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COMMUNICATION

One-pot preparation of piperazines by regioselective ring-opening of non-activated arylaziridines†

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Herein we report a new straightforward synthesis of *cis* and *trans* 2,5-disubstituted *N*,*N*-dialkylpiperazines, even in enantioenriched form, by reacting non-activated *N*-alkyl arylaziridines in the presence of a catalytic amount of a Lewis acid. A stereochemical and NMR investigation revealed useful mechanistic insights for this process.

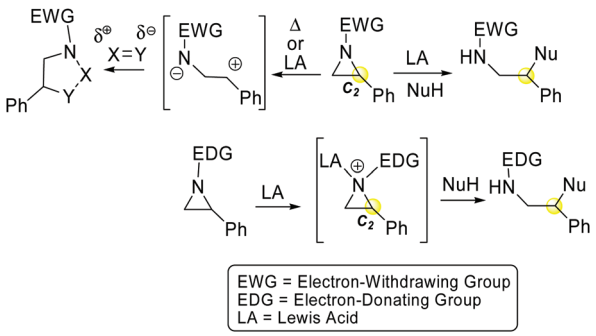
Aziridines are widely used versatile building blocks for the synthesis of a variety of biologically and pharmaceutically important molecules.[1] Several synthetic methods for aziridines have been developed and their use as chiral building blocks has also emerged recently.[2] In the past decades, much interest has been devoted to the development of new synthetic methodologies based on aziridine reactivity. Well established synthetic routes are based either on the nucleophilic ring-opening[3] of this spring-loaded heterocyclic system or on the regioselective metalation–electrophile trapping sequence without ring-opening.[4] However, where the aziridine reactivity is concerned, the nature of the nitrogen substituent can play a pivotal role. With reference to ring-opening reactions, aziridines have been classified as "activated" (those bearing an electron-withdrawing group) and "non-activated" (those bearing an electron-donating group) depending on the nature of the *N*-substituent.[5] Activated 2-phenylaziridines, in the presence of a Lewis acid (LA) or heat, undergo formal [3 + 2] cycloaddition reactions with non-activated alkenes, nitriles and ketones[6,7] through the corresponding masked 1,3-dipole; instead, in the presence of a LA and a nucleophile, a regioselective attack at the benzylic position (C_2) is often observed (Scheme 1).[8]

Non-activated 2-phenylaziridines, upon *N*-complexation with a LA, react with a nucleophile almost exclusively at the benzylic position, while reactivity as a formal 1,3-dipole obtained by a C–N bond cleavage, to the best of our knowledge, has never been reported (Scheme 1).[9]

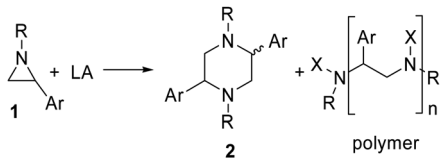
During our investigations on the chemistry of *N*-alkyl-2-arylaziridines, we found that the use of BH_3 as the LA gave stable complexes amenable to further elaboration.[10] Nevertheless, it was found that in the presence of metal halides, the same non-activated aziridines of the kind **1** underwent either dimerization to the corresponding piperazines **2** or polymerization depending on the reaction conditions (Scheme 2).

A look into the literature revealed an old report by Dick[11] on the formation of piperazinium halides from *C*-unsubstituted *N*-alkylaziridines, while De Kimpe exploited the reactivity of β-chloro- or β-tosyloxyethylamines in the preparation of *C*-unsubstituted piperazines.[12] Moreover, He *et al.*[13] reported *N*,*N*′-diethyl piperazines as side products (<15% yield) in reactions of *N*-alkyl C_2-substituted aziridines with CO_2.

Since the piperazine ring is found in a large number of biologically active compounds,[14] and this heterocycle finds use as a ligand in asymmetric catalysis,[15] we decided to investigate this



Scheme 1 Reactivity of "activated" and "non-activated" aziridines.



