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Diastereoselective synthesis of 2-oxiranyl and 2-aziridinyl thiazoles

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Abstract—2-Chloroalkylthiazolyllithiums, prepared by deprotonating the 2-chloroalkylthiazoles with *n*-BuLi at −78°C in THF, add to ketones or imines affording in 'one-pot' oxiranes and aziridines in a *Z* stereoselective manner.

1. Introduction

2-Oxiranyl and aziridinyl thiazoles represent a versatile class of intermediates in synthetic organic chemistry. The high degree of ring strain of the oxiranyl and aziridinyl rings,[1] which gives them the propensity to undergo ring opening reactions, jointly with the susceptibility of the thiazole moiety to be elaborated (thiazole is a masked carbonyl function)[2] makes them particularly appealing in synthetic organic chemistry for the preparation of a variety of organic compounds, such as α-hydroxy-β-amino and α-amino-β-hydroxyaldehydes.[3]

The synthesis of 2-benzothiazolyl,[4] 2-oxazolinyl,[5] 2 (3 and 4)-pyridinyl[4b,6] oxiranes and aziridines, based on the coupling reaction of α-heteroarylchloromethyllithium which acts as a Darzens reagent, with carbonyl compounds or imines has been reported. These reactions were almost always characterized by a high *E* diastereoselectivity.

Despite their synthetic potential, few papers have been reported on the synthesis of oxiranyl and aziridinyl thiazoles. Recently, thiazolyl epoxides and aziridines have been stereoselectively obtained by the coupling of thiazolyllithium, generated by deprotonation of the 2-unsubstituted thiazole with *n*-BuLi, with α-chloroketones and α-chloroimines.[7] The number, however, of thiazolyl epoxides and aziridines that could be synthesized by this procedure is limited by the commercial availability of α-chloroketones and α-chloroimines.

We now describe a rather general method of preparation of various thiazolyl oxiranes and aziridines based on the lithiation of 2-chloroalkylthiazoles and subsequent coupling with carbonyl compounds and imines.

2. Results and discussion

The precursors 2-chloroalkylthiazoles **1a–c** were first synthesized. 2-(Chloromethyl)-4-methylthiazole **1a** was prepared by formylation[8] of 4-methylthiazole, reduction[9] of the obtained 2-thiazolylaldehyde and halogenation[10] of the corresponding 2-thiazolylcarbinol. 2-(1-Chloroethyl)-4-methylthiazole **1b** and 2-(chloro-phenyl-methyl)-4-methylthiazole **1c** were prepared by the coupling reaction of 2-(4-methyl)thiazolyllithium with acetaldehyde and benzaldehyde respectively,[11] and successive halogenation[10] of the resulting 2-thiazolylcarbinols. Lithiation of **1a** with *n*-BuLi at −78°C in THF produced a dark brown solution of 2-(4-methyl)thiazolylchloromethyllithium **1a′** (Scheme 1).

The addition of cyclohexanone **2a** to the solution of **1a′**, gave the 2-thiazolyloxirane **3a** in high yield (Table 1: entry 1).

Lithiation of **1b** and **1c** followed by the coupling with ketones **2a–c** produced oxiranes **3c–e**, **3h**, respectively (entries 3–5, 8). The coupling reaction of lithiated chloroalkyllithiums **1a′–c′** with asymmetrically substituted carbonyl compounds proceeded with a stereochemistry which was different with respect to that of the reported heteroarylmethyllithiums,[4a,5a,6] which afforded oxiranyl derivatives of *E* configuration exclusively. Indeed, using acetaldehyde **2d** and benzaldehyde **2e**, the coupling reactions of **1a′–c′** afforded a mixture of isomeric epoxides

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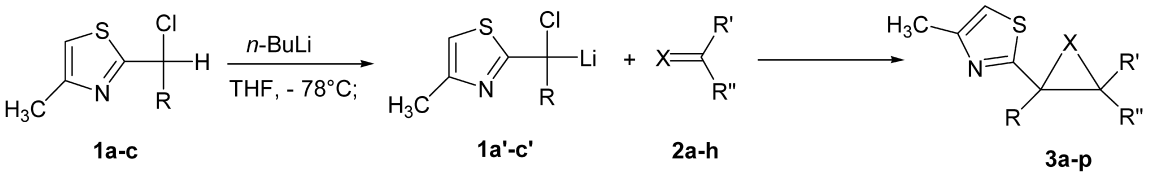


1a': R = H **2a:** X = O; R'= R''= -$(CH_2)_5$- **3a:** X = O; R = H; R'= R''= -$(CH_2)_5$-

1b': R = CH_3 **2b:** X = O; R'= R''= CH_3 **3b:** ***Z***: X = O; R = R''= H; R'= Ph
E: X = O; R = R'= H; R''=Ph

1c': R = Ph **2c:** X = O; R'= R''=  **3c:** X = O; R = CH_3; R'= R''= -$(CH_2)_5$-

