Check for updates

ACES Asian Chemical Editorial Society

Ammonium Zincates as Catalysts for the Microwave-Enhanced Synthesis of Symmetric Piperazines by Regioselective Opening of Aziridines

Matteo Alberti,[a] Andrea Dariol,[a] Nicola Panza,[a] Giorgio Abbiati,[b] and Alessandro Caselli*[a]

2,5-disubstituted *N,N'*-alkylpiperazines represent an interesting target in organic synthesis both for pharmaceutical or agrochemical applications and as a promising class of ligands in coordination chemistry. We report here a microwave-enhanced synthesis of these compounds starting from non-activated *N*-alkyl aziridines in the presence of catalytic amounts of simple ammonium metallates. A remarkable TOF of 2787.9 h^{-1} has been observed in the case of [TBA]$_2$[ZnI$_4$] as the catalyst (catalyst loading 0.1 mol%) and with an almost complete selectivity (up to 97%) in favor of both diastereoisomers (*meso* and chiral form) of the target 2,5-disubstituted piperazines, obtained in 1:1 ratio. The two isomers are easily separated, because the *meso* form precipitates in pure from the reaction crude. A stereochemical investigation and the unprecedented isolation of 2,6-disubstituted *N,N'*-alkylpiperazines allowed us to shed light on the reaction mechanism.

Introduction

The synthesis of symmetric and unsymmetric piperazines through the ring opening of aziridines under the action of nucleophiles represents an important and versatile transformation in organic chemistry.[1–3] Piperazines are heterocyclic compounds widely utilized in pharmaceuticals,[4] agrochemicals,[5] and materials science[6] due to their diverse biological and chemical properties.[7] The ability to selectively and efficiently construct piperazines is of great significance in drug discovery, as these compounds often serve as key structural motifs in bioactive molecules.[8] The synthetic versatility of symmetric piperazines makes them valuable building blocks, providing rigid scaffolds for the design and development of drug candidates, imparting desirable pharmacokinetic and pharmacodynamic properties.[9] Moreover, their symmetrical nature allows for the creation of chiral compounds, enabling the exploration of stereochemical effects on biological activity.[10]

Aziridines, on the other hand, are three-membered heterocyclic amines that are known for their strained nature.[11,12] The reactivity associated with this strain makes aziridines attractive starting materials for synthesizing various nitrogen-containing compounds.[13] Ring-opening reactions of aziridines have emerged as powerful tools for constructing complex molecular architectures[14–22]

The ring-opening process typically involves the cleavage of one of the carbon-nitrogen bonds in the aziridine ring.[14,23] Various nitrogen nucleophiles such as amines,[24,25] hydrazones,[26] and amino alcohols[27] have been successfully employed in these transformations, allowing for the introduction of different functionalities and structural variations.

In this context, the development of efficient and selective methods for the synthesis of symmetric piperazines *via* aziridine dimerization remains a quite neglected field,[28] despite the fact that early studies have shown that LiI in refluxing THF promotes efficiently the ring opening to yield a mixture of piperazine stereoisomers.[29] In addition, piperazines are often cited as common by-products in the synthesis of oxazolidinones by the cycloaddition of CO_2 to aziridines.[30–33]

Some years ago our group found that Zn(II)[34] and Fe(III)[35] complexes of Pyclen ligands are suitable catalysts for the CO_2 cycloaddition to epoxides to give cyclic carbonates. Inspired by these positive results, we explored the possibility of using simpler catalytic systems such as ammonium ferrate[36] and ammonium zincate salts,[37] obtaining excellent yields and selectivities under quite mild conditions. The proposed mechanism has been supported by theoretical calculations both by semiempirical tight-binding based quantum chemistry (QC) method GFNn-xTB and DFT simulations, adopting the B3LYP hybrid functional.[36] A natural evolution of these studies was the use of ammonium ferrates as catalysts for the CO_2 coupling with aziridines, and also in this case we were able to obtain 5-substituted 1,3-oxazolidin-2-ones under mild conditions (*i.e.*, rt, CO_2 0.1 MPa).[38] Interestingly, during these studies, we observed that these reactions produce as the only by-products a low amount of a diastereoisomeric mixture of two symmetrically

[a] M. Alberti, A. Dariol, N. Panza, A. Caselli
Department of Chemistry, Università degli Studi di Milano and CNR-SCITEC, Via Golgi 19, 20133 Milano, Italy
Phone: +39 02 50314372
E-mail: alessandro.caselli@unimi.it

[b] G. Abbiati
Dipartimento di Scienze Farmaceutiche - Sezione di Chimica Generale e Organica "A. Marchesini", Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy

substituted piperazines, derived from the homocoupling of two aziridine molecules (Scheme 1). As a consequence, we were interested on improving the yield of these products, and we report here the catalytic efficiency of butyl ammonium zincate in the synthesis of symmetric piperazines through the ring opening of aziridines.

Results and Discussion

As discussed in the introduction, symmetrically substituted piperazines are the only by-products observed by us in the synthesis of 5-substituted 1,3-oxazolidin-2-ones catalyzed by ammonium ferrates starting from CO_2 and aziridines (Scheme 1). Although the formation of these by-products can be suppressed almost completely by fine-tuning the reaction conditions, we were interested in their isolation in pure form to shed light on the reaction mechanism underlying their formation. During the optimization of the reaction condition for

the synthesis of 1,3-oxazolidin-2-ones, we observed that higher reaction temperatures (*i.e.* 75 °C) promote the homocoupling process with formation of piperazine *meso*-**2**, which spontaneously precipitated from the reaction crude and thus was easily separated in pure form, especially when using ammonium zincates as the catalysts. Based on these premises, we started our optimization study for the synthesis of symmetrically substituted piperazines according to the experimental knowledge acquired in the oxazolidinone synthesis, employing a series of tetrabutylammonium metallates. Best results were obtained with zincates **[TBA]$_2$[ZnX$_4$]**, (2.5 mol%) in CH_3CN. 1-Methyl-2-phenylaziridine, **1 a**, was chosen as the model substrate and the reaction temperature was set to 75 °C for 16 h. The results are reported in Table 1.

