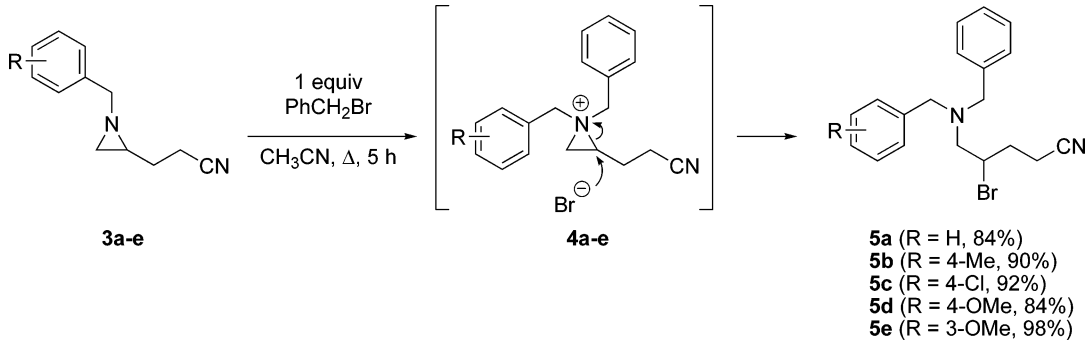
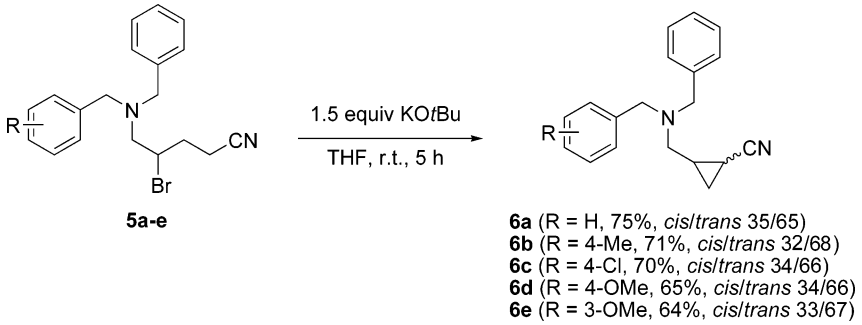
**SCHEME 2**




**SCHEME 3**




more hindered aziridine carbon atom, affording $\beta$-bromoamines **5** as the sole reaction products in high purity. Detailed spectral analysis confirmed the structural identity of these novel *N*-(2-bromo-4-cyanobutyl)amines **5**, excluding the formation of the corresponding regioisomers.

It should be remarked that this novel approach offers a direct method toward a functionalized $\gamma$-bromonitrile moiety, which is a new structural entity suitable for further elaboration and difficult to prepare via other routes. Only one alternative approach toward 5-amino-4-bromopentanenitriles can be found in the literature, involving an exchange reaction of xanthates with bromine in refluxing chlorobenzene.[21]

The presence of this $\gamma$-bromonitrile moiety in aminonitriles **5** allows a formal 1,3-intramolecular ring closure toward cyclopropanecarbonitriles upon α-deprotonation with respect to the nitrile moiety and subsequent bromide expulsion through nucleophilic displacement. In accordance with the previously reported 3-*exo*-*tet* ring closure of *N*-[2-chloro-1-(cyanomethyl)-ethyl]benzimidates toward *N*-(2-cyanocyclopropyl)benzimidates,[5] the premised cyclization of $\gamma$-bromonitriles **5** proceeded very nicely utilizing 1.5 equiv of KO*t*Bu in THF at room temperature for 5 h, affording novel 2-(aminomethyl)cyclopropanecarbonitriles **6** in good yields (Scheme 3). Almost no information regarding this type of compounds can be found in the literature,[22] and no general synthetic approach toward 2-(aminomethyl)cyclopropanecarbonitriles is available to date. These constrained carbocycles can be considered as precursors of the corresponding biologically relevant 2-(aminomethyl)-cyclopropanecarboxylic acids with diverse applications in medicinal and peptide chemistry.

