C–C bond cleavage of keto-aziridines; synthesis of oxazoles *via* regio-controlled ring expansion

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The ring expansion of keto-aziridines to the corresponding 2,5-diaryloxazoles in the presence of iodine in refluxing dimethyl sulfoxide, is described. A plausible mechanism for the synthesis of 2,5-diaryloxazoles is proposed.

Keywords: keto-aziridine, ring expansion, oxazoles, iodine, regio-controlled reaction, C–C bond cleavage

The oxazole core is found in a diverse array of structures, including biologically active agents such as anti-cancer,[1] anti-tubercular,[2] antibacterial,[3] anti-inflammatory[4] and anti-HIV agents,[5]. They are most commonly obtained by the Hantzsch reaction.[6] Other processes including aza-Wittig reactions,[7] Schmidt rearrangements,[8] Friedel–Crafts/Robinson–Gabriel reactions,[9] the cyclodehydration of β-ketoamides,[10] the use of isocyanides,[11] the dehydrogenation of oxazolines,[12] cyclo-isomerisation of *N*-propargyl amides[13] and decomposition of α-diazoketones in nitriles,[14] have also been developed for the synthesis of oxazoles.

In addition, ring expansion of aziridines is an attractive method for the preparation of a wide variety of five-membered ring aza-heterocycles *via* a C–C or C–N bond cleavage.[15,16] Ring-opening reaction of aziridines, predominantly involves cleavage of the C–N bond of the ring,[17–22] although a few isomerisations are known in which the C–C bond of the ring is broken.[23–27]

Despite numerous reports on the application of *N*-aryl, *N*-alkyl or *N*-acyl aziridines in C–N or C–C bond cleavage,[17–27] the synthesis of oxazoles from *N*-H aziridines by a C–C bond cleavage has not yet been reported.

In continuation of our efforts in the development of the chemistry of keto-aziridines,[28–30] as well as the ring expansion of keto-aziridines for the preparation of regio-isomers of *trans*-oxazolines,[31–34] we now report the C–C bond cleavage of *N*-H aziridines and synthesis of the corresponding diaryloxazoles in the presence of iodine. A similar role of iodine was also reported by Padwa and co-workers.[35]

trans-2-Aroyl-3-arylaziridines **1** were prepared following a known synthetic procedure,[32] by bromination of the appropriate α,β-unsaturated carbonyl compounds, followed by reaction with ammonia solution (*i.e.* aqueous ammonia) in methanol at room temperature.

The initial purpose of this research was to develop a new method to synthesise oxazoles from the reaction of keto-aziridines. Initial studies were aimed at finding optimal conditions for the C–C bond cleavage of keto-aziridines. We examined the reaction of 2-benzoyl-3-phenylaziridine (1 mmol) in different solvents such as EtOH, DMSO (dimethyl sulfoxide), DEG (diethylene glycol), DMAC (*N*,*N*-dimethylacetamide), CH_3CN or THF under reflux without any catalyst. However, under these conditions a small amount of 2,5-diphenyloxazole together with chalcone **2a** were obtained (Table 1, entries 1–6). The results are summarised in Table 1.

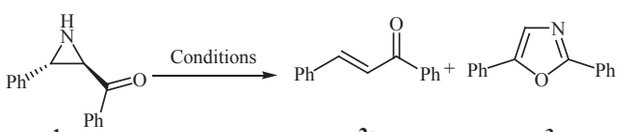
Further studies were aimed at exploring the effect of iodine as a catalyst for the ring cleavage of the aziridines. Therefore, we considered the possibility of ring expansion of 2-benzoyl-3-phenylaziridine **1a** in the presence of iodine as a catalyst in some refluxing solvents. Treatment of **1a** with iodine in refluxing EtOH, DEG, DMAC, CH_3CN or THF gave only a trace amount 2,5-diphenyloxazole (14–38%) (Table 1, entries 7–11). However, the best result for the conversion of 2-benzoyl-3-phenylaziridine **1a** to 2,5-diphenyloxazole **3a** was achieved in the presence of iodine in refluxing DMSO (entry 12, 73% yield). In another attempt, we examined treatment of **1a** in DMSO and in the presence of some other catalysts such as $ZnCl_2$, $AlCl_3$, $BF_3.OEt_2$, but none of them gave a reasonable yield of oxazole (Table 1, entries 13–15).

