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Transformations of 3-aryl-2-chloro-2-imidoylaziridines: novel entries to 4-chloro-2,5-diaryl-1*H*-imidazoles and 2-chloro-2-acylaziridines

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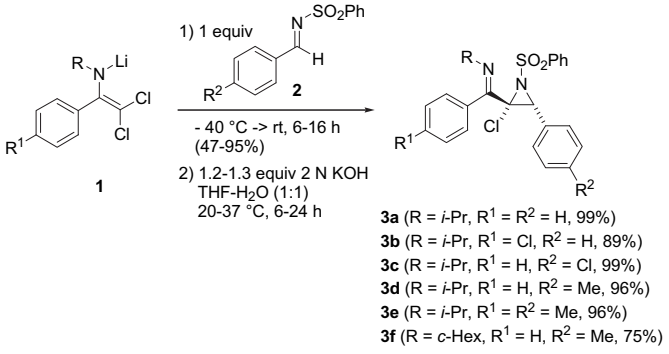
ABSTRACT

The reactivity of stereochemically defined 3-aryl-2-chloro-2-imidoylaziridines, an unexplored class of substituted aziridines, was investigated under various reaction conditions. 2-Chloro-2-imidoylaziridines underwent a novel thermal rearrangement by reflux in acetonitrile via C–C bond cleavage to 4-chloro-2,5-diarylimidazoles in high yield. Alternatively, a novel efficient entry toward 2-aroyl-2-chloroaziridines was based on the chemoselective hydrolysis of 2-chloro-2-imidoylaziridines with hydrochloric acid in aqueous tetrahydrofuran.

1. Introduction

Functionalized aziridines are versatile building blocks in the synthesis of acyclic nitrogen-containing compounds and azaheterocycles via cleavage of the C–N or C–C bond and via elaboration of functionalized substituents.[1] As such, a strong interest among experimental and theoretical chemists exists to obtain a better understanding of the reactivity of aziridines, which depends strongly on the substitution pattern of the aziridines and the reaction conditions.[2] The further development of aziridine-mediated synthesis of heavily functionalized compounds relies, of course, on the availability of stereochemically defined highly substituted aziridines and the ability to control their further transformations in the desired way. The synthesis of *cis*-3-aryl-2-chloro-2-imidoylaziridines **3a**–**c** and the unreported aziridines **3d**–**f**, representing interesting and novel examples of stable 2-chloroaziridines,[3] was described via aza-Darzens type reaction of 3,3-dichloro-1-azaallylic anions **1** and *N*-sulfonylaldimines **2** (Scheme 1).[4] The aziridines **3** belong to a class of aziridines **4** or **5** bearing an imidoyl or carbonyl functionality at the 2-position leading to an interesting substitution pattern, which opens up a whole range of further possible transformations (Scheme 2). Nucleophilic addition (path a) across the imino group in aziridines **4** (Y=NR′) is possible as previously demonstrated by the stereoselective synthesis of 2-(aminomethyl) aziridines via reaction of aziridines **3** with sodium cyanoborohydride in the presence of acetic acid.[4]



Scheme 1.

The thermal formation of azomethine ylides **7** (path b) can be envisioned due to the presence of the inductively electron-withdrawing 2-imidoyl and 2-chloro substituents, which stabilize the carbanionic center, and the 3-aryl group, which stabilizes the benzylic cationic center in azomethine ylides **7**. Subsequent 1,5-dipolar electrocyclization of the generated azomethine ylides **7** would lead to the formation of 1*H*-imidazoles **9** (Y=NR′). 1*H*-Imidazoles are a very important class of heterocycles due to their known biological activity and diverse medical uses, explaining that the synthesis of substituted 1*H*-imidazoles has received significant

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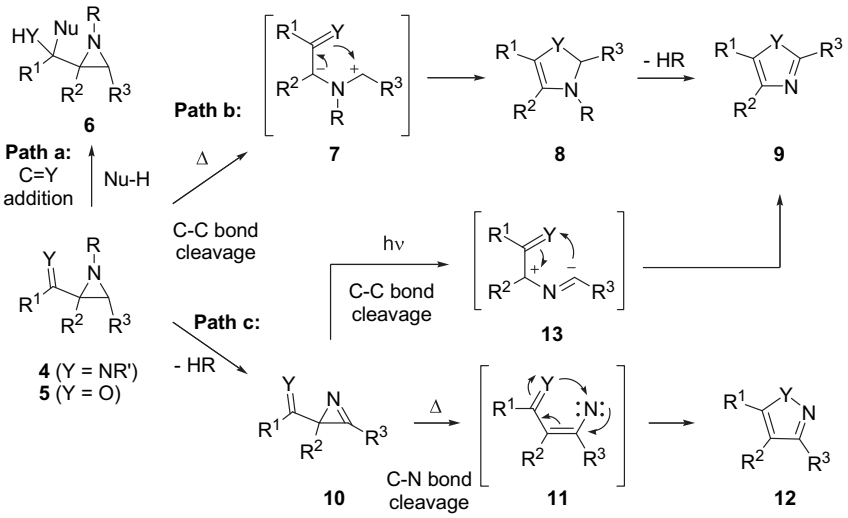


Scheme 2.

attention.[5,6] 1*H*-Imidazoles are nonpeptide angiotensin II receptor antagonists for the treatment of hypertension,[7] as well as inhibitors of p38 MAP kinase, implicated with the release of the pro-inflammatory cytokine TNF-α.[8] Naturally occurring imidazoles include the amino acid histidine, and purines, important bases in nucleic acids. 2,5-Diarylimidazoles are responsible of the modulation of the NPY5 receptor, involved in regulating the food intake and body weight, and several derivatives have anorexic effects in rodents, especially when an electron-withdrawing group was introduced at the aromatic ring at carbon-5.[9]

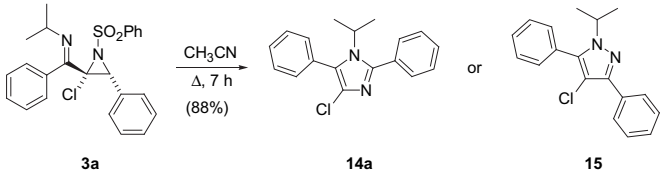
The investigation of the thermal rearrangement of 2-imidoylaziridines **4** to imidazole derivatives **9** lacks a comprehensive study.[10] The thermal ring transformation of α-imidoylaziridines into pyrroles has been described previously.[11] The limited reports on the rearrangement of 2-imidoylaziridines are probably due to the difficulty to access these functionalized strained heterocycles. In fact, the synthesis of ketimines derived from 2-acylaziridines cannot be performed at high temperature, i.e., in hot toluene or benzene, because intramolecular rearrangement to oxazole derivatives is in competition with the imine condensation.[12] Few examples of thermal reactions of 2-aroylaziridines were described. The synthesis of 2,5-diaryloxazole derivatives (R^1=R^3=aryl) from the thermally induced rearrangement of aroylaziridines **5** (Y=O) was reported.[12,13]