Scheme 2 Reactivity of *N*-alkylaziridines with LAs.

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reaction with the aim to improve the yields of piperazine while reducing the amount of the polymeric by-products.

In order to find the optimal reaction conditions for this dimerization, aziridines **1a–e** were first investigated. Several LAs were tested ($ZnCl_2$, $MgBr_2$, CsF, $CeCl_3$, CuBr, $(NH_4)_2Ce(NO_3)_6$, $InCl_3$) against different reaction conditions (solvent, temperature and LA amount), and it was found that the use of $MgBr_2$ in acetonitrile at 60 °C furnished appreciable yields of the corresponding piperazines **2a–d** as a 1 : 1 mixtures of two easily separable diastereoisomers (Table 1). The $MgBr_2$ was tested either in stoichiometric or catalytic (5%) amount. As can be seen in Table 1, the use of a catalytic amount of the LA gave faster reactions and higher conversions of the starting material. However, with a sterically demanding *N*-substituent, such as the *tert*-butyl group, the reaction did not take place with 1 equiv. of LA and occurred to a small extent with 5% of LA (Table 1). The structure and stereochemistry of diastereoisomeric piperazines **2a–d** and *meso*-**2a–d** were ascertained by NMR and HPLC analysis.[16] The stereochemistry of *meso*-**2a,n** and **2f** were confirmed by X-ray analysis.[17] It is worth pointing out that a 2,3-substitution was erroneously assigned to reported piperazine **2b**,[13a] and that the stereochemistry of this kind of piperazines has never been assessed before.

Under the optimized conditions (5% $MgBr_2$, CH_3CN, 60 °C), the scope of the reaction was investigated using *N*-methyl-2-aryl aziridines **1f–r**. As reported in Table 2, the reaction occurred with good yields, furnishing mixtures of diastereoisomeric piperazines **2f–r** and *meso*-**2f–r**.[18] However, they were easily separable and their stereochemistry was assigned by analogy to **2a–d** and *meso*-**2a–d**.[19]

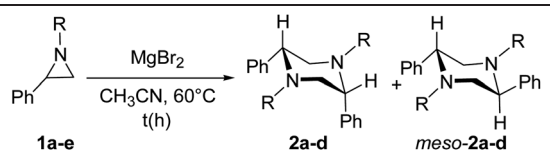
Next, we turned our attention to the reactivity of enantioenriched aziridines (*S*)-**1a,h** and (*R*)-**1a,i** (er >98 : 2) with the aim to prepare optically active piperazines, and disclose useful mechanistic information.

When chiral aziridines (*S*)-**1a,h** and (*R*)-**1a,i** reacted with a catalytic amount of $MgBr_2$ (5%), chiral piperazines (*S*,*S*)-**2a,h** and (*R*,*R*)-**2a,i** together with *meso*-**2a,h,i** were obtained, respectively (Scheme 3).[20] The absolute configuration of chiral piperazines (*S*,*S*)-**2a** and (*R*,*R*)-**2a** suggested that the reaction occurred with net retention of configuration with respect to the starting aziridines.[21]

The results obtained with chiral aziridines were a little surprising. With the exception of (*R*,*R*)-**2i**,[22] erosion of the enantiomeric ratio occurred to a small extent in chiral piperazines (*S*,*S*)-**2a,h** and (*R*,*R*)-**2a**, and the presence of the *meso* form, requiring an inversion of configuration at the benzylic carbon, should be explained.