With the optimal reaction conditions in hand, the scope of the ring expansion reaction of some keto-aziridines **1** was explored by variation of substitution pattern, in the presence of iodine in refluxing DMSO, and the results are summarised in Table 2. All the products were characterised by ^1H, ^{13}C NMR and IR spectra.

It is interesting to note that the yield of products is dependent upon the substituents in the aryl groups. With a nitro group (entries h and i) no oxazoles were obtained, instead both aziridines gave 3-nitrobenzaldehyde upon treatment with iodine.

Although the exact mechanism for this oxazole synthesis is not clear, a proposed pathway for this synthesis is shown in Scheme 1. First, iodine behaves as a Lewis acid to promote C–C bond cleavage of the aziridine by coordinating with the

Table 1 Transformation of *trans*-2-benzoyl-3-phenylaziridine **1a** to the corresponding oxazole **3a** under different conditions



1a **2a** **3a**

Entry	Conditions[b]	Time/h	Yield/%[a]	
			2	3
1	EtOH	5	0	0
2	DEG	5	24	8
3	DMAC	8	22	36
4	THF	5	12	5
5	CH_3CN	8	0	0
6	DMSO	8	0	0
7	CH_3CN/I_2	8	33	38
8	THF/I_2	8	18	14
9	$EtOH/I_2$	8	26	19
10	$DMAC/I_2$	8	18	41
11	DEG/I_2	8	37	18
12	**$DMSO/I_2$**	**5**	**15**	**73**
13	$DMSO/ZnCl_2$	8	15	21
14	$DMSO/BF_3.OEt$	8	31	24
15	$DMSO/AlCl_3$	8	26	9

[a]Isolated yield after purification.

[b]All reactions were performed in refluxing solvents.

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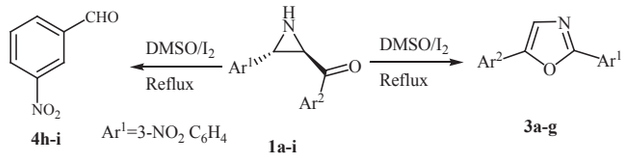
Table 2 Synthesis of oxazoles **3** from the corresponding *trans*-2-aroyl-3-arylaziridines **1**



Ar^1=3-NO_2 C_6H_4

Entry	Ar^1	Ar^2	Time/h	Yield/%[a]
a	C_6H_5	C_6H_5	6	73[9,18]
b	2-4-$Cl_2C_6H_3$	4-ClC_6H_4	5	71
c	4-ClC_6H_4	4-ClC_6H_4	6	77
d	C_6H_5	4-BrC_6H_4	4	68[9]
e	2,4-$Cl_2C_6H_3$	C_6H_5	5	62
f	4-ClC_6H_4	C_6H_5	8	65
g	4-$MeOC_6H_4$	C_6H_5	6	66[18]
h	3-$NO_2C_6H_4$	4-ClC_6H_4	10	0[b]
i	3-$NO_2C_6H_4$	C_6H_5	10	0[b]

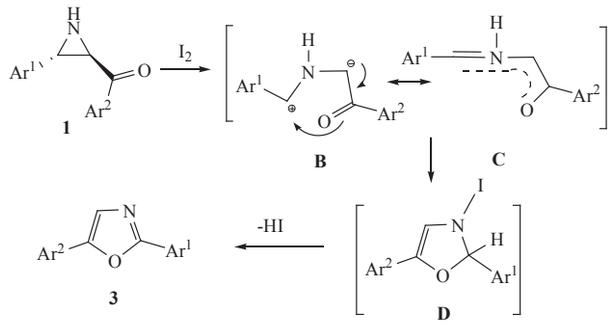
[a]Isolated yield after purification.
[b]3-Nitrobenzaldehyde was obtained in low yields (9–11%).

nitrogen to give an intermediate **B** or **C**, Such coordination can induce cleavage of the C–C bond of the strained aziridine ring.