2*H*-Azirines are important building blocks in heterocyclic synthesis,[14] and they were found in some natural products, e.g., azirinomycin.[15] *N*-(Benzenesulfonyl)aziridines **4** (R=SO_2Ph) are prone to elimination of benzenesulfinate when treated with base (path c) and thus, 2*H*-azirines **10** can be obtained in this way.[16] One of the possible ways of constructing 1*H*-pyrazoles **12** involves the thermal rearrangement of 2-imidoyl-2*H*-azirines **10** (Y=NR′) via nitrene intermediates **11**.[17–19] 1*H*-Pyrazoles were found to be active as antihypertensives,[7] in the cure of gout,[20] as well as anti-inflammatory agents[21] and herbicides.[22] In contrast, the photochemical rearrangement 2-imidoyl-2*H*-azirines **10** has led to 1*H*-imidazoles **9**.[17,19]

Therefore an evaluation of the reactivity of 3-aryl-2-chloro-2-imidoylaziridines **3** is of significant synthetic and mechanistic interest and will fill up important gaps in heterocyclic chemistry.

2. Results and discussion

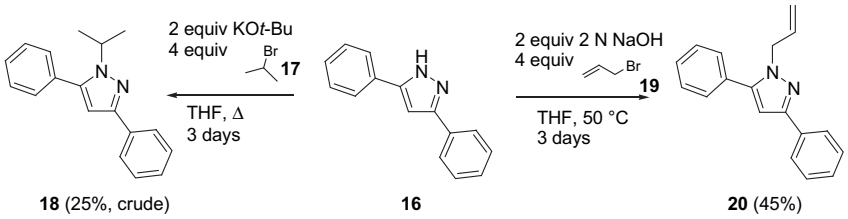
In an initial experiment, 2-chloro-2-imidoylaziridine **3a** was heated under reflux in acetonitrile for 7 h resulting in a complete rearrangement to a diazaaromatic compound as the only reaction product in 88% yield (Scheme 3). ^{1}H NMR and ^{13}C NMR spectral data did not show any aliphatic signals except for the aliphatic substituent at nitrogen. As previously highlighted, either the formation of a pyrazole **15** or an imidazole **14a** can be justified by thermal rearrangement of 2-imidoylaziridines. The obtained reaction product definitely represented a tetrasubstituted diazole derivative, as confirmed by spectroscopic and combustion elemental analysis. Further, comparison of the literature data of substituted 1*H*-imidazoles and 1*H*-pyrazoles were useful during the structure elucidation.



Scheme 3.

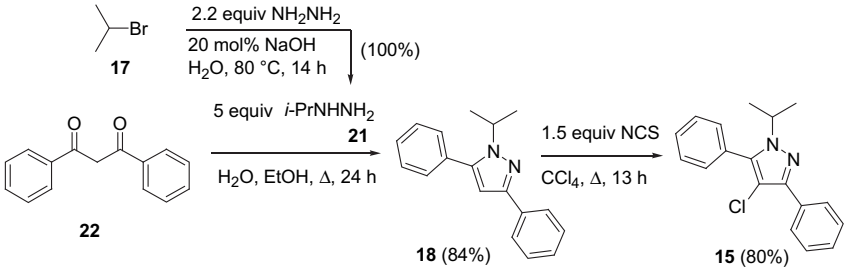
At first, analyses of the ^{13}C NMR data of some imidazole derivatives[5,23] showed that for imidazoles related to the present compound **14a** only carbon-2 is subjected to a low field shift, as can be easily predicted as a result of its position in between two nitrogen atoms. The presence of a resonance signal at 146.5 ppm in the ^{13}C NMR spectrum of our compound **14a** (or **15**) gave a first indication of an imidazole ring.

To establish the structure of the reaction product of the thermal rearrangement of aziridine **3a** as a 1*H*-imidazole **14a** (or a 1*H*-pyrazole **15**), without any reasonable doubt, an authentic sample of 1-isopropyl-4-chloro-1*H*-imidazole **14a** or 1-isopropyl-4-chloro-1*H*-pyrazole **15** was needed. At the moment that the structural attribution of the unknown diazole was not performed yet, it was decided to start with a new synthesis of 4-chloro-3,5-diphenyl-1-isopropyl-1*H*-pyrazole **15**. First attempts directed at the N-alkylation of the commercially available 3,5-diphenyl-1*H*-pyrazole **16** afforded 1-isopropyl-1*H*-pyrazole **18** in low yields (Scheme 4). Reaction of pyrazole **16** with 2-bromopropane **17** in the presence of potassium *tert*-butoxide in tetrahydrofuran under reflux resulted in poor yield of the desired *N*-isopropyl-1*H*-pyrazole **18** (25%), along with starting material. The use of allyl bromide **19** as an electrophile in tetrahydrofuran at 50 °C for 3 days in the presence of 2 equiv of 2 N sodium hydroxide gave *N*-allylpyrazole **20** and starting product **16** (ratio 1/1) (Scheme 4), confirming the reluctant behavior of the pyrazole **16** toward N-alkylation.



Scheme 4.

Although chlorination of *N*-alkylated 1*H*-pyrazole **18** should afford the 4-chloro-3,5-diphenylpyrazole **15** useful for structural elucidation, this N-alkylation strategy of pyrazole **16** was not continued because of the poor results. However, a different strategy for the synthesis of 4-chloro-3,5-diphenylpyrazole **15** was applied. Knowing that 3,5-diphenyl-1*H*-pyrazoles were synthesized via the condensation of arylhydrazones and dibenzoylmethane,[24] also the reaction of *N*-isopropylhydrazine and dibenzoylmethane would give the desired *N*-isopropyl-1*H*-pyrazole **18** (Scheme 5). An independent synthesis of *N*-isopropylhydrazine **21** started with hydrazine and 2-bromopropane **17** followed by distillation to yield *N*-isopropylhydrazine **21** as a 24% w/w solution in water. Therefore, distilled *N*-isopropylhydrazine was condensed with dibenzoylmethane **22** in ethanol under reflux for 24 h to afford crystalline *N*-isopropylpyrazole **18** in 84% yield (Scheme 5). The resulting *N*-isopropylpyrazole **18** was chlorinated at the 4-position with *N*-chlorosuccinimide in carbon tetrachloride at reflux overnight, as previously performed with 3,5-diphenylisoxazole analogues,[25] to give 4-chloropyrazole **15** in 80% yield.