2d: X = O; R'= H; R''= CH_3 **3d:** X = O; R = R'= R''= CH_3

2e: X = O; R'= H; R''= Ph **3e:** X = O; R = CH_3; R'= R''= 

2f: X = N-Ph; R'= H; R''= Ph **3f:** ***Z***: X = O; R = R'= CH_3; R''= H
E: X = O; R = R''= CH_3; R'= H

2g: X = N-Ph; R'= R''= -$(CH_2)_5$- **3g:** ***Z***: X = O; R = CH_3; R'= Ph; R''= H
E: X = O; R = CH_3; R'= H; R''= Ph

3h: X = O; R = Ph; R'= R''= -$(CH_2)_5$-

3i: ***Z***: X = O; R = Ph; R'= CH_3; R''= H
E: X = O; R = Ph; R'= H; R''= CH_3

3l: ***Z***: X = O; R = R'= Ph; R''= H
E: X = O; R = R''= Ph; R'= H

3m: ***Z***: X = N-Ph; R = R''= H; R'= Ph
E: X = N-Ph; R = R'= H; R''= Ph

3n: ***Z***: X = N-Ph; R = CH_3; R'= Ph; R''= H
E: X = N-Ph; R = CH_3; R'= H; R''= Ph

3o: ***Z***: X = N-Ph; R = R'= Ph; R''= H
E: X = N-Ph; R = R''= Ph; R'= H

3p: X = N-Ph; R = CH_3; R'= R''= -$(CH_2)_5$-

Scheme 1.

Table 1. The coupling reactions between lithiated thiazolylalkylchlorides and carbonyl and imine compounds affording thiazolyl oxiranes and aziridines

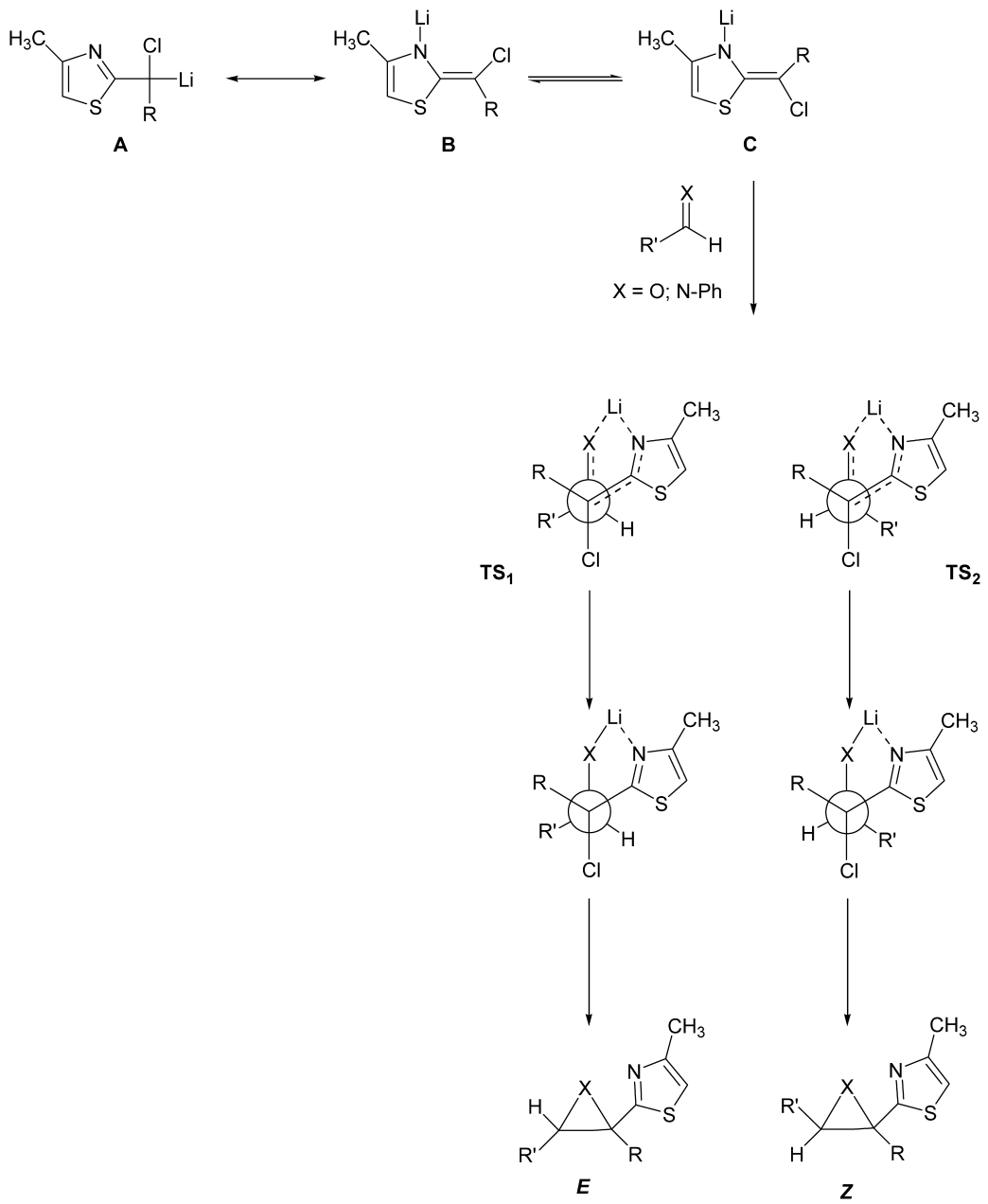
Entry	Reagents	Products	Yield (%)[a]	dr[b] (*Z*/*E*)
1	**1a′+2a**	**3a**	90	–
2	**1a′+2e**	**3b**	80	25:75
3	**1b′+2a**	**3c**	80	–
4	**1b′+2b**	**3d**	63	–
5	**1b′+2c**	**3e**	70	–
6	**1b′+2d**	**3f**	70	32:68
7	**1b′+2e**	**3g**	76	95:5
8	**1c′+2a**	**3h**	73	–
9	**1c′+2d**	**3i**	90	80:20
10	**1c′+2e**	**3l**	78	70:30
11	**1a′+2f**	**3m**	40	65:35
12	**1b′+2f**	**3n**	84	100:0
13	**1c′+2f**	**3o**	50	40:60
14	**1b′+2g**	**3p**	50	–

