Reaction of Halogenated Cyclopropanes and Nitrosyl Cation: Preparation of Isoxazoles

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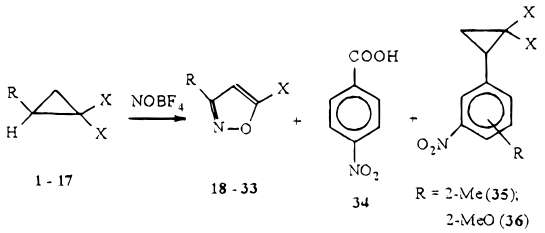
Introduction

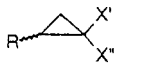
Isoxazole derivatives have anticonvulsant,[1] antibacterial,[2] antiasthmatic,[3] and other pharmacological activities.[3] Isoxazoles are typically prepared by the reaction of nitrile oxides with alkynes or by cyclization of the adducts of α,β-unsaturated ketones (or aldehydes) and hydroxylamines.[4] More recently, isoxazolines have been prepared by the nitrosation of cyclopropanes using a mixture of sodium nitrite and trifluoroacetic acid,[5] dinitrogen tetraoxide,[6] cupric nitrate in acetic anhydride,[7] and nitrosyl cation in acetonitrile.[8] These isoxazolines can be converted into isoxazoles via dehydrogenation. In our previous work, we prepared 5-halogenoisoxazoles by the nitration of dihalogenated cyclopropanes using a mixture of nitric acid and sulfuric acid at room temperature.[9] This process takes place only when the phenyl group bears a strong electron-withdrawing group, such as NO_2 or CN. We can now prepare the isoxazoles by the reaction of dihalogenocyclopropane and nitrosyl cation, taking advantage of the halogen as a leaving group (Scheme 1). In contrast to previous reports that cyclopropanes must contain aryl groups for rearrangement,[5−9] these isoxazoles were formed by the reaction of nitrosyl cation with either the arylcyclopropanes or alkylcyclopropanes.

Results and Discussion

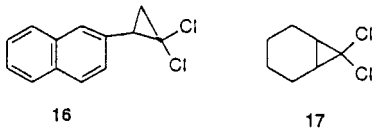
Halogenated cyclopropanes were reacted with nitrosyl tetrafluoroborate (1.2 equiv) in acetonitrile solution at room temperature for 2 h. During this reaction, the color of the solution changed from yellow for the initial mixture to a final green color, which depended on the nature of the substituent of the phenyl ring. The yields of the isoxazoles obtained by reacting 17 cyclopropanes with nitrosyl cation are summarized in Table 1. As this table shows, the yields of the various isoxazoles depended on the nature and the position of the substituents on the phenyl ring. Lower yields of isoxazoles were obtained with *ortho*-substituents, possibly because that the *ortho*-substituents hinder the formation of a coplanar transition state between the phenyl ring and the cyclopropane ring. Coplanarity of the two rings seems to be an essential transition state for the ring-opening of a cyclopropane ring.[9] Meanwhile, the aryl ring can delocalize the anion at the benzylic position for the electrophilic attack of the nitrosyl cation, as shown in Scheme 1. Aryl-nitrated products were obtained as the major or even sole products from 2-methyl- (**11**) or 2-methoxy- (**14**) phenyldichlorocyclopropanes (eq 1). The regioselectivity of nitration is



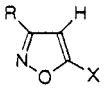
controlled by activation of the phenyl ring by a methoxyl (or methyl) group and the cyclopropyl ring as well as by a steric effect which reduces the possibility of the formation of a coplanar state between the two rings for the nucleophilic reaction of the cyclopropyl ring. The donor nature of the dihalogenocyclopropyl ring has been demonstrated by character of examining SCS (substituent chemical shifts) in ^{13}C NMR analyses.[10] As expected, treating 1-bromo-2-phenylcyclopropane with the nitrosyl salt yields 3-phenylisoxazole as the major product along with benzoic acid from the oxidation reaction. In this study, we found that 2,2-dichlorobicyclo[4.1.0]heptane (**17**) can undergo a similar reaction to give alkyl-substituted isoxazoles **33**. It is important to note that this is in contrast to previous reports that have stated that only the cyclopropyl rings which contain an aryl group are subjected to opening and the formation of isoxazolines or isoxazoles.[5−9]