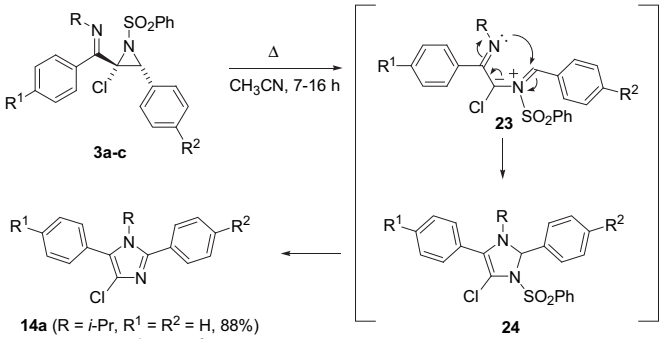
Scheme 5.

1-Alkyl-4-chloropyrazoles are interesting compounds for biological screening, as some 1,5-diarylpyrazoles were found active as anti-inflammatory agents, e.g., in the cure of arthritis.[21,26] Previously, 4-bromo- and 4-fluoro-1*H*-pyrazoles were generated by condensation of 2-bromo- or 2-fluoro-1,3-propanediones and phenylhydrazines.[27,28] A drawback of the latter procedure was the formation of mixtures of isomers when unsymmetrical propane-1,3-dione derivatives were used.

After spectroscopic characterization of the 4-chloro-1*H*-pyrazole **15**, it was clear that the latter synthesized 4-chloro-1*H*-pyrazole had different spectroscopic features than the former unknown compound **14a**. The ^{13}C NMR data of the 4-chloropyrazole **15** were in agreement with a previously synthesized 1-alkyl-4-chloropyrazole.[29] Looking into the details of the NMR spectra it was clear that the ^{1}H NMR spectra of 4-chloropyrazole **15** and compound **14a** were quite alike, while their ^{13}C NMR spectra revealed more differences. In the ^{13}C NMR spectrum of pyrazole **15** a shielded signal appeared at 106.1 ppm (tetramethylsilane as reference), attributed to the C-4 of the pyrazole ring, while the C-3 and C-5 were found at lower field, 146.1 and 140.2 ppm, respectively. In contrast, in the ^{13}C NMR spectrum of compound **14a** no shielded resonance signal around 105 ppm is present, and its ^{13}C NMR data are in agreement with previously reported spectra of related imidazoles.[5,23] Finally, 1*H*-pyrazole derivatives showed to be unstable under *hv*, i.e., the conversion of substituted pyrazoles into imidazoles via 2-imidoyl-2*H*-azirine intermediates.[30] This fact contrasts with the chemical behavior of compound **14a**, which is a stable compound, i.e., by photochemical irradiation or simply upon heating. Compound **14a** was stable in daylight in tetrahydrofuran and $CDCl_3$ solutions, as well as on heating, e.g., in acetic acid or tetrahydrofuran for 3 days at reflux.

In conclusion, spectroscopic data, in particular ^{13}C NMR, as compared to the spectra of synthesized 4-chloro-3,5-diphenylpyrazole **15**, along with its chemical behavior, ascertained the identification of the compound from the thermal rearrangement of 2-imidoylaziridine **3a** as 4-chloro-2,5-diphenyl-1*H*-imidazole **14a**.

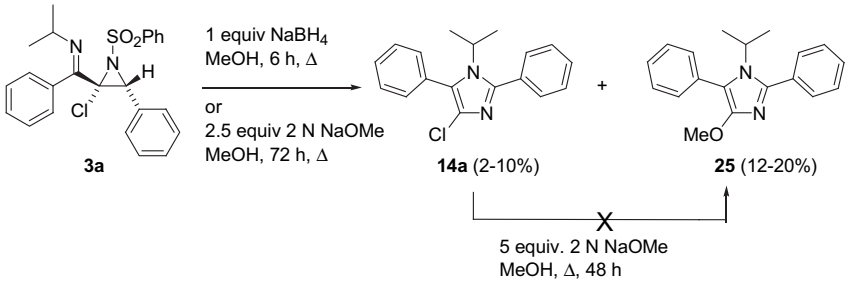
The previously described route to 4-chloroimidazole **14a** was evaluated during the synthesis of some derivatives by varying the aromatic substituents and the *N*-substituent. Thus, 2-chloroaziridines **3b**–**f** were converted to 4-chloroimidazoles in acetonitrile at reflux for 7–16 h in generally good yields (Scheme 6). Importantly, 4-chloroimidazole **14b** was obtained on leaving the aziridine **3b** in chloroform for 24 h at room temperature, albeit in lower yield (47%). Finally, 1*H*-imidazole **14a** was also obtained in lower yields when imidoylaziridine **3a** was refluxed in mixtures of



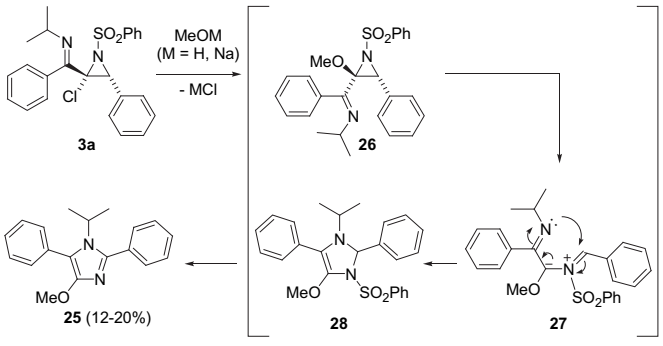
Scheme 6.

methanol–tetrahydrofuran (1/1) (40–70%) along with mixtures of unidentified reaction products. The structures of 4-chloroimidazole derivatives **14b–f** (vide infra) were confirmed as their spectroscopic data were in analogy with data of 4-chloro-2,5-diphenyl-1*H*-imidazole **14a**.