To shed light on the mechanism of this reaction and also on the role of the LA, an NMR investigation was undertaken. Racemic and enantioenriched aziridines were analyzed by ^1H NMR in CD_3CN at 60 °C in the presence of catalytic (5%) and stoichiometric amounts of $MgBr_2$, respectively. From the ^1H NMR analysis of **1a** it was found that in the presence of a

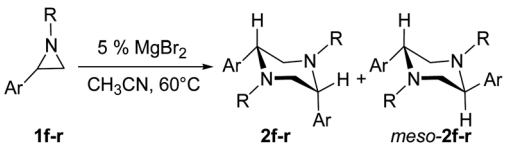
Table 1 Dimerization of aziridines **1a–e**



Aziridine **1**	R	*t* (h)	$MgBr_2$ (equiv.)	Yield[a,b] (%)	SM[c] (%)
1a	Me	15	1	85	15
1a	Me	5	0.05	90	<2
1b	Et	65	1	54	46
1b	Et	20	0.05	90	5
1c	n-Pr	89	1	45	55
1c	n-Pr	5	0.05	70	20
1d	i-Pr	90	1	76	24
1d	i-Pr	20	0.05	80	20
1e	*t*-Bu	90[c]	1	Nr	100[e]
1e	*t*-Bu	53	0.05	<5[d]	90

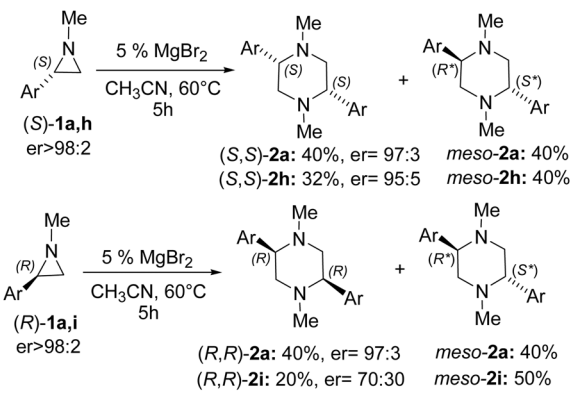
[a] Overall isolated yields of the two diastereoisomers. [b] As a 1 : 1 diastereomeric mixture of **2a–d**/*meso*-**2a–d**. [c] Recovered starting material (SM). [d] The corresponding piperazines were detected only by GC-MS analysis. [e] The starting material was recovered unchanged.

Table 2 Dimerization of aziridines **1f–r**



Aziridine **1**	R	Ar	Yield[a,b] (%)
1f	Me	4-ClC_6H_4	75
1g	Me	4-BrC_6H_4	75
1h	Me	2-BrC_6H_4	70
1i	Me	2-MeC_6H_4	73
1j	Me	2,4,6-$(Me)_3C_6H_2$	75
1k	Me	2-Naphthyl	80
1l	Me	3-$MeOC_6H_4$	60
1m	Me	4-$MeOC_6H_4$	60
1n	Me	2-$(CH_2{=}CHCH_2)C_6H_4$	65
1o	Me	3-$CF_3C_6H_4$	80
1p	Me	4-$CF_3C_6H_4$	80
1q	Me	2-*n*-PrC_6H_4	75
1r	Me	2-Me-5-FC_6H_3	50[c]

[a] Overall yields of the two diastereoisomers. [b] As a 1 : 1 diastereomeric mixture of **2f–r**/*meso*-**2f–r**. [c] After flash chromatography only the *meso* form was isolated.



Scheme 3 Synthesis of enantioenriched piperazines.

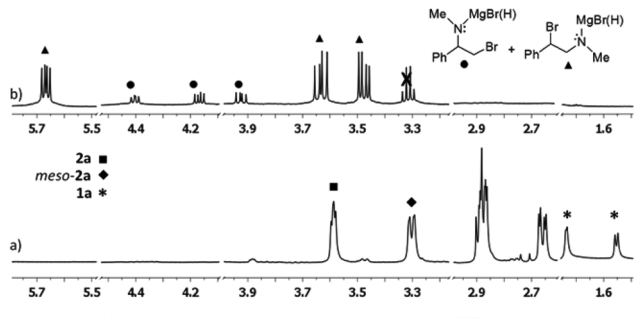


Fig. 1 ^{1}H NMR investigation on aziridine **1a** (partial spectra shown for clarity). (a) Aziridine **1a** + 5% $MgBr_2$, CD_3CN, 60 °C after 30 min, signals of **1a**, **2a** and *meso*-**2a** are shown. (b) Aziridine **1a** + 100% $MgBr_2$, CD_3CN, 60 °C, CH–CH_2 patterns are shown.