[a] Isolated yields.
[b] Diastereomeric ratio.

(entry 2, *Z*/*E*∼1:3; entry 6, *Z*/*E*∼1:2; entry 9, *Z*/*E*∼4:1; entry 10, *Z*/*E* 2:1). The reaction of **1b′** with benzaldehyde **2e** led almost exclusively to the epoxide **3g** showing *Z* configuration (entry 7, *Z*/*E*∼95:5).

2-Aziridinyl thiazoles could be prepared by the coupling reaction of 2-chloroalkylthiazoles **1a′**–**c′** with imines. We found that 2-chloroethylthiazolyllithium **1b′** at −78°C in THF reacts with imine **2g** giving aziridine **3p** (entry 14) and with imine **2f** to give stereoselectively aziridine **3n** showing *Z* configuration (entry 12). The coupling reactions of **1a′** and **1c′** with **2f** produced an isomeric mixture of aziridines: *Z*/*E*=65:35 (entry 11) and 40:60 (entry 13) respectively, while the reactions of heteroarylmethyllithiums, as reported,[4b,5a] gave aziridines of *E* configuration exclusively.

The stereochemistry of epoxide **3b** and aziridine **3m** was assigned on the basis of the ^{1}H NMR coupling constants between the two oxiranyl or aziridinyl hydrogens[12] (J_{cis}> J_{trans}); the configurations of oxiranes **3f** and **g**, **3i**–**l**, and



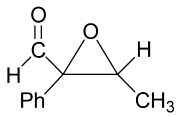
Scheme 2.

aziridines **3n** and **o** were established on the basis of an upfield shift for a CH_3 group and H in the case of a *cis* relationship with a Ph group or with a CH_3 group. Indeed, it has been reported that a high field displacement occurs when a CH_3 group is on the same side of a Ph group, while a smaller upfield shift is observed when two Me groups are on the same side.[13] The configuration assignment was confirmed, for oxirane **3g** and aziridine **3n**, by ^{13}C NMR spectroscopy.[14] Indeed, in the $^{13}C-H$ coupled spectrum the $^3J_{CH3-H}$ (1.76 Hz) of the *Z* isomer (having the CH_3 and the ring hydrogen on the same side) was found to be larger than that of the *E* isomer ($^3J_{CH3-H}\sim 0$ Hz).

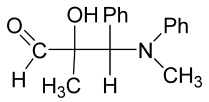
A possible explanation of the results reported here might be given by considering the structure of the heteroarylchloroalkyllithiums **1a′–c′** and the rate-determining step in the reactions leading to oxiranes and aziridines. There is spectroscopic evidence[15] that in heterocyclic azines and azoles, as in compounds **1a′–c′**, a substantial proportion of the negative charge is delocalized on the aza-heterocyclic system. Such propensity of heterocyclic groups to delocalize negative charge is responsible for the double bond fixation of the exocyclic C=C bond in anions **1a′–c′**. Chloroalkyllithiums **1a′–c′**, therefore, should exist as an equilibrium of the isomeric forms B and C (which resonate with A; Scheme 2). Considering the experimental conditions of the Darzens reaction of **1a′–c′**, the B/C ratio should be substantially shifted toward the stereomeric form C.[16] We presume that the reacting carbanionic species C may discriminate between the two enantiotopic faces of the electrophile leading to transition states TS_1 and TS_2. These are both stabilized by the intramolecular chelation of lithium, but one of the two should be energetically favoured in view of the R and R′ groups steric interaction (Scheme 2).

In particular, when R=H, TS_1, which would evolve to the *E* oxirane or aziridine, is evidently for steric reasons of lower energy than transition state TS_2, which would lead to the *Z* form (entry 2). Instead, when R=CH_3, TS_2 could become energetically favoured providing, therefore, the *Z* diastereomer exclusively (entry 12). Moreover, the R′ structure could sterically influence the transition state formation, and consequently the *Z*/*E* ratio, as showed by the remaining results.

The *E* epoxide **3i** and *Z* aziridine **3n** were unmasked upon thiazole ring opening according to a known protocol.[2c] While the oxirane **3i** gave the expected oxiranyl adehyde **4a**, as reported,[7] the aziridine **3n** gave the hydroxyaminoaldehyde **4b** through the opening of both the thiazole and the aziridine ring.



