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Highly Diastereoselective Baldwin Rearrangement of Isoxazolines into *cis*-Acylaziridines

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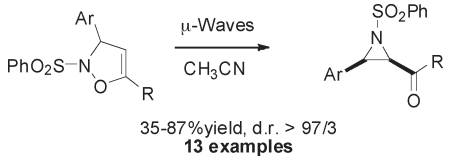

An atom-economical and practical synthesis of *cis*-*N*-benzenesulfonamide acylaziridines through the Baldwin rearrangement of various *N*-benzenesulfonamide isoxazolines has been reported. A detailed experimental study revealed the beneficial effect of microwaves and pointed out the crucial role of the temperature in the reaction course. Moderate to good yields and excellent *cis* stereoselectivities were achieved for 13 examples.

In 1968, Baldwin and co-workers postulated that the weakness of the nitrogen−oxygen bond would allow the thermal rearrangement of isoxazoline into acylaziridine.[1,2] A short experimental study validated this initial hypothesis and highlighted the crucial role of the nature of the substituents on the course of the reaction (Scheme 1). If the transformation has been made object of mechanistical studies,[2a,3] the potential of this synthetic tool has been poorly exploited perhaps because of the scarcity of described examples (three substrates) in the seminal paper and because a further rearrangement of the acylaziridine into oxazoline is sometimes observed. In 2002, Saito and co-workers described a rearrangement promoted by a stoichiometric amount of Co(0), leading to the corresponding *N*-benzyl-substituted acylaziridine with moderate to good selectivities.[4] As part of a program aimed at developing gold and iron reactions,[5] we recently described a straightforward synthesis of *N*-sulfonyl 2,3-dihydroisoxazoles from propargylic alcohols (Scheme 2).[6] We anticipated that such compounds may undergo rearrangement into *N*-sulfonylaziridines. To the best of our knowledge, no systematic study on the influence of the isoxazoline substituents on the course of the reaction has been realized and, in particular, on the effect of a EWG, such as a sulfonyl, on the nitrogen. Moreover, this transformation could lead to functionalized sulfonyl aziridines, which are valuable intermediates in organic synthesis.[7] In this paper, we disclose our results on this Baldwin rearrangement.

We first investigated the thermal rearrangement of isoxazoline **2a** (Ar = *p*-tolyl, R = *n*-Bu) chosen as model substrate (Scheme 3). The influence of three parameters (solvent, temperature, time) was investigated. Results are summarized in Table 1.

The reaction gave predominantly one diastereomer, in 83/17 to >95/5 diastereomeric ratio (dr). The *cis* relative strereochemistry of the major compound has been assigned from the comparison of the ^3J value (7.9 Hz) with previously reported data for acylaziridine analogues.[3a] This assumption was further confirmed from an X-ray analysis of product *cis*-**3l**[8] (vide infra) and is in full agreement with previously reported DFT studies where *N*-sulfonylaziridines adopt a *trans*/*trans* conformation between C and N substituents in order to minimize steric effects.[9] The 4.2 Hz ^3J constant value of the minor compound indicates a *trans* relationship between the C substituents.

The reaction is slow, and the diastereomeric ratio increases with time (Table 1, entries 1−3). The polarity of the solvent

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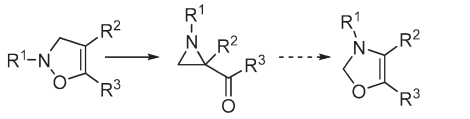
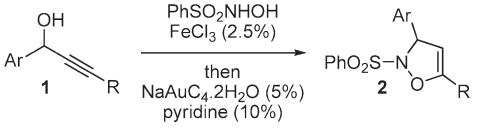
SCHEME 1. Baldwin Rearrangement of Isoxazoline



