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Thermal Rearrangement of Azido Ketones into Oxazoles via Azirines: One-Pot, Metal-Free Heteroannulation to Functionalized 1,3-Oxazoles

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Dedicated to Professor Goverdhan Mehta

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α-Azidoacetophenones were converted into 2-aryl-1,3-oxazole-4-carbaldehydes through rearrangement of the carbon framework upon exposure to DMF/$POCl_3$. The unprecedented rearrangement occurs via alkenyl azides and 2*H*-azirines. A mechanism for this unusual reaction was proposed and evidenced.

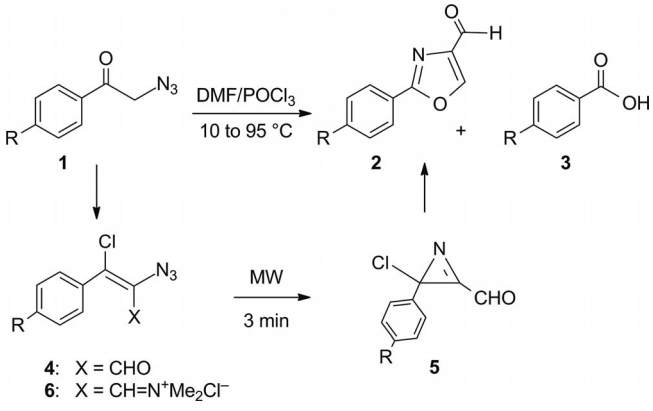
Introduction

1,3-Oxazoles are prominent five-membered heterocyclic compounds.[1] Recent interest in these heterocycles was spurred by the isolation of a number of bioactive 1,3-oxazoles[2] and by their use as ligands in asymmetric synthesis[3] and as protective groups.[4] We report an unusual synthesis of 2-aryl-1,3-oxazole-4-carbaldehydes from α-azidoacetophenones[5,6] and propose a mechanism to rationalize the transformation that involves an unprecedented thermal rearrangement of the carbon skeleton. 2-Substituted 4-formyloxazoles are biosynthetically formed by the action of nonribosomal peptide synthetase (NRPS) and polyketide synthase (PKS). They are intermediates in the biosynthesis of many natural oxazoles.[7] Oxazoles possessing a functional group are indeed versatile intermediates[8] for the synthesis of differently substituted 1,3-oxazoles and for the construction of other five- and six-membered heterocycles of interest in medicinal chemistry.[8d]

In the context of a medicinal chemistry project aimed at designing new heterocyclic entities useful in the treatment of metabolic disorders,[9] we required 1,3-oxazoles with different substitution patterns. There are several methods for their synthesis, most of which require advanced starting materials and many involve transition metal-catalyzed reactions.[10]

Results and Discussion

The Vilsmeier reagent is one of the most versatile and widely used reagents, not only for the formylation of activated aromatic and vinylic compounds but also in the synthesis of various heterocycles.[11] While studying the reaction of α-azido ketones **1a**–**e**[12] under Vilsmeier conditions (DMF/$POCl_3$, 90–95 °C) that was reported to yield 5-aryl-4-formyl-1,3-oxazoles,[10j] we observed the unexpected formation of 2-aryl-4-formyl-1,3-oxazoles **2a**–**e** in moderate yields (Scheme 1; Table 1).



Scheme 1. Rearrangement of α-azido ketones into 1,3-oxazoles via azirines.

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Table 1. 2-Aryl-1,3-oxazole-4-carbaldehydes **2a**–**e**.

Compound [17]	R	Yield[a] [%]	M.p.[b] [°C]
2a[17c]	H	42	94
2b[17b]	CH_3	31	90
2c[17a]	OCH_3	29	121
2d[17b]	Br	52	135
2e[17a,17b]	Cl	48	130

[a] Unoptimized, isolated yield from α-bromoketones. [b] Uncorrected in open capillary.

As byproducts, benzoic acids **3** (Scheme 1) were isolated. Prompted by the difficulties in differentiating between the formylated isomeric 1,3-oxazoles by NMR spectroscopy, the structure of oxazole **2d** was established by single-crystal X-ray analysis[18] (Figure 1).