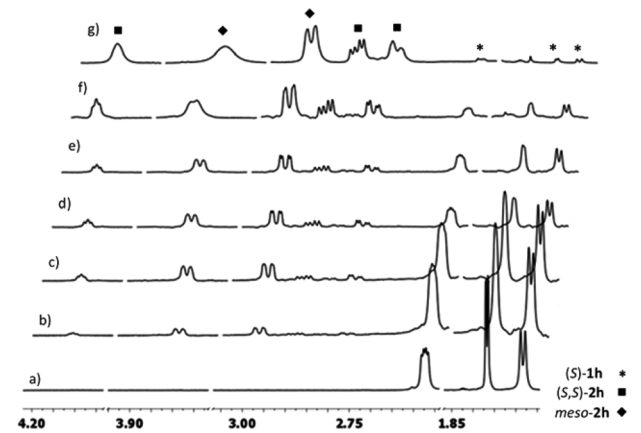


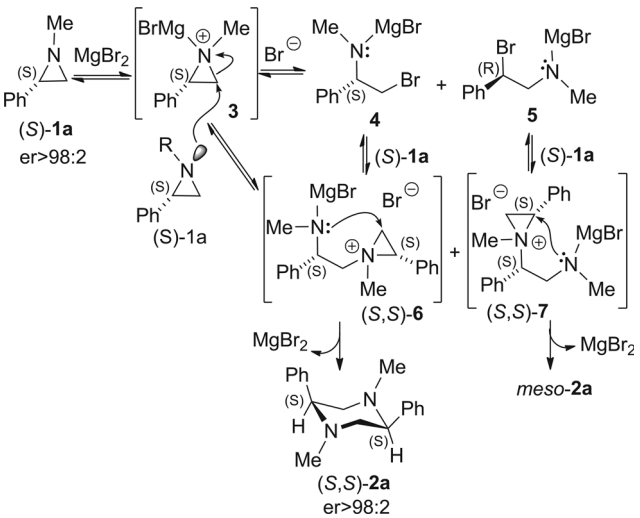
Fig. 2 ^{1}H NMR investigation on chiral aziridine (*S*)-**1h** + 5% $MgBr_2$, CD_3CN, 60 °C (partial spectra shown for clarity).

stoichiometric amount of $MgBr_2$ a fast and quantitative bromide-promoted ring-opening reaction occurred leading to the corresponding bromo amines or amides[23] (Fig. 1b). The ring-opening reaction occurred with a preference for the benzylic position and the reaction mixture remained unchanged even after 24 h at 70 °C.[24,25]

In striking contrast, in the presence of a catalytic amount of $MgBr_2$ a mixture of piperazines and starting aziridine was observed after 30 min and complete conversion was obtained in 2 h. Under these conditions, the ring-opening product was not observed even in trace amounts (Fig. 1a).

The NMR investigation on chiral aziridine (*S*)-**1h** in the presence of a catalytic amount of $MgBr_2$ gave results similar to those observed for **1a** (Fig. 2). After mixing of (*S*)-**1h** and $MgBr_2$ (5%), the spectra recorded at 5 min showed the presence of (*S*)-**1h**, *meso*-**2h** and traces of (*S*,*S*)-**2h** (Fig. 2). However, the conversion of (*S*)-**1h** into the corresponding piperazines was complete in 5 h, and still there was no evidence for ring-opening derivatives (Fig. 2).