4a



4b

3. Conclusion

In conclusion, thiazolyl chloroalkyllithiums **1a′**–**c′**, easily available by lithiation of chloroalkanes **1a**–**c**, react as Darzens-type reagents with ketones and imines, sometimes in a stereoselective way, to form substituted thiazolyl oxiranes and aziridines, which are potentially useful intermediates for the synthesis of pharmacologically and biologically interesting compounds.

4. Experimental

n-Butyllithium (*n*-BuLi) was bought as a commercial solution in hexanes (Aldrich) and titrated with *N*-pivaloyl-*o*-toluidine prior to use.[17] THF, 4-methylthiazole, cyclohexanone, acetone, adamantanone, dichloromethane, triethylamine, lithium diisopropylamine were of commercial grade (Aldrich), and they were used without further purification. Acetaldehyde and benzaldehyde of commercial grade (Aldrich), were purified by distillation prior to use. Petroleum ether refers to the 40–60°C boiling fraction. The ^{1}H and the ^{13}C NMR spectra were recorded on a Bruker AC200 apparatus (200 and 50.3 MHz, for ^{1}H and ^{13}C, respectively); with $CDCl_3$ as solvent and TMS as internal standard (δ_H=7.24 for ^{1}H spectra; δ_H=77.0 for ^{13}C spectra). The IR spectra were recorded on a Perkin–Elmer spectrometer Model 283. GC-MS analyses were performed with Hewlett–Packard HP-5890 series II gas chromatograph (5% phenyl-methylsiloxane capillary column, 30 m, 0.25 mm i.d.), equipped with an HP 5971 mass-selective detector operating at 70 eV (EI). The electrospray ionisation (HR-ESI-MS) experiments were carried out in a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) equipped with an ion spray ionisation source. MS (+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL), dissolved in solution 0.1% acetic acid, methanol/water 50:50 at the optimum ion voltage of 4800 V. The nitrogen gas flow was set at 30 psi (pounds per square inch) and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50, and 25 V relative to ground, respectively. Melting points were determined using an electrothermal melting point apparatus and were uncorrected. TLC were performed on Merck silica gel plates with F-254 indicator; viewing was by UV light (254 nm). Column chromatographies were performed on silica gel (63–200 μm) using petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware using syringe/septum cap techniques. Microanalyses were performed on a Carlo Erba C, H, N, analyzer.

4.1. General procedure for the preparation of 2-thiazolyl oxiranes (3a–l)

A stirred solution of 2 mmol of **1a**–**c** in THF (30 mL), at −78°C was treated with *n*-BuLi in hexanes (2.5 M, 1 mL, 2.5 mmol), and then a solution of the electrophile **2a**–**h** (2 mmol) in THF (5 mL) was added dropwise, under N_2. The reaction mixtures were kept at −78°C for 30 min, and then warmed and kept to room temperature for 10–12 h, quenched with water (10 mL), and extracted with Et_2O (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 8:2) to afford the pure thiazolyl oxiranes (colourless oils), yields: 63–90%.

4.1.1. 4-Methyl-2-(1-oxa-spiro[2.5]oct-2-yl)-thiazole (3a). Yield: 376.2 mg, (90%), oil. IR (film): 3100, 3060, 2920, 2845, 1515, 1440, 1300, 1225, 910, 730 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.52–1.86 (m, 10H), 2.46 (d, 3H, *J*=0.9 Hz), 4.08 (s, 1H), 6.85 (q, 1H, *J*=0.9 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 15.2, 24.5, 24.9, 25.3, 28.6, 35.0, 62.4, 65.8, 113.3, 153.0, 171.0. GC-MS (70 eV) *m*/*z* (rel. int.): 209 (33, M^+), 192 (62), 180 (42), 164 (45), 152 (13), 128 (100), 112 (24), 100 (44). HR-ESI-MS: *m*/*z* calcd for $C_{11}H_{16}NOS$: 210.0953, $[M+H]^+$; found 210.0980.

4.1.2. 4-Methyl-2-(3-phenyl-oxiranyl)-thiazole (3b). Overall yield: 347.2 mg (80%), oil. *Z*. Yield: 86.8 mg (25%), oil. IR ($CHCl_3$): 3030, 2930, 2860, 1610, 1450, 1300, 1035, 860, 760, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.34 (d, 3H, *J*=0.8 Hz), 4.49 (d, 1H, *J*=4.1 Hz), 4.60 (d, 1H, *J*=4.1 Hz), 6.65 (q, 1H, *J*=0.8 Hz), 7.25–7.36 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 16.8, 57.8, 60.4, 114.2, 127.1, 128.0, 128.2, 133.0, 152.6, 167.0. GC-MS (70 eV) *m*/*z* (rel. int.): 217 (7, M^+), 200 (95), 188 (100), 167 (3), 147 (3), 126 (8), 105 (9), 91 (24). HR-ESI-MS: *m*/*z* calcd for $C_{12}H_{12}NOS$: 218.0640, $[M+H]^+$; found 218.0612. *E*. Yield: 260.4 mg (75%), oil. IR ($CHCl_3$): 3030, 2930, 2860, 1610, 1450, 1300, 1035, 860, 760, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42, (d, 3H, *J*=0.8 Hz), 4.08 (d, 1H, *J*=1.8 Hz), 4.18 (d, 1H, *J*=1.8 Hz), 6.84 (q, 1H, *J*=0.8 Hz), 7.2–7.3 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 22.6, 59.9, 63.3, 113.7, 125.6, 128.7, 128.8, 135.5, 153.4, 167.0. GC-MS (70 eV) *m*/*z* (rel. int.): 217 (11, M^+), 200 (90), 188 (100), 167 (4), 147 (3), 126 (10), 105 (10), 91 (26). HR-ESI-MS: *m*/*z* calcd for $C_{12}H_{12}NOS$: 218.0640, $[M+H]^+$; found 218.0620.