SCHEME 2. Dual Iron/Gold-Catalyzed One-Pot Synthesis of Isoxazolines



SCHEME 3. Rearrangement of 2a into *cis*-3a and *trans*-3a

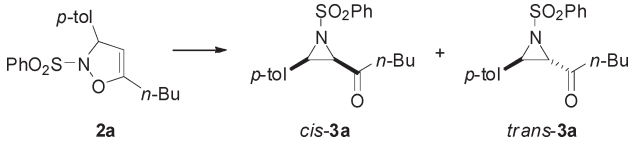


TABLE 1. Thermal Rearrangement of 2a: Solvent Study

entry	solvent	T (°C)	time	*cis*-**3a**/ *trans*-**3a**[a]	transf (%)[b] (yield, %)[c]
1	toluene	110	2 h	83/17	100 (86)
2			4 h	92/8	100 (75)
3			16 h	>95/5	100 (45)
4	dioxane	100	8 h	92/8	50 (nd)
5	MeCN	85	45 min	84/16	11 (nd)
6			1 h 30	91/9	50 (nd)
7			3 h	>95/5	40 (nd)
8			6 h	>95/5	80 (nd)
9			8 h	>95/5	85 (52)
10	*n*-PrCN	125	2 h	95/5	80 (nd)
11			4 h	>95/5	100 (57)

[a]Determined by ^{1}H NMR of the crude product. [b]Product/(starting material + product) percentage determined by ^{1}H NMR of the crude product. [c]Isolated yield.

has a moderate influence on the conversion (compare entries 1 and 10) but has a significant effect on the dr. In more polar solvent, higher selectivities are observed (compare entries 1, 6, and 10). High reaction temperatures are generally required to obtain good conversions (entries 1, 4, 6, and 10), but prolonged heating time result in a drastic drop of the yield due to decomposition. These results are not that surprising in light of previous reported examples where strong donating nitrogen substituents appear to favor the rearrangement.[1] In our case, the presence of the sulfonyl group may explain the hard reaction temperatures needed. In order to maintain high yields and selectivities, the use of microwaves was thus envisioned. Microwave activation in organic synthesis has become an increasingly used technique for the preparation of new molecules.[10] Reactions are generally faster, cleaner, and very often more selective. Furthermore, the focused heating generated by the microwaves enables a high temperature to be reached in a short time. Hence, this technique should be particularly adapted to the rearrangement described herein which necessitates elevated temperature and short reaction time to avoid side reactions.[11] Working with a microwave synthesizer dedicated to chemistry, in a sealed-vessel configuration, also provided the possibility of heating the reaction samples above the solvent boiling point in a safe manner.[12]

TABLE 2. Microwaves Rearrangement of 2a: Solvent Study

entry[a]	solvent	*cis*-**3a**/*trans*-**3a**[b]	conv[c] (%)	transf[d] (%)
1	CH_3CN	97/3	40	34
2	toluene	85/15	22	20
3	H_2O	>97/3	90	63
4	DMF	94/6	38	36
5	DMSO	>97/3	68	49
6	DCE	93/7	33	28
7	EtOH	97/3	39	30
8	*i*-PrOH	88/12	34	28
9	neat		degradation	

[a]Reaction conditions: 0.125M, 5 min reaction on a 0.125 mmol scale. [b]Determined by ^{1}H NMR of the crude product. [c]Determined by ^{1}H NMR of the crude product using 4-ethynylnitrobenzene as internal standard. [d]Product/(starting material + product) percentage determined by ^{1}H NMR analysis of the crude product.

TABLE 3. Microwave-Assisted Rearrangement of 2a in CH_3CN: Time and Temperature Study

entry	time (min)	T (°C)	*cis*-**3a**/ *trans*-**3a**[a]	conv[b] (%)	transf[c] (%)
1	5	90	93/7	8	6 (nd)
2	5	100	95/5	18	14 (nd)
3	5	110	97/3	40	34 (nd)
4	5	120	>97/3	75	61 (nd)
5	5	130	>97/3	97	68 (nd)
6	10	110	>97/3		60 (nd)
7	15	110	>97/3		73 (nd)
8	30	110	>97/3		100 (67)

[a]Determined by ^{1}H NMR of the crude product. [b]Determined by ^{1}H NMR of the crude product using 4-ethynylnitrobenzene as internal standard. [c]Product/(starting material + product) percentage determined by ^{1}H NMR of the crude product.