All ammonium zincates proved to be active in the dimerization of aziridines, in decreasing order **[TBA]$_2$[ZnI$_4$]** > **[TBA]$_2$[ZnBr$_4$]** > **[TBA]$_2$[ZnCl$_4$]**, which reflects the leaving group ability of the anion and not its nucleophilic character (Table 1, entries 1–3). Regardless of the employed catalyst, *meso*-**2 a** and
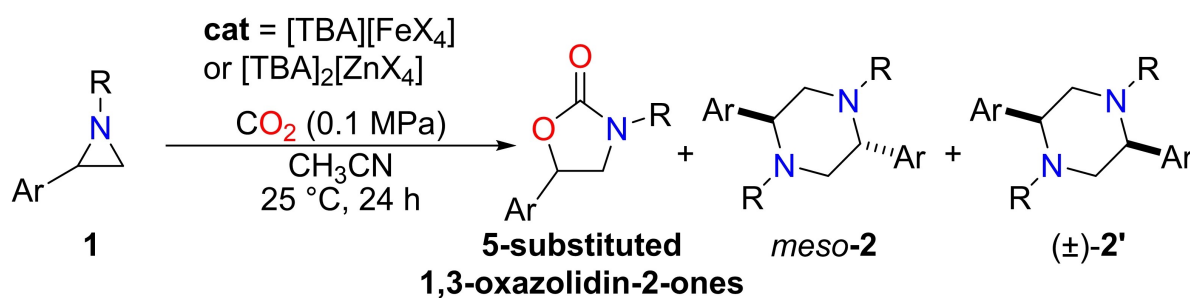
Scheme 1. [TBA][FeX$_4$] catalyzed synthesis of 5-substituted 1,3-oxazolidin-2-ones by reaction of aziridines with CO_2 under mild reaction conditions (RT, 0.1 MPa of CO_2) and formation of symmetric pyperazines **2** and **2′** as by-products.

Table 1. Synthesis of symmetric piperazines *meso*-**2a** and (±)-**2a** (*meso*-1,4-dimethyl-2,5-diphenylpiperazine and (±)-1,4-dimethyl-2,5-diphenylpiperazine, respectively) catalyzed by ammonium zincates, **[TBA]$_2$[ZnX$_4$]**.[a]

Entry	Catalyst	Cat. Loading (mol %)	Con.[b] **1 a** %	Sel.[c] **2 a** %	TOF[d] (h^{-1})
1	**[TBA]$_2$[ZnCl$_4$]**	2.5	11	90	0.3
2	**[TBA]$_2$[ZnBr$_4$]**	2.5	34	90	0.9
3	**[TBA]$_2$[ZnI$_4$]**	2.5	80	85	2.0
4	**[TBA][FeBr$_4$]**	2.5	>99	27	2.5
5	**ZnI$_2$**	2.5	>99	33	2.5
6	**TBACl**	5	<5	–	–
7	**TBAB**	5	12	50	0.2
8	**TBAI**	5	43	62	0.5
9	**none**	–	<1	–	–

[a] Reaction conditions: 1-methyl-2-phenyl aziridine, **1 a**, (1 mmol) and catalyst (x mol%) in CH_3CN (1 mL) at T = 75 °C, t = 16 h. [b] Conversion determined by GC using DMT as IS. [c] Selectivity determined by ^{1}H NMR using DMT as IS. Selectivity reported as the sum of *meso*-**2 a** and (±)-**2 a**, obtained as 1:1 mixture. [d] Turnover frequency (mol$_{1a(converted)}$ mol$_{cat}^{-1}$·reaction time^{-1}).

(±)-**2a** were always formed in an equimolar ratio. A full conversion of the starting aziridine was observed when employing **[TBA][FeBr₄]** as the catalyst, but selectivity was very poor (Table 1, entry 4).

In all cases, besides the two major products *meso*-**2a** and (±)-**2a**, traces of other isomers, tentatively attributed to 2,6-disubstituted *N,N*-dialkylpiperazines (*Vide Infra*) were also detected in the reaction crude. When selectivity was lower than 85%, polymeric or oligomeric materials were also observed.

As known from the literature, catalytic amounts of Lewis acids can catalyze the dimerization of non-activated aziridines to yield a *cis/trans* mixture of the symmetrically 2,5-disubstituted piperazines.[28] For this reason, **ZnI₂** was also tested as the catalyst, but despite a very high conversion of starting aziridine **1a** was observed, uncharacterized oligomeric and/or polymeric materials were the major products recovered at the end of the reaction (Table 1, entry 5). The same trend in reactivity and selectivity reported for the corresponding metallate salts but with lower yields in **2** was observed using the corresponding halide ammonium salts as catalyst (in this case a 5 mol% loading of the catalyst was used to preserve the stoichiometry ratio compared with ammonium zincates, Table 1, entries 6–8). Under otherwise identical conditions, no aziridine conversion was observed in the absence of any catalyst, proving the stability of 1a in dry CH₃CN at 75°C (Table 1, entry 9).

Reaction Optimization

Having assessed that a cooperative effect between the Lewis acidity of the metal center and the nucleophilic character/ leaving group ability of the halide ion is beneficial for the piperazine formation and that bromine and iodine are far superior with respect to chlorine in this regard, we next turned our attention to the optimization of the catalytic system. To boost the reaction rate, we shifted to a more efficient energy source as dielectric heating using closed vessels, which allowed us to raise the reaction temperature above the acetonitrile boiling point and shorten the reaction times.

