An Exploration of the Metal Oxide-assisted Decomposition and Rearrangement of *N*-Acyl-1,3-oxazolidin-2-ones Leading to 2-Aryl-2-oxazolines [1]

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An exploration into the utility of the thermally-induced (metal oxide-mediated) CO_2 extrusion and subsequent rearrangement of *N*-acyl-1,3-oxazolidin-2-ones to form 2-aryl(alkyl)-2-oxazolines is described. The reaction is found to give moderate yields of the corresponding 2-oxazolines. Attempts to employ the above methodology to give enantiopure (*R*)- or (*S*)-2,5-diphenyl-2-oxazoline (the latter form being the natural product Oxytriphine) from enantiopure (and crystallographically characterised) (*S*)-*N*-benzoyl-5-phenyl-2-oxazolidinone led to the isolation of an essentially racemic product. These protocols are compared to other common methods used to form the oxazoline ring system and are placed into context with previous investigations of such ring forming reactions.

Key words: 2-Oxazoline, Oxazolidone, Crystal Structure, Oxazole, Rearrangement

Introduction

The 2-oxazoline (*i. e.*, 4,5-dihydro-1,3-oxazole) ring system is found in a number of natural products and is a component of a large array of important ligands that find use in transition metal and main group chemistry. 2-Oxazolines are also a component of a wide variety of monomer scaffolds used in the production of synthetic polymers [4 – 16]. The late Albert I. Meyers pioneered the use of oxazolines as selective directing agents for both regio- and enantio-selective C–C bond forming reactions [17 – 19]. Following the seminal work of Meyers, chiral oxazolines have since taken on a pivotal role as ligands in transition metal-mediated reactions, specifically those employing Lewis acid catalysts [9]. This has led to many oxazolines being routinely "screened" for their effectiveness in enantioselective substrate modification. As a result, novel chiral and achiral 2-oxazolines are still being produced in large numbers, and the ring system is now being explored in more detail in coordination chemistry, materials science and medicinal chemistry [20 – 29].

As part of a program in such medicinal inorganic chemical syntheses, we required a number of 2-aryl oxazolines which were devoid of further substitution at oxazoline ring position C-4. There are a number of methodologies that can be used to yield such an oxazoline. These include the high-temperature dehydrative coupling of benzoic acids and amino-alcohols [30 – 34], Lewis acid-catalysed addition and subsequent ring closure of a combination of aryl-nitriles and amino-alcohols [35, 36], or ring expansion *via* the rearrangement of *N*-acylaziridines [37]. Oxazoline rings can also be produced *via* *N*-(2-hydroxyethyl)amides promoted by reagents such as DAST [38 – 40], Deoxo-Fluor [40], $SnCl_2Bu_2$ [41], the Vilsmeier reagent [42], Martin's Sulfurane [43], substituted triazines [44], the Burgess reagent [45, 46], PPh_3/CCl_4 [47], molybdenum oxides [48], arylboronic acids [49], zeolites [50], and TsOH [51], among others [52].

Certainly all of the above methods can be used effectively for 2-oxazoline production, and all have their unique advantages and disadvantages. Of the latter, several involve expensive and stoichiometric reagents, high molar mass leaving groups (*n. b.*, poor atom economy), environmentally hazardous solvents and/or extended reaction times. Hence, there is still a need for cheap and simple methods for the synthesis of 2-oxazolines. Some twenty-five years ago, Mundy and Kim [53] reported that solid calcium ox-

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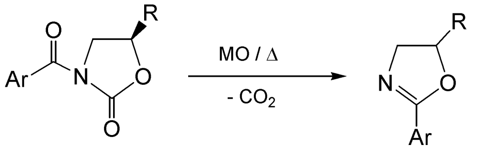


(1)

