Aziridination of 2-(Phenylsulfinyl)-2-cycloalkenones with Arylsulfonyloxycarbamates

Stefania Fioravanti,*[a] M. Gabriella Mascia,[a] Alberto Morreale,[a] Lucio Pellacani,*[a] and Paolo A. Tardella*[a]

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Highly functionalised aziridines are easily obtained with high levels of diastereoselectivity (up to 98%) from 2-(phenylsulfinyl)-2-cycloalkenones by treatment with arylsulfonyloxycarbamates in the presence of bases under mild conditions.

Aziridines are important targets and valuable intermediates and their synthesis is an important topic in preparative organic chemistry.[1]

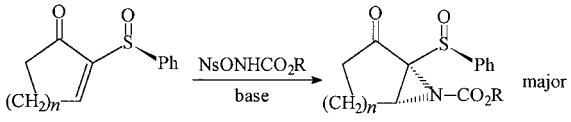
We have previously described the aziridination of nitroalkenes by ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = 4-nitrophenylsulfonyl) in the presence of inorganic bases. The stereochemical outcome and the selectivity of attack on substrates containing either conjugated or unconjugated double bonds suggested an aza-Michael reaction.[2]

Recently we reported that nosyloxycarbamates very efficiently aziridinate olefins bearing two geminal electron-withdrawing groups[3] and high levels of diastereoselectivity have been reached with optically active α-carbonyl enoates.[4]

Lately we have focused our interest on sulfinyl groups, widely used in several important chemical transformations. Moreover, the usefulness of this group as a chiral auxiliary in various reactions is extensively reported in the literature.[5] The reactivity of derivatives of β-oxo sulfinyl compounds has been studied to obtain chiral 2-amino sulfoxides.[6]

Examples of the preparation of optically active aziridines bearing a sulfinyl group by transfer of the methylene group of achiral ylide reagents to chiral sulfinylimines have been reported in the literature. These reactions, performed under various conditions, gave the expected aziridines in moderate yields and with diastereomeric excesses of up to 70%.[7–9]

Here we describe the results obtained in the direct aziridination of 2-(phenylsulfinyl)-2-cycloalkenones with ethyl and *tert*-butyl nosyloxycarbamate (Scheme 1).



1 $n = 1$ **3** $n = 2$ **5** $n = 3$ — **2a,b** **4a,b** **6a,b** — **a** R = Et **b** R = *t*Bu

Scheme 1

We tested rings of different size under different mild conditions. Results are collected in Table 1.

The molar ratios and reaction times reported in Table 1 are the conditions that gave the highest diastereomeric ratios and yields. On the basis of previous results regarding Michael additions of similar substrates,[10] we tentatively propose that the major diastereomer should be the one displayed in Scheme 1. Diastereomeric ratios were calculated by integration of the characteristic aziridine proton signals in the NMR spectra.

Reactions performed in the absence of CH_2Cl_2 (Table 1, Entries 2, 4, 6, 9, 11, 13) usually disfavour diastereoselectivity and yields.[11] Another noteworthy point is the inversion of diastereoselectivity (as shown by HPLC analysis) in the reaction carried out in the presence of triethylamine under homogeneous reaction conditions (Table 1, Entry 7). This particular behaviour has been observed previously on different substrates and we have tentatively suggested an explanation. It is probable that inorganic bases might also act

[a] Dipartimento di Chimica, Università degli Studi di Roma La Sapienza,
P.le Aldo Moro 2, 00185 Roma, Italy
Fax: (internat.) + 39-06/490631
E-mail: lucio.pellacani@uniroma1.it

Table 1. Direct aziridination of 2-(phenylsulfinyl)-2-cycloalkenones with nosyloxycarbamates

Entry	Substrate	R	Solvent	Molar ratios substrate/ CaO/$NsONHCO_2R$	Reaction times [h]	Product	Yields (%)	*dr*[a] (%)
1	**1**	Et	CH_2Cl_2	1:1.5:1.5	2	**2a**	94	71:29
2	**1**	Et	−	1:2:2	1	**2a**	45	50:50
3	**1**	*t*Bu	CH_2Cl_2	1:3:2	24	**2b**	29	70:30
4	**1**	*t*Bu	−	1:1.5:1.5	1	**2b**	99	50:50
5	**3**	Et	CH_2Cl_2	1:5:4	25	**4a**	traces	−
6	**3**	Et	−	1:2:2	1	**4a**	26	70:30
7	**3**	Et	CH_2Cl_2	1:1:1[b]	3.5	**4a**	90	27:73
8	**3**	*t*Bu	CH_2Cl_2	1:3:3	22	**4b**	99	80:20
9	**3**	*t*Bu	−	1:3:3	1	**4b**	74	67:33
10	**5**	Et	CH_2Cl_2	1:4:4	22	**6a**	83	80:20
11	**5**	Et	−	1:3:3	2	**6a**	59	63:37
12	**5**	*t*Bu	CH_2Cl_2	1:4:4	22	**6b**	96	92:8
13	**5**	*t*Bu	−	1:3:3	2	**6b**	93	55:45

[a] Diastereomeric ratios as gauged by ^1H and ^{13}C NMR and HPLC analyses on the crude reaction mixtures. [b] Et_3N instead of CaO.