A study of the reaction conditions under microwave irradiation was thus undertaken, and the results are summarized in Table 2. We first examined the effect of solvent on the rearrangement of **2a** in the following conditions: 0.125 M, 5 min reaction, 110 °C, and on a 0.125 mmol scale (Table 2). As previously observed in thermal reactions, apolar solvents give lower *cis*/*trans* selectivities (see entries 2 and 6). Among the various polar solvents tested, water and DMSO allow a good level of conversion (90 and 68%, respectively) but, unfortunately, also induce the formation of extensive amounts of degradation products (63 and 43% transformation, respectively, see entries 3 and 5). As compared to the other solvents used, CH_3CN finally offers the better compromise in term of efficiency (selectivity, conversion, and transformation) and of practical convenience. Indeed, at the end of the reaction, the solvent is removed in vacuo and the residue is directly loaded on silica gel for purification, which

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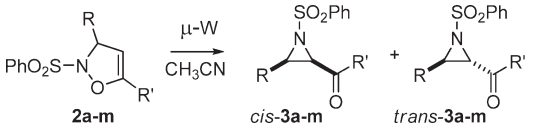
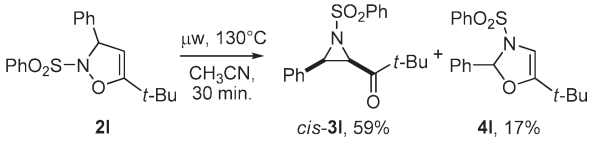
TABLE 4. Microwaves Rearrangement of Isoxazolines: Scope and Limitations



entry	R	R′	*T* (°C)	time (min)	pdt (*cis*)	dr[a]	yield[b] (%)
1	*p*-tol	*n*-Bu	110	30	**3a**	>97/3	67
2	*o*-tol	*n*-Bu	110	30	**3b**	>97/3	80
3	*m*-tol	*n*-Bu	110	30	**3c**	>97/3	87
4	Ph	*n*-Bu	130	15	**3d**	>97/3	70
5	*p*-F-Ph	*n*-Bu	130	15	**3e**	>97/3	74
6	*p*-Ph-Ph	*n*-Bu	120	20	**3f**	>97/3	66
7	2-Napht	*n*-Bu	120	20	**3g**	>97/3	63
8	*p*-Br-Ph	*n*-Bu	130	20	**3h**	>97/3	64
9	*p*-MeOPh	*n*-Bu	110	20	**3i**	>97/3	35
10	Ph	*c*-Pr	130	15	**3j**	>97/3	68
11	Ph	*i*-Pr	130	20	**3k**	>97/3	71
12	Ph	*t*-Bu	130	30	**3l**	>97/3	59
13	Ph	Ph	130	30	**3m**	>97/3	71

[a]Determined by ^{1}H NMR of the crude product. [b]Isolated yield.

SCHEME 4. Transformation of 2l into *cis*-3l and 4l



avoids an aqueous workup. The reaction conducted in the absence of solvent resulted in the complete degradation of the starting material.

We thus next evaluated the influence of reaction conditions (time and temperature) using CH_3CN as solvent (Table 3).