To our pleasure, we discovered that using microwave radiation and with 2.5 mol% of **[TBA]₂[ZnI₄]**, the conversion observed was 68% in just 20 mins at 100°C and in 5 mins rising the temperature at 120°C, keeping a good selectivity (Table 2, entries 1 and 2). Both **[TBA]₂[ZnBr₄]** and **[TBA]₂[ZnI₄]** gave almost quantitative conversions at 120°C, although the selectivity and thus the piperazine yield were better with the latter (Table 2, entries 4 and 6) in 20 min, and a further increase of the reaction time to 1 h did not affect too much the selectivity (Table 2, entry 5), proving that piperazines **2a** are stable at this temperature. Next, we monitored the effect of the catalyst loading, and we found out that a quantitative conversion could be obtained with 1 mol% **[TBA]₂[ZnI₄]** at T = 120°C (Table 2, entry 7), and that in the presence of 0.1 mol% of an almost complete conversion (92%) of the starting aziridine **1a** was still observed (corresponding to a TOF of 2790 h⁻¹), with a remarkable 97% selectivity in just 20 mins (Table 2, entry 8).

Table 2. Optimization of the synthesis of symmetric piperazines *meso*-**2a** and (±)-**2a** (*meso*-1,4-dimethyl-2,5-diphenylpiperazine and (±)-1,4-dimethyl-2,5-diphenylpiperazine, respectively) under microwave heating.[a]

Entry	Catalyst	Cat. Loading (mol %)	T (°C)	T (min)	Con.[b] **1a** %	Sel.[c] **2a** %	TOF[d] (h⁻¹)
1	[TBA]₂[ZnI₄]	2.5	100	20	68	81	81.6
2	[TBA]₂[ZnI₄]	2.5	120	5	68	85	326.4
3	[TBA]₂[ZnI₄]	2.5	120	10	78	88	187.2
4	[TBA]₂[ZnI₄]	2.5	120	20	**96**	**94**	115.2
5	[TBA]₂[ZnI₄]	2.5	120	60	>99	77	40.0
6	[TBA]₂[ZnBr₄]	2.5	120	20	>99	75	120.0
7	[TBA]₂[ZnI₄]	1	120	20	>99	82	300.0
9	[TBA]₂[ZnI₄]	0.1	120	20	**93**	**97**	**2790**
10	ZnI₂	1	120	20	94	79	282.0
11	TBAI	1	120	20	96	73	288.0
12	[TMA]₂[ZnI₄]	2.5	120	20	95	80	114.0
13	none	–	120	20	62	66	–

[a] Reaction conditions: 1-methyl-2-phenyl aziridine, **1a**, (1 mmol) and catalyst (x mol%) in CH₃CN (1 mL). [b] Conversion determined by GC using DMT as IS. [c] Selectivity determined by ¹H NMR using DMT as IS. Selectivity reported as the sum of *meso*-**2a** and (±)-**2a**, obtained as 1:1 mixture. [d] Turnover frequency (mol₁ₐ₍converted₎·mol_cat⁻¹·reaction time⁻¹).

Worth noting, under dielectric heating, **ZnI₂** and, **TBAI** are also competent catalysts, and very high conversion values are observed albeit with worst selectivities (significant amounts of polymeric materials were observed to account for the rest of the reaction mass balance) (Table 2, entries 10 and 11). Moreover, the advantage of using ammonium zincates instead of zinc salt or ammonium halides is related to their easier handling and their less pronounced hydrophilic nature.[36] Furthermore, all the metallate salts are known to be excellent microwave absorbers, due to their ionic nature. To investigate if the chosen ammonium cation could influence the reaction outcome, we synthesized and tested **[TMA]₂[ZnI₄]** (TMA = tetramethyl ammonium), obtaining, as expected almost identical results (Table 2, entry 12). The coupling reaction of two aziridine molecules under those conditions occurs to some extent also in the complete absence of any catalyst (Table 2, entry 13). However, it should be pointed out that, in the absence of any catalyst, some polymeric materials were also observed to account for the rest of the mass balance.
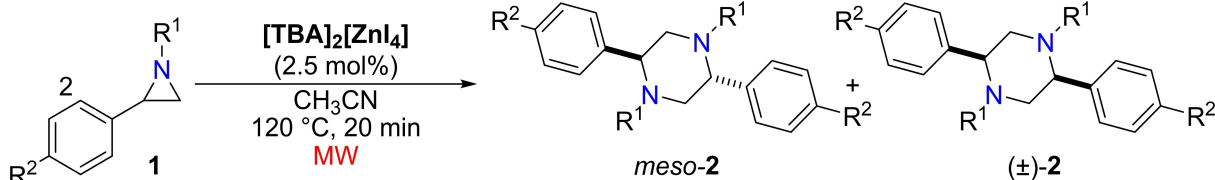
Piperazine *meso*-**2a** spontaneously precipitated from the reaction crude. Under the reaction conditions employed for entry 4 in Table 2, *meso*-**2a** was recovered pure in 44% yield, whereas the pure racemic form of piperazine (±)-**2a** was isolated in 27% yield after column chromatography (see Table 3, entry 1). The proposed structures for both diastereoisomers were determined by NMR analysis and confirmed by comparison with literature data (see SI for details). A minority fraction of (±)-**2a** (ca. 10%) was obtained contaminated with a

different by-product with a very similar elution coefficient, that we were not able to isolate in pure form, but whose ¹H NMR signals are in agreement with a 2,6-disubstituted *N,N*-dialkylpiperazine,(±)-**3a**. Finally, a third product with lower RF was isolated in 1% yield, whose stereochemistry and structure were proposed based on NMR and MS analysis to correspond to product *meso*-**3a** (see SI). These two 2,6-disubstituted piperazines were also formed in 1:1 mixture and, to the best of our knowledge their formation has never been proposed before in the literature.

