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Graphical Abstract

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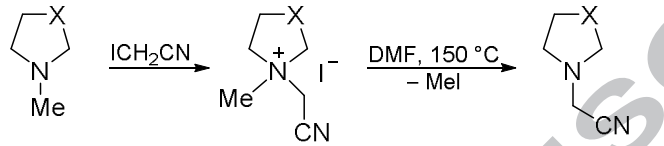

X = O, CH_2, $(CH_2)_2$

36–69%
overall yields

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Novel synthesis of aminoacetonitriles *via* the selective demethylation of quaternary ammonium salts

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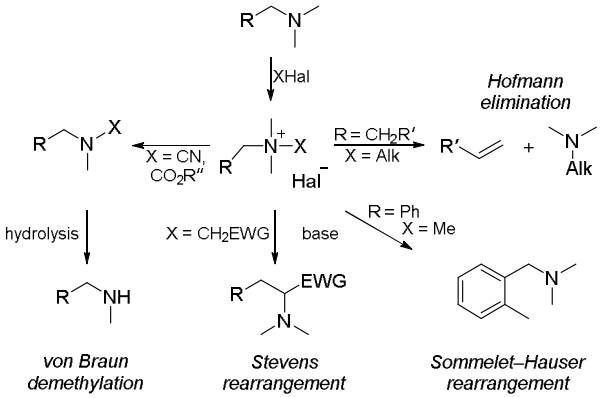
ABSTRACT

N-Methyl cyclic amines readily formed quaternary ammonium salts upon treatment with iodoacetonitrile in high yields (70–96%). The latter were selectively demethylated by heating in dimethylformamide to give aminoacetonitriles in moderate to good overall yields (36–69%).

Amines are one of the most valuable classes of organic compounds; they represent a significant part of modern pharmaceuticals and are widespread in Nature.[1] In this context, there are many methods for the synthesis and modification of amines.[2] In particular, a common way to modify an amine structure is quaternization by an alkylating reagent, followed by removal or transformation of its substituents. Such reactions include the Hofmann elimination,[3] [1,2]- (Stevens) and [2,3]- (Sommelet-Hauser) sigmatropic rearrangements,[4] von Braun demethylation using BrCN[5] and a related demethylation using highly electrophilic chloroformates ($ClCO_2R$)[6] (Scheme 1). Despite the abundance of known methods, many of them possess synthetic limitations and require the utilization of expensive or dangerous reagents. In light of these aspects, the development of new and simple methods for amine modification is still in demand.

The main focus of our research is devoted to the synthesis of various aza-heterocycles and acyclic amines using the synthetic potential of nonstabilized azomethine ylides in combination with simple 1–3 stage modifications of the primary cycloadducts.[7] In our investigation on the development of oxazolidine chemistry, we were interested in examining the possibility of Stevens sigmatropic rearrangement of previously obtained fluorene-oxazolidine **1a**.[8] To test the feasibility of this idea, quaternary ammonium salt **2a** was obtained in high yield by treating oxazolidine **1a** with iodoacetonitrile in diethyl ether at room temperature (Scheme 2). Contrary to our intentions, we discovered that the known reaction conditions for Stevens rearrangement (stirring a quaternary ammonium salt in a two-phase aqueous $NaOH/CH_2Cl_2$ system) did not result in the formation of cyanomorpholine **3a** (Scheme 2, Table 1, entry 1). Additionally, heating salt **2a** with *t*-BuOK in toluene was not successful and resulted in the formation of a mixture of dealkylation products **1a** and **4a** with a predominance of starting oxazolidine **1a** (Table 1, entry 2). An unexpected, but more promising, finding was the selective formation of demethylated product **4a** after heating oxazolidine salt **2a** in DMF at 150 °C in the presence of Hünig's base in a microwave reactor. Novel α-aminonitrile **4a** was successfully isolated and purified by column chromatography in 57% yield (Table 1, entry 3). Further experiments showed that the presence of a base and microwave irradiation was not necessary for this reaction (Table 1, entry 4). Moreover, selective demethylation can be accomplished in other



Scheme 1. Selected reactions of quaternary ammonium salts.