4.1.3. 4-Methyl-2-(2-methyl-1-oxa-spiro[2.5]oct-2-yl)-thiazole (3c). Yield: 356.8 mg (80%), oil. IR ($CHCl_3$):

3100, 3060, 3000, 2920, 2850, 1500, 1420, 1200, 1030 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.2–1.8 (m, 10H), 2.0 (s, 3H), 2.4 (d, 3H, J=0.85 Hz), 6.81 (q, 1H, J=0.85 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.1, 21.7, 21.8, 25.5, 27.3, 31.2, 31.9, 72.0, 76.4, 114.0, 152.8, 170.2. GC-MS (70 eV) *m/z* (rel. int.): 223 (26, M^+), 204 (7), 180 (100), 152 (23), 126 (45), 124 (44). HR-ESI-MS: *m/z* calcd for $C_{12}H_{18}NOS$: 224.1110, $[M+H]^+$; found 224.1136.

4.1.4. 4-Methyl-2-(2,3,3,trimethyl-oxiranyl)-thiazole (3d). Yield: 230.6 mg (63%), oil. IR ($CHCl_3$): 3020, 2960, 2920, 2880, 1530, 1440, 1370, 1300, 1200, 1140, 1050 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.45 (s, 3H), 1.73 (s, 3H), 2.42 (d, 3H, J=0.8 Hz), 6.77 (q, 1H, J=0.8 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.1, 19.4, 20.7, 21.0, 65.4, 65.8, 113.0, 153.0, 172.0. GC-MS (70 eV) *m/z* (rel. int.): 183 (34, M^+), 168 (54), 142 (100), 100 (36), 72 (67). HR-ESI-MS: *m/z* calcd for $C_9H_{14}NOS$: 184.0793, $[M+H]^+$; found 184.0815.

4.1.5. 3′-Methyl-3′-[2-(methylthiazolyl)]-2′spiroadamantan-oxirane (3e). Yield: 385 mg (70%), oil. IR ($CHCl_3$): 2910, 2850, 1530, 1450, 1375, 1300, 1070, 1050 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.26–2.1 (m, 14H), 1.75 (s, 3H), 2.45 (d, 3H, J=0.8 Hz), 6.78 (q, 1H, J=0.8 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.7, 18.7, 27.1, 27.3, 32.5, 33.3, 35.3, 35.5, 36.1, 36.6, 36.8, 67.2, 75.3, 113.4, 153.3, 172.0. GC-MS (70 eV) *m/z* (rel. int.): 275 (38, M^+), 233 (40), 232 (100), 142 (10), 125 (15), 91 (16), 72 (16). HR-ESI-MS: *m/z* calcd for $C_{16}H_{22}NOS$: 276.1423, $[M+H]^+$; found 276.1462.

4.1.6. 2-(2,3-Dimethyl-oxiranyl)-4-methyl-thiazole (3f). Overall yield: 236.6 mg (70%), oil. *Z*. Yield: 75.7 mg (32%), oil. IR (film): 3100, 2960, 2925, 2880, 1530, 1450, 1385, 1300, 1270, 1070, 810 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.15 (d, 3H, J=5.5 Hz), 1.7 (s, 3H), 2.38 (d, 3H, J=0.8 Hz), 3.20 (q, 1H, J=5.5 Hz), 6.7 (q, 1H, J=0.8 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.6, 17.2, 22.6, 59.5, 63.0, 113.4, 153.3, 174.1. GC-MS (70 eV) *m/z* (rel. int.): 169 (50, M^+), 154 (100), 142 (20), 126 (70), 72 (90). HR-ESI-MS: *m/z* calcd for $C_8H_{12}NOS$: 170.0640, $[M+H]^+$; found 170.0630. *E*. Yield: 161.0 mg (68%), oil. IR (film): 3100, 2960, 2925, 2880, 1530, 1450, 1385, 1300, 1270, 1070, 810, 750 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (d, 3H, J=5.4 Hz), 1.7 (s, 3H), 2.35 (d, 3H, J=0.8 Hz), 3.13 (q, 1H, J=5.4 Hz), 6.7 (q, 1H, J=0.8 Hz). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.0, 15.7, 17.1, 60.1, 64.0, 113.2, 152.9, 173.0. GC-MS (70 eV) *m/z* (rel. int.): 169 (55, M^+), 154 (100), 142 (22), 126 (70), 72 (92). HR-ESI-MS: *m/z* calcd for $C_8H_{12}NOS$: 170.0640, $[M+H]^+$; found 170.0675.