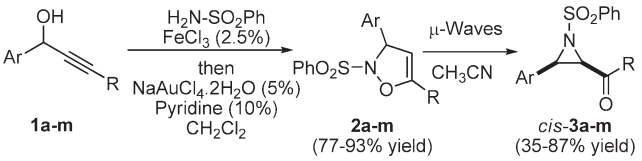
The reaction is highly sensitive to temperature, as shown in Table 3, entries1−5. For the rearrangement of **2a**, the best results are obtained when the reaction is carried out above the solvent boiling point, at 110 °C (entry 3). At 90 °C, a slow conversion is observed (entry 1), whereas from 120 to 130 °C, product decomposition is detrimental to the transformation (entries 4 and 5). In order to ensure complete conversion, a 30 min reaction time is required (entry 8). Under these optimized conditions (CH_3CN as solvent, 110 °C, 30 min), *cis*-**3a** is isolated as a single diastereoisomer in 67% yield.

The possible influence of the nature of the aromatic and the acetylenic substituents was next studied. In all cases, compounds *cis*-**3a**−**m** have been obtained as a single diastereoisomer, but careful optimization of temperature (110 to 130 °C) and reaction time (15 to 30 min) for each starting material proved to be necessary to ensure good isolated yields (see Table 4).

Studies on starting materials bearing a *n*-Bu in the acetylenic position show that good yields are obtained whatever the position (*ortho*, *meta*, *para*) and the nature (Me, Ph, F, Br, naphthyl) of the substituents on the aromatic ring (see entries 1−8), which allows further functional modifications. A notable exception is the use of the methoxy group in the *para* position, where a poor 35% yield is obtained due to the competitive formation of unidentified side products.

The substituents on the olefinic moiety have little influence on the reaction course, and when primary and secondary

SCHEME 5. Straightforward Access of Acylaziridines *cis*-3a−m from the Corresponding Propargylic Alcohols 1a−m



alkyl and phenyl groups are used, the corresponding acylaziridines *cis*-**3d**,**j**,**k**,**m** are obtained in 68−71% yields (entries 4, 10, 11, and 13). The lower yield obtained for the *t*-Bu-substituted *cis*-**3l** is explained by the competitive formation of corresponding oxazoline **4l**, isolated in 17% yield. It is interesting to note that the presence of a bulky substituent on the alkene has such a dramatic effect that the rate of the oxazoline formation step becomes close to that of the acylaziridine step (Scheme 4). Indeed, with an isopropyl substituent the oxazoline **4k** is isolated in 10% yield, whereas only a trace amount (< 3%) of **4** could be observed for nonbulky substituents, including the cyclopropyl group.

In conclusion, this study expands the thermal rearrangement of isoxazolines into acylaziridines initially reported by Baldwin and demonstrates a possible clean and highly diastereoselective rearrangement induced by microwave irradiation. Combined with our recently developed dual gold−iron-catalyzed synthesis of isoxazolines, this methodology allows an efficient atom-economical access to *N*-benzenesulfonamide acylaziridines with high *cis* selectivity in two steps from readily available propargylic alcohols (Scheme 5).[13]

Experimental Section

Typical Procedure A: Preparation of 5-Butyl-3-(naphthalen-2-yl)-2-(phenylsulfonyl)-2,3-dihydroisoxazole (2g). To a solution of 1-(naphthalen-2-yl)hept-2-yn-1-ol (**1g**) (603 mg, 2.5 mmol, 1.2 equiv) in dichloromethane (5 mL) were added *N*-hydroxybenzenesulfonamide (365 mg, 1 mmol, 1 equiv) and $FeCl_3$ (11 mg, 2.5 mol %) at room temperature. The mixture was refluxed for 1 h, $NaAuCl_4 \cdot 2H_2O$ (52 mg, 5 mol %) and pyridine (41 μL, 0.1 mmol) were added, and the reflux was maintained for an additional 2 h. After reaction completion (TLC monitoring), the mixture was concentrated under vacuum and the crude material was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5) to give the corresponding isoxazoline **2g** (643 mg, 1.63 mmol, yield: 78%) as a pale yellow solid: mp 84−85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.88 (t, J = 7.6 Hz, 3H), 1.23−1.45 (m, 4H), 2.00−2.17 (m, 2H), 4.62 (m, 1H), 5.97 (m, 1H), 7.47−7.52 (m, 3H), 7.56−7.61 (m, 2H), 7.68−7.73 (m, 1H), 7.79−7.88 (m, 4H), 8.03−8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.7, 22.2, 25.4, 28.4, 68,9, 95.9, 127.1 (2C), 127.4, 127.5 (2C), 127.6 (2C), 128.8 (2C), 129.0 (2C), 129.5 (2C), 134.1, 134.2, 138.9, 140.7, 141.4, 156.6; IR (KBr) ν (cm^{-1}) 3057, 2957, 2871, 1687, 1601, 1509, 1447, 1361, 1171, 1088, 1020, 900, 860, 801, 751, 726, 688, 631, 579, 555, 477; MS (ESI$^+$) m/z 787 (30, $[2M + H]^+$), 394 (100, $[M + H]^+$), 301 (75), 255 (15), 221 (45); HRMS (ESI$^+$) m/z 394.1479, calcd for $C_{23}H_{23}NO_3S + H^+$ 394.1477.