As proven by our previous work,[36] and also well documented in the literature,[33] the regioselectivity of the ring opening reaction of non-activated 2-phenyl substituted aziridines by a nucleophilic addition is favored at the benzylic position; however, in the case of LA-promoted reaction, the nucleophilic attack involving the unsubstituted position has been also observed.[28] We believe that in this case, products (±)-**3a** and *meso*-**3a** are by-products formed by the coupling of two aziridine molecules **1a**, one that undergoes the ring-opening process at the benzylic position (more favored) and the second at the terminal position (*Vide infra* for mechanistic considerations).

We also checked the effect of a scale-up/scale-down of the reaction (from 0.2 mmol/0.2 mL–2 mmol/2 mL) and of the starting aziridine concentration (from 0.1 M–2 M) (see SI, Table S3). No particular effect was noted by scaling the reaction, whilst the selectivity dropped dramatically when decreasing the aziridine concentration.

Table 3. Reaction scope.[a]

Entry	R¹	R²	Piperazine	yield[b] *meso*-2%	yield[c] (±)-2%
1	Me	H	**2a**	44	27
2	*n*Bu	H	**2b**	27	20
3	H	H	**2c**	n.d.	n.d.
4	*s*Bu	H	**2d**	n.d	n.d.
5	CH₂Ph	H	**2e**	13	8
6	CH₂CHCH₂	H	**2f**	15	12
7	CH₂CH₂NHTs	H	**2g**	n.d.	n.d.
8	Me	Me	**2h**	46	36
9	Me	*t*Bu	**2i**	31	21
10	Me	Br	**2l**	20	17
11	Me	F	**2m**	14	6
12	*n*Bu	Me	**2n**	15	7
13	*n*Bu	Cl	**2o**	8	4
14	*n*Bu	F	**2p**	n.d.	n.d.

[a] Reaction conditions: aziridine, **1**, (1 mmol) and catalyst (2.5 mol%) in CH₃CN (1 mL). Isolated yields. [b] The *meso*-**2** products were collected as white solids after filtration of the reaction crude at the end of the reaction. [c] Pure (±)-**2** fractions were obtained after column chromatography, see SI for details.

Next, the solvent effects on the catalytic reaction were studied. Solvent polarity plays a major role in the nucleophilic ring opening of aziridines[39] and with microwave heating this becomes even more significant since the more polar is the reaction media,[40] the greater is its ability to absorb microwave energy. However, being our catalyst an ionic compound, it could itself enhance the rapid temperature rise and consequently result in faster reaction rates. We thus chose solvents with different dielectric constants and dipole moment to compare results in terms of conversion and selectivity, by employing the optimized conditions (1 mmol of aziridine **1a**, 1 M in the solvent, 2.5 mol% catalytic loading, T = 120 °C and t = 20 min). When using a 2.5 mol% loading of our catalyst, which, as already stated, is a good microwave absorber, also toluene could be employed to reach the target temperature; on the other hand, in the absence of [TBA]$_2$[ZnI$_4$] or at lower catalyst loadings (0.1 mol%) solvents with low dielectric constant failed to reach 120 °C. Obtained results are reported in Table S4, ordered in increasing dielectric constant. Although all conversion values obtained are very high and thus a clear correlation cannot be drawn, it is evident that the dielectric constant of the solvent is not the limiting factor governing the ring opening of the aziridine. However, observed selectivity changes dramatically along the series, and the best result was obtained with acetonitrile, which also has the advantage of leading to the spontaneous quantitative precipitation of the *meso* form of the aziridine, facilitating its separation in pure form at the end of the reaction.

Reaction Scope

With the best catalyst and the optimal reaction conditions in hand (Table 2, entry 4), we explored the scope and limitations of the approach. Starting aziridines were synthesized according to published procedures. We also ran parallel reactions, under otherwise identical conditions, but in the absence of the catalyst, and only in cases of entries 1, 2, and 8 homocoupling products were observed, albeit in very modest yield (see SI, Table S5). All yields refer to isolated products; the *meso* form spontaneously precipitated from the reaction crude and was recovered by filtration as a pure white powder, whilst the racemic piperazines were purified and isolated by column chromatography (see SI for experimental details). Worth noting, the NMR analysis of the reaction crudes always showed an equimolar amount of the two diastereoisomers of the desired piperazines and that means that the recovery by chromatography of the racemate is always incomplete. In any case, uncharacterized oligomeric and polymeric materials were also detected to account for the rest of the mass balance.

Initially, we checked differently *N*-substituted aziridines. Slightly worse results in terms of global isolated yields were obtained when employing 1-Butyl-2-phenylaziridine, **1b**, whilst, more sterically hindered 1-(1-methylpropyl)-2-phenylaziridine, **1d**, failed to give the desired coupling products (Table 3, entries 2 and 4). In this case, unreacted aziridine (35%) was recovered at the end of the reaction, along with polymerization

products. Contrary to our expectations, a similar negative result was observed also for 2-phenylaziridine **1c** (Table 3, entry 3). This may be traced to the presence of a N–H functionality, which favors the polymerization process. A similar result was observed also starting from commercially available 7-azabicyclo[4.1.0]heptane. Low yields of the pure piperazines were observed for benzyl and allyl-substituted aziridines, but it should be pointed out that isolation of these compounds proved to be more problematic and most probably real yields are underestimated (Table 3, entries 5 and 6). Traces of benzaldehyde, most probably formed by hydrolysis of the Schiff base obtained from the ring opening of the aziridine, were also detected.