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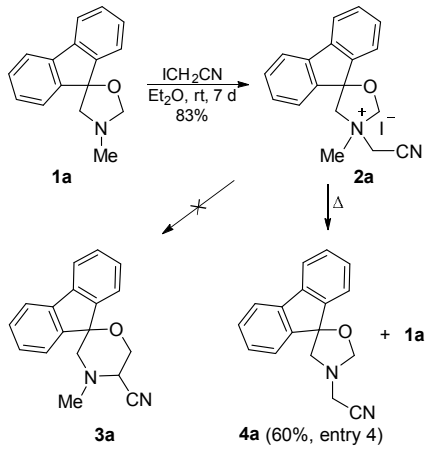
solvents, such as 1-methyl-2-pyrrolidone (NMP) and DMSO, albeit in lower yields (Table 1, entries 5, 6). The use of nucleophilic piperidine in DMF mainly resulted in removal of the cyanomethyl group and the formation of starting oxazolidine **1a** (Table 1, entry 7). In general, the most convenient experimental conditions were heating quaternary ammonium salt **2a** in DMF for 15 min at 150 °C which led to α-aminonitrile **4a** in 50% overall yield. This two-stage synthesis can be considered as equivalent to a formal C–H functionalization of the *N*-methyl group by a CN group.



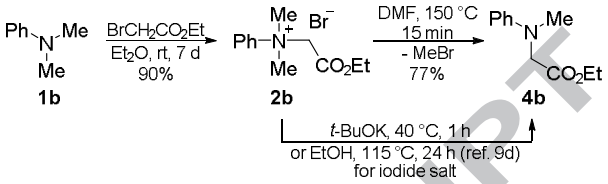
Scheme 2. Synthesis of aminoacetonitrile **4a**.

Table 1. Optimisation of the reaction conditions.

Entry	Conditions	NMR ratio **1a** : **4a**	Yield **4a** (%)[a]
1	50% NaOH aq. (10 equiv.), CH_2Cl_2, 40 °C, 2 h	Traces of **4a**	–
2	*t*-BuOK (3 equiv.), PhMe, 60 °C, 2 h	96 : 4	–
3	DIPEA (1.05 equiv.), DMF, MW, 150 °C, 15 min	0 : 100	57
4	**DMF, 150 °C, 15 min**	**0 : 100**	**60**
5	DIPEA (1.05 equiv.), NMP, 150 °C, 15 min	0 : 100	40
6	DMSO, 150 °C, 15 min	0 : 100	49
7	piperidine (5 equiv.), DMF, MW, 150 °C, 15 min	92 : 8	–
8	EtOH, MW, 150 °C, 30 min	–[b]	–

[a] Isolated yield of chromatographically purified product based on starting quaternary ammonium salt **2a**.
[b] Complex mixture of side products.

Previously, a small number of examples of quaternary ammonium salt demethylation reactions were reported in the literature.[9] Probably, the most similar conditions were used for the demethylation of a salt of 5-((dimethylamino)methyl)oxazolidin-2-one.[9c] Kuninobu and co-workers carried out the selective demethylation of the ammonium salt, obtained from *N*,*N*-dimethylaniline (**1b**) and ethyl iodoacetate, with prolonged heating in EtOH at 115 °C (Scheme 3).[9d] Nonetheless, we determined that heating quaternary ammonium salt **2a** in EtOH in a microwave reactor at 150 °C for 30 min did not result in the dealkylation product (Table 1, entry 8). To clarify this contradiction, the quaternization of *N*,*N*-dimethylaniline (**1b**) was performed using ethyl bromoacetate in 90% yield. Heating salt **2b** under the previously found conditions (DMF, 150 °C, 15 min) gave the expected ethyl *N*-methyl-*N*-phenylglycinate (**4b**) in 69% overall yield (Scheme 3). However, this product was also obtained by treating **2b** with potassium *tert*-butoxide at room temperature. These results presumably reflect the difference in the dealkylation selectivities of conformationally free ammonium salt **2b** and conformationally fixed **2a** (Table 1, entries 2 and 8).