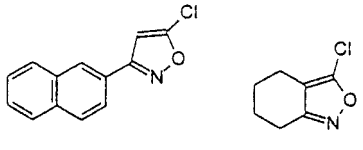
R, X', X" : C_6H_5, Cl, Cl (**1**); C_6H_5, Br, Br (**2**); 4-O_2N-C_6H_4, Cl, Cl (**3**); 3-O_2N-C_6H_4, Cl, Cl (**4**); 2-O_2N-C_6H_4, Cl, Cl (**5**); 4-Cl-C_6H_4, Cl, Cl (**6**); 3-Cl-C_6H_4, Cl, Cl (**7**); 4-Br-C_6H_4, Cl, Cl (**8**); 4-Me-C_6H_4, Cl, Cl (**9**); 3-Me-C_6H_4, Cl, Cl (**10**); 2-Me-C_6H_4, Cl, Cl (**11**); 4-MeO-C_6H_4, Cl, Cl (**12**); 3-MeO-C_6H_4, Cl, Cl (**13**); 2-MeO-C_6H_4, Cl, Cl (**14**); C_6H_5, H, Br (**15**)



16 **17**



R, X : C_6H_5, Cl (**18**); C_6H_5, Br (**19**); 4-O_2N-C_6H_4, Cl (**20**); 3-O_2N-C_6H_4, Cl (**21**); 2-O_2N-C_6H_4, Cl (**22**), 4-Cl-C_6H_4, Cl (**23**); 3-Cl-C_6H_4, Cl (**24**); 4-Br-C_6H_4, Cl (**25**); 4-Me-C_6H_4, Cl (**26**); 3-Me-C_6H_4, Cl (**27**); 2-Me-C_6H_4, Cl (**28**); 4-MeO-C_6H_4, Cl (**29**); 3-MeO-C_6H_4, Cl (**30**); C_6H_5, H (**31**)



32 **33**

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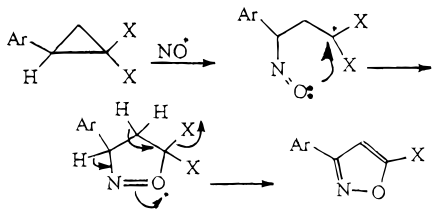
Table 1. Physical Properties and Spectral Data of Compounds 18−33