In order to rationalize all the above results, the mechanism reported in Scheme 4 is proposed taking into consideration the stereochemistry of the process with reference to (*S*)-**1a**. Intermediate (*S*,*S*)-**6**, which should derive from nucleophilic attack of (*S*)-**1a** at the terminal position of **3** or by a nucleophilic



Scheme 4 Proposed mechanism for the conversion of aziridines into piperazines.

substitution on **4**,[26] would give chiral piperazine (*S*,*S*)-**2a** *via* an intramolecular nucleophilic attack at the terminal position of the aziridinium ion.[27] Instead, intermediate (*S*,*S*)-**7**, which should derive from **5**, undergoes intramolecular nucleophilic attack at the benzylic position of the aziridinium ion to give *meso*-**2a**.[28] In this mechanism, the excess of free aziridine is required for the reaction to occur.[29] In addition, the regioselectivity of the ring-opening reaction, involving the terminal position, is quite unusual for non-activated aziridines.

In conclusion a new straightforward synthesis of 2,5-disubstituted piperazines starting from readily available *N*-alkyl aziridines has been developed. Further investigations are underway in order to expand the applicability of this process and control the stereoselectivity.

Acknowledgements

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16 Piperazines **2a–d** with a *cis* relationship between substituents in 2,5 positions (axial–equatorial relationship) were mixtures of two enantiomers. Instead, a *trans* substitution (diequatorial relationship) gave *meso* piperazines **2a–d**.
17 The ^{1}H NMR analysis revealed characteristic spectroscopic patterns for piperazines **2a–d** and *meso*-**2a–d**. In particular, racemic **2a–d** always showed a deshielded benzylic CH proton (3.5–3.8 ppm) with respect to *meso*-**2a–d** (3.2–3.6 ppm) (see the ESI†).
18 Attempts to use *N*-alkylaziridines bearing a C_2-alkyl group failed, and only complex mixtures were recovered.
19 The relative stereochemistry was assigned by comparison of the ^{1}H NMR chemical shifts of the benzylic protons (see ref. 16).
20 The absolute configuration of chiral piperazine (*R*,*R*)-**2a** was confirmed by comparison of the optical rotation of the corresponding mono hydrochloride ($[\alpha]_D$ −56.6, *c* 0.15, H_2O), with the reported value ($[\alpha]_D$ −64.0, *c* 0.3, H_2O); (see K. Fuji, K. Tanaka and H. Miyamoto, *Tetrahedron: Asymmetry*, 1993, **4**, 247–259).
21 Opposite optical rotation values were found for (*S*,*S*)-**2a** ($[\alpha]_D$ +56.4, *c* 0.5, $CHCl_3$) and (*R*,*R*)-**2a** ($[\alpha]_D$ −56.4, *c* 0.5, $CHCl_3$).
22 It is likely that the *ortho* substituent could affect the reaction stereoselectivity (see mechanism and ref. 25).
23 An ESI-MS analysis of the reaction mixture collected directly from the NMR tube revealed the presence of the bromo amines.
24 It has been demonstrated that, with a stoichiometric amount of $MgBr_2$, the work-up procedure with water always gave a mixture of piperazines and starting aziridine so justifying the results reported in Table 1 with 1 equiv. of $MgBr_2$.
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26 Aziridine (*S*)-**1a** should attack mainly the terminal position of **3**. Attack at the benzylic position, occurring with inversion of configuration, would give (*S*,*R*)-**7** which would generate (*S*,*R*)-2,6-disubstituted piperazine (not observed) and (*R*,*R*)-**2a** to a small extent.
27 Nucleophilic attack at the benzylic position would lead to (*S*,*R*)-2,6-disubstituted piperazine which has not been observed.
28 Nucleophilic attack at the terminal position would lead to (*S*,*S*)-2,6-disubstituted piperazine which has not been observed.
29 However, we cannot rule out the regioselective ring opening of the aziridinium ions of (*S*,*S*)-**6**,**7** by the bromide, followed by an intramolecular nucleophilic substitution. For a similar example see: M. Yu. Moskalik and B. A. Shainyan, *Russ. J. Org. Chem.*, 2011, **47**, 568–571.