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Novel rearrangement of 4-aroyloxy-3-bromomethyl-2-isoxazolines to 3-aroyloxymethylisoxazoles and a mechanistic study

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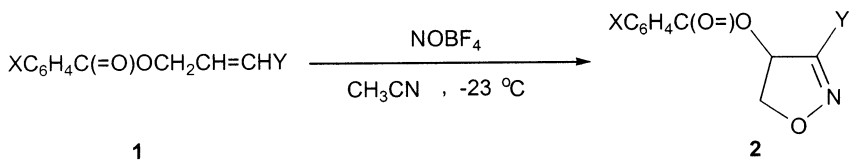
Abstract

Treatment of 4-aroyloxy-3-bromomethyl- and 4-aroyloxy-3-aroyloxymethyl-2-isoxazolines with $NaHCO_3$ in DMF at 120°C gave 3-aroyloxymethylisoxazoles in moderate to good yields. A concerted mechanism is proposed to explain the formation of the rearrangement products.

Keywords: isoxazolines; isoxazoles; deprotonation; labeling; rearrangements.

2-Isoxazolines are useful for the synthesis of various functionalized organic compounds. Their synthetic methods including 1,3-dipolar cycloaddition involving nitrile oxides and alkenes have been extensively studied.[1] A survey of the recent literature shows some interesting methods for the synthesis of 2-isoxazolines which include nitrosative cyclization of 3-chloro-1-nitropropane using sodium nitrite and *n*-propyl nitrite in DMSO,[2] the reactions of 3-isoxazolin-5-one with olefins,[3] photochemical reactions of 1,2-disubstituted cyclopropanes with $NOBF_4$,[4] deprotonation of 2-isoxazolines by a strong base, followed by addition of alkyl iodides.[5]

More recently we reported synthesis of 3-substituted 4-aroyloxy-2-isoxazolines **2** by treatment of allylic arenecarboxylates **1** with $NOBF_4$ in CH_3CN at −23°C[6] (Scheme 1). Of them,



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Scheme 1. **a**. Y = H; **b**. Y = CH_2Br; **c**. Y = $XC_6H_4C(=O)OCH_2$

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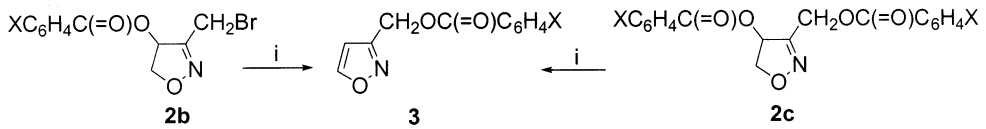
compound **2b** attracted our attention since it was expected that replacement of the bromine atom with appropriate nucleophiles would give various 3-substituted 4-aroyloxy-2-isoxazolines.

In the course of our study on the nucleophilic displacement of the bromine atom of **2b**, we found that treatment of **2b** (X = H) with $NaHCO_3$ in DMF at 120°C afforded 3-benzoyloxymethylisoxazole **3a** (X = H) in 53% yield (Scheme 2). Similarly the reaction of compound **2c** (X = H) under the same conditions afforded **3a** (48%). The results led us to investigate the reactions with other 2-isoxazoline derivatives **2b** and **2c**.



Scheme 2. *Reagents and conditions*: (i) $NaHCO_3$, DMF, 120°C

Typical procedure: to a solution of **2b** in DMF (10 mL) was added $NaHCO_3$ (5 equiv.). The mixture was heated at 120°C for an appropriate time, followed by addition of water (30 mL), which was extracted with CH_2Cl_2 (30 mL×2). The extracts were worked up as usual and the residue was chromatographed on a silica gel (70 ~ 230 mesh, ASTM) column.

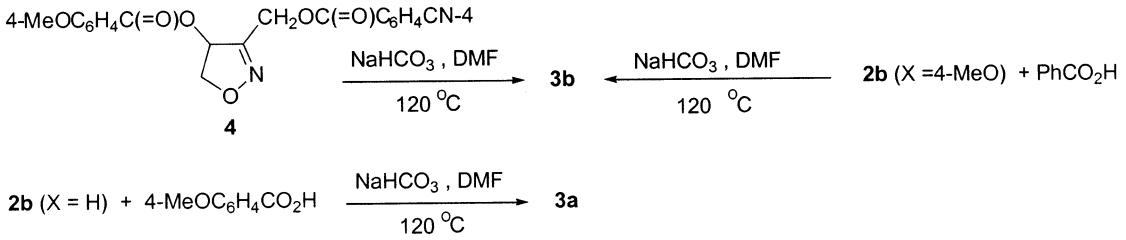
Elution with a mixture of *n*-hexane and EtOAc (5:1) gave **3**. Reaction times, yields and mps of 3-aroyloxymethylisoxazoles **3** are summarized in Table 1.