During the course of our investigation on the thermal rearrangement, it was found that 2-chloroaziridine **3a** led to mixtures of 4-chloroimidazole **14a** and 4-methoxyimidazole **25** when **3a** was treated with sodium borohydride in methanol or 2 N sodium methoxide in methanol under reflux (Scheme 7). The methoxy substituent at position 4 of the imidazole ring **25** is not generated by a direct substitution from the 4-chloroimidazole **14a**, because a direct conversion of **14a** into **25** with sodium methoxide in methanol under reflux did not give 4-methoxyimidazole **25**. Therefore, the methoxylation resulted from a substitution of the aziridine **3** rather than from the 4-chloro-1*H*-imidazole **14a**. A reasonable mechanism for the synthesis of 4-methoxyimidazole **25** involved the displacement of the chloride ion by addition of sodium methoxide or methanol, which gave 2-methoxyaziridine **26** (Scheme 8). Although not proven, the substitution reaction of **3a** probably occurs via stereoselective addition of methoxide or methanol to afford the intermediate **26** with a trans relationship of the phenyl and methoxy substituents.[3]



Scheme 7.



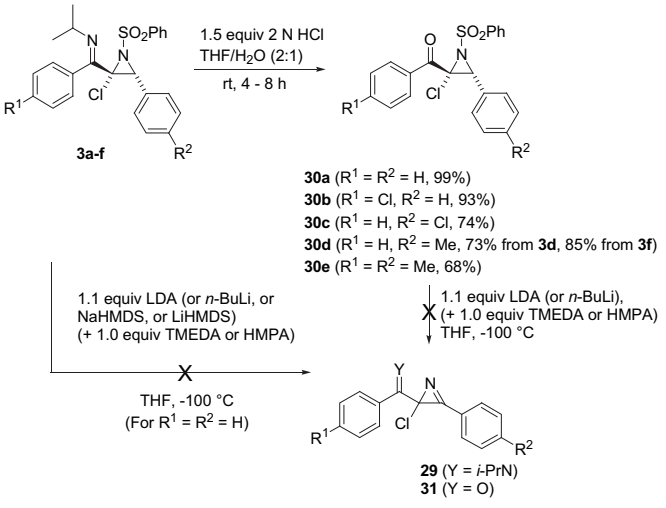
Scheme 8.

The aziridine **26** underwent ring opening to dipolar intermediate **27** followed by intramolecular ring closure to give imidazoline **28**, which after loss of benzenesulfinate afforded 4-methoxyimidazole **25**.

After having evaluated the thermal behavior of aziridines **3**, some efforts were directed toward the generation of 2-chloro-2*H*-azirines **29** through the use of strong bases (lithium diisopropylamide, butyl lithium, sodium, and lithium hexamethyldisilazide).[16,31] 2-Halo-2*H*-azirines are a class of not well studied azaheterocycles with a unique reactivity due to the presence of the highly strained unsaturated three-membered ring and the halogen substituent.[32]

Despite all efforts and a range of reaction conditions investigated, the elimination of benzenesulfinic acid from aziridine **3a** to the desired 2*H*-azirine **29** could not be achieved, even when TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), or HMPA (hexamethylphosphor(V) amide), was used as co-solvent,[16] as complex reaction mixtures were obtained instead (Scheme 9). At present, some 2-acyl-2-halo-2*H*-azirines have been synthesized.[32] Therefore our efforts moved toward the synthesis of 2-aroyl-2-chloro-2*H*-azirines from 2-chloro-2-imidoylaziridines **3**. An additional hydrolysis step was required to synthesize 2-aroyl-2-chloro-2*H*-azirines. The latter chemoselective hydrolysis of ketimines **3** was simply accomplished by 1.5 equiv of 2 N hydrochloric acid in tetrahydrofuran–water (1/1) at room temperature, giving (1-benzenesulfonyl-2-chloro-3-arylaziridin-2-yl)(aryl)methanones **30a–e** in 68–99% yield (Scheme 9).

Unfortunately, also the attempted elimination reactions performed from **30a** with 1.1 equiv of LDA in tetrahydrofuran, with and without TMEDA, at low temperature (−100 °C) were not successful to give 2-chloroazirine **31**.



Scheme 9.

3. Conclusion

As conclusion, the reactivity of a new class of stereochemically defined densely functionalized *cis*-3-aryl-2-chloro-2-imidoyl-1-(phenylsulfonyl)aziridines was evaluated. The thermal rearrangement of the 2-chloro-2-imidoylaziridines via cleavage of the C–C bond gave unreported 4-chloro-2,5-diarylimidazoles upon reflux in acetonitrile. Novel chlorinated 2-aroylaziridines were generated in good yields (68–99%) via selective acid hydrolysis of the imidoyl functionality of the aziridines. Neither the 2-imidoylaziridines nor the 2-aroylaziridines gave the corresponding 2*H*-azirine derivatives when treated with strong bases to induce elimination of the *N*-substituent.