Table 2. Direct aziridination of 2-(phenylsulfinyl)-2-cycloalkenones with *tert*-butyl tosyloxycarbamate

Entry	Substrate	Solvent	Molar ratios substrate/ NaH/$TsONHCO_2tBu$	Reaction times [h]	Product	Yields (%)	*dr*[a] (%)
1	**1**	THF	1:1.5:1	2 at −40 °C, 2.5 at room temp.	**2b**	93	99:1
2	**3**	THF	1:1.5:1	2 at −40 °C, overnight at room temp.	**4b**	96	99:1
3	**5**	THF	1:1.5:1	2 at −40 °C, overnight at room temp.	**6b**	94	63:37

[a] Diastereomeric ratios as gauged by ^1H and ^{13}C NMR and HPLC analyses on the crude reaction mixtures.

as a solid support, absorbing the reagents and then modifying the difference in energy between the two transition states.[12]

We next considered a different carbamate − namely *tert*-butyl tosyloxycarbamate ($TsONHCO_2tBu$) − and the use of low temperatures, in THF as the solvent and with NaH as the base[13] (Table 2). These conditions had been used by Hanessian to bring about alkoxyaminocarbonylation on β-dicarbonyl compounds.

This use of *tert*-butyl tosyloxycarbamate (Table 2, Entries 1 and 2) provided the best results in terms both of chemical yields and of diastereomeric ratios (up to 96% and 99:1, respectively). The substrate **5** (Table 1, Entry 12) was aziridinated in good yields and diastereomeric ratios with *tert*-butyl nosyloxycarbamate, but with CH_2Cl_2 as the solvent, CaO as the base and working at room temperature.

In conclusion, the simple procedure reported here allows highly diastereoselective aziridination in very good yields through the use of the directing effect of a resident phenylsulfinyl group. Attempts to elaborate polyfunctionalised aziridines are in progress.

Experimental Section

General: GC analyses were performed with an HP 5890 series II gas chromatograph with a capillary column (methyl silicone, 12.5 m × 0.2 mm). GC-MS was carried out with an HP G1800A GCD system with a capillary column (phenyl methyl silicone, 30 m × 0.25 mm). HPLC separations were performed with a Varian 9001 instrument equipped with a Varian RI-4 differential refractometer. The column was an analytical Waters μPorasil (3.9 mm × 300 mm), the flow was 1.3 mL/min with a hexane/ethyl acetate mixture (80:20, HPLC-grade) as eluent. The substrates,[14] $NsONHCO_2Et$,[15] $NsONHCO_2tBu$[16] and $TsONHCO_2tBu$[17] were synthesised as reported in the literature. IR: Perkin−Elmer 1600 series FTIR spectrophotometer. NMR: Varian Mercury 300 and Gemini 200, with $CDCl_3$ as the solvent and $CHCl_3$ as the internal standard.

General Procedure for the Synthesis of Aziridines: CaO or Et_3N and $NsONHCO_2R$ were added portionwise over 1 h at room temp., in the molar ratios reported in Table 1, to a stirred solution of substrate (10 mmol) in 10 mL of CH_2Cl_2. In the reactions carried out without solvent, the reagents were ground together in a mortar. The reaction was monitored by TLC and GC, and CH_2Cl_2 (50 mL) was added to the crude mixture upon completion. After filtration and solvent evaporation under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 6:4).