Scheme 3. Synthesis of ethyl *N*-methyl-*N*-phenylglycinate (**4b**).

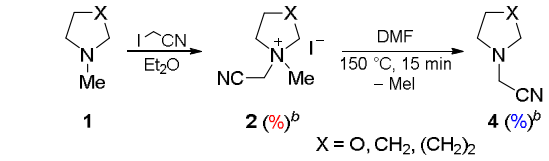
It can be concluded that heating the conformationally fixed quaternary salt **2a** in weak nucleophilic solvents (DMF, DMSO, NMP) in the absence of strongly nucleophilic reagents leads to selective demethylation and the formation of aminoacetonitrile **4a** (Scheme 2, Table 1). At the same time, the presence of nucleophiles in the reaction mixture, such as the hydroxide anion, secondary amines or alcohols, leads either to removal of the cyanomethyl group and formation of starting oxazolidine **1a** or does not lead to the dealkylation.

To investigate the scope and limitations, the functionalization of diethyl 1-methylpyrrolidine-3,3-dicarboxylate[10] by the cyano group was carried out utilizing the optimised conditions; novel aminoacetonitrile **4c** was successfully obtained in 55% overall yield (Table 2). This result reveals that β-hydrogens in the starting amine do not promote the Hofmann-type elimination and do not prevent the observed demethylation of the quaternary ammonium salt. Moreover, the described method was tolerant of a β-phenyl moiety, which increased the β-CH acidity of the ammonium salt obtained from 1-methyl-4-phenylpyrrolidine-3,3-dicarbonitrile. The presence of two CN groups in the latter substrate, potentially able to act as leaving groups, also did not prevent the demethylation stage in the synthesis of aminonitrile **4d**, which was isolated in 58% overall yield. Thus, our approach for amine functionalization is sufficiently mild and selective.

Further work was focused on the functionalization of other pyrrolidines for the synthesis of various α-aminonitriles. The latter have attracted attention due to their broad utility in organic synthesis.[11] It should be pointed out that a number of starting *N*-methyl heterocycles can be obtained *via* [3+2]-cycloaddition of the azomethine ylide derived from sarcosine and formaldehyde or from spiroanthraceneoxazolidine.[2a,7] Modification of these compounds possessing a pharmacophore phenethylamine moiety with a cyano group appears to be a promising direction for the preparation of building blocks for the synthesis of pharmaceutical compounds. It should be noted that the direct synthesis of *N*-cyanomethyl heterocycles by 1,3-dipolar cycloaddition is difficult, and to the best of our knowledge no examples have been reported. Moreover, the synthesis of the obvious precursors of such aminonitriles, *N*-unsubstituted azaheterocycles, by the [3+2]-cycloaddition of nonstabilized azomethine ylides or by other reactions is also a laborious task. In a continuation, substrates bearing aryl, heteroaryl moieties or a benzopyran annulated system were chosen for further investigation. As expected, *N*-cyanomethylpyrrolidines **4e**–**h** were obtained in 56–69% overall yield (Table 2). Next, the quaternary ammonium salt of 2-methyl-4-phenyltetrahydroisoquinoline was examined,[7a] which is presumably able to undergo Stevens rearrangement upon heating with base.[12] Nevertheless, heating in DMF gave α-aminonitrile **4i** in 41% overall yield. We also functionalized a similar tetrahydroisoquinoline bearing an electron-donating dioxolane moiety and obtained novel nitrile **4j** in moderate yield.

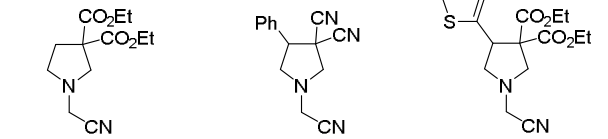
3-Methyl-5-phenyloxazolidine and naphtho[1,2-*e*][1,3]oxazine were successfully involved in the developed process to form α-aminonitriles **4k** and **4l**, respectively, in good overall yields.