4. Experimental

4.1. General

Flame-dried glassware was used for all non-aqueous reactions. Commercially available solvents and reagents were purchased from common chemical suppliers and used without further purification, unless stated otherwise. Tetrahydrofuran was distilled from sodium and sodium benzophenone ketyl. Dichloromethane was distilled over calcium hydride. Petroleum ether and chloroform were dried and purified by washing with concentrated sulfuric acid and distilled. Methanol was dried with magnesium and distilled. Hexamethylphosphor(V) amide (HMPA) was dried over CaH_2 and distilled, then stored over molecular sieves. Flash chromatography was carried out using a glass column filled with silica gel (Acros, particle size 0.035–0.070 mm, pore diameter ca. 6 nm). TLC was performed on glass-backed silica plates (Merck Kieselgel 60 F_{254}, precoated 0.25 mm), which were developed using standard visualization techniques or agents: UV fluorescence (254 nm and 366 nm), coloring with iodine vapor, permanganate solution/Δ or 50% aqueous sulfuric acid/Δ. The purity of the synthesized compounds or reaction mixtures was monitored by gas chromatography, using a Hewlett-Packard 6890 GC Plus coupled with a FID Detector equipped with a CIS-4-PTV (Programmed Temperature Vaporization) Injector (Gerstel), and EC5 capillary column (fused silica, AT-1, film thickness 0.25 μm, length 30 m, i.d. 0.25 mm, N_2 as carrier gas, FID, H_2 gas) and Agilent 6890 Series gas chromatograph (fused silica, AT-5, film thickness 0.25 μm, length 30 m, i.d. 0.25 mm, He as carrier gas, FID, H_2 gas). ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run with a Jeol Eclipse FT 300 NMR spectrometer at room temperature unless otherwise specified. Peak assignments were performed with the aid of DEPT, 2D-HETCOR and 2D-COSY NMR techniques when required. The compounds were diluted in deuterated chloroform, quoted in parts per million (ppm) and referenced to tetramethylsilane (TMS, δ=0) or the appropriate residual solvent peak. Infrared spectra were obtained from a Perkin–Elmer Spectrum One FT-IR spectrometer. For liquid samples, the spectra were recorded by preparing a thin film of compound between sodium chloride plates. Solid compounds were mixed with potassium bromide and pressed at high pressure until a transparent disc was obtained. IR spectra were also obtained from samples in neat form with an ATR (Attenuated Total Reflectance) accessory. Only selected absorbances (ν_{max}/cm^{-1}) are reported. LC–MS was performed with Agilent 1100 Series VL (ES, 4000V) equipment or Agilent 1100 Series SL (ES, 4000V) equipment, performing electrospray ionization at 4 kV (positive mode) or 3.5 kV (negative mode) and fragmentation at 70 eV, with only molecular ions ([MH]$^+$), and major peaks being reported with intensities quoted as percentage of the base peak, using either an LC–MS coupling or a direct inlet system. GC–MS was performed with Hewlett-Packard 6890 GC Plus coupled with a FID Detector equipped with a CIS-4-PTV (Programmed Temperature Vaporization) Injector (Gerstel), and HP5-MS capillary column (fused silica, AT-1, film thickness 0.25 μm, length 30 m, i.d. 0.25 mm, He as carrier gas), ionization EI at 70 eV. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and were not corrected. The elemental analysis of new compounds was performed with an Anca-NT System Elemental Analyzer.

4.2. Synthetic procedures

*4.2.1. Synthesis of 2-imidoylaziridines **3**.* Aziridines **3** were prepared according to the method described previously.[4]

*4.2.1.1. N-{(1E)-1-[cis-1-Benzenesulfonyl-2-chloro-3-p-tolylaziridin-2-yl](phenyl)methylidene}isopropylamine **3d**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.13 (d, 3H, J=6.1 Hz, CH_3), 1.28 (d, 3H, J=6.1 Hz, CH_3), 2.29 (s, 3H, CH_3), 3.65 (sept, 1H, J=6.1 Hz, *CH*N=), 4.86 (s, 1H, CH*p*-Tol), 6.97 (d, 2H, J=8.3 Hz, $CH_{arom.}$), 7.05 (d, 2H, J=8.3 Hz, $CH_{arom.}$), 7.41–7.62 (m, 8H, $CH_{arom.}$), 7.99–8.04 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2, 22.9, 23.4, 51.0, 53.5, 73.4, 127.5, 127.6, 128.05, 128.11, 128.4, 128.6, 128.8, 129.0, 133.5, 134.8, 138.3, 140.0, 159.6; IR (ATR): ν=1637 (C=N), 1344 and 1166 (S=O); MS (ES$^+$): m/z (%)=453/455 (MH$^+$, 29), 298/300 (100). Mp=46.3–46.9 °C. Yield 96%, brown crystals. Anal. Calcd for $C_{25}H_{25}ClN_2O_2S$: C, 66.28; H, 5.56; N, 6.18. Found: C, 66.03; H, 5.75; N, 6.01.

*4.2.1.2. N-{(1E)-1-[cis-1-Benzenesulfonyl-2-chloro-3-p-tolylaziridin-2-yl](p-tolyl)methylidene}isopropylamine **3e**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.12 (d, 3H, J=6.1 Hz, CH_3), 1.28 (d, 3H, J=6.1 Hz, CH_3), 2.29 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.68 (sept, 1H, J=6.1 Hz, *CH*N=), 4.85 (s, 1H, CH*p*-Tol), 6.98 (d, 2H, J=7.7 Hz, $CH_{arom.}$), 7.05 (d, 2H, J=8.3 Hz, $CH_{arom.}$), 7.28 (d, 2H, J=7.7 Hz, $CH_{arom.}$), 7.39 (d, 2H, J=7.7 Hz, $CH_{arom.}$), 7.47–7.62 (m, 3H, $CH_{arom.}$), 8.01 (d, 2H, J=7.2 Hz, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2, 21.4, 23.0, 23.4, 51.0, 53.4, 73.6, 127.5, 127.6, 128.0, 128.6, 128.8, 129.0, 131.8, 133.4, 138.3, 139.0, 140.1, 159.6; IR (ATR): ν=1636 (C=N), 1344 and 1166 (S=O); MS (ES$^+$): m/z (%)=467/469 (MH$^+$, 100). Mp=59.2–59.6 °C. Yield 96%, yellow crystals. Anal. Calcd for $C_{26}H_{27}ClN_2O_2S$: C, 66.87; H, 5.83; N, 6.00. Found: C, 66.54; H, 5.99; N, 6.09.

*4.2.1.3. N-{(1E)-1-[cis-1-Benzenesulfonyl-2-chloro-3-p-tolylaziridin-2-yl](phenyl)methylidene}cyclohexylamine **3f**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.03–1.90 (m, 10H, 5×CH_2), 2.29 (s, 3H, CH_3), 3.31–3.40 (m, 1H, *CH*N=), 4.91 (s, 1H, CH*p*-Tol), 6.97 (d, 2H, J=8.3 Hz, $CH_{arom.}$), 7.05 (d, 2H, J=8.3 Hz, $CH_{arom.}$), 7.42–7.63 (m, 8H, $CH_{arom.}$), 7.99–8.04 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2, 24.0, 24.1, 25.7, 32.7, 33.3, 51.0, 61.5, 73.6, 127.5, 128.0, 128.1, 128.3, 128.6, 128.8, 129.0, 133.4, 134.8, 138.3, 140.1, 159.6; IR (ATR): ν=1637 (C=N), 1345 and 1166 (S=O); MS (ES$^+$): m/z (%)=493/495 (MH$^+$, 100). Mp=72.1–72.3 °C. Yield 75%, yellow crystals. Anal. Calcd for $C_{28}H_{29}ClN_2O_2S$: C, 68.21; H, 5.93; N, 5.68. Found: C, 67.95; H, 6.12; N, 5.51.

