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A facile and novel method for the synthesis of 2-isoxazolines

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Abstract

Treatment of allylic esters such as allyl benzoate (3a), allyl phenylacetate (4), allyl 3-phenylpropanoate (5), crotyl esters 14, 4-bromo-2-butenyl esters 15, and 1,4-bis(aroyloxy)-2-butenes 16 with NOBF₄ in CH₃CN at -23° C gave alkanoyloxy (or aroyloxy)-2-isoxazolines and 3-substituted 4-alkanoyloxy (or aroyloxy)-2-isoxazolines, depending on the allylic esters. © 1999 Elsevier Science Ltd. All rights reserved.

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2-Isoxazolines are versatile synthetic intermediates which have been extensively used for introducing synthetically useful functionalities such as β -hydroxy ketones,¹ γ -amino alcohols,² β -hydroxynitriles,³ β -hydroxy acids,⁴ α , β -unsaturated ketones,⁵ etc. The 1,3-dipolar addition of a nitrile oxide to a double bond is a well-known method for the synthesis of 2-isoxazolines.⁶ In addition, there are some other methods which have been less frequently used, i.e., nitrosative cyclization using a DMSO solution of sodium nitrite and *n*-propyl nitrite,^{6b,7} treatment of isoxazolin-5-one with olefins,⁸ the reactions of 2,3-disubstituted cyclopropanes with NOBF₄,⁹ and deprotonation of 3-substituted 2-isoxazolines with LDA, followed by addition of electrophiles,¹⁰ all of the reactions gave 2-isoxazolines having one or more substituent(s) at C-3, C-4 and/or C-5, depending on the methods.

In a continuation of our study exploring the synthetic utility of nitrosonium ions (NO⁺) having a non-nucleophilic counter anion,¹¹ we became interested in the examination of a possible interaction between the cation formed by addition of NO⁺ to the olefinic double bond and non-bonding electrons in oxygen at either the γ or δ position from the cationic center. The oxygen atom would be expected to stabilize the cation by forming a five- or six-membered cyclic intermediate depending on the site where the oxygen atom presents. Subsequently the cyclic intermediate might be attacked by the oxime hydroxy group to give 2-isoxazolines. Therefore, other reactions besides cyclization, leading to 4*H*-5,6-dihydro-1,2-oxazine^{11b} and 2-alkyl-*N*-hydroxyimidazolium tetrafluoroborates¹² in addition to the formation of nitrolic acids^{11c}, would be expected to occur. With this in mind, the reactions of various esters 1–5 with NOBF₄ were studied. Our preliminary results are disclosed herein.

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Treatment of 1 with a slight excess molar amount of NOBF₄ in CH₃CN at -23°C for 4 h exhibited a series of color changes, i.e., colorless \rightarrow yellow \rightarrow pale blue \rightarrow yellow. Quenching the yellow solution with water resulted in a colorless solution from which *N*-benzylacetamide (6) (43%), an unknown mixture and unreacted 1 (48%) were isolated. Compound 6 is envisaged to be formed by a kind of Ritter-type reaction of benzyl cation in CH₃CN.¹³ The reaction of 2 under the same conditions gave unreacted 2 (12%) and a complex mixture from which no pure product was isolated. On the other hand, the reaction of **3a** under the same conditions gave 4-benzoyloxy-2-isoxazoline (**7a**) (34%).¹⁴ The structure of **7a** was determined based on the spectroscopic (¹H and ¹³C NMR, IR, MS) data and elemental analyses. The possible formation of the structural isomers **8** and **9** was eliminated based on the HMBC spectrum of **7a** which clearly shows the correlation between the carbonyl carbon and a proton at C-4 of **7a**. Similarly, the reactions of phenylacetate ester **4** and 3-phenylpropanoate ester **5** under the same conditions gave 4-phenylacetoxy- (**10**)¹⁵ and 4-(3-phenylpropanoyloxy)-2-isoxazolines (**11**)¹⁶ in 13 and 12% yields, respectively.



The formation of compounds 7a, 10, and 11 indicates that the length of the carbon chain between phenyl and carbonyl groups of the esters 3a, 4, and 5 is not important despite the variable yields of 2-isoxazolines. However, the reaction of allyl 2-phenethyl ether (12) under the same conditions gave 2-phenethyl alcohol (16%) and an unknown mixture in addition to unreacted 12 (28%). Surprisingly, the reaction with 1-phenyl-4-penten-1-one (13) under the same conditions gave ethyl benzoate (20%) and benzoic acid (50%). The results suggest that the ester functionality is requisite for the formation of 2-isoxazolines.

In order to obtain further evidence to support the necessity of ester functionality, crotyl esters 14, 4bromo-2-butenyl esters 15, and 1,4-bis(aroyloxy)-2-butenes (16) were synthesized. Treatment of 14–16 with NOBF₄ under the same conditions as for 3 gave the corresponding 2-isoxazolines 17–19 (Scheme 1). Reaction times and yields of 2-isoxazolines 17–19 are summarized in Table 1. The table shows that the yields of 2-isoxazolines are independent of the substituents in the aryl group. However, there is a tendency for the reactions to proceed faster in the presence of an electron-donating group in the aryl group (cf. 7b and 7d, 17b and 17d, 18b and 18d, 19b and 19d). It is noteworthy that compounds 16, which have two aroyloxy groups at C-1 and C-4 of butene, undergo reactions at similar rates to those of 3 despite having two large groups around the C=C double bond, which might cause steric hindrance. Nevertheless, yields of 19 are much higher than those of 7, 17, and 18.