1a: Ar = *p*-Cl-Ph; R = H;	**1b**: Ar = *p*-Cl-Ph; R = H
2a: Ar = *p*-MeO-Ph; R = H;	**2b**: Ar = *p*-MeO-Ph; R = H
3a: Ar = *p*-Me-Ph; R = H;	**3b**: Ar = *p*-Me-Ph; R = H
4a: Ar = *p*-F-Ph; R = H;	**4b**: Ar = *p*-F-Ph; R = H
5a: Ar = *m*-Cl-Ph; R = H;	**5b**: Ar = *m*-Cl-Ph; R = H
6a: Ar = *m*-Me-Ph; R = H;	**6b**: Ar = *m*-Me-Ph; R = H
7a: Ar = *p*-O_2N-Ph; R = H;	**7b**: Ar = *p*-O_2N-Ph; R = H
8a: Ar = R = Ph	**8b**: Ar = R = Ph

Scheme 1. The reaction equation and the numbering scheme for the compounds discussed herein; MO = metal oxide.

ide could be used to yield 2-oxazolines *via* thermally induced CO_2 extrusion from readily obtained *N*-acyl-2-oxazolidones (*i. e.*, *N*-acyl-1,3-oxazolidin-2-ones, Scheme 1). This process occurs rapidly under solvent-free conditions in what is now sometimes referred to as a "one-pot" synthesis; heat is added to the system using a small flame such as a Bunsen burner which is held briefly beneath the reaction vessel. This direct methodology does not appear to have been further explored or exploited for oxazoline synthesis since this early report [54]. Herein, we examine the application of the Mundy-Kim protocol to yield 2-aryl-2-oxazolines and compare this to other common methods for oxazoline synthesis.

Table 1. Synthesis and yields of oxazolines **1b** – **8b** prepared according to Scheme 1.[a]

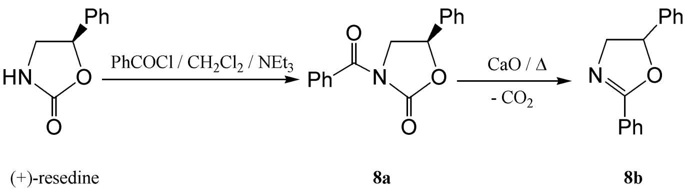
Entry	Product	Yield (%)	Entry	Product	Yield (%)
1[b]	**1b**	12	8[e]	**5b**	26
2[c]	**1b**	15	9[e]	**6b**	55
3[d]	**1b**	25	10[e]	**7b**	0[f]
4[e]	**1b**	27	11[e]	**8b**	50
5[e]	**2b**	35	12[e,g]	2-phenyl-2-oxazoline	65
6[e]	**3b**	54	13[e,g]	2-(*o*-anisolyl)-2-oxazoline	∼ 67[h]
7[e]	**4b**	32	14[e,g]	2-methyl-2-oxazoline	∼ 25[h]

[a] Conditions: A sample of the respective *N*-acyl-2-oxazolidinone (4.4 mmol) and MO (1 g) were mixed together in the solid state and then heated under an atmosphere of N_2 (*g*) (using a small Bunsen burner) past the melting point of the mixture. The resulting products were then isolated by distillation and/or extraction (EtOAc) followed by flash chromatographic separation. Yields refer to isolated and purified products except where noted; [b] MO = MgO; [c] MO = BaO; [d] MO = ZnO; [e] MO = CaO; [f] see text; [g] ref. [53]; [h] estimated yield: other unidentified products also produced [53].

Results and Discussion

Our initial examination of the reaction shown in Scheme 1 (Eq. 1) involved a study of the effect of the nature of the metal oxide on the yield of the resulting oxazoline (Table 1, entries 1 – 4). The use of the aryl group derived from 4-chlorobenzoyl chloride was employed due to availability and ease of NMR characterisation [54]. The results indicate that CaO is superior in terms of isolated yields of product to both MgO and BaO; ZnO gives comparable yields. The former was therefore chosen for the remaining experiments to allow for a direct comparison with the Mundy and Kim study [53]. There is a trend in which the presence of electron-donating groups on the aromatic ring seems to lead to an increase in overall yield (Table 1: entries 5, 6 and 9) when compared with electron-withdrawing groups (Table 1, entries 1 – 4, 7, 8). This suggests an electron demand during the yield-determining transformation. Our attempts to use a nitro-containing aryl group (*i. e.*, R = -C_6H_4-*p*-NO_2: Table 1, entry 10) resulted in rapid decomposition of the acyl starting material with the production of smoke and in-extractable black tar-like materials under the experimental conditions. *Caution! It is therefore advised that nitro-containing N-acyl-2-oxazolidinones should not be used under the conditions of Scheme 1.* These results suggest that this methodology, although rapid and effective, does so at a sacrifice of yield *vs.* methods such as the high-temperature catalytic (*e. g.*, ZnX_2) formation of 2-oxazolines [35, 36, 55] from the combination of amino-alcohols and arylnitriles.