4.1.7. 4-Methyl-2-(2-methyl-3-phenyl-oxiranyl)-thiazole (3g). Overall yield: mg 351.1 (76%), oil. *Z*. Yield: 333.6 mg (95%), oil. IR ($CHCl_3$): 3060, 2920, 2850, 1600, 1490, 1450, 1100, 1070 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.89 (s, 3H), 2.46 (d, 3H, J=0.8 Hz), 5.23 (s, 1H), 6.86 (q, 1H, J=0.8 Hz), 7.25–7.28 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.1, 28.6, 72.8, 80.3, 114.6, 127.6, 128.1, 128.2, 138.1, 152.8, 173.1. GC-MS (70 eV) *m/z* (rel. int.): 231 (100, M^+), 230 (51), 213 (26), 202 (36), 154 (60), 125 (73), 124 (64). HR-ESI-MS: *m/z* calcd for $C_{13}H_{14}NOS$: 232.0797, $[M+H]^+$; found 232.0780. *E*: traces identified in reaction mixture with *Z* form. ^1H NMR (200 MHz, $CDCl_3$): δ 1.62 (s, 3H), 2.46 (s, 3H), 5.25 (s, 1H), 6.87 (s, 1H), 7.25–7.28 (m, 5H). GC-MS (70 eV) *m/z* (rel. int.): 231 (100, M^+), 213 (25), 202 (38), 154 (58), 125 (73), 124 (67). HR-ESI-MS: *m/z* calcd for $C_{13}H_{14}NOS$: 232.0797, $[M+H]^+$; found 232.0765.

4.1.8. 4-Methyl-2-(2-phenyl-1-oxa-spiro[2.5]oct-2-yl)-thiazole (3h). Yield: 416 mg (73%), oil. IR ($CHCl_3$): 3060, 3030, 2940, 2850, 1600, 1520, 1490, 1450, 1300, 1130 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.3–1.7 (m, 10H), 2.42 (d, 3H, J=0.8 Hz), 6.75 (q, 1H, J=0.8 Hz), 7.25–7.40 (m, 3H), 7.68–7.70 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.2, 24.4, 24.5, 25.2, 30.8, 30.9, 69.5, 71.8, 113.2, 127.2, 127.6, 127.9, 137.0, 153.0, 169.4. GC-MS (70 eV) *m/z* (rel. int.): 285 (66, M^+), 268 (12), 205 (100), 187 (41), 186 (36), 147 (42), 105 (34). HR-ESI-MS: *m/z* calcd for $C_{17}H_{20}NOS$: 286.1267, $[M+H]^+$; found 286.1292.

4.1.9. 4-Methyl-2-(3-methyl-2-phenyl-oxiranyl)-thiazole (3i). Overall yield: 415.8 mg (90%), oil. *Z*. Yield: 332.6 mg (80%), oil. IR ($CHCl_3$): 3050, 2960, 2920, 2850, 1600, 1530, 1445, 1370, 1290, 1010, 750, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.33 (d, 3H, J=5.3 Hz), 2.50 (s, 3H), 3.46 (q, 1H, J=5.3 Hz), 6.86 (s, 1H), 7.28–7.41 (m, 3H), 7.58–7.64 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.6, 17.2, 64.0, 64.7, 114.4, 126.3, 128.0, 128.1, 138.1, 153.2, 167.0. GC-MS (70 eV) *m/z* (rel. int.): 231 (68, M^+), 202 (100), 186 (70), 147 (94), 105 (79). HR-ESI-MS: *m/z* calcd for $C_{13}H_{14}NOS$: 232.0797, $[M+H]^+$; found 232.0840. *E*. Yield: 83.2 mg (20%), oil. IR ($CHCl_3$): 3100, 3060, 2960, 2920, 2850, 1600, 1530, 1445, 1370, 1290, 1010, 750, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.15 (d, 3H, J=5.3 Hz), 2.43 (s, 3H), 3.88 (q, 1H, J=5.3 Hz), 6.80 (s, 1H), 7.28–7.41 (m, 3H), 7.58–7.64 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 14.6, 17.2, 63.4, 64.7, 113.7, 126.3, 128.1, 128.2, 138.1, 153.2, 167.0. GC-MS (70 eV) *m/z* (rel. int.): 231 (60, M^+), 202 (90), 186 (65), 147 (100), 105 (70). HR-ESI-MS: *m/z* calcd for $C_{13}H_{14}NOS$: 232.0797, $[M+H]^+$; found 232.0820.

4.1.10. 2-(2,3-Diphenyl-oxiranyl)-4-methyl-thiazole (3l). Overall yield: 457.1 mg (78%), oil. *Z*. Yield: 320 mg (70%), oil. IR ($CHCl_3$): 3060, 3030, 2940, 2850, 1600, 1520, 1490, 1450 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.23, (d, 3H, J=0.8 Hz), 4.4 (s, 1H), 6.74 (q, 1H, J=0.8 Hz), 7.10–7.71 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.1, 66.1, 68.7, 113.6, 126.6, 127.7, 127.8, 128.3, 128.4, 128.8, 140.0, 152.8, 170.1. GC-MS (70 eV) *m/z* (rel. int.): 293 (20, M^+), 264 (27), 186 (25), 167 (100), 147 (36), 105 (30). HR-ESI-MS: *m/z* calcd for $C_{18}H_{16}NOS$: 294.0954, $[M+H]^+$; found 294.0967. *E*. Yield: 137 mg (30%), oil. IR ($CHCl_3$): 3060, 3030, 2940, 2850, 1600, 1520, 1490, 1450 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.49, (d, 3H, J=0.8 Hz), 4.91 (s, 1H), 6.87 (q, 1H, J=0.8 Hz), 7.10–7.71 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.2, 66.5, 67.5, 114.8, 126.2, 126.7, 127.8, 128.0, 128.3, 128.6, 128.9, 134.0, 153.7, 170.1. GC-MS (70 eV) *m/z* (rel. int.): 293 (22, M^+), 264 (24), 186 (25), 167 (100), 147 (39), 105 (30). HR-ESI-MS: *m/z* calcd for $C_{18}H_{16}NOS$: 294.0954, $[M+H]^+$; found 294.0980.