Table 2. Synthesis of aminoacetonitriles **4**.[a]



1 **2** (%)[b] **4** (%)[b]

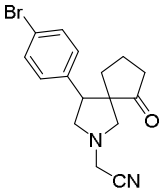
X = O, CH_2, $(CH_2)_2$



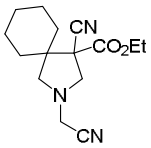
4c (84%, 65%, 55%)

4d (91%, 64%, 58%)

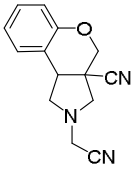
4e (86%, 65%, 56%)



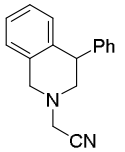
4f (94%, 73%, 69%)[c]



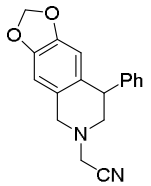
4g (94%, 71%, 67%)



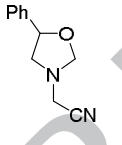
4h (87%, 70%, 61%)[c]



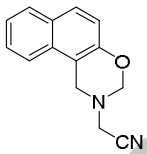
4i (94%, 44%, 41%)



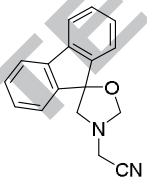
4j (96%, 37%, 36%)



4k (81%, 59%, 48%)



4l (70%, 57%, 40%)



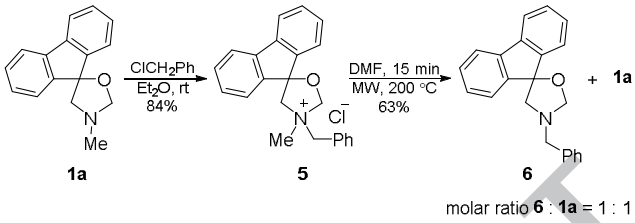
4a (83%, 60%, 50%)

[a] Reagents and conditions: amine **1** (5.0 mmol), ICH_2CN (5.5 mmol, 919 mg), Et_2O (15 mL), rt, 3–14 d; then salt **2,** DMF (2 mL per 1 mmol of salt **2**) 150 °C, 15 min.

[b] Isolated yields (quaternary ammonium salt **2**, %; chromatographically purified demethylated product **4**, %; overall yield **4**, % after two steps) are specified.

[c] Compounds **4f**,**h** were isolated without column chromatography purification.

Next, we examined the possibility of methyl group substitution by a benzyl group. Salt **5** was obtained from the reaction of fluorene-oxazolidine **1a** and benzyl chloride in 84% yield (Scheme 4). However, attempted demethylation under the optimised conditions (DMF, 150 °C, 15 min) was unsuccesful and starting ammonium salt **5** was recovered. Increasing the reaction temperature to 200 °C resulted in the formation of both dealkylated oxazolidines **6** and **1a** (the molar ratio of **6** and **1a** was 1:1 as determined by ^{1}H NMR spectroscopy) with a mixture of side products. This result indicates that replacement of the cyanomethyl group in the starting quaternary ammonium salt by a benzyl group, which is more similar to the initial methyl group, leads to the complete absence of selectivity in the observed reaction.



1a **5** **6**

Scheme 4. Dealkylation of salt **5**.

In summary, we report a new method for the functionalization of various *N*-methylazaheterocycles by substitution of the methyl group by a cyanomethyl moiety. The proposed strategy is based on the selective demethylation of readily available quaternary ammonium salts of starting amines under the simple conditions. In view of the broad possibilities for the 1,3-dipolar cycloaddition of azomethine ylides in obtaining various *N*-methylazaheterocycles, this concept allows easy access to a wide range of α-aminonitriles and is expected to find application in the synthesis and the modification of natural and pharmaceutical compounds. Further investigation of the aminoacetonitriles is underway in our laboratory and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

A selective demethylation of quaternary ammonium salt as a method for *N*-heterocycle functionalization.
A new substitution of the methyl group by cyanomethyl moiety in *N*-methylazaheterocycle.
A formal C–H functionalization of N-methyl group by CN group.