Halogenation of Vinyl Ketoximes. Synthesis of Isoxazoles and Preparation and Silver Ion-Promoted Reactions of 4-Halo-2-isoxazolines

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Reaction of several α,β-unsaturated ketoximes with *N*-bromosuccinimide (NBS) gave isoxazoles, but yields were lower and the reaction less general than a similar transformation using iodine under basic conditions. With β,β-disubstituted oximes, 4-halo-5,5-disubstituted-2-isoxazolines were obtained using NBS, iodine, or *N*-chlorosuccinimide. Treatment of the 4-bromoisoxazolines with silver acetate or silver nitrate caused either elimination with rearrangement to give isoxazoles or substitution at C-4, depending upon the nature of the substituents at C-5.

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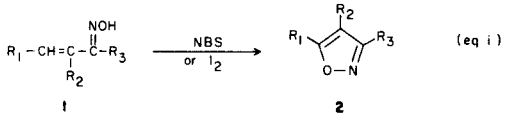
We have described in a preliminary communication the reaction of some α,β-unsaturated oximes with *N*-bromosuccinimide (NBS) to give isoxazoles or 4-bromoisoxazolines, depending upon the structure of the oxime (2). We now wish to report the results of our further investigations into the scope and limitations of this reaction, along with our observations on the reaction of the 4-bromo-2-isoxazolines with silver acetate or silver nitrate.

The reaction of several oximes of structure **1** in benzene



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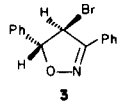

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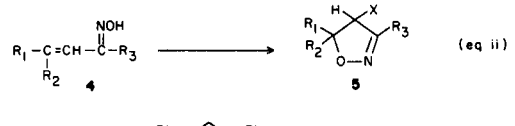
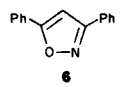
with NBS gave the isoxazoles **2** (equation i). It seemed likely that this reaction was closely analogous to a similar oxidative transformation using iodine under mildly basic conditions which has been reported by Büchi and Vederas (3), and a comparison of the two methods for isoxazole synthesis was carried out. The results of this study, shown in Table I, clearly indicate that the method of Büchi and Vederas is superior for isoxazole synthesis. In nearly every instance higher yields were obtained using iodine, while in some cases NBS failed entirely, which is consistent with the report of Büchi and Vederas (3) that donors of "positive" chlorine or bromine failed to effect isoxazole formation in the cases they investigated. A few examples of the reaction of **1** with *N*-chlorosuccinimide were examined, but the reaction proceeded much more slowly than with NBS, and the yields of isoxazoles were lower.

Various mechanistic alternatives have been discussed by Büchi and Vederas (3) for the iodine-induced cyclization, including the possible intermediacy of 4-iodo-2-isoxazolines, which they were unable to isolate. In the preparation of the isoxazoles with NBS, intermediates could be detected by thin layer chromatography in some instances but could not isolated (4). It seems likely that these intermediates were 4-bromo-2-isoxazolines analogous to the intermediates proposed by Büchi and Vederas (3) since the reaction of chalcone oxime **1** ($R_1 = R_3 = Ph$, $R_2 = H$) with NBS gave the known *trans*-4-bromo-3,5-diphenyl-2-isoxazoline (**3**) (5,6) as the major product in moderate yield. The unique stability of **3** compared with the presumed 4-bromo-2-isoxazoline intermediates in the formation of **2a-2i** may be due to the lack of strain in **3**, where the bulky phenyl and bromo substituents are *trans*, while the geometric relationship between bromine and the C-5 hydrogen is unfavorable for an E_2 elimination of hydrogen bromide. The contrasting ease of elimination from the presumed intermediate 4-bromo-2-isoxazolines to give the isoxazoles in Table I during reaction and subsequent workup may be the result of steric crowding of R_1 with R_2 or bromine, the stabilizing influence of additional substituents on the developing isoxazole, or a favorable *trans* relationship between bromine and C-5 hydrogen (*i.e.*, in the formation of **2f**) which facilitates dehydrobromination.