*4.2.2. Synthesis of 2,5-diaryl-1H-imidazoles **14**.* Procedure A: a solution of 2-chloro-2-imidoylaziridine **3** (2 mmol) in 10 mL of acetonitrile was heated under reflux for 7–16 h (the reaction was followed up via TLC). After usual workup (diethyl ether—aqueous extraction), 1*H*-imidazole **14** was isolated in pure form after recrystallization from methanol.

Procedure B: aziridine **3** (1 mmol) was dissolved in $CHCl_3$ (2 mL) and stirred at room temperature for 24–48 h. After workup by water and $CHCl_3$ extraction, evaporation of the solvent gave a nearly pure crude sample, that was recrystallized from methanol.

*4.2.2.1. 1-Isopropyl-4-chloro-2,5-diphenyl-1H-imidazole **14a**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.26 (d, 6H, J=6.7 Hz, 2×CH_3), 4.51 (sept, 1H, J=6.7 Hz, *CH*N), 7.39–7.50 (m, 8H, $CH_{arom.}$), 7.55–7.57 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.4, 50.4, 127.6, 128.5, 128.6, 129.1, 129.3, 129.9, 131.3, 131.7, 146.5; IR (KBr): ν=1688 (C=N), 1606, 1482, 1448; MS (EI): m/z (%)=296/298 (M$^+$, 75), 254/256 (100), 227/229 (20), 192 (10), 150 (10), 124 (8), 104 (6), 89 (18), 77 (5). Mp (MeOH)=103.8–105.0 °C. Yield 88%, white crystals. Anal. Calcd for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; N, 9.44. Found: C, 72.72; H, 5.65; N, 9.49.

*4.2.2.2. 1-Isopropyl-4-chloro-5-(4-chlorophenyl)-2-phenyl-1H-imidazole **14b**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.25 (d, 6H, J=6.9 Hz, 2×CH_3), 4.51 (sept, 1H, J=6.9 Hz, *CH*N), 7.39–7.48 (m, 2H, $CH_{arom.}$), 7.38–7.41 (m, 5H, $CH_{arom.}$), 7.51–7.60 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.3, 50.4, 128.1, 128.4, 128.5, 128.8, 129.4, 129.7, 130.0, 132.9, 135.3, 146.8; IR (KBr): ν=1687 (C=N), 1601, 1481, 1446; MS (EI): m/z (%)=330/332/334 (M$^+$, 50), 288/290/292 (100), 226/

228 (14), 207 (5), 150/152 (6), 89 (10), 43 (5). Mp (MeOH)=120.7–122.5 °C. Yield 89%, white crystals. Anal. Calcd for $C_{18}H_{16}Cl_2N_2$: C, 65.27; H, 4.87; N, 8.46. Found: C, 65.19; H, 4.62; N, 8.40.

4.2.2.3. 1-Isopropyl-4-chloro-2-(4-chlorophenyl)-5-phenyl-1H-imidazole ***14c***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.23 (d, 6H, J=6.9 Hz, 2×CH_3), 4.47 (sept, 1H, J=6.9 Hz, CHN), 7.40–7.56 (m, 9H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.4, 50.5, 128.6, 128.8, 129.2, 129.7, 131.1, 131.7, 135.6, 145.3; IR (KBr): ν=1662 (C=N), 1485, 1450; MS (EI): m/z (%)=330/332/334 (M^+, 51), 288/286/284 (100), 226/228 (14), 123 (6), 89 (9), 43 (5). Mp (MeOH)=146.1–147.4 °C. Yield 84%, white crystals. Anal. Calcd for $C_{18}H_{16}Cl_2N_2$: C, 65.27; H, 4.87; N, 8.46. Found: C, 65.12; H, 4.67; N, 8.39.

4.2.2.4. 1-Isopropyl-4-chloro-5-phenyl-2-p-tolyl-1H-imidazole ***14d***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.24 (d, 6H, J=6.6 Hz, 2×CH_3), 2.42 (s, 3H, CH_3), 4.51 (sept, 1H, J=7.0 Hz, *CH*N), 7.27 (d, 2H, J=7.7 Hz, $CH_{arom.}$), 7.41–7.50 (m, 7H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.4, 23.3, 50.3, 127.4, 128.2, 128.4, 129.0, 129.1, 129.6, 129.9, 131.6, 139.2, 146.6; IR (ATR): ν=1731, 1482, 1443; MS (ES^+): m/z (%)=311/313 (MH^+, 100). Mp=143.9–144.3 °C. Yield 92%, yellow crystals. Anal. Calcd for $C_{19}H_{19}ClN_2$: C, 73.42; H, 6.16; N, 9.01. Found: C, 73.31; H, 6.45; N, 8.87.

4.2.2.5. 1-Isopropyl-4-chloro-2,5-di-p-tolyl-1H-imidazole ***14e***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.25 (d, 6H, J=6.6 Hz, 2×CH_3), 2.42 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.50 (sept, 1H, J=6.9 Hz, *CH*N), 7.24–7.34 (m, 6H, $CH_{arom.}$), 7.43–7.48 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.39, 21.44, 23.2, 50.2, 126.8, 127.4, 128.3, 128.4, 129.1, 129.2, 129.6, 131.5, 138.9, 139.2, 146.4; IR (ATR): ν=1682 (C=N), 1498, 1454; MS (ES^+): m/z (%)=325/327 (MH^+, 100). Mp=132.8–133.1 °C. Yield 95%, light brown crystals. Anal. Calcd for $C_{20}H_{21}ClN_2$: C, 73.95; H, 6.52; N, 8.62. Found: C, 73.80; H, 6.69; N, 8.41.

4.2.2.6. 1-Cyclohexyl-4-chloro-5-phenyl-2-p-tolyl-1H-imidazole ***14f***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.67–1.14 (m, 3H, CH_2, and C*H*H), 1.41–1.85 (m, 7H, 3×CH_2, and CH*H*), 2.42 (s, 3H, CH_3), 3.98–4.08 (m, 1H, *CH*N), 7.26 (d, 2H, J=7.7 Hz, $CH_{arom.}$), 7.39–7.49 (m, 7H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.4, 24.9, 26.0, 33.5, 59.1, 127.6, 128.2, 128.3, 128.9, 129.1, 129.6, 130.0, 131.7, 139.1, 146.7; IR (ATR): ν=1684 (C=N), 1485, 1442; MS (ES^+): m/z (%)=351/353 (MH^+, 100). Mp=149.3–149.5 °C. Yield 76%, yellow crystals. Anal. Calcd for $C_{22}H_{23}ClN_2$: C, 75.31; H, 6.61; N, 7.98. Found: C, 75.02; H, 6.84; N, 7.91.