Of practical interest is the formation of chiral species *via* these reaction conditions. Although chiral centres located at ring position C-4 of the oxazoline product will presumably be unaffected by cyclisation of enantiopure *N*-acyl-4-*R*-2-oxazolidinones under these conditions, it is unclear as to the result at ring position C-5. A recent disclosure by Hoye *et al.* [56] has demonstrated that the reaction depicted in Scheme 1 can be performed at lower temperatures using a combination of LiI and DBU as mediators. Unfortunately, this method was ineffective in the formation of 5-substituted oxazolines such as 5-methyl-2-phenyl-2-oxazoline. Other published methods which facilitate ring formation *via* closure involving the oxazoline ring position C-5 carbon centre have shown that both inversion (for example: [38 – 40, 43, 45 – 47, 49]) or retention (*e. g.*, [30, 51]) of configuration can be mandated. The use of a small Bunsen burner flame here can be compared to such reactions under very high temperature conditions, such as those employed under FVP protocols [57]. The natural product Oxytri-



Scheme 2. The formation of **8a** and Oxytriphine (**8b**) *via* (+)-resedine.

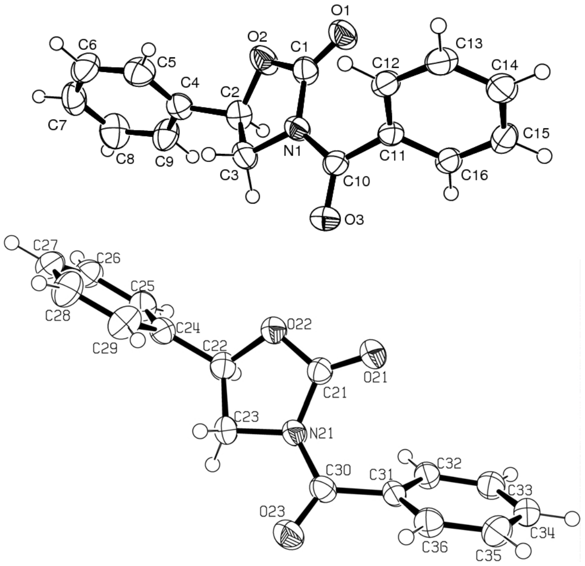


Fig. 1. ORTEP representation of the molecular structures of molecules A (top) and B (bottom) of compound **8a** that are found in the unit cell.

Table 2. Selected bond lengths (Å), angles (deg) and dihedral angles (deg) for the two crystallographically independent molecules of compound **8a** with estimated standard deviations in parentheses (see Fig. 1).

Molecule A			
Bond lengths		Bond angles	
O1–C1	1.193(4)	C1–N1–C10	128.4(3)
O2–C1	1.351(4)	O2–C1–N1	108.7(3)
N1–C1	1.386(4)	Dihedral angles	
N1–C10	1.386(5)	C10–N1–C1–O1	−9.6(7)
O3–C10	1.219(4)	C10–N1–C1–O2	171.1(4)
		N1–C10–C11–C12	60.6.(5)
		O2–C2–C4–C5	74.4(5)
Molecule B			
O21–C21	1.199(4)	C21–N21–C30	126.7(3)
O22–C21	1.354(4)	O22–C21–N21	108.1(3)
N21–C21	1.398(5)	Dihedral Angles	
N21–C30	1.390(4)	C30–N21–C21–O21	7.5(6)
O23–C30	1.220(4)	C30–N21–C21–O22	−170.4(3)
		N21–C30–C31–C32	−47.3(5)
		O22–C22–C24–C25	106.1(4)