4 **5**



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A number of examples were investigated using oximes of type **4**, and the 4-bromo-2-isoxazolines **5** (X = Br) could be isolated (equation ii). The absence of hydrogen at C-5 precludes elimination of hydrogen bromide in these cases. A similar attempt to isolate a stable 4-iodo-2-isoxazoline has been described by Büchi and Vederas (3), who

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Table I

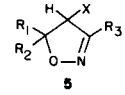
Synthesis of Isoxazoles **2** from Vinyl Ketoximes

Compound (a)	R_1	R_2	R_3	M.p. (°C)	Yield (b) Method A	Yield (b) Method B
2a	Ph	Ph	Ph	212-213	83	97
2b	Ph	Me	Ph	122-123	43	78
2c	Ph	Me	Me	49-51	40	72
2d (c)	Me	Me	Ph	32-33	65	75
2e (d)	Ph	Ph	Me	93-94	19	85
2f	H	H	Ph	(e)	16	67
2g	Ph	Br	Ph	133-135	57	47
2h	Ph	Br	Me	25-26	42	52
2i	Ph	$-(CH_2)_4-$		65-66	39	76
2j	Ph	$-(CH_2)_3-$		107-109	0	18
2k	Ph	H	Me	67-68	0	67
2l	Ph	H	H	(f)	0	15 (g)

(a) Most of the isoxazoles are known compounds which were identified by literature comparison or independent synthesis by reported methods. (b) Method A. NBS in benzene, room temperature; Method B. Iodine-potassium iodide in refluxing aqueous sodium bicarbonate and tetrahydrofuran, see Reference 3. (c) *Anal.* Calcd.: C, 76.28; H, 6.40; N, 8.08. Found: C, 76.17; H, 6.31; N, 8.33. (d) *Anal.* Calcd.: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.58; H, 5.52; N, 5.81. (e) Liquid, b.p. 68-70° at 0.06 torr. (f) Liquid, b.p. 130° at 11 torr. (g) Mixture of isoxazole and cinnamonitrile, 2:1.

Table II

Preparation of 4-Halo-2-isoxazolines (**5**)



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Compound	R_1	R_2	R_3	X	Yield	M.p. (°C)	Pmr (δ) (*inter alia*) (a) C-4 H	R_1	R_2	R_3	Analysis Calcd. (Found) C	H	N
5a	Me	Me	Me	Br	18	(b)	4.72	1.59	1.34	2.13	37.52 (37.74)	5.25 (5.21)	7.29 (7.50)
5b	Me	Me	Ph	Br	54	75-76	5.14	1.70	1.38		51.99 (51.95)	4.76 (4.80)	5.51 (5.72)
5c	Me	Ph	Ph	Br	70	140-141	5.51	1.97			60.78 (61.10)	4.46 (4.47)	4.42 (4.27)
5d	Ph	Ph	Me	Br	32	149-151	5.53			2.03	60.78 (60.82)	4.46 (4.43)	4.42 (4.53)
5e	Ph	Ph	Ph	Br	69	189-191	6.07				66.66 (66.99)	4.29 (4.51)	3.70 (3.67)
5f	Ph	H	Ph	Br	64	156-157	5.33 (c)		6.01 (c,d)				
5g	Me	Ph	Ph	Cl	35	123-124	5.42	1.91			70.72 (70.95)	5.19 (5.20)	5.15 (5.42)
5h	Ph	Ph	Ph	Cl	51	180-182	5.98				75.56 (75.67)	4.83 (4.59)	4.20 (4.23)
5i	Me	Ph	Ph	I	60	134-136	5.67	2.03			52.91 (53.01)	3.88 (3.95)	3.86 (3.88)
5j	Ph	Ph	Ph	I	39	135-138	6.26				59.31 (59.21)	3.79 (3.70)	3.29 (3.51)

(a) Signals for phenyl groups fell in the usual range; when R_3 = Ph, the two *ortho* protons of that ring were deshielded, appearing at δ 7.7-7.8. (b) Liquid, b.p. 36-37° at 0.05 torr. (c) Doublet, J = 2 Hz. (d) In a sample of **5** (R_1 = R_3 = Ph; R_2 = D) this signal was absent.

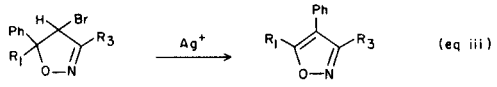
reported the recovery of starting material when mesityl oxide oxime **4** (R_1 = R_2 = R_3 = Me) was reacted with iodine under the usual conditions (3). Although the cyclization failed for that example, we found that 4-iodo-2-isoxazolines could indeed be prepared in some other instances. This provides further indication of the close analogy of the NBS and iodine-induced cyclization processes, and it supplies direct evidence to support the intermediacy of 4-iodo-2-isoxazolines in the isoxazole synthesis as proposed by Büchi and Vederas (3). Some examples of 4-chloro-2-isoxazolines **5** (X = Cl) were prepared using *N*-chlorosuccinimide, but once again the reaction was slower and the yields lower than with NBS. The results of the preparation of 4-halo-2-isoxazolines and some properties of the compounds are described in Table II.