4.2.3. Synthesis of N-isopropylhydrazine ***21***. To hydrazine (64% in water) (5.0 g, 0.1 mol) was added 2-bromopropane (0.04 mol, 4.88 g) followed by aqueous 2 N sodium hydroxide (10 mL, 0.02 mol). The reaction mixture was heated under reflux for 14 h, then distilled to give *N*-isopropylhydrazine **21** as a 24% w/w solution in water in quantitative yield (bp 103.0 °C/1 atm).

4.2.4. Synthesis of 1-isopropyl-1H-pyrazole ***18***. To dibenzoylmethane **22** (0.44 g, 2.0 mmol) in ethanol (10 mL) was added aqueous isopropylhydrazine **21** (24% w/w; 3.0 g, 10 mmol). After 24 h under reflux, 40 mL of water was added to the reaction mixture followed by extraction with diethyl ether (3×40 mL), and washing of the combined organic layers with brine. After drying the combined organic phases over magnesium sulfate, filtration, and removal of the solvent in vacuo, a crude yellow oil was isolated. After addition of methanol, pyrazole **18** (0.44 g) was isolated as colorless crystals (84% yield).

4.2.4.1. 1-Isopropyl-3,5-diphenyl-1H-pyrazole ***18***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.51 (d, 6H, J=6.6 Hz, 2×CH_3), 4.55 (sept, 1H, J=6.6 Hz, *CH*N), 6.52 (s, 1H, 4-CH), 7.29–7.46 (m, 8H, $CH_{arom.}$), 7.85–7.88 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.0, 50.2, 102.9, 125.6, 127.3, 128.4, 128.5, 128.7, 129.0, 131.2, 134.0, 143.9, 150.2; IR (KBr): ν=1606, 1482, 1460; MS (ES^+): m/z=263 (MH^+). Mp (MeOH)=57.6–58.9 °C. Yield 84%, colorless crystals. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68. Found: C, 82.23; H, 6.98; N, 10.73.

4.2.5. Synthesis of 4-chloropyrazole ***15***. To pyrazole **18** (0.26 g, 1.0 mmol) in carbon tetrachloride (5 mL) was added *N*-chlorosuccinimide (0.20 g, 1.5 mmol). After 13 h under reflux the reaction was cooled to room temperature, the precipitate was filtered and rinsed with carbon tetrachloride. After removal of the solvent in vacuo, the crude 4-chloropyrazole **15** together with 7% unreacted pyrazole **18** was obtained. Further purification by flash chromatography gave pure pyrazole **15** (0.24 g) as a yellow oil (80% yield).

4.2.5.1. 1-Isopropyl-4-chloro-3,5-diphenyl-1H-pyrazole ***15***. Spectral data obtained from the 93/7 mixture of 4-chloropyrazole **15** and pyrazole **18**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.48 (d, 6H, J=6.6 Hz, 2×CH_3), 4.45 (sept, 1H, J=6.6 Hz, *CH*N), 7.34–7.56 (m, 8H, $CH_{arom.}$), 7.95–7.99 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=22.7, 51.2, 106.1, 127.4, 127.8, 128.3, 128.5, 128.8, 129.1, 129.9, 132.4, 140.2, 146.1; IR (KBr): ν=1773, 1700, 1605, 1483, 1456; MS (EI): m/z (%)=296/298 (M^+, 79), 281/283 (63), 254/256 (100), 225 (8), 189 (24), 104 (12), 77 (10). Yield 80%. Anal. Calcd for $C_{18}H_{17}ClN_2$: C, 72.84; H, 5.77; N, 9.44. Found: C, 72.65; H, 5.81; N, 9.47.

4.2.6. Synthesis of 2,5-diphenyl-4-methoxy-1H-imidazole ***25***. Procedure A: to aziridine **3a** (1.0 mmol, 0.44 g) in methanol (5 mL) was added 2 N sodium methoxide in methanol (2.5 mmol, 1.25 mL). After 72 h under reflux the reaction mixture was neutralized with aqueous ammonium chloride, then the solvent was partially evaporated under vacuo. The residue was washed with water (20 mL) and extracted with diethyl ether (3×20 mL), then washed with brine. After drying the combined organic phases over magnesium sulfate, filtration and removal of the solvent in vacuo, a crude yellow oil was obtained. Chromatographic purification over silica gel (petroleum ether–ethyl acetate 9/1, R_f=0.30) gave crystalline imidazole **25** (0.06 g, 20% yield) and imidazole **14a** (0.03 g, 10%).

Procedure B: to a solution of aziridine **3a** (1 mmol, 0.44 g) in 5 mL of methanol at 0 °C, $NaBH_4$ (1.0 mmol, 38 mg) was added portionwise. The mixture was allowed to reach room temperature in 10 min, then refluxed for 6 h. Workup started with pouring the reaction mixture into an ice cooled solution of water (10 mL), and extraction with dichloromethane (3×60 mL). After drying of the combined extracts with magnesium sulfate and evaporation of the solvent in vacuo, the crude reaction mixture was purified by flash chromatography.

4.2.7. 1-Isopropyl-4-methoxy-2,5-diphenyl-1H-imidazole ***25***. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.26 (d, 6H, J=7.0 Hz, 2×CH_3), 3.90 (s, 3H, OCH_3), 4.48 (sept, 1H, J=7.0 Hz, *CH*N), 7.38–7.45 (m, 8H, $CH_{arom.}$), 7.55–7.57 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=23.5, 23.8, 49.7, 56.9, 112.4, 127.9, 128.4, 128.5, 128.8, 130.0, 130.9, 131.6, 132.4, 142.1, 153.0; IR (KBr): ν=1688 (C=N), 1609, 1368; MS (ES^+): m/z=293 (MH^+). Mp=109.5–110.3 °C (flash chromatography, petroleum ether–ethyl acetate 9/1, R_f=0.30). Yield 20%, white crystals. Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.91; H, 6.94; N, 9.50.