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Scheme 1.

Ar	7 (X = H)			17 (X = Me)			$18 (X = CH_2Br)$			$19 (X = CH_2O_2CAr)$		
	time (h)		Yield "(%)	time (h)		Yield" (%)	time (h)		Yield" (%)	time (h)		Yield" (%)
Ph	3	a	34	4	a	31	4	a	63	2	a	61
4-MeOC₅H₄	1.5	b	41	2	b	60	2	b	58	2	b	83
4-MeC ₆ H₄	2	с	56	4	c	49	4	c	65	2	с	74
4-O ₂ NC ₆ H ₄	6	d	47	4 1	đ	12 18°	5	d	36	4	đ	83
1-Naphthyl	2	е	47	4	e	30	4	e	50	4	e	64

Table 1Reaction times and yields of 2-isoxazolines 7, 17, 18, and 19

" Isolated yields. The starting ester 14 (Ar = $4-O_2NC_6H_4$, X = Me) was recovered (32%).

The mechanism for the formation of 2-isoxazolines may be explained by assuming an intermediate **20** in which the cation formed by addition of NO⁺ to the C=C double bond is stabilized by the interaction of the ester carbonyl group. Subsequent nucleophilic attack of the hydroxy group on C-5 of the oxonium ion occurs simultaneously with cleavage of the C-O bond to give 2-isoxazolines (Scheme 2). High yields of **19** may be attributable to two aroyloxy groups, which stabilize the cation formed regardless of regiochemistry when the addition of NO⁺ to the double bond takes place.



Scheme 2.

In summary, we have developed a new synthetic method for 2-isoxazolines having an alkanoyloxy or aroyloxy group at C-4 and for 3-substituted 2-isoxazolines bearing the same alkanoyloxy or aroyloxy group at C-4 from allylic esters and NOBF₄ in CH₃CN at -23° C.

The synthetic utility of the 3 and/or 4-substituted 2-isoxazolines prepared and the scope of the reactions will be reported in due course.

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- 14. Typical procedure: To a solution a NOBF₄ (884 mg, 7.57 mmol) in dried CH₃CN (20 mL) was added dropwise, with stirring, a solution of allyl benzoate (1.050 g, 6.47 mmol) in dried CH₃CN (10 mL) over a period of 10 min at -23° C under a nitrogen atmosphere. The mixture was stirred for 3 h, followed by addition of water and extracted with CH₂Cl₂ (30 mL×2). The extracts were dried over MgSO₄, concentrated in vacuo, and chromatographed on a silica gel column (2×10 cm). Elution with a mixture of *n*-hexane and EtOAc (3:1) gave 4-benzoyloxy-2-isoxazoline (**7a**) (420 mg, 34%): white solid; mp 84–86°C (*n*-hexane); ¹H NMR (300 MHz, CDCl₃) δ 4.39 (1H, dd, *J*=11.1, 7.9 Hz), 4.49 (1H, dd, *J*=11.3, 3.4 Hz), 6.19 (1H, dd, *J*=7.9, 3.4 Hz), 7.43–8.04 (5H, m), 7.49 (1H, s); ¹³C NMR (75 MHz, CDCl₃) δ 72.60, 78.69, 128.98, 129.15, 130.24, 134.17, 144.54, 166.00; IR (KBr) 1715, 1590, 1440, 1350, 1315 cm⁻¹. Anal. calcd for C₁₀H₉NO₃: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.91; N, 7.18.
- 15. Compound 10: colorless liquid; ¹H NMR (300 MHz, CDCl₃) δ 4.09 (2H, s), 4.18 (2H, d, J=5.8 Hz), 5.92 (1H, t, J=5.8 Hz), 5.84 (1H, t, J=5.7 Hz), 7.14–7.34 (5H, m), 7.27 (1H, s); IR (KBr) 1731, 1597, 1488, 1443, 1367 cm⁻¹; MS(EI) *m/z* 205 (M⁺, 3.8%), 176 (1.6), 136 (13), 91 (100). Anal. calcd for C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.50; H, 5.28; N, 6.75.
- 16. Compound 11: colorless liquid; ¹H NMR (300 MHz, CDCl₃) δ 2.59 (2H, t, J=7.3 Hz), 2.87 (2H, t, J=7.6 Hz), 4.16 (2H, d, J=5.6 Hz), 5.84 (1H, t, J=5.7 Hz), 7.10–7.29 (5H, m), 7.29 (1H, s); IR (KBr) 1728, 1590, 1488, 1443, 1408, 1370 cm⁻¹. Anal. calcd for C₁₂H₁₃NO₃: C, 65.74; H, 5.98; N, 6.89. Found: C, 62.65; H, 6.05; N, 6.50.