We next studied electronic effects by tuning the properties of the phenylic ring with *p*-substituents. We chose not to study *o*-substituted and *m*-substituted 2-phenylaziridines, because in the first case, the electronic effect cannot be separated from the steric one, and in the second negligible effects are to be expected. Electron withdrawing groups such as Br, Cl, and F resulted in a drop in the observed yield (Table 3, entries 10, 11, 13 and 14). On the other hand 1-methyl-2-(4-methylphenyl)aziridine, **1h**, gave the best result and (±)-**2h** and *meso*-**2h** were isolated in a global 84% yield (Table 3, entry 8). No other products were detected in this case.

Finally, to investigate a useful protecting group at the nitrogen atom that could be subsequently cleaved at a later stage, we turned our attention to deactivated *N*-tosyl substituted aziridines, which are easier to synthesize and handle. In particular, we tested the coupling reaction of 1-tosylaziridine, **1r**, 2-phenyl-1-tosylaziridine, **1s**, and 2-(1,1-dimethylethyl)-1tosylaziridine, **1t** (see SI, Table S6). A 25% isolated yield of 1,4-bis(tosyl)piperazine **2r**, that spontaneously precipitated out from the reaction mixture was obtained only in the case of the completely unsubstituted N-tosyl protected aziridine (Scheme 2), whilst in the other cases, steric hindrance in the 2-position led to complete polymerization of the starting material.

Mechanistic Considerations

In the case of MgBr$_2$ catalyzed coupling,[28] it has been proposed that the activated aziridine, after coordination to the electrophilic LA would undergo nucleophilic attack either by a free aziridine or by a free halogen anion moiety, that after a nucleophilic substitution, followed by a second intramolecular ring opening, would lead to the observed 1 to 1 diastereomeric mixture of the piperazines.
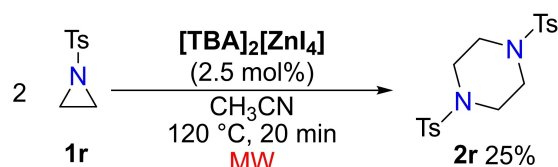
Scheme 2. [TBA]$_2$[ZnI$_4$] catalyzed synthesis of 1,4-bis(tosyl)piperazine **2r**.

Our previous experience in the use of ammonium metallate salts, corroborated by DFT calculations, supports the presence of an equilibrium in solution between the "ate" complex and the metallic salt plus the free halide nucleophile X⁻.[36] We have recently reported that, in the case of related ammonium ferrates, the nucleophilic attack of a free bromine atom on the LA-activated aziridine occurs almost barrierless (overall, the process that leads to the opened aziridine is exothermic with an enthalpy of −18.1 kcal/mol).[38] Attack by the nucleophile on the terminal carbon atom is less favored. It is reasonable to assume that even in this case, the first reaction step is represented by the fast nucleophilic attack of I⁻ to the benzylic position of the LA-activated aziridine to lead to intermediate **5a**, as shown in Scheme 3.

Formation of a minor amount of intermediate **5b** due to the attack of the nucleophile on the less hindered position would be responsible for the formation of the 2,6-disubstituted diastereoisomers **3a**. Next, intermediate **5a** could either undergo a nucleophilic substitution, **Path A** in Scheme 3, leading to intermediate **6a**, which would finally lead to piperazine **2** via a nucleophilic attack by the amido anion on the benzylic position

of the aziridinium ion. Alternatively, a direct nucleophilic attack of the amido intermediate **5a** to a free aziridine molecule on the more substituted carbon atom, **Path B** in Scheme 3, would lead to intermediate **6b**, which undergoes concerted ring closure with iodine elimination to finally yield the piperazine.

All these nucleophilic substitution reactions are believed to occur with a S_N2 mechanism,[2] also consistent with the low dependence of the reaction outcome observed in solvents with very different dielectric constants.