In addition, the formation of ylide **B** or **C** can be envisioned as being due to the presence of the electron-withdrawing carbonyl group, which stabilises the carbanionic centre, and 3-aryl group which stabilises the benzylic cationic centre in the azomethine ylide. The reaction then proceeds by ring closure to a 2,3-dihydrooxazole **D** in the presence of iodine. Subsequent elimination of HI gives the oxazole **3** (Scheme 1).

The intermediacy of this dipolar spices is supported by the fact aziridine containing a nitro group (entries h and i), which destabilises the carbocationic centre, did not give any oxazole. According to the mechanism presented in Scheme 2 for the conversion of the 3-(3-nitrophenyl)aziridines (entries h and i) to aldehyde there are two possible routes. In route **I**, the aziridine in the presence of iodine gives intermediate **B** which then reacts with residual H_2O in DMSO to produce intermediate **F**. Protonation of the amino function will generate a good leaving group (a protonated hemi-aminal) from which elimination of the aldehyde can now occur. Whereas in route **II**, It can be deduced that the electron-withdrawing nitro-group destabilises the carbocationic centre in intermediate **B**, which is less likely to be formed. However, the aziridine in the presence of iodine reacts with H_2O faster than an intramolecular reaction to afford intermediate **F**, which gives the aldehyde *via* a C–N bond cleavage.

To further investigate the proposed mechanism we examined the reaction of 2-benzoyl-3-(3-nitrophenyl)aziridine in the



Scheme 1 A proposed mechanism for synthesis of oxazoles from the corresponding keto-aziridines.

presence of iodine in DMSO-H_2O (1:1). The reaction afforded 3-nitrobenzaldehyde (39%) and a mixture of products.

In summary, we report an efficient and novel method for the synthesis of 2,5-diaryloxazoles by C–C bond cleavage of *trans*-2-benzoyl-3-arylaziridines in a completely regio-controlled reaction in the presence of iodine in refluxing DMSO. The synthesis of oxazoles from *N*-H aziridines by a C–C bond cleavage has not been reported so far.

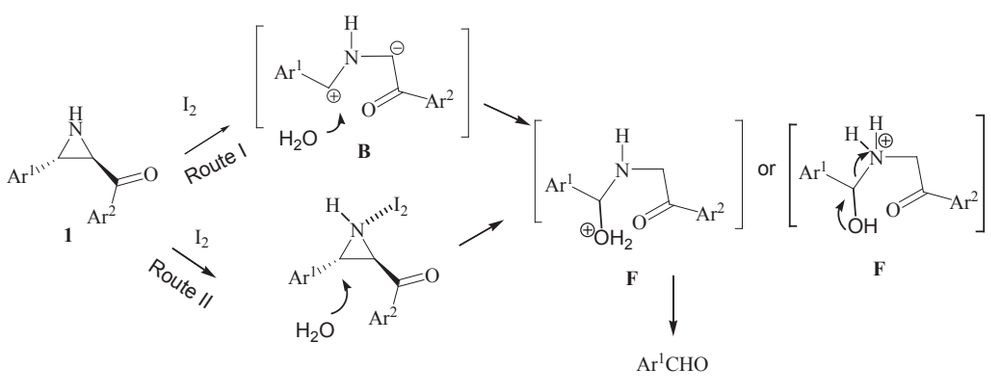
Experimental

All yields refer to isolated products after purification by column chromatography or distillation in vacuum. Products were characterised by IR, ^{1}H NMR and ^{13}C NMR spectra, TLC and melting points. NMR spectra were recorded on a Bruker AMX-400 spectrometer (^{1}H at 400 MHz and ^{13}C at 100 MHz) in $CDCl_3$ with chemical shift values in ppm downfield from TMS. IR spectra were recorded on a JASCO, FT/IR-6300 spectrophotometer. All solvents used were dried and distilled according to standard procedures.