Typical Procedure B: Preparation of 1-(Phenylsulfonyl)-3-(*p*-tolylaziridin-2-yl)pentan-1-one (*cis*-3a). Isoxazoline **2a** (1.5 mmol, 535 mg) was dissolved in acetonitrile (12 mL) and was heated in a sealed vessel at 110 °C during 30 min under microwave irradiation

(13) Attempts of a one pot sequential synthesis of the acyl-aziridine *cis*-**3a** from the corresponding propargylic alcohol under microwave irradiation and in CH_3CN gave *cis*-**3a** in 35% isolated yield as compare to an overall 60% for the two step procedure.

(400 W, temperature-controlled mode). The resulting reaction mixture was concentrated under vacuum and the crude material directly purified by flash chromatography on silica gel (cyclohexane/ether 9/1) to give the acylaziridine **3a** (359.7 mg, 67%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.66 (t, J = 7.2 Hz, 3H), 0.91−1.01 (m, 2H), 1.11−1.30 (m, 2H), 1.94 (ddd, J = 6.5, 8.1, 17.5 Hz, 1H), 2.13 (ddd, J = 6.3, 8.1, 17.5 Hz, 1H), 2.28 (s, 3H), 3.65 (d, J = 7.9 Hz, 1H), 4.14 (d, J = 7.9 Hz, 1H), 7.04−7.09 (m, 4H), 7.57−7.61 (m, 2H), 7.66−7.71 (m, 1H), 8.04−8.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 13.5, 21.1, 21.8, 24.6, 40.7, 45.8, 48.8, 127.2 (2C), 128.1 (2C), 128.2, 129.2 (2C), 129.3 (2C), 134.1, 137.1, 138.5, 202.6; IR (neat) ν (cm^{-1}) 3066, 2957, 1712, 1448, 1330, 1164, 1090, 1023, 916, 818, 752, 688, 600, 564; MS (ESI$^+$) m/z 715 (15, $[2M + H]^+$), 358 (100, $[M + H]^+$), 274 (5), 6 (5); MS (ESI$^-$) m/z 356 (85, $[M - H]^-$), 227 (100), 175 (30), 156 (20), 113 (50), 61 (5); HRMS (ESI$^+$) m/z 358.1480, calcd for $C_{20}H_{23}NO_3S + H^+$ 358.1477.

2,2-Dimethyl-3-phenyl-1-((phenylsulfonyl)aziridin-2-yl)propan-1-one (*cis*-3l) and 4-*tert*-Butyl-2-phenyl-3-(phenylsulfonyl)-2,3-dihydrooxazole (4l). According to typical procedure B (on 0.5 mmol scale, 130 °C, 30 min), 102.6 mg of compound **3l** (0.299 mmol, 59% yield) as a white solid (mp 125−126 °C) and 29.0 mg of compound **4l** (0.084 mmol, 17% yield) as a white solid (mp 119 °C) were obtained. *cis*-**3l** and **4l** were separated by flash chromatography on silica gel (cyclohexane/ether 9/1, R_f (silica, pentane/ether 8/2) = 0.33, UV/PMA).