Starting from a racemate, both these mechanisms would lead to a 1:1 ratio of the *meso* and the racemic diastereoisomers of the piperazines, as experimentally observed. To shed light on the reaction mechanism, we performed the reaction employing the enantiomerically pure (*S*)-1-methyl-2-phenylaziridine, **1a**, prepared by a well-established literature procedure. The result was unexpected and very different from what was previously reported for the same reaction catalyzed by MgBr₂.[28] The obtained isolated products, on repeated trials, were again *meso*-**2a** and the racemic form of piperazine (±)-**2a** but formed in a 2.2:1 ratio in favor of the *meso* form as the main product. This result can be only rationalized by taking into account a
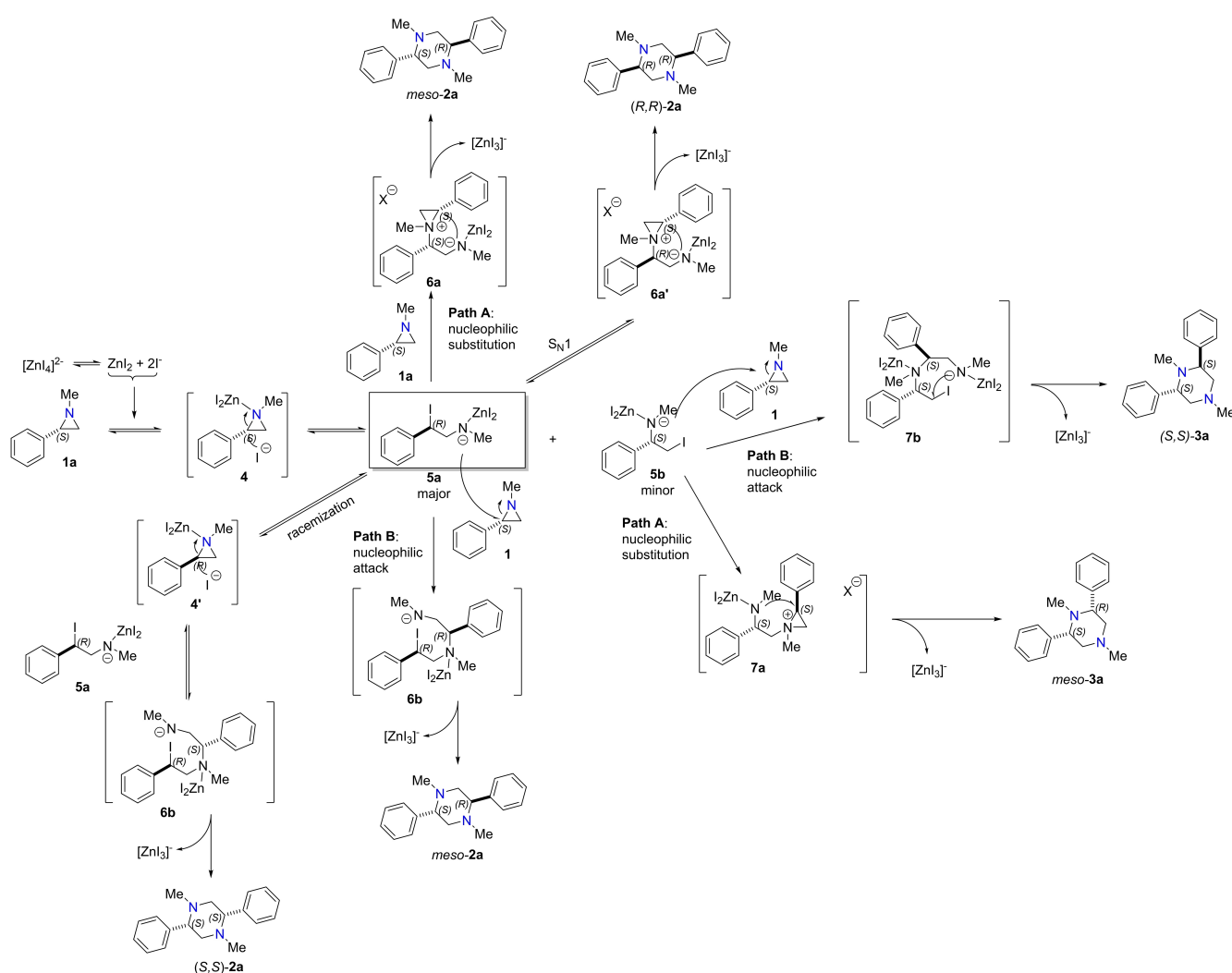
Scheme 3. Proposed mechanism for the aziridine dimerization to piperazines catalyzed by [TBA][ZnI₄]²⁻.

concurrent S_N1 mechanism for the nucleophilic substitution reaction, leading to intermediate **6 a'**, or by a racemization pre-equilibrium reaction of the starting aziridine (intermediate **4'**). The occurrence of such a process aligns with the experimental observation that the order of reactivity is **[TBA]$_2$[ZnI$_4$]** > **[TBA]$_2$[ZnBr$_4$]** > **[TBA]$_2$[ZnCl$_4$]**, which is consistent with the leaving group ability in the halide series and is the opposite with respect to their nucleophilic behavior. Both these possibilities would explain the fact that the chiral form of the piperazine is obtained as a racemate even if starting from an enantiomerically pure aziridine. This would also imply, however, that the most favored pathways are those depicted in Scheme 3 as **Path A** or **Path B**, leading both to *meso*-**2 b** as the main product. Data in our hands at the present stage are not sufficient to discriminate between these two hypotheses.

Although we could not follow the reaction *in situ*, due to the microwave heating, we have conducted a series of reactions under identical reaction conditions but checking the aziridine conversion at different reaction times, as detailed in the supporting information. A clear correlation could not be drawn, due to experimental limitations, but a second order fit in aziridine conversion could be observed in the first 10 minutes of reaction (See Figure S7), consistent with our mechanistic proposal. Worth to note, a fit could also be obtained taking into account even higher orders in the aziridine concentration, which could be explained with the partial formation of oligomeric and polymeric materials as by-products.

Conclusions

In conclusion, we have reported here a microwave-enhanced synthesis of 2,5-disubstituted piperazines starting from *N*-substituted aziridines. Apart from the synthetic value of the produced piperazines, which are obtained as 1:1 ratio of the easy-to-separate *meso* and chiral form, this work intends to shed light on the activation of *N*-alkyl aziridines by the dual activity of a LA and a nucleophile, a reaction that has wide implications in the synthesis of many pharmaceutically interesting compounds. To the best of our knowledge, the formation of 2,6-diarylsubstituted piperazines as a mixture of diastereoisomers through nucleophilic dimerization of aziridines has never been previously proposed in the literature.[30] Isolation and characterization of *meso*-**3 a** and the concurrent characterization of the (±)-**3 a** isomer allow for a better insight into the reaction mechanism and of possible competitive pathways.

Experimental Section

General Considerations

All chemicals and solvents were commercially available and used as received except where specified. ^{1}H NMR analyses were performed with 400 MHz spectrometers at room temperature. The coupling constants (J) are expressed in hertz (Hz), and the chemical shifts (δ) in ppm. Catalytic tests were analyzed by ^{1}H NMR spectroscopy and by GC using DMT (dimethylterephthalate) as IS (internal standard).