Based on literature data, it is generally observed that the substituted cyclopropane carbon atoms in trans-disubstituted cyclopropane derivatives are characterized by a downfield shift in $^{13}$C NMR as compared to their cis isomers.[5,23] Also in 2-(aminomethyl)cyclopropanecarbonitriles **6**, the C2-carbon atoms (*C*HCH$_2$N) of the major isomers resonated at considerably higher $\delta$ values (19.1−19.2 ppm, $CDCl_3$) as compared to the minor isomers (17.0 ppm, $CDCl_3$), confirming the formation of *trans*-2-(aminomethyl)cyclopropanecarbonitriles **6** as the major constituents. The trans isomers of compounds **6a**−**e** were obtained in pure form after separation by means of column chromatography on silica gel (hexane/EtOAc 14/1), allowing full spectroscopic characterization. The diastereomeric ratio of cyclopropanes **6** (cis/trans 32−35/65−68) was determined by means of $^1$H NMR. This ratio appeared to be independent of the reaction temperature, as the same values were obtained upon treatment with 1.5 equiv of KO*t*Bu in THF after reflux for 30 min or after stirring at 0 °C for 6 h.

In conclusion, 1-arylmethyl-2-(bromomethyl)aziridines have been converted into 2-(2-cyanoethyl)aziridines upon treatment with α-lithiated trimethylsilylacetonitrile in THF in an efficient and straightforward approach. The latter novel aziridines can serve as substrates for the preparation of a variety of aminonitrile derivatives via elaboration of the aziridine moiety. 1-Arylmethyl-2-(2-cyanoethyl)aziridines were further transformed into 5-amino-4-bromopentanenitriles through a regiospecific ring opening of intermediate aziridinium salts upon treatment with benzyl bromide in acetonitrile. The latter $\gamma$-bromonitriles proved to be excellent substrates for the 1,3-intramolecular ring closure toward novel 2-(aminomethyl)cyclopropanecarbonitriles by means of KO*t*Bu in THF. The net conversion of this methodology concerns a novel ring transformation of an aziridine into an (aminomethyl)cyclopropane derivative.

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## Experimental Part

**Synthesis of 1-Arylmethyl-2-(2-cyanoethyl)aziridines 3.** General procedure: To an ice-cooled solution of trimethylsilylacetonitrile (7.5 mmol, 1.5 equiv) in dry THF (10 mL) was added *n*-BuLi (1.5 equiv, 2.5 M) via a syringe under nitrogen atmosphere, and the resulting solution was stirred for 1 h at 0 °C. Subsequently, a solution of 1-arylmethyl-2-(bromomethyl)aziridine **2** (5 mmol) in THF (10 mL) was added via a syringe at 0 °C, followed by heating under reflux for 4 h. The reaction mixture was poured into a 1 N $NaOH_{aq}$ solution (25 mL) and extracted with $Et_2O$ (3 × 20 mL). Drying ($MgSO_4$), filtration of the drying agent, and evaporation of the solvent afforded 1-arylmethyl-2-(2-cyanoethyl)aziridine **3**, which was purified by means of column chromatography on silica gel. **1-Benzyl-2-(2-cyanoethyl)aziridine 3a.** Yellow oil. Yield: 45%. $R_f$ = 0.43 (hexane/EtOAc/$Et_3N$ 40/10/1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.45−1.52 (1H, m); 1.56 (1H, d, $J$ = 6.1 Hz); 1.60−1.67 (1H, m); 1.75 (1H, d, $J$ = 3.3 Hz); 1.83−1.94 (1H, m); 2.17 (1H, d × d × d, $J$ = 16.9, 7.9, 7.0 Hz); 2.26 (1H, d × d × d, $J$ = 16.9, 7.2, 6.0 Hz); 3.22 and 3.64 (2H, 2 × d, $J$ = 12.8 Hz); 7.26−7.39 (5H, m). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 15.3 ($CH_2$), 29.0 ($CH_2$), 34.4 ($CH_2$), 37.5 (CH), 64.9 ($CH_2$), 119.5 (C), 127.5 (CH), 128. 5 (CH), 128.7 (CH), 138.9 (C). IR (NaCl, cm$^{-1}$): $\nu_{CN}$ = 2246. MS (70 eV) *m*/*z*: 187 ($M^+$ + 1, 100). Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.54; H, 7.77; N, 14.93.