reactant	product	mp/°C (color)	yield (%)	molecular formula	anal. found (calcd) C, H, N	^{1}H NMR ($CDCl_3$)
1	**18**	42 (white)[a]	89	C_9H_6NOCl	60.24, 3.32, 6.20 (60.19, 3.37, 6.25)	6.48 (1H, s); 7.46 (3H, m), 7.73 (2H, m)
2	**19**	40.2−42.0 (white)	83	C_9H_6NOBr	48.33, 2.89, 6.42 (48.25, 2.70, 6.25)	6.60 (1H, s); 7.45 (3H, m); 7.63 (2H, m)
3	**20**	169.9−171.3[b] (yellow)	82[c]			6.58 (1H, s); 7.94 (2H, d, J = 8.8 Hz); 8.33 (2H, d, J = 8.8 Hz)
4	**21**	147.0[d] (white)	82			6.59 (1H, s), 7.68 (1H, t, J = 8.0 Hz), 8.14 (1H, d, J = 10.9 Hz), 8.32 (1H, d, J = 10.9 Hz), 8.57 (1H, s)
5	**22**	61.5−62.0[e] (white)	65			6.31 (1H, s), 7.68 (3H, m), 8.05 (1H, m)
6	**23**	98.6 (white)	97	$C_9H_5NOCl_2$	50.53, 2.45, 6.67 (50.50, 2.35, 6.54)	6.47 (1H, s), 7.44 (2H, d, J = 8.5 Hz); 7.69 (2H, d, J = 8.5 Hz)
7	**24**	59.5 (white)	95	$C_9H_5NOCl_2$	50.46, 2.48, 6.55 (50.50, 2.35, 6.54)	6.47 (1H, s); 7.42 (2H, m); 7.63 (1H, dd, J = 1.9, 7.0 Hz); 7.75 (1H, d, J = 1.9 Hz)
8	**25**	99.5 (yellow)	85	$C_9H_5NOBrCl$	41.80, 1.99, 5.45 (41.82, 1.95, 5.42)	6.46 (1H, s), 7.62 (4H, m)
9	**26**	40.7 (yellow)	66	$C_{10}N_8NOCl$	62.21, 4.20, 7.18 (62.03, 4.16, 7.23)	2.24 (3H, 2); 6.45 (1H, s); 7.26 (2H, d, J= 8.0 Hz); 7.64 (2H, d, J = 8.0 Hz)
10	**27**	43.4 (yellow)	65	$C_{10}H_8NOCl$	62.09, 4.19, 7.20 (62.03, 4.16, 7.23)	2.41 (3H, s); 6.47 (1H, s); 7.33 (2H, d, J = 7.3 Hz); 7.49 (1H, d, J = 7.3 Hz); 7.58 (1H, s)
11	**28**	viscous liq orange	55[f]	$C_{10}H_8NOCl$	62.14, 4.26, 7.33 (62.03, 4.16, 7.23)	2.46 (3H, s); 6.35 (1H, s); 7.27−7.36 (3H, m), 7.44−7.47 (1H, m)
12	**29**	57.8−59.0 (yellow)	63	$C_{10}H_8NO_2Cl$	57.44, 3.89, 6.64 (57.30, 3.85, 6.68)	3.86 (3H, s), 6.40 (1H, s), 6.98 (2H, d, J = 9.0 Hz), 7.68 (2H, d, J = 9 Hz)
13	**30**	viscous liq (yellow)	60	$C_{10}H_8NO_2Cl$	57.26, 3.89, 6.59 (57.30, 3.85 6.68)	3.86 (3H, s); 6.47 (1H, s); 7.02 (2H, m); 7.34 (2H, m)
14			46[g]			
15	**31**	viscous liq (colorless)	45[h]	C_9H_7NO	74.40, 4.89, 9.71 (74.46, 4.86, 9.65)	5.00 (1H, d, J = 3.5 Hz), 5.84 (1H, d, J = 3.5 Hz), 7.28 (2H, m), 7.37 (3H, m)
16	**32**	101.5−102.9 (yellow)	73	$C_{13}H_8NOCl$	68.06, 3.64, 6.18 (67.99, 3.51, 6.10)	6.63 (1H, s); 7.55 (3H, m); 7.90 (3H, m); 8.20 (1H, s)
17	**33**	34.2−35.8 (white)	43	C_7C_8NOCl	53.38, 5.01, 8.99 (53.35,5.12, 8.89)	1.76 (4H, m); 2.43 (2H, m); 2.70 (2H, m)

[a] Literature[16] 45−47 °C. [b] Literature[9] 167−169 °C. [c] 5% of nitrobenzoic acid (**34**) as a byproduct. [d] Literature[9] 147.5−148.9 °C. [e] Literature[9] 59 °C. [f] 17% of 1-(2-methyl-5-nitrophenyl)-2,2-dichlorocyclopropane (**35**) as a byproduct from 1-(2-methylphenyl)-2,2-dichlorocyclopropane: yellow powder, mp 90.7 °C; ^{1}H NMR 1.99 (1H, dd, J = 7.6, 16.1 Hz), 2.12 (1H, d, J = 7.6 Hz), 2.56 (3H, s), 2.81 (1H, t, J = 16.1 Hz), 7.12 (1H, d, J = 8.5 Hz), 7.90 (1H, s), 8.10 (1H, d, J = 8.5 Hz); MS (relative intensity) m/z 245 (M^+, 7), 129 (100). Anal. Calcd (found) for $C_{10}H_9NO_2Cl_2$; C 48.80 (48.75), H 3.69 (3.76), N 5.69 (5.61). [g] 46% of 1-(2-methoxy-5-nitrophenyl)-2,2-dichlorocyclopropane (**36**) was obtained as the only product with 38% of the starting compound recovered from 1-(2-methoxyphenyl)-2,2-dichlorocyclopropane: red solid, mp. 124 °C; ^{1}H NMR 1.88−2.08 (2H, m), 2.89 (1H, dd, J = 9.5, 19.0 Hz), 4.05 (3H, s), 7.05 (1H, d, J = 9.0 Hz), 7.90 (1H, d, J = 2.7 Hz), 8.24 (1H, dd, J = 2.7, 9.0 Hz); MS (relative intensity) m/z 261 (M^+, 23), 145 (100). Anal. Calcd (found) for $C_{10}N_9NO_2Cl_2$: C 45.83 (45.89), H 3.46 (3.55), N 5.34 (5.28). [h] 17% of benzoic acid (**37**) as a byproduct.