phine (*i. e.*, 2,5-diphenyl-2-oxazoline; Scheme 2: **8b**) is an ideal candidate [58] to investigate the stereochemical outcome of the Mundy-Kim method as the optical properties of the enantiopure (5*S*)-(+) isomer are well-known [59]. The precursor to **8b**, *i. e.* **8a**, is readily obtained by the treatment of (+)-resedine [60] with benzoyl chloride (Scheme 2) in the presence of base. Compound **8a** has been further characterised by single crystal X-ray diffraction methods. *N*-Acyl-2-oxazolidinones analogous to **8a** have been the subjects of detailed computational, structural and reactivity studies as reported by Seebach *et al.* [61]; hence this solid-state investigation adds to the database of such materials [61, 62].

Compound **8a** crystallises in the space group $P2_1$ with four molecules in the unit cell. Selected bond lengths and angles are tabulated in Table 2, and an ORTEP [63] presentation of the two independent molecules of **8a** that are found in the unit cell is shown in Fig. 1. The two structural forms of **8a** differ only in the torsion angles involving the two aromatic rings (Fig. 1, Table 2 and CCDC 740139). The oxazolidinone ring system is structurally almost identical in the two isomers. These data are comparable to the variety of other *N*-acyl-2-oxazolidinones that are found in the literature [61, 62] and are otherwise unsurprising.

The heating (Bunsen) of samples of **8a** with CaO (*vide supra*) leads to the isolation of Oxytriphine (**8b**), and yields are reproducibly about 50 % (±15 %: the result of three determinations). However, optical rotation data was found to be variable and difficult to reproduce with % *ee* values ranging from 50 % to as low as 10 % in preference for the (–)-isomer (*i. e.*, inversion) [64]. We have made a cursory investigation of this solid-state reaction using TGA and have found that the reaction appears to initiate at temperatures around 200 °C. However, attempts to use high-temperature solvents *in lieu* of flame heating did not improve the outcome of the reaction. The application of naphthalene (b. p. 218 °C) as solvent gave no yield of oxazoline product **8b**. In contrast, a reaction of **8a** (*vide infra*) and CaO in DMSO (reflux temperature, 30 h) gave **8b** but in a very disappointing 18 % yield and low % *ee* (< 5 %). Thus, it appears that this synthetic methodology is inappropriate under the conditions tested for the production of enantiopure oxazolines with desired chirality installed at ring position C-5. In the field of chiral oxazoline synthesis, perhaps the best solvent-free method, and one that is rarely employed today, is the anhydrous $Zn(OAc)_2$-mediated dehydration of *N*-acyl-β-hydroxyamines [30]. This method leads to enantiopure products with complete retention of configuration *at both* oxazoline ring positions C-4 and C-5 under solventless conditions and without the necessity of FVP temperatures [57].

Conclusion

An investigation of the high-temperature (Bunsen flame) and solvent-free production of 2-aryl-2-oxazolines from *N*-acyl-2-oxazolidinones has revealed that although the method is rapid and cost effective, this comes at a sacrifice in yield of product *vs.* that of other reported methods. In the case of 2,5-diphenyl-2-oxazoline produced by this protocol, considerable loss of enantiopurity is noted at ring position C-5 of this product when it is derived from optically pure *N*-benzoyl-5-phenyl-2-oxazolidinone. The (+)-(*S*)-isomer of this latter material has been further structurally characterised by single crystal X-ray diffraction methods.

Experimental Section

All reactions were carried out using standard bench-top and Schlenk techniques. ^{1}H NMR spectra were recorded at room temperature (r. t.) from samples in $CDCl_3$ solution using a Bruker Avance 300 MHz NMR spectrometer. Chemical shifts are referenced to residual non-deuterated $CHCl_3$ at δ = 7.24 ppm relative to that of external TMS (δ = 0.00 ppm). Compounds **1a** – **7a** [53, 54] and (+)-resedine (**8a**) [60d] were synthesised and analysed (m. p., ^{1}H NMR, $[\alpha]_D$) as previously reported [60]. The purity and identity of oxazolines **1b** – **7b** were confirmed relative to their previously published characteristics [53, 54]. Oxytriphine (**8b**) was produced from (+)-(5*S*)-5-phenyl-*N*-benzoyl-2-oxazolidinone (**8a**) using the method of Mundy and Kim [53] and identified spectroscopically [58, 59a].