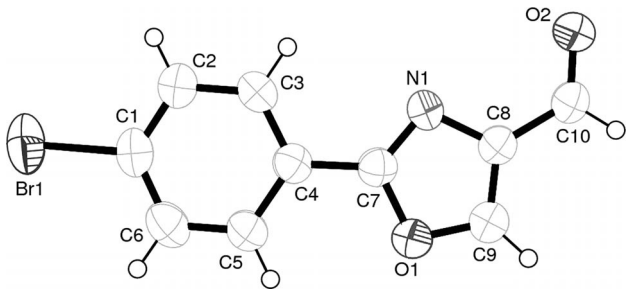


Figure 1. ORTEP diagram of oxazole **2d** (R = Br). Only one of the two symmetry-independent molecules is shown.

To rationalize the formation of **2** from the azido ketones, we examined the unprecedented transformation more closely. An intermediate was observed after the addition of $POCl_3$ and upon warming the reaction mixture from 0 °C to room temperature. It was identified as 2-azido-3-chloro-3-arylpropenal (**4**),[10j] which is the hydrolysis product of expected intermediate **6** of a typical Vilsmeier reaction. The structure of **4** was confirmed by X-ray analysis[19] of needles of **4d** (Figure 2).

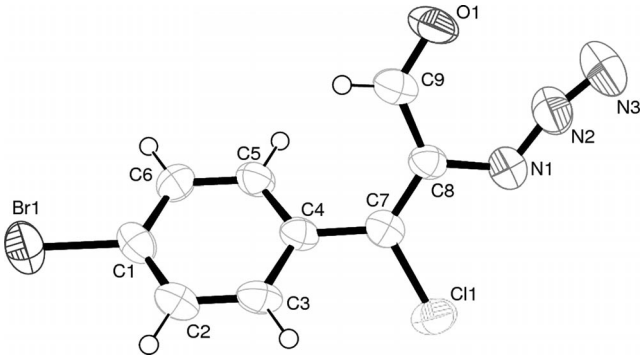
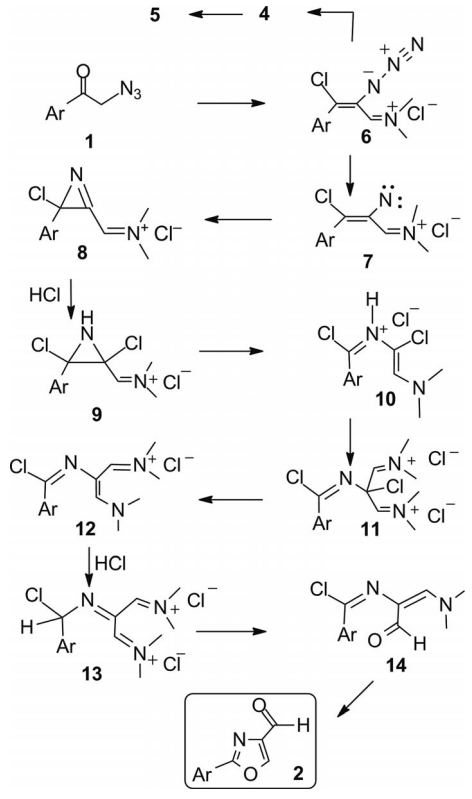


Figure 2. ORTEP diagram of alkenyl azide **4d** (R = Br).

Intermediate **4a** (liquid) was converted into azirine **5a** under the thermal conditions of GC, as evidenced by the most abundant mass peak at m/z = 179 with the expected isotopic peaks;[13] this suggests the transformation of intermediate **4** into **5** when performing the Vilsmeier reaction of **1** at 90–95 °C. The same result was observed when **4d** was subjected to ESI mass analysis with a higher source temperature (350 °C). The azirine hypothesis was reasserted when alkenyl azide **4d** was smoothly transformed into corresponding azirine **5d** under microwave conditions.[13,14c] The synthesis of 2*H*-azirines by thermolysis of vinyl azides is well precedented.[14] This preparative experiment helped us to study the spectral characteristics[13] of the azirines. The IR spectrum of **5d** (liquid) shows sharp bands at 1759, 1735, 1587, and 1068 cm^{-1} and the absence of the azide band at 2112 cm^{-1}, which is observed for **4d**. The ^{13}C NMR spectrum has typical signals at δ = 192.4 (CHO), 163.2 (C=N of azirine), and 60.8 (C_{sp^3} of 2*H*-azirine) in addition to the signals of the aromatic carbon atoms.

Hydrolysis of iminium cations **6** may have occurred during isolation of intermediate **4** or in situ, as larger amounts of benzoic acids and lower yields of 1,3-oxazoles were obtained when the solvent was used as received without further drying. Exposure of intermediate **4** to the original reaction conditions (DMF/$POCl_3$, 90–95 °C) resulted in the same products in nearly the same proportion as that obtained from **1**, which is consistent with either (partial) hydrolysis and further transformation of **4** or the reversibility of hydrolysis by the excess amount of the Vilsmeier reagent.