Gas-chromatographic analyses were performed with the GC-FAST technique using a GC equipped with a Supelco SLBTM-5 ms capillary column. Low-resolution MS spectra were recorded with instruments equipped with ESI/ion trap sources. High-resolution MS spectra were acquired at the COSPECT Unitech (Unimi) on a Q-ToF SYNAPT G2-Si HDMS 8 K instrument (Waters) equipped with a ZsprayTM ESI source (Waters). The values are expressed as mass-charge ratio and the relative intensities of the most significant peaks are shown in brackets. Elemental analyses were recorded in the analytical laboratories of Università degli Studi di Milano. Catalytic experiments under microwave heating were carried out in a 300 W Personal Chemistry "Emrys creator" single-mode micro-wave synthetizer at 2450 MHz. Aziridines, except for commercially available **1 r**, were synthesized according to published procedures: **1 b**, **1 e**, **1 f**, and **1 n**;[41] **1 a**, **1 c** and **1 l**;[42] **1 d**;[43] **1 m**;[44] **1 o**;[45] **1 p**;[46] and **1 s**.[47] Synthesis and characterization of aziridines **1 g**–**1 i** and of the ammonium zincates is detailed in the supporting information.

General Procedure for Aziridine Dimerization to Yield Symmetric Piperazines

Method A (Thermal Heating)

The catalyst (0.025 mmol), acetonitrile (1 mL), and the substrate (1 mmol) were added in this order in a round bottom pressure tube. Each piece of glassware was previously dried in an oven at 120 °C. The reaction mixture was stirred for 16 hours at 75 °C in a preheated hot bath.

Method B (Microwave Heating)

The catalyst (0.025 mmol), acetonitrile (1 mL), and the substrate (1 mmol) were added in this order in a microwave vial. The reaction was stirred for 20–80 mins (according to the specific experiment) at 100–140 °C.

GC Analysis

At the end of the reaction, the mixture was diluted with ethyl acetate in a 10 mL volumetric flask. 0.1 mL were taken and further diluted with ethyl acetate in a volumetric 10 mL volumetric flask to obtain a concentration of analytes in the range of 0.1–0.3 mg/mL. Before completing dilution, 0.1 mL of a solution of DMT in acetonitrile (10 mg/mL) was added as internal standard (IS), to obtain a final IS concentration of 0.1 mg/mL. **NMR yield with IS**: At the end of the reaction, the reaction mixture was diluted with ethyl acetate in a 10 mL volumetric flask. 5 mL were taken and 24.3 mg (0.125 mmol) of DMT were added as IS. The solvent was evaporated under reduced pressure, and about 750 μL of CDCl$_3$ was added for ^{1}H-NMR analysis.

Supporting Information Summary

Supplementary data associated with this article, including full tables of the optimization procedures, synthetic details and full characterization of ammonium zincates, aziridines **1 g**--**1 i** and all newly synthesized piperazines can be found in the Supporting Information. The authors have cited additional references within the Supporting Information.[28,37,41–47]

Conflict of Interests

There are no conflicts to declare.

Data Availability Statement

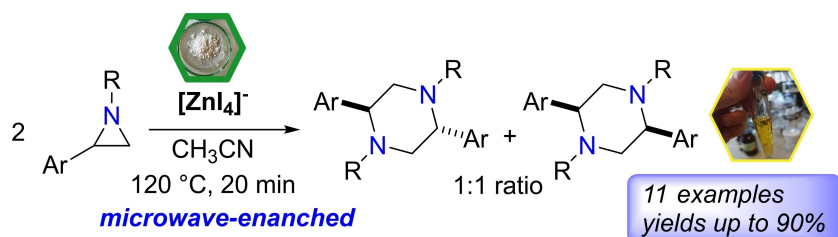The data that support the findings of this study are available in the supplementary material of this article.