*(+)-(5S)-5-Phenyl-N-benzoyl-2-oxazolidinone (*8a*)*

A 0.50 g sample of (+)-resedine (3.1 mmol) and benzoyl choride (1.26 g, 9.0 mmol) were dissolved in dichloromethane (40 mL) with stirring and the mixture cooled to 0 °C on an ice bath. Triethylamine (0.62 g, 6.0 mmol) dissolved in 10 mL of CH_2Cl_2 was then added to the mixture in a drop-wise fashion. Stirring of the mixture was continued at this temperature for 10 min and then the flask was allowed to slowly reach r. t.; this was followed by heating of the contents to reflux temperature for a period of 18 h. The mixture was then cooled again to r. t., and an additional 30 mL of fresh CH_2Cl_2 was added. The organic layer was then washed with 15 mL of 5 % aq. HCl, followed by 30 mL of sat. aq. $NaHCO_3$, 30 mL of water and finally 30 mL of brine. The organic layer was then isolated and dried with $MgSO_4$. Compound **8a** was then isolated in the form of a white solid by flash column chromatography (EtOAc/hexanes: 1 : 3 v/v as eluent; R_f = 0.28) following evaporation of the solvents (*vacuo*). Yield: 0.55 g (54 %). A voucher sample, also suitable for X-ray diffraction study (*vide infra*), was obtained by recrystallisation (95 % aq. EtOH) of a sample of **8a** isolated above. – M. p. 139 – 141 °C (uncorrected). – ^{1}H NMR (300 MHz, $CDCl_3$, 23 °C): δ = 4.13 (m, 1H, NC*H*), 4.53 (m, 1H, NC*H*), 5.70 (pseudo-triplet, 1H, C*H*Ph), 7.47 (m, 7H, Ar*H*), 7.59 (m, 1H, Ar*H*), 7.71 (m, 2H, Ar*H*). – $[\alpha]_D$ = +80° ($CHCl_3$, *c* = 0.992). – $C_{16}H_{13}NO_3$ (267.27): calcd. C 71.90, H 4.90, N 5.24; found C 71.82, H 4.74, N 5.27.

X-Ray structure determination of **8a**

The data for compound **8a** was collected at −100 °C on a Nonius Kappa CCD diffractometer, using the COLLECT program [65]. Cell refinement and data reductions used the programs DENZO and SCALEPACK [66]. SIR97 [67] was used to solve the structure, and SHELXL97 [68] was used to refine the structure. ORTEP-3 for Windows [63] was used for molecular graphics (Fig. 1), and PLATON [69] was used to prepare material for publication. The H atoms were placed in calculated positions with U_{iso} constrained to be 1.2 times U_{eq} of the carrier atom for all hydrogen atoms.

The data were collected with MoK_α radiation. Since the crystal contained no heavy atoms, the absolute configuration could not be determined from the data, but the absolute configuration was known from the synthetic procedure. Friedel pairs were therefore merged before refinement. The crystal was sufficiently small and contained only light atoms, thus no absorption correction was deemed necessary. $C_{16}H_{13}NO_3$, M_r = 267.27, crystal size = 0.12 × 0.07 × 0.07 mm^3, monoclinic crystal system, space group $P2_1$, a = 5.6326(3), b = 18.9526(10), c = 12.2105(9) Å, β = 92.608(4)°, V = 1302.15(14) Å^3, T = 173(2) K, Z = 4, ρ_{calc} = 1.363 g cm^{-3}, $\lambda(\text{Mo}K_\alpha)$ = 0.71073 Å, $F(000)$ = 560, *hkl* range = ±7, −24/ + 21, ±15, refls. measured = 5213, refls. unique = 3058, R_{int} = 0.0449, parameters refined = 362, $R(F)/wR(F^2)$ (all refls.) = 0.0787/0.1083, $GoF(F^2)$ = 1.049, $\Delta\rho_{\text{fin}}$ (max./min.) = 0.226/−0.176 e Å^{-3}.

CCDC740139 contains 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.

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