Table 1
Reaction times, yields, and mps of isoxazoles **3**

Compd	X	Time (days)		Yield[a] (%)		Mp (°C)
		Y = CH_2Br	Y = $XC_6H_4CO_2CH_2$	Y = CH_2Br	Y = $XC_6H_4CO_2CH_2$	
3a	H	1.5	2	53	48	Liquid
3b	4-MeO	1	1.5	72	65	73–74[b]
3c	4-Me	1.5	1	65	54	Liquid
3d	2-Br	2	1.5	43	42	Liquid
3e	4-Cl	1.5	2	56	52	Liquid
3f	2-Ph	2	2	70	53	Liquid
3g	4-O_2N	3[c]	0.5	[d]		
3h	1-Naphthyl	1	1.5	77	58	102–104[b]
3i	4-NC		1	[e]	13	Liquid

[a] Isolated yields.
[b] Recrystallized from *n*-hexane.
[c] Hours.
[d] 4-Nitrobenzoic acid was isolated in 85% yield.
[e] Compound **2b** (X = 4-CN) was not prepared. Compounds **3** were characterized satisfactorily by the spectroscopic (IR, ^1H and ^{13}C NMR, MS) and analytical data.

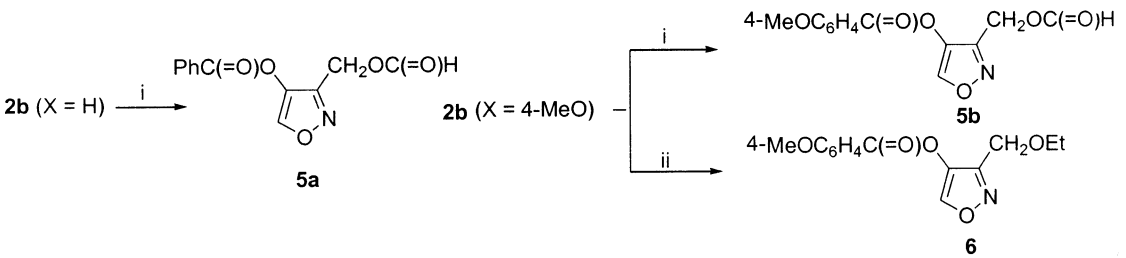
For mechanistic information on the conversion of either compounds **2b** or **2c** into **3**, 2-isoxazoline **4**, which possessed two different aryloxy groups, was subjected to the same reaction conditions. From the reaction only **3b** (63%) was isolated. No 4-cyanobenzolyoxy incorporated product was detected (Scheme 3).



Scheme 3.

The reaction of **2b** (X = H) in the presence of *p*-anisic acid (2 equiv.) under the same conditions afforded only **3a** (44%). Similarly only **3b** (62%) was obtained from the reaction of **2b** (X = 4-MeO) in the presence of benzoic acid under the same conditions. No 4-anisic acid and benzoic acid derived products were detected from the former and the latter reactions, respectively. The results suggest that the aroyloxy group at C-4 of 2-isoxazolines migrates to the methylene carbon atom at C-3, presumably by a concerted mechanism.

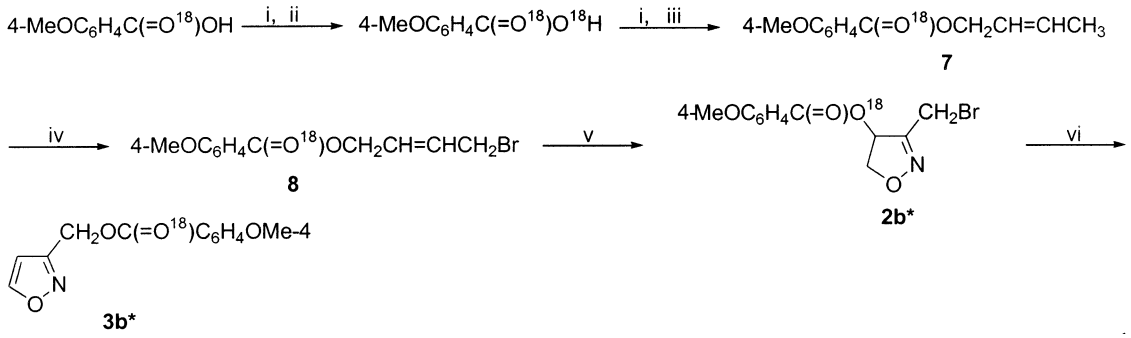
The reaction of **2b** did not proceed in the absence of $NaHCO_3$, whereas substitution of $NaHCO_3$ for organic bases such as pyridine and *N*,*N*-dimethylaniline under the same conditions led to decreased yields of **3b** in 27 and 28%, respectively, indicating the efficiency of $NaHCO_3$ compared with the organic bases for the formation of **3**. Unexpectedly treatment of **2b** (X = H, 4-MeO) with $AgNO_3$ in DMF at rt afforded formates **5a** and **5b** in 29 and 83% yields, respectively (Scheme 4). Since DMF was envisaged to be involved as a source of formyl group, DMF was substituted for EtOH as a solvent.