cis-**3l**: ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 0.97 (s, 9H), 4.11 (d, J = 7.7 Hz, 1H), 4.24 (d, J = 7.7 Hz, 1H), 7.24−7.28 (m, 5H,), 7.53−7.57 (m, 2H), 7.62−7.66 (m, 1H), 8.04−8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 25.6, 43.7, 46.6, 47.0, 127.5 (2C), 127.8 (2C), 128.1 (2C), 128.5, 129.1 (2C), 131.1, 133.9, 137.6, 202.7; IR (KBr) ν (cm^{-1}) 3066, 3033, 2969, 2933, 2871, 1716, 1478, 1448, 1367, 1329, 1170, 1091, 1072, 996, 912, 885, 802, 754, 731, 698, 688, 606, 577, 547; MS (ESI+) m/z 344 (100, $[M + H]^+$), 316 (28), 260 (57); MS (ESI−) m/z 342 (31, $[M - H]^-$), 326 (35), 286 (20), 283 (22), 255 (36); HRMS (ESI+) m/z 344.1323, calcd for $C_{19}H_{21}NO_3S + H^+$ 344.1320. Crystal data for *cis*-**3l**: CCDC 777638, formula = $C_{19}H_{21}N_1O_3S_1$, T = 175 K, M_r = 343.45 g mol^{-1}, crystal size = 0.150 × 0.200 × 0.400 mm^3, orthorhombic, space group *Pbca*, a = 16.2244(6) Å, b = 11.0860(5) Å, c = 19.8492(8) Å, α = 90°, β = 90°, γ = 90°, V = 3570.2(3) $Å^3$, Z = 8, ρ_{calcd} = 1.278 g cm^{-3}, μ = 0.197 mm^{-1}, θ_{max} = 29.189°, experimental resolution 0.77 Å, 41166 reflections measured, 4435 unique, 2339 with $I > 2\sigma(I)$, R_{int} = 0.091, $<\sigma(I)/I>$ = 0.041, refined parameters = 217, $R_1(I > 2\sigma(I))$ = 0.0449, w$R_2(I > 2\sigma(I))$ = 0.0782, R_1(all data) = 0.1008, wR_2 (all data) = 0.0782, GOF = 0.9584, $\Delta\rho$(min/max) = −0.51/0.28 e $Å^{-3}$.

4l: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.90 (s, 9H), 5.63 (s, 1H), 6.64 (s, 1H), 7.33−7.40 (m, 3H), 7.53−7.58 (m, 4H), 7.63−7.67 (m, 1H), 7.88−7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 26.1 (3C), 30.0, 91.3, 99.3, 124.5 (2C), 127.2 (2C), 127.3 (2C), 127.7 (2C), 127.9, 132.4, 134.2, 137.0, 159.7; IR (KBr) ν (cm^{-1}) 2967, 1645, 1445, 1347, 1212, 1169, 1088, 1026, 986, 919, 890, 851, 742, 723, 688, 674, 630, 596, 573, 556; MS (ESI+) m/z 687 (10, $[2M + H]^+$), 445 (15), 344 (100, $[M + H]^+$), 202 (55), 167 (15), 102 (8); MS (ESI−) m/z 428 (20), 400 (15), 356 (15), 336 (10), 286 (80), 227 (55), 219 (40), 175 (30), 157 (50), 113 (100); HRMS (ESI+) m/z 344.1324, calcd for $C_{19}H_{21}NO_3S + H^+$ 344.1320.

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Supporting Information Available: Spectral and analytical and experimental procedures for compounds **2b**,**c**,**f**,**g**, *cis*-**3a**−**m**, and **4l**, **4k**; X-ray data for acylaziridine *cis*-**3l**. This material is available free of charge via the Internet at http://pubs.acs.org.