4.2. General procedure for the preparation of 2-thiazolyl aziridines (3m–3p)

A solution of *n*-BuLi in hexane (2.5 M, 1 mL, 2.5 mmol) was added to 10 mL of THF, at −78°C, under N_2, and then a solution of 2-thiazolyl derivatives **1a–c** (2 mmol) and the electrophiles **2f** and **g** (2 mmol) in THF (5 mL) were added dropwise. The reaction mixtures were kept at −78°C for 30 min, and then warmed and kept to room temperature for 5–6 h, quenched with 50 mL of a saturated aqueous NH_4Cl solution, and extracted with Et_2O (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 7:3) to afford the pure thiazolyl aziridines (oils), yields: 40–84%. GC-MS data are not available because of the on column cleavage of the aziridinic ring. However, the empirical formulae were confirmed by microanalyses.

4.2.1. 2-(1,3-Diphenyl-aziridin-2-yl)-4-methyl-thiazole (3m). Overall yield: 160 mg (40%), oil. *Z*. Yield: 104 mg (65%), oil. IR ($CHCl_3$): 3060, 3030, 2960, 2920, 2840, 1495, 1450, 1350, 1270 cm^{-1}. ^1H NMR (200 MH, $CDCl_3$): δ 2.44, (d, 3H, *J*=0.8 Hz), 3.26 (d, 1H, *J*=15.1 Hz), 3.96 (d, 1H, *J*=15.1 Hz), 6.71 (q, 1H, *J*=0.8 Hz), 6.9–7.4 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.0, 46.9, 49.8, 113.4, 113.8, 119.7, 123.4, 127.6, 128.0, 128.2, 129.3, 147.6, 152.3, 166.5. HR-ESI-MS: *m/z* calcd for $C_{18}H_{17}N_2S$: 293.1114, $[M+H]^+$; found 293.1080. Anal. calcd for $C_{18}H_{16}N_2S$ (292.325): C, 73.96; H, 5.52; N, 9.58; S, 10.97; found: C, 73.69; H, 5.48; N, 9.47; S, 10.88. *E*. Yield: 56 mg (35%)104, oil. IR ($CHCl_3$): 3060, 3030, 2960, 2920, 2840, 1495, 1450, 1350, 1270 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.35 (d, 3H, *J*=0.8 Hz), 3.80 (d, 1H, *J*=6.3 Hz), 3.97 (d, 1H, *J*=6.3 Hz,), 6.67 (q, 1H, *J*=0.8 Hz), 6.85–7.45 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.0, 52.6, 52.8, 113.8, 114.3, 120.3, 123.3, 127.5, 127.8, 128.1, 129.1, 147.6, 152.2, 166.2. HR-ESI-MS: *m/z* calcd for $C_{18}H_{17}N_2S$: 293.1112, $[M+H]^+$; found 293.1127. Anal. calcd for $C_{18}H_{16}N_2S$ (292.403): C, 73.94; H, 5.52; N, 9.58; S, 10.96; found: C, 73.72; H, 5.58; N, 9.49; S, 10.85.

4.2.2. 4-Methyl-2-(2-methyl-1,3-diphenyl-aziridin-2-yl)-thiazole (3n). Yield: 514.1 mg (84%), oil. *Z*. Yield: 514.1 mg (100%), oil. IR ($CHCl_3$): 3060, 3030, 2940, 2920, 2860, 1600, 1490, 1450, 1380, 1240, 1070, 1030, 760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.65 (s, 3H), 2.24 (d, 3H, *J*=0.8 Hz), 3.60 (s, 1H), 6.45 (q, 1H, *J*=0.8 Hz), 6.96–7.40 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.0, 18.8, 50.2, 54.6, 113.5, 120.0, 122.8, 127.2, 127.8, 128.9, 135.0, 148.2, 152.6, 170.8. HR-ESI-MS: *m/z* calcd for $C_{19}H_{19}N_2S$: 307.1270, $[M+H]^+$; found 307.1250. Anal. calcd for $C_{19}H_{18}N_2S$ (306.430): C, 74.47; H, 5.92; N, 9.14; S, 10.46; found: C, 74.55; H, 5.80; N, 8.99; S, 10.28.