Scheme 4. *Reagents and conditions*: (i) $AgNO_3$, DMF, rt, 12 h. (ii) $AgNO_3$, EtOH, rt, 12 h

The bromine atom of **2b** (X = 4-MeO) was then replaced by an ethoxy group, leading to compound **6** in 55% yield. No rearranged product such as **3b** was detected. The results suggest that generation of an electron deficient center at the migration terminus by the interaction of the bromine atom of **2b** with Ag^+ ion does not act as a driving force for the migration of the aryloxy group at C-4 in the molecules. In order to confirm the migrating oxygen atom, the ^{18}O-enriched compound **2b*** prepared (Scheme 5) was subjected to the same conditions mentioned foregoing to trace where the ^{18}O is.

The enrichment of ^{18}O in the labeling compounds compared with the normal (unlabeling) compounds was compared by mass spectroscopy. By introducing % (M^++2) obtained from the abundances of M^+ and M^++2 ions into the following equation,[7] one can calculate α values that represent the contribution of % ^{18}O in % (M^++2) in ^{18}O-enriched molecular ion and its fragmented ions.



Scheme 5. *Reagents and conditions*: (i) $SOCl_2$, reflux, 4 h. (ii) H_2O^{18} (10 mol%). (iii) Crotyl alcohol, 5 h. (iv) NBS, CCl_4, reflux, 12 h. (v) $NOBF_4$, CH_3CN, −23°C. (vi) $NaHCO_3$, DMF, 120°C

$$\%\ (M^+{+}2) = [(1.1\times a)^2 + (0.016\times b)^2]/200 + 0.2\times c + \alpha$$

a: number of C atoms in the molecule; b: number of H atoms in the molecule

c: number of O atoms in the molecule; α: contribution of ^{18}O to % $(M^+{+}2)$

× in the molecule

% $(M^+{+}2)$ and α values calculated based on the abundances of M^+, $M^+{+}2$ ions of labeled and normal compounds **7**, a fragment $(MeOC_6H_4C(=O)OCH_2CH=CHCH_2)^+$ from the molecule **8**, a fragment $(MeOC_6H_4C(=O)OH)^{+\bullet}$ from the molecule **2b*** and a fragment $(MeOC_6H_4C(\equiv O^+))$ from the molecule **3b*** are summarized in Table 2.

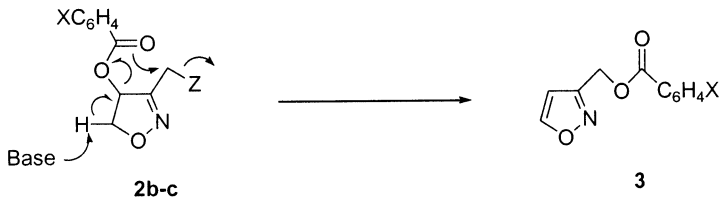
Table 2
Percent $(M^+ + 2)$ and α-values

Ions	**7**$^{+\bullet}$		(**8**-Br)$^{+\bullet}$		$(MeOC_6H_4C(=O)O^{18}H)^{+\bullet}$[a]		$MeOC_6H_4C(\equiv O^{18+})$[b]	
	Labeled	Normal	Labeled	Normal	Labeled	Normal	Labeled	Normal
% $(M^+ + 2)$	3.69	1.33	6.65	1.60	3.58	1.05	2.21	0.76
α	2.42	1.44	2.33	1.47	2.78	0.99	1.62	0.79

[a] A fragment ion from **2b***.
[b] A fragment ion from **3b***.

In order to avoid the interference of ^{91}Br in the calculations of % $(M^+{+}2)$ of compounds **8** and **2b***, the α values ions were calculated based on the abundances of fragments $(MeOC_6H_4C(=O)OCH_2CH=CHCH_2)^+$ and $(MeOC_6H_4C(=O)OH)^{+\bullet}$ derived from the molecular ions of **8** and **2b***, respectively. The data clearly show that fragments from labeled compound possess a higher ^{18}O than the corresponding fragments from normal molecule. Indeed, the α value (1.62) obtained from labeled *p*-methoxybenzoyl cation generated from **3b*** is higher than that (0.79) obtained from the corresponding unlabeled ion. This result clearly indicates that the ^{18}O atom in the molecule **2b*** becomes the carbonyl oxygen of **3b***.

Based on the data in hand, the rearrangement can be explained by deprotonation from C-5 of 2-isoxazolines, concomitant with migration of electrons to form a C=C double bond, followed by an intramolecular nucleophilic attack of the carbonyl oxygen to the carbon atom bearing a leaving group (Z = Br, ArC(=O)O) to give **3** (Scheme 6).



Scheme 6.

Acknowledgements

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