**Synthesis of 5-[Bis(arylmethyl)amino]-4-bromopentanenitriles 5.** General procedure: To a stirred solution of 1-arylmethyl-2-(2-cyanoethyl)aziridine **3** (5 mmol) in acetonitrile (10 mL) was added benzyl bromide (5 mmol, 1.0 equiv), and the resulting mixture was heated under reflux for 5 h. Evaporation of the solvent afforded 5-[bis(arylmethyl)amino]-4-bromopentanenitrile **5**, which was purified by means of column chromatography on silica gel (hexane/EtOAc 9/1) in order to obtain an analytically pure sample. **5-[Bis(benzyl)amino]-4-bromopentanenitrile 5a.** Yellow oil. Yield: 84%. $R_f$ = 0.24 (hexane/EtOAc 9/1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 1.75−1.88 (1H, m); 2.12−2.40 (3H, 2 × m); 2.78 and 2.88 (2H, 2 × d × d, $J$ = 13.4, 9.5, 5.4 Hz); 3.49 and 3.72 (4H, 2 × d, $J$ = 13.2 Hz); 3.91−3.99 (1H, m); 7.22−7.38 (10H, m). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 15.1 ($CH_2$), 31.5 ($CH_2$), 50.9 (CH), 59.6 ($CH_2$), 60.1 ($CH_2$), 119.1 (C), 127.6 (CH), 128.6 (CH), 129.2 (CH), 138.7 (C). IR (NaCl, cm$^{-1}$): $\nu_{CN}$ = 2250. MS (70 eV) *m*/*z*: 357/9 ($M^+$ + 1, 24), 277 (100). Anal. Calcd for $C_{19}H_{21}BrN_2$: C, 63.87; H, 5.92; N, 7.84. Found: C, 64.02; H, 6.05; N, 7.71.

**Synthesis of 2-[*N*,*N*-Bis(arylmethyl)aminomethyl]cyclopropanecarbonitriles 6.** General procedure: To a solution of 5-[bis(arylmethyl)amino]-4-bromopentanenitrile **5a** (2 mmol) in dry tetrahydrofuran (15 mL) was added potassium *tert*-butoxide (3 mmol, 1.5 equiv) at room temperature. After being stirred for 5 h at room temperature, the reaction mixture was poured into water (30 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with water (2 × 50 mL) and brine (1 × 50 mL). Drying ($MgSO_4$), filtration of the drying agent, and removal of the solvent afforded 2-[*N*,*N*-bis(arylmethyl)-aminomethyl]cyclopropanecarbonitrile **6** as a mixture of cis/trans isomers. The trans isomer was isolated in pure form by means of column chromatography on silica gel (hexane/EtOAc 14/1). ***trans*-2-[*N*,*N*-Bis(benzyl)aminomethyl]cyclopropanecarbonitrile *trans*-6a.** Colorless oil. $R_f$ = 0.15 (hexane/EtOAc 14/1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.65−0.72 (1H, m); 0.82−0.95 (1H, m); 1.10−1.28 (1H, m); 1.53−1.63 (1H, m); 2.33 and 2.38 (2H, 2 × d × d, $J$ = 13.8, 6.6, 6.1 Hz); 3.60 and 3.64 (2 × 2H, 2 × d, $J$ = 13.6 Hz); 7.19−7.37 (10H, m). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 2.4 (CH), 13.2 ($CH_2$), 19.2 (CH), 55.6 ($CH_2$), 58.6 ($CH_2$), 121.7 (C), 127.3 (CH), 128.6 (CH), 129.8 (CH), 139.3 (C). IR (NaCl, cm$^{-1}$): $\nu_{CN}$ = 2238. MS (70 eV) *m*/*z*: 277 ($M^+$ + 1, 100). Anal. Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.73; H, 7.44; N, 10.07. ***cis*-2-[*N*,*N*-Bis(benzyl)aminomethyl]cyclopropanecarbonitrile *cis*-6a.** Colorless oil. $R_f$ = 0.05 (hexane/EtOAc 14/1). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 0.73−0.79 (1H, m); 0.83−0.90 (1H, m); 1.10−1.17 (1H, m); 1.35−1.42 (1H, m); 2.61 and 2.77 (2H, 2 × d × d, $J_{gem}$ = 13.4, 5.6, 5.0 Hz); 3.65 and 3.72 (2 × 2H, 2 × d, $J$ = 13.8 Hz); 7.21−7.42 (10H, m). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 2.4 (CH), 13.3 ($CH_2$), 17.0 (CH), 54.9 ($CH_2$), 58.7 ($CH_2$), 120.3 (C), 127.1 (CH), 128.4 (CH), 128.8 (CH), 139.5 (C). IR (NaCl, cm$^{-1}$): $\nu_{CN}$ = 2238. MS (70 eV) *m*/*z*: 277 ($M^+$ + 1, 100).

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**Supporting Information Available:** Spectroscopic data of compounds **3b**−**e**, **5b**−**e**, and **6b**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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