Synthesis of oxazoles **3a–g** *from the corresponding keto-aziridines* **1a–g***; general procedure*

Iodine (0.24 g, 1 mmol) was added to a solution of the keto-aziridine (1.0 mmol) in DMSO (15 mL) and the mixture was stirred at reflux for 4–8 h. The progress of the reaction was monitored by TLC (EtOAc-hexane: 1:4). After completion of the reaction, EtOAc (15 mL) and water (15 mL) was added to the mixture. The organic layer was separated and rinsed twice with water and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure and subsequent purification of the residue by column chromatography (silica gel, EtOAc-hexane: 1:4) provided the 2,5-diaryloxazoles **3** (62–77%) (Table 2).

5-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)oxazole (**3b**): Yellow solid, m.p. 136–139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 2.1 Hz, 1H), 7.44 (s, 1H), 7.36



Scheme 2 A proposed mechanism for the conversion of aziridines containing nitro groups (entries h and i) to the corresponding aldehydes.

(d, J = 8.7 Hz, 2H), 7.30 (dd, J = 8.5, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 151.5, 136.4, 135.6, 134.1, 131.7, 129.5, 129.7, 128.5, 128.9, 127.7, 125.6, 123.1. Anal. Calcd for $C_{15}H_8Cl_3NO$: C, 55.50; H, 2.48; N, 4.32. Found: C, 55.56; H, 2.47; N, 4.22%.

2,5-Bis(4-chlorophenyl)oxazole (**3c**): Yellow solid, m.p. 125–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J = 8.60 Hz, 2H), 7.66 (d, J = 8.57 Hz, 2H), 7.37 (d, J = 8.60 Hz, 2H), 7.35 (s, 1H), 7.32 (d, J = 8.60 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 150.5, 136.6, 134.4, 130.9, 129.3, 129.2, 128.9, 127.6, 125.4, 123.9. Anal. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; N, 4.83. Found: C, 62.13; H, 3.16; N, 4.84%.

2-(2,4-Dichlorophenyl)-5-phenyloxazole (**3e**): Yellow solid, m.p. 90–92 °C; IR (KBr): ν_{max}/cm^{-1} 3064, 1662, 1590, 1482, 1101, 867, 828, 756, 685; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.26 (m, 1H), 7.38–7.33 (m, 2H), 7.44 (s, 1H), 7.47 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 152.4, 148.7, 131.8, 130.0, 129.2, 129.1, 129.0, 127.4, 124.6, 124.5, 123.8, 121.2. Anal. Calcd for $C_{15}H_9Cl_2NO$: C, 62.09; H, 3.13; N, 4.83. Found: C, 62.13; H, 3.15; N, 4.78%.

2-(4-Chlorophenyl)-5-phenyloxazole (**3f**):Yellow solid, m.p. 100–102 °C; IR (KBr): ν_{max}/cm^{-1} 3064, 2993, 1656, 1586, 821, 756, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 7.50, 2H), 7.84–7.62 (m, 3H), 7.52–7.33 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 151.5, 136.4, 130.1, 129.1, 128.9, 127.8, 127.5, 125.9, 124.2, 123.5. Anal. Calcd for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.04; H, 3.90; N, 5.18%.