Ethyl 2-Oxo-1-phenylsulfinyl-6-azabicyclo[3.1.0]hexane-6-carboxylate (2a). Major Diastereomer: IR (CCl_4): $\tilde{\nu}$ = 1722, 1048 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.95 (t, *J* = 7.3 Hz, 3 H), 1.80−2.70 (m, 4 H), 3.78 (d, *J* = 2.9 Hz, 1 H), 3.89−4.10 (m, 2 H), 7.45−7.65 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 13.8, 18.9, 33.8, 51.0, 63.2, 66.7, 125.1, 128.6, 131.4, 139.7, 157.1, 201.6 ppm. GC-MS: *m*/*z* (%) = 293 (1.7) [M^+], 204 (82), 173 (35), 147 (22), 126 (55), 125

(100), 109 (28), 97 (25), 84 (73), 78 (82), 77 (53), 73 (52), 68 (29), 54 (70), 51 (33), 42 (24), 41 (57). $C_{14}H_{15}NO_4S$ (293.339): calcd. C 57.32, H 5.15, N 4.77, S 10.93; found C 57.25, H 5.13, N 4.75, S 10.90. **Minor Diastereomer:** IR (CCl_4): $\tilde{\nu}$ = 1724, 1050 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.25 (t, *J* = 7.3 Hz, 3 H) 1.85−2.63 (m, 4 H), 3.87 (d, *J* = 3.7 Hz, 1 H), 4.10−4.40 (m, 2 H), 7.75−7.90 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 18.8, 33.6, 51.9, 63.6, 65.0, 125.8, 128.8, 132.8, 139.7, 157.2, 200.2 ppm. GC-MS: *m*/*z* (%) = 293 (1.9) [M^+], 281 (24), 221 (21), 207 (33), 204 (84), 173 (33), 147 (36), 126 (53), 125 (100), 110 (21), 109 (31), 97 (27), 84 (76), 78 (80), 77 (59), 73 (84), 68 (30), 54 (78), 51 (38), 42 (24), 41 (60).

Ethyl 2-Oxo-1-phenylsulfinyl-7-azabicyclo[4.1.0]heptane-7-carboxylate (4a). Major Diastereomer: IR (CCl_4): $\tilde{\nu}$ = 1739, 1081 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.98 (t, *J* = 7.3 Hz, 3 H), 1.20−2.63 (m, 6 H), 3.63 (t, *J* = 2.2 Hz, 1 H), 3.93 (q, *J* = 7.3 Hz, 2 H), 7.40−7.90 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 18.0, 21.1, 37.5, 46.5, 62.2, 63.5, 126.5, 128.5, 132.0, 141.0, 155.2, 201.0 ppm. GC-MS: *m*/*z* (%) = 307 (1) [M^+], 289 (20), 281 (25), 207 (36), 181 (24), 154 (56), 150 (24), 147 (33), 136 (95), 126 (100), 125 (35), 122 (20), 110 (58), 109 (74), 108 (32), 98 (41), 97 (22), 83 (32), 82 (57), 80 (30), 78 (76), 77 (51), 73 (65), 65 (29), 55 (63), 54 (24), 53 (21), 51 (34). $C_{15}H_{17}NO_4S$ (307.366): calcd. C 58.61, H 5.57, N 4.56, S 10.43; found C 58.54, H 5.55, N 4.55, S 10.42. **Minor Diastereomer:** IR (CCl_4): $\tilde{\nu}$ = 1736, 1049 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7.3 Hz, 3 H), 1.40−2.45 (m, 6 H), 3.81 (t, *J* = 2.2 Hz, 1 H), 4.25 (q, *J* = 7.3 Hz, 2 H), 7.40−7.70 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 16.9, 22.4, 34.9, 38.8, 62.1, 63.6, 124.19, 132.2, 140.5, 155.5, 200.6 ppm. GC-MS: *m*/*z* (%) = 307 (1) [M^+], 281 (41), 221 (23), 207 (68), 147 (40), 136 (65), 126 (86), 125 (40), 110 (40), 109 (44), 108 (24), 98 (46), 97 (20), 83 (25), 82 (64), 78 (79), 73 (100), 55 (77), 54 (23), 51 (26).

Ethyl 2-Oxo-1-phenylsulfinyl-8-azabicyclo[5.1.0]octane-8-carboxylate (6a). Major Diastereomer: IR (CCl_4): $\tilde{\nu}$ = 1736, 1049 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.90−1.45 (m, 3 H), 1.60−2.87 (m, 8 H), 3.38 (d, *J* = 4.8 Hz, 1 H), 4.00−4.50 (m, 2 H), 7.40−8.00 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 22.7, 23.1, 24.2, 26.6, 41.7, 62.8, 65.0, 123.8, 128.4, 131.3, 139.4, 158.0, 205.5 ppm. GC-MS: *m*/*z* (%) = 321 (2) [M^+ − 45], 136 (54), 113 (100), 110 (66), 109 (47), 85 (24), 67 (78), 57 (23), 41 (29). $C_{16}H_{19}NO_4S$ (321.392): calcd. C 59.79, H 5.96, N 4.36, S 9.98; found C 59.72, H 5.95, N 4.34, S 9.95. **Minor Diastereomer:** IR (CCl_4): $\tilde{\nu}$ = 1734, 1054 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.93−1.50 (m, 3 H), 1.60−2.90 (m, 8 H), 3.58 (d, *J* = 4.2 Hz, 1 H), 4.10−4.60 (m, 2 H), 7.32−7.90 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 22.3, 23.1, 24.2, 27.0, 41.1, 63.0, 66.1, 124.0, 127.9, 130.7, 139.2, 158.2, 205.2 ppm.