4.2.3. 4-Methyl-2-(1,2,3-triphenyl-aziridin-2-yl)-thiazole (3o). Overall yield: 368 mg (50%), oil. *Z*. Yield: 147.2 mg (40%), oil. IR ($CHCl_3$): 3060, 3030, 2940, 2840, 1600, 1495, 1450, 1375, 1210, 1050 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.40 (d, 3H, *J*=0.8 Hz), 4.20 (s, 1H), 6.75–7.47 (m, 16H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.3, 61.4, 68.2, 113.9, 115.4, 118.5, 124.1, 127.1, 127.2, 127.6, 128.1, 128.7, 128.8, 129.0, 129.5, 138.1, 152.9, 173.1. HR-ESI-MS: *m/z* calcd for $C_{24}H_{21}N_2S$: 369.9939, $[M+H]^+$; found 369.9914. Anal. calcd for $C_{24}H_{20}N_2S$ (368.490): C, 78.23; H, 5.47; N, 7.60; S, 8.70; found: C, 78.30; H, 5.39; N, 7.49; S, 8.69. *E*. Yield: 220.2 mg (60%), oil. IR ($CHCl_3$): 3060, 3030, 2940, 2840, 1600, 1495, 1450, 1375, 1210, 1050 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.38 (d, 3H, *J*=0.8 Hz), 4.80 (s, 1H), 6.74–7.50 (m, 16H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.2, 60.1, 63.8, 113.8, 114.3, 118.5, 124.1, 127.0, 127.4, 127.5, 128.2, 128.7, 128.9, 129.0, 129.2, 141.1, 153.0, 173.4. HR-ESI-MS: *m/z* calcd for $C_{24}H_{21}N_2S$: 369.1421, $[M+H]^+$; found 369.1430. Anal. calcd for $C_{24}H_{20}N_2S$ (368.501): C, 78.22; H, 5.47; N, 7.60; S, 8.70; found: C, 78.20; H, 5.49; N, 7.45; S, 8.59.

4.2.4. 2-Methyl-2-(4-methyl-thiazol-2-yl)-1-phenyl-1-aza-spiro[2.5]octane (3p). Yield: 298 mg (50%), oil. IR ($CHCl_3$): 3030, 2920, 2860, 1600, 1490, 1450, 1370, 1220, 1050 cm^{-1}. ^1H NMR (200 MH, $CDCl_3$): δ 1.58 (s, 3H), 2.47 (d, 3H, *J*=0.8 Hz), 1.40–1.86 (m, 10H), 6.76 (q, 1H, *J*=0.8 Hz), 6.95–6.99 (m, 3H), 7.26–7.29 (m, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.1, 21.7, 21.8, 25.6, 27.3, 31.0, 31.9, 52.6, 77.3, 113.3, 120.8, 121.7, 129.3, 146.4, 153.4, 171.1. HR-ESI-MS: *m/z* calcd for $C_{18}H_{23}N_2S$: 299.1582, $[M+H]^+$; found 299.1600. Anal. calcd for $C_{18}H_{22}N_2S$ (298.450): C, 72.44; H, 7.43; N, 9.39; S, 10.74; found: C, 72.50; H, 7.35; N, 9.30; S, 10.80.

4.3. Thiazolyl ring opening reaction

The ring-opening reaction was carried out according to Dondoni's method[2c] on 1 mmol of **3i** and **3n**.

4.3.1. 3-Methyl-2-phenyl-oxirane-2-carboxyaldehyde (4a). Yield: 145 mg (90%), oil. IR ($CHCl_3$): 3060, 3040, 2990, 2820, 1730, 1500, 1450, 1420, 1375, 1240, 1100 cm^{-1}. ^1H NMR (200 MH, $CDCl_3$): δ 1.12 (d, 3H, *J*=5.0 Hz), 3.56 (q, 1H, *J*=5.0 Hz), 7.33–7.45 (m, 5H), 9.2 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 13.6, 58.1, 64.2, 127.7, 127.8, 128.1, 128.4, 197.6. GC-MS (70 eV) *m/z* (rel. int.): 162 (26, M^+), 147 (27), 105 (100), 90 (35), 89 (35), 77 (42). HR-ESI-MS: *m/z* calcd for $C_{10}H_{11}O_2$: 163.0759, $[M+H]^+$; found 163.0765. Anal. calcd for $C_{10}H_{10}O_2$ (162.188): C, 74.06; H, 6.21; found: C, 74.15; H, 5.35.

4.3.2. 2-Hydroxy-2-methyl-3-(methyl-phenyl-amino)-3-phenyl-proprionaldehyde (4b). Yield: 107 mg (40%), oil. IR (film): 3350 (broad), 3060, 2920, 2850, 1695, 1590, 1485, 1375, 1365, 1200, 1100 cm^{-1}. ^1H NMR (200 MH, $CDCl_3$): δ 1.57 (s, 3H), 2.92 (s, 3H), 3.3 (s, broad, 1H), 5.27 (s, 1H), 6.6–7.5 (m, 10H), 10.0 (s, 1H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 17.0, 29.7, 52.5, 61.1, 120.8, 125.9, 128.7, 128.8, 128.9, 129.1, 129.7, 131.3, 192.1. HR-ESI-MS: *m/z* calcd for $C_{17}H_{20}NO_2$: 270.1495, $[M+H]^+$; found 270.1480. Anal. calcd for $C_{17}H_{19}NO_2$ (269.344): C, 75.81; H, 7.11; N, 5.20; found: C, 75.70; H, 7.05; N, 5.15.

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