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References

1 X.H. Liu, P.C. Lv, J.Y. Xue, B.A. Song and H.L. Zhu, *Eur. J. Med. Chem*., 2009, **44**, 3930.
2 X.A. Dominguez, G. De la Fuente, A.G. Gonzalez, M. Reina and I. Timon, *Heterocycles*, 1988, **27**, 35.
3 A.C. Giddens, H.I.M. Boshoff, S.G. Franzblau, C.E. Barry and B.R. Copp, *Tetrahedron Lett*., 2005, **46**, 7355.
4 K.N. Venugopala and B.S. Jayashree, *Indian. J. Heterocycl. Chem*., 2003, **12**, 307.
5 F.W. Bell, A.S. Cantrell, M. Hoegberg, S.R. Jaskunas, N.G. Johansson, Ch. L. Jordan, *et al. J. Med. Chem*., 1995, **38**, 4929.
6 T.R. Kelly and F. Lang, *J. Org. Chem*., 1996, **61**, 4623.
7 H. Takeuchi, S.-I. Yanagida, T. Ozaki, S. Hagiwara and S. Eguchi, *J. Org. Chem*., 1989, **54**, 431.
8 M. Lautens and A. Roy, *Org. Lett*., 2000, **2**, 555.
9 M. Keni and J.J. Tepe, *J. Org. Chem*., 2005, **70**, 4211.
10 P. Wipf and C.P. Miller, *J. Org. Chem*., 1993, **58**, 3604.
11 S.-X. Wang, M.-X. Wang, D.-X. Wang and J. Zhu, *Org. Lett*., 2007, **9**, 3615.
12 A.J. Phillips, Y. Uto, P. Wipf, M.J. Reno and D.R. Williams, *Org. Lett*., 2000, **2**, 1165.
13 E.M. Beccalli, E. Borsini, G. Broggini, G. Palmisano and S.J. Sottocornol, *J. Org. Chem*., 2008, **73**, 4746.
14 M.P. Doyle, W.E. Buhro, J.G. Davidson, R.C. Elliott, J.W. Hoekstra and M. Oppenhuizen, *J. Org. Chem*., 1980, **45**, 3657.
15 B. Zwanenburg, *Pure Appl. Chem*., 1999, **71**, 423.
16 B. Zwanenburg, *Pure Appl. Chem*., 1996, **68**, 735.
17 A. Padwa and W. Eisenhardt, *J. Am. Chem. Soc*., 1971, **93**, 1400**.**
18 E.V. Beletskii and M.A. Kuznetsov, *Russ. J. Org. Chem*., 2009, **45**, 1229.
19 J.W. Lown and J.P. Moser, *J. Chem. Soc., Chem. Commun*., 1970, 247.
20 M.A. Kuznetsov and V.V. Voronin, *Chem. Heterocycl. Compd*., 2011, **47**, 173.
21 B.F. Bonini, M. Fochi, M. Comes-Franchini, A. Ricci, L. Thijs and B. Zwanenburg, *Tetrahedron: Asymmetry*, 2003, **14**, 3321.
22 G. Cardillo, L. Gentilucci and A. Tolomelli, *Tetrahedron,* 1999, **55**, 15151.
23 P.D. Pohlhaus, R.K. Bowman and J.S. Johnson, *J. Am. Chem. Soc*., 2004, **126**, 2294.
24 L. Li, X. Wu and J. Zhang, *Chem. Commun*., 2011, **47**, 5049.
25 X. Wu, L. Li and J. Zhang, *Chem. Commun*., 2011, **47**, 7824.
26 L.; Li and J. Zhang, *Org. Lett*., 2011, **13**, 5940.
27 X. Wu and J. Zhang, *Synthesis*, 2012, **14**, 2147.
28 Z. Jiang, J. Wang, P. Lu and Y. Wang, *Tetrahedron*, 2011, **67**, 9609.
29 H.A. Samimi, M. Mamaghani, K. Tabatabeian and H.R. Bijanzadeh, *J. Iran. Chem. Soc*., 2010, **7**, 185.
30 H.A. Samimi, Z. Shams and A.R. Momeni, *J. Iran. Chem. Soc*., 2012, **9**, 705.
31 H.A. Samimi and S. Mohammadi, *J. Iran. Chem. Soc*. (in press).
32 H.A. Samimi and Z. Shams, *J. Heterocyclic Chem*. (in press).
33 H.A. Samimi, M. Mamaghani and Kh. Tabatabeian, *J. Heterocyclic Chem*., 2008, **45**, 1765.
34 M. Mamaghani, Kh. Tabatabeian and H.A. Samimi, *Z. Kristallogr. NCS*, 2008, **223**, 390.
35 A. Padwa, D. Eastman and L. Hamilton, *J. Org. Chem*., 1968, **33**, 1317.