***tert*-Butyl 2-Oxo-1-phenylsulfinyl-8-azabicyclo[5.1.0]octane-8-carboxylate (6b). Major Diastereomer:** IR (CCl_4): $\tilde{\nu}$ = 1736, 1700, 1051 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.49 (s, 9 H), 1.65−2.86 (m, 8 H), 3.31 (d, *J* = 5.1 Hz, 1 H), 7.43−7.91 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.9, 24.3, 26.7, 27.8, 42.0, 41.2, 66.4, 82.4, 126.4, 128.4, 131.3, 140.1, 156.5, 205.7 ppm. GC-MS: *m*/*z* (%) = 304 (1) [M^+ − 45], 303 (39), 247 (100), 230 (22), 218 (20), 202 (22), 161 (21), 110 (41), 109 (44), 77 (27), 65 (21), 57 (82), 55 (28), 41 (42). $C_{18}H_{23}NO_4S$ (349.446): calcd. C 61.87, H 6.63, N 4.01, S 9.18; found C 61.80, H 6.62, N 3.99, S 9.16. **Minor Diastereomer:** IR (CCl_4): $\tilde{\nu}$ = 1738, 1049 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.53 (s, 9 H), 1.61−2.83 (m, 8 H), 3.60 (d, *J* = 4.1 Hz, 1 H), 7.42−7.90 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.4, 23.3, 27.3, 27.9, 38.4, 41.9, 65.8, 83.0, 125.4, 128.1, 128.7, 142.4, 156.7, 205.5 ppm.

Synthesis of Aziridines with $TsONHCO_2tBu$ in the Presence of NaH: Fresh NaH (15 mmol) was added at −40 °C to a stirred solution of substrate (10 mmol) in anhydrous THF (10 mL). After 30 min, $TsONHCO_2tBu$ (10 mmol) in anhydrous THF (10 mL) was added portionwise over 20 min. After stirring for an additional 1 h at −40 °C, the mixture was allowed to warm to room temperature and stirred for the times reported in Table 2. The crude mixture was then poured into aqueous NH_4Cl and extracted with ethyl acetate. After the organic layer had been dried with Na_2SO_4 and concentrated in vacuo, the product was collected by flash chromatography on silica gel (hexane/ethyl acetate, 6:4) in the yields and with the diastereomeric ratios reported in Table 2.

***tert*-Butyl 2-Oxo-1-phenylsulfinyl-6-azabicyclo[3.1.0]hexane-6-carboxylate (2b):** IR (CCl_4): $\tilde{\nu}$ = 1723, 1055 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.12 (s, 9 H), 1.70−2.57 (m, 4 H), 3.74−3.75 (d, *J* = 3.3 Hz, 1 H), 7.48−7.82 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 19.0, 27.4, 34.2, 51.0, 60.3, 83.0, 125.2, 128.5, 131.3, 140.0, 155.5, 201.6 ppm. GC-MS: *m*/*z* (%) = 263 (100) [M^+ − 58], 109 (98), 65 (23). $C_{16}H_{19}NO_4S$ (321.392): calcd. C 59.79, H 5.96, N 4.36, S 9.98; found C 59.71, H 5.94, N 4.35, S 9.96.

***tert*-Butyl 2-Oxo-1-phenylsulfinyl-7-azabicyclo[4.1.0]heptane-7-carboxylate (4b):** IR (CCl_4): $\tilde{\nu}$ = 1727, 1055 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.12 (s, 9 H), 1.28−2.60 (m, 6 H), 3.65 (t, *J* = 2.6 Hz, 1 H), 7.43−7.85 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 17.5, 20.4, 27.4, 37.1, 45.8, 62.2, 82.7, 126.2, 128.2, 131.0, 140.5, 155.0, 200.4 ppm. GC-MS: *m*/*z* (%) = 335 (< 1) [M^+], 126 (45), 110 (30), 109 (21), 69 (20), 57 (100), 55 (32), 43 (21), 41 (31). $C_{17}H_{21}NO_4S$ (335.419): calcd. C 60.87, H 6.31, N 4.18, S 9.56; found C 60.81, H 6.29, N 4.16, S 9.53.

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