Scheme 1



X :Cl, Br

NMR and mass spectra were used to characterize these isoxazole products. In general, the chemical shifts of the C(4)-H appear as a singlet in the range from 6.30 to 6.60 ppm and slightly depend on the nature and the position of the substituent in the phenyl ring. The ^{13}C NMR chemical shifts of the C(3) and C(5) were assigned to the two most downfield signals due to the nature of the heterocyclic ring and the electron-withdrawing effect of the chlorine atom.[11] The chemical shifts of C(3) and C(5) slightly depend on the nature of the substituent on the phenyl ring. This might be due to the large remote distance from the substituent to both C(3) and C(5). The increment of chemical shift for the phenyl ring is found to be increased by −0.4, −1.7, 0.6, and 2.1 with the addition of the 5-chloroisoxazole group to C1, C2, C3, and C4 of the phenyl ring, respectively. In the mass spectra, the fragmentation of this series of compounds is relatively simple. The major fragments are the molecular ion $[M - Cl]^+$ (as the base peak), $[M - Cl - CO]^+$ **c**, and $[M - Cl - CO - HCN]^+$ (presumably a benzocyclopropenium cation).[12] The formation of $[M - Cl]^+$ as a base peak occurs because the chlorine atom is an ionization center as well as the fragmentation center in this series.

Conclusion

The reaction of the halogenated cyclopropanes with nitrosyl cation is a feasible and effective method for preparing isoxazoles. The formation of isoxazole instead of the isoxazoline is due to the halogen group acting as an adequate leaving group in the formation of isoxazoline. These results demonstrate that this process can be extended to a cyclopropane ring which does not bear an aryl ring.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded at 250 MHz and at 62.86 MHz, respectively, at an ambient temperature with

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deuteriochloroform as the solvent. 1-Aryl-2,2-dichlorocyclopropanes were prepared by treating styrene derivatives with $CHCl_3$ in pentane in the presence of $KOBu^t$ as described in the literature procedures.[13]

1-(2-Nitrophenyl)- and 1-(4-nitrophenyl)-2,2-dichlorocyclopropanes were prepared directly by nitrating of 1-phenyl-2,2-dichlorocyclopropane in acetic anhydride at −50 °C.[14] 1-Bromo-2-phenylcyclopropanes were prepared by reducing 1,1-dibromo-2-phenylcyclopropane using diethyl phosphite as a reducing agent.[15] Acetonitrile was dried and stored over CaH_2 before use.

Typical Procedure for the Reaction of 1-Aryl-2,2-dichlorocyclopropane and Nitrosyl Tetrafluoroborate. To a two-necked flask containing $NOBF_4$ (1.2 equiv, caution: very hygroscopic, after opening must be stored over P_4O_{10}) was added cyclopropane (50 mmol) in a dry acetonitrile solution (30 mL). The solution was stirred at rt for 1.5 h and then quenched with water. The subsequent solution was extracted with ethyl acetate (50 mL × 3). The combined organic solution was washed with water (50 mL × 3) and then dried over $MgSO_4$. After filtration and evaporation of the solvent, the resultant solid was recrystallized from methanol, and the liquid products (**18**, **30**, **31**) were purified by means of thin-layer chromatography (SiO_2) with *n*-hexane/EtOAc as an eluent. The yields, physical properties, and the spectroscopic data of the products are summarized in Table 1.

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Supporting Information Available: Tables of the mass spectral and ^{13}C NMR spectral data and a possible fragmentation mechanism of arylisoxazoles under EI conditions (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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