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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 $NOBF_4$ in CH_3CN at −23°C gave alkanoyloxy (or aroyloxy)-2-isoxazolines and 3-substituted 4-alkanoyloxy (or aroyloxy)-2-isoxazolines, depending on the allylic esters.

Keywords: 2-isoxazoline; nitrosonium tetrafluoroborate; allylic ester.

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 $NOBF_4$,[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 tetrafluoroborates[12] 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 $NOBF_4$ were studied. Our preliminary results are disclosed herein.

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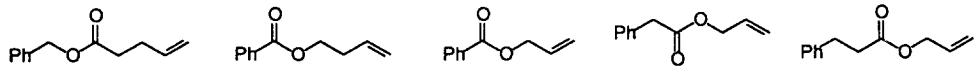
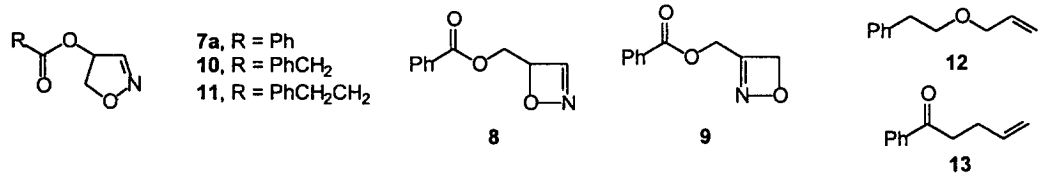


1 2 3a 4 5

Treatment of **1** with a slight excess molar amount of $NOBF_4$ in CH_3CN at −23°C for 4 h exhibited a series of color changes, i.e., colorless→yellow→pale blue→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 CH_3CN.[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 ^{13}C 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.

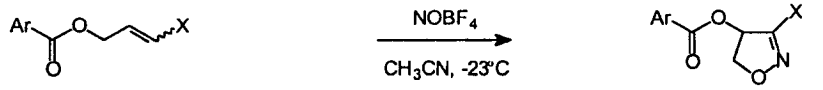


7a, R = Ph
10, R = $PhCH_2$
11, R = $PhCH_2CH_2$

8 9 12 13

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**, 4-bromo-2-butenyl esters **15**, and 1,4-bis(aroyloxy)-2-butenes (**16**) were synthesized. Treatment of **14–16** with $NOBF_4$ 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**.



3, Ar = aryl, X = H **14**, Ar = aryl, X = Me
15. Ar = aryl, X = CH_2Br **16**, Ar = aryl, X = CH_2O_2CAr

7, X = H **17**, X = Me
18, X = CH_2Br **19**, X = CH_2O_2CAr

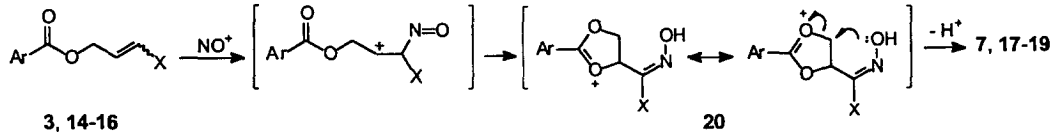
Scheme 1.

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

Ar	7 (X = H)			17 (X = Me)			18 (X = CH_2Br)			19 (X = CH_2O_2CAr)		
	time (h)		Yield[a] (%)	time (h)		Yield[a] (%)	time (h)		Yield[a] (%)	time (h)		Yield[a] (%)
Ph	3	**a**	34	4	**a**	31	4	**a**	63	2	**a**	61
4-$MeOC_6H_4$	1.5	**b**	41	2	**b**	60	2	**b**	58	2	**b**	83
4-MeC_6H_4	2	**c**	56	4	**c**	49	4	**c**	65	2	**c**	74
4-$O_2NC_6H_4$	6	**d**	47	4	**d**	12	5	**d**	36	4	**d**	83
				1		18[b]						
1-Naphthyl	2	**e**	47	4	**e**	30	4	**e**	50	4	**e**	64

[a] Isolated yields. [b]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 $NOBF_4$ in CH_3CN 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 $NOBF_4$ (884 mg, 7.57 mmol) in dried CH_3CN (20 mL) was added dropwise, with stirring, a solution of allyl benzoate (1.050 g, 6.47 mmol) in dried CH_3CN (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 CH_2Cl_2 (30 mL×2). The extracts were dried over $MgSO_4$, 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); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.90; H, 4.91; N, 7.18.
15. Compound **10**: colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) 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 $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.50; H, 5.28; N, 6.75.
16. Compound **11**: colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) 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 $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.89. Found: C, 62.65; H, 6.05; N, 6.50.