[1] S. S. Sajadikhah, M. Nassiri, *Chem. Heterocycl. Compd.* **2021**, *57*, 905–907.
[2] N. Chauhan, S. Pradhan, M. K. Ghorai, *J. Org. Chem.* **2019**, *84*, 1757–1765.
[3] B. K. Das, S. Pradhan, T. Punniyamurthy, *Org. Lett.* **2018**, *20*, 4444–4448.
[4] M. Al-Ghorbani, A. Bushra Begum, Z. Zabiulla, S. V. Mamatha, S. A. Khanum, *Res. J. Pharm. Technol.* **2015**, *8*, 611–628.
[5] Y. Zhang, X. Liu, Y. Zou, S. Wang, H. Song, Q. Cai, J. Peng, C. Yi, J. Chen, *J. Heterocycl. Chem.* **2023**, *60*, 1826–1837.
[6] S. Shao, F. Zeng, L. Long, X. Zhu, L. E. Peng, F. Wang, Z. Yang, C. Y. Tang, *Environ. Sci. Technol.* **2022**, *56*, 12811–12827.
[7] K. J. McCullough, in *Rodd's Chem. Carbon Compd.*, 2nd ed., (Eds. M .F. Ansell), Elsevier B.V, Amsterdam **1975**, pp. 93–191.
[8] V. Sharma, R. Das, D. Sharma, S. Mujwar, D. K. Mehta, *J. Mol. Struct.* **2023**, *1292*, 136089.
[9] M. Al-Ghorbani, M. A. Gouda, M. Baashen, O. Alharbi, F. A. Almalki, L. V. Ranganatha, *Pharm. Chem. J.* **2022**, *56*, 29–37.
[10] S. K. Manna, G. Panda, *RSC Adv.* **2013**, *3*, 18332–18338.
[11] L. Degennaro, P. Trinchera, R. Luisi, *Chem. Rev.* **2014**, *114*, 7881–7929.
[12] C. Dank, L. Ielo, *Org. Biomol. Chem.* **2023**, *21*, 4553–4573.
[13] J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247–258.
[14] X. E. Hu, *Tetrahedron* **2004**, *60*, 2701–2743.
[15] S. Stanković, M. D'Hooghe, N. De Kimpe, *Org. Biomol. Chem.* **2010**, *8*, 4266–4273.
[16] P. Lu, *Tetrahedron* **2010**, *66*, 2549–2560.
[17] X. Du, S. Yang, J. Yang, Y. Liu, *Chem. - A Eur. J.* **2011**, *17*, 4981–4985.
[18] Y. Xu, L. Lin, M. Kanai, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2011**, *133*, 5791–5793.
[19] S. Nagamalla, A. A. Thomas, A. K. Nirpal, J. T. Mague, S. Sathyamoorthi, *J. Org. Chem.* **2023**, *88*, 15989–16006.
[20] W. N. Sun, G. J. Mei, S. K. Jia, *ChemCatChem* **2024**, *16*, DOI 10.1002/cctc.202301431.
[21] C. X. Ma, Q. Hu, H. L. Qin, G. Yang, Z. Chai, *Adv. Synth. Catal.* **2024**, *366*, 1654–1660.
[22] P. García-Martínez, O. Bernardo, J. Borge, J. González, L. A. López, *Adv. Synth. Catal.* **2024**, *366*, 1007–1012.
[23] R. Akhtar, S. A. R. Naqvi, A. F. Zahoor, S. Saleem, *Mol. Divers.* **2018**, *22*, 447–501.
[24] T. Isobe, T. Oriyama, *Tetrahedron Lett.* **2016**, *57*, 2849–2852.
[25] Y. Y. Huang, Z. C. Lv, X. Yang, Z. L. Wang, X. X. Zou, Z. N. Zhao, F. Chen, *Green Chem.* **2017**, *19*, 924–927.
[26] L. Crespin, L. Biancalana, T. Morack, D. C. Blakemore, S. V. Ley, *Org. Lett.* **2017**, *19*, 1084–1087.
[27] J. K. Loh, N. Asad, T. B. Samarakoon, P. R. Hanson, *J. Org. Chem.* **2015**, *80*, 9926–9941.
[28] P. Trinchera, B. Musio, L. Degennaro, A. Moliterni, A. Falcicchio, R. Luisi, *Org. Biomol. Chem.* **2012**, *10*, 1962–1965.
[29] W. Chamchaang, A. R. Pinhas, *J. Org. Chem.* **1990**, *55*, 2943–2950.
[30] Y. Du, Y. Wu, A. H. Liu, L. N. He, *J. Org. Chem.* **2008**, *73*, 4709–4712.
[31] Y. Wu, L. N. He, Y. Du, J. Q. Wang, C. X. Miao, W. Li, *Tetrahedron* **2009**, *65*, 6204–6210.
[32] R. A. Watile, D. B. Bagal, K. M. Deshmukh, K. P. Dhake, B. M. Bhanage, *J. Mol. Catal. A Chem.* **2011**, *351*, 196–203.
[33] Y. Xie, C. Lu, B. Zhao, Q. Wang, Y. Yao, *J. Org. Chem.* **2019**, *84*, 48.
[34] M. Cavalleri, N. Panza, G. Biase, G. Tseberlidis, S. Rizzato, G. Abbiati, A. Caselli, *European J. Org. Chem.* **2021**, *2021*, 2764–2771.
[35] N. Panza, A. Biase, E. Gallo, A. Caselli, *J. CO2 Util.* **2021**, *51*, 101635.
[36] N. Panza, R. Soave, F. Cargnoni, M. I. Trioni, A. Caselli, *J. CO2 Util.* **2022**, *62*, 102062.
[37] N. Panza, M. Alberti, C. Damiano, A. Caselli, *Front. Catal.* **2022**, *2*, 991270.
[38] N. Panza, M. Alberti, S. Galiè, C. Damiano, F. Cargnoni, M. I. Trioni, A. Caselli, *Eur. J. Org. Chem.* **2022**, DOI: 10.1002/EJOC.202200908.
[39] T. Qadir, A. Amin, D. Sarkar, K. P. Sharma, *Curr. Org. Chem.* **2021**, *25*, 1868–1893.
[40] A. M. Rodríguez, P. Prieto, A. De La Hoz, Á. Díaz-Ortiz, D. R. Martín, J. I. García, *ChemistryOpen* **2015**, *4*, 308–317.
[41] D. Carminati, E. Gallo, C. Damiano, A. Caselli, D. Intrieri, *Eur. J. Inorg. Chem.* **2018**, *2018*, 5258–5262.
[42] G. Bresciani, M. Bortoluzzi, G. Pampaloni, F. Marchetti, *Org. Biomol. Chem* **2021**, *19*, 4152.
[43] P. Sonzini, N. Berthet, C. Damiano, V. Dufaud, E. Gallo, *J. Catal.* **2022**, *414*, 143–154.
[44] F. Sebest, L. Casarrubios, H. S. Rzepa, A. J. P. White, S. Díez-González, *Green Chem.* **2018**, *20*, 4023–4035.
[45] M. Sengoden, M. North, A. C. Whitwood, *ChemSusChem* **2019**, *12*, 3296–3303.
[46] M. Prieschl, D. Cantillo, C. O. Kappe, *J. Flow Chem.* **2021**, *11*, 117–125.
[47] A. K. Ravn, M. B. T. Vilstrup, P. Noerby, D. U. Nielsen, K. Daasbjerg, T. Skrydstrup, *J. Am. Chem. Soc.* **2019**, *141*, 11821–11826.

RESEARCH ARTICLE

M. Alberti, A. Dariol, N. Panza, G. Abbiati, A. Caselli*

1 – 9

Ammonium Zincates as Catalysts for the Microwave-Enhanced Synthesis of Symmetric Piperazines by Regioselective Opening of Aziridines

A microwave-enhanced protocol for aziridine dimerization to yield symmetric piperazines with zincates as eco-sustainable catalyst is reported. A remarkable TOF of 2787.9 h^{-1} has been observed and with an almost complete selectivity (up to 97%) in favor of both diastereoisomers (*meso* and chiral form) of the target 2,5-disubstituted piperazines, obtained in 1:1 ratio. Preliminary mechanistic studies are also discussed.