4.2.8. Synthesis of cis-(3-aryl-2-chloroaziridin-2-yl)(aryl)methanones ***30***. A solution of 2-chloro-2-imidoylaziridines **3** (2 mmol) in tetrahydrofuran (20 mL) was added to an equal amount of water (20 mL) and 2 N hydrochloric acid in water (3 mmol, 1.5 mL). After stirring at room temperature (4–8 h) the reaction was neutralized with 2 N aqueous sodium hydroxide and extracted with diethyl

ether, then washed with water and brine. After drying ($MgSO_4$) and evaporation of solvents in vacuo, a crude solid material was isolated. Recrystallization from methanol gave pure aziridines **30**.

*4.2.8.1. cis-[2-Chloro-1-(phenylsulfonyl)-3-phenylaziridin-2-yl](phenyl)methanone **30a**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.74 (s, 1H, C*H*Ph), 7.32–7.34 (m, 4H, CH), 7.47–7.53 (m, 4H, CH), 7.60–7.65 (m, 2H, CH), 7.92–7.95 (m, 2H, CH), 8.13–8.16 (m, 2H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=49.1, 70.2, 127.9, 128.3, 128.5, 128.6, 129.2, 129.3, 130.4, 130.8, 132.7, 134.4, 134.5, 137.9, 185.8; IR (KBr): ν=1692 (C=O); MS (ES^+): *m*/*z*=398 (MH^+, 46), 256 (20), 105 (100). Mp (MeOH)=102.1–103.0 °C. Yield 99%, white crystals. Anal. Calcd for $C_{21}H_{16}ClNO_3S$: C, 63.39; H, 4.05; N, 3.52. Found: C, 63.21; H, 4.16; N, 3.60.

*4.2.8.2. cis-[2-Chloro-1-(phenylsulfonyl)-3-phenylaziridin-2-yl](4-chlorophenyl)methanone **30b**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.74 (s, 1H, *CH*Ph), 7.32–7.34 (m, 4H, CH), 7.47–7.53 (m, 4H, CH), 7.60–7.65 (m, 2H, CH), 7.92–7.95 (m, 2H, CH), 8.13–8.16 (m, 2H, CH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=49.3, 70.0, 127.8, 128.3, 128.5, 129.0, 129.1, 129.2, 129.5, 130.2, 132.3, 134.6, 137.7, 141.1, 184.7; IR (KBr): ν=1687 (C=O); MS (ES^+): *m*/*z*=432/434/436 (MH^+, 45), 139/141 (100). Mp (Et_2O)=182.1–182.5 °C. Yield 93%, white crystals. Anal. Calcd for $C_{21}H_{15}Cl_2NO_3S$: C, 58.34; H, 3.50; N, 3.24. Found: C, 58.18; H, 3.61; N, 3.40.

*4.2.8.3. cis-[2-Chloro-1-(phenylsulfonyl)-3-(4-chlorophenyl)aziridin-2-yl](phenyl)methanone **30c**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.69 (s, 1H, C*H*Ar), 7.24–7.35 (m, 4H, $CH_{arom.}$), 7.48–7.58 (m, 4H, $CH_{arom.}$), 7.62–7.69 (m, 2H, $CH_{arom.}$), 7.91–7.94 (m, 2H, $CH_{arom.}$), 8.12–8.16 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=48.4, 70.1, 128.3, 128.6, 128.8, 129.0, 129.2, 129.4, 130.8, 132.6, 134.55, 134.61, 135.2, 137.7, 185.5; IR (KBr): ν=1696 (C=O); MS (ES^+): *m*/*z*=432/434/436 (MH^+, 40), 290/292 (22), 105 (100). Mp (Et_2O)=132.5–133.6 °C. Yield 74%, white crystals. Anal. Calcd for $C_{21}H_{15}Cl_2NO_3S$: C, 58.34; H, 3.50; N, 3.24. Found: C, 58.20; H, 3.41; N, 3.32.

*4.2.8.4. cis-[2-Chloro-1-(phenylsulfonyl)-3-p-tolylaziridin-2-yl](phenyl)methanone **30d**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.34 (s, 3H, CH_3), 4.69 (s, 1H, C*Hp*-Tol), 7.13–7.23 (m, 4H, $CH_{arom.}$), 7.47–7.67 (m, 6H, $CH_{arom.}$), 7.93–7.96 (m, 2H, $CH_{arom.}$), 8.13–8.16 (m, 2H, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.2, 49.1, 70.1, 127.2, 127.6, 128.1, 128.4, 129.1, 129.2, 130.7, 132.6, 134.2, 134.4, 137.8, 139.0, 185.7; IR (ATR): ν=1687 (C=O); MS (ES^+): *m*/*z*=429/431 ($M+NH_4^+$, 100), 411/413 (MH^+, 26). Mp (MeOH)=119.0–119.3 °C. Yield 73% from **3d**, 85% from **3f**, yellow crystals. Anal. Calcd for $C_{22}H_{18}ClNO_3S$: C, 64.15; H, 4.40; N, 3.40. Found: C, 63.82; H, 4.56; N, 3.57.

*4.2.8.5. cis-[2-Chloro-1-(phenylsulfonyl)-3-p-tolylaziridin-2-yl](p-tolyl)methanone **30e**.* ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.33 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 4.66 (s, 1H, C*Hp*-Tol), 7.14 (d, 2H, *J*=8.3 Hz, $CH_{arom.}$), 7.19 (d, 2H, *J*=8.3 Hz, $CH_{arom.}$), 7.30 (d, 2H, *J*=8.3 Hz, $CH_{arom.}$), 7.48–7.53 (m, 2H, $CH_{arom.}$), 7.60–7.65 (m, 1H, $CH_{arom.}$), 7.94 (d, 2H, *J*=7.2 Hz, $CH_{arom.}$), 8.06 (d, 2H, *J*=8.3 Hz, $CH_{arom.}$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.3, 21.9, 49.1, 70.2, 127.3, 127.6, 128.2, 129.1, 129.2, 130.1, 130.9, 134.2, 137.9, 139.0, 145.6, 185.3; IR (ATR): ν=1688 (C=O); MS (ES^+): *m*/*z*=443/445 ($M+NH_4^+$, 100), 426/428 (MH^+, 22). Mp (MeOH)=145.1–145.3 °C. Yield 68%, yellow crystals. Anal. Calcd for $C_{23}H_{20}ClNO_3S$: C, 64.86; H, 4.73; N, 3.29. Found: C, 64.74; H, 4.96; N, 3.04.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.11.082.

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