The rearrangement is thus rationalized by a mechanism consistent with the above observations, as depicted in Scheme 2. Initial Vilsmeier product **6** generates azirine **8**, presumably via nitrene **7** or via a triazine, or in a concerted manner[5,15] by analogy to the Neber rearrangement. Addition of HCl to **8** affords aziridine **9**, which undergoes ring opening to give **10**. Intermediate **10** reacts with a further



Scheme 2. Proposed mechanism depicting the rearrangement of azido ketones into1,3-oxazoles via azirines.

equivalent of the Vilsmeier reagent to generate intermediate **11**. Reductive dechlorination (by an X-philic reaction)[16] generates **12** that is protonated to **13** and partially hydrolyzed to **14**. Ring closure of **14** followed by hydrolysis finally leads to oxazole **2**.[17] The observed side products, the benzoic acids, could be formed by hydrolysis of intermediates **10**–**14** before heterocyclization. Donor substituents resulted in lower yields of the desired product, as seen by comparing **2b** and **2c** to **2a**, whereas halogen substituents led to higher yields of products **2d** and **2e** (Table 1).

Conclusions

In summary, a moderate yielding, one-pot synthesis of 2-aryloxazole-4-carbaldehydes from readily available, inexpensive reagents involves an unprecedented rearrangement occurring via 2*H*-azirines and constitutes a metal-free heteroannulation to functionalized 1,3-oxazoles.

Experimental Section

General Procedure for the Synthesis of 2-Aryloxazole-4-carbaldehydes 2a–e: In a 250-mL, two-necked, round-bottomed flask, sodium azide (3.16 g, 55 mmol) was added in one portion to an ice-cooled (10–15 °C), magnetically stirred solution of arylacyl bromide (50 mmol) in DMF (50 mL). After stirring for 30 min, the acyl bromide was completely converted into the phenacyl azide (TLC 10% EtOAc in petroleum ether). Then, $POCl_3$ (14 mL, 150 mmol) was added dropwise at 10–15 °C within 30–45 min. The reaction mixture was allowed to attain room temperature (30 °C) and was stirred for 3–4 h. After this time, the reaction mixture was heated slowly to 90–95 °C and stirred for 2–3 h. The reaction mixture was then cooled to room temperature and poured into an ice–water mixture (500 mL). The mixture was stirred for 1 h and extracted with $CHCl_3$ (3× 100 mL). The organic layer was washed with aqueous $NaHCO_3$ solution to remove the formed benzoic acid and with water and brine and then dried with anhydrous Na_2SO_4. The solvent was removed, and the residue was chromatographed (5% EtOAc/petroleum ether) to yield 2-aryloxazole-4-carbaldehydes **2a**–**e** as crystalline products.

CCDC-817127 (for **2d**) and -887930 (for **4d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Supporting Information (see footnote on the first page of this article): Representative experimental procedures and spectral analytical data for all the compounds.

Acknowledgments

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[18] **2d**: CCDC-817127; molecular formula: $C_{10}H_6Br_1N_1O_2$; monoclinic; a = 3.9271(5) Å; b = 34.3676(40) Å; c = 7.0792(8) Å; β = 95.169(2)°; V = 951.56(3) Å^3; T = 295(1) K; space group, $P2_1$, Z = 4; $\rho_{calcd.}$ = 1.76 g cm^{-3}; μ(Mo-K_α) = 4.289 mm^{-1}; reflns measured, 10082; unique reflns, 3863; no. of parameters = 253; R_{obs} = 0.047; wR_{2obs} = 0.108; $\Delta\rho_{min,max}$ = –0.220, 0.416 e Å^{-3}; gof = 1.031.
[19] **4d**: CCDC-887930; molecular formula: $C_9H_5Br_1Cl_1N_3O_1$; monoclinic; a = 10.2287(33) Å; b = 4.0564(13) Å; c = 12.9024(43) Å; β = 100.314(5)°, V = 526.69(6) Å^3; T = 295(1) K; space group, $P2_1$, Z = 2; $\rho_{calcd.}$ = 1.93 g cm^{-3}; μ(Mo-K_α) = 4.136 mm^{-1}; reflns measured, 3666; unique reflns, 2005; no. of parameters = 136; R_{obs} = 0.041; wR_{2obs} = 0.088; $\Delta\rho_{min,max}$ = –0.242, 0.572 e Å^{-3}; gof = 0.99.

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