In the case of **5c**, **5g**, and **5i** (see Table II), two geometric isomers are possible, but only a single product was observed in each instance. Furthermore, the oximes of both *cis*- and *trans*-dypnone **4** (R_1 = Me; R_2 = R_3 = Ph) were prepared by the method of Lutz (7), and both oximes yielded the same product upon treatment with NBS. This may indicate that the cyclization process is not stereospecific, but the possibility of isomerization of the *cis* isomer to the more stable *trans*-dypnone oxime before

cyclization cannot be ruled out. Büchi and Vederas (3) has shown that iodine-induced cyclization proceeds readily for either the (*E*)- or the (*Z*)-oxime of β-ionone (3), and the cyclization with NBS also seems to be independent of oxime geometry about the carbon-nitrogen bond. For example, the oximes used in the preparation of **5d** and of **3** are known to have a *syn* relationship between the hydroxyl group and the olefinic bond, while these groups have an *anti* relationship in the oximes used to prepare **2a** and **2g** (8).

Crabbé, *et al* (9), has demonstrated the conversion of a 4-iodo-2-isoxazoline to an isoxazole using silver acetate-assisted elimination of hydrogen iodide. A similar transformation could be effected for **3** (entry **5f** in Table II) by heating with silver acetate in acetic acid or with ethanolic silver nitrate to give 3,5-diphenylisoxazole (**6**). The other 4-bromo-2-isoxazolines **5a-e** cannot undergo such an elimination, since they lack the necessary hydrogen atom at C-5. The reactions observed for those compounds with silver ion were dependent on the nature of the substituents present at C-5.

In the cases of **5c**, **5d**, and **5e**, all of which bear phenyl substituents at C-5, rearrangement occurred. Elimination with phenyl migration was observed for these compounds to give the 4-phenylisoxazoles **7** in good yield (equation iii). A process similar to the pinacolic rearrangement of



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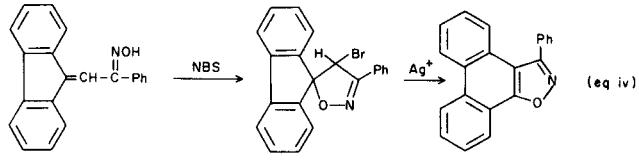
bromohydrins (10) is suggested in this reaction. This process might involve formation of the discrete carbonium ion **8**, through abstraction of bromide by silver ion followed by phenyl migration to **9**. Alternatively, an anchimeric effect might be involved, with concerted bromide abstraction and phenyl migration to give **9** directly. Loss of the C-4 proton from **9** would give **7**. The overall process of acid-catalyzed elimination with rearrangement to give an aromatic product is reminiscent of the familiar dienol-benzene rearrangement (11).

A further interesting example of this rearrangement was observed for the spiro-fused isoxazoline **11** to give the phenanthro[9,10-*d*]isoxazole **12** (equation iv). The oxime **10** was first converted to **11** with NBS, and **12** was formed upon heating with silver nitrate in ethanol. The structures of **11** and **12** were assigned on the basis of satisfactory elemental analyses and spectral data.

The 5,5-dimethyl-4-bromo-2-isoxazolines **5a** and **5b** behave quite differently. Upon reaction with silver ion, silver bromide was formed, but no rearrangement to the 4,5-dimethylisoxazole could be detected by gas chromatographic analysis. With ethanolic silver nitrate, a mixture of products was obtained which could not be conveniently separated (12). With silver acetate in acetic acid, however, the only products obtained were the 4-acetoxy-2-isoxazolines **13**. The structures of **13a** and **13b** followed from satisfactory elemental analyses and from the appearance of signals in the ir at 1740 cm^{-1} (carbonyl stretch). The pmr spectra included signals around δ 2.1 for the acetyl methyl groups and otherwise closely resembled the spectra of the 4-bromo-2-isoxazolines.



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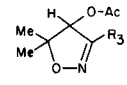

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a, R_3 = Me
b, R_3 = Ph

EXPERIMENTAL

Melting points were determined with a Thomas Hoover Uni-Melt apparatus in open capillary tubes. Ir spectra of liquids were determined as neat films, solids as Nujol mulls with a Perkin-Elmer 700 or 710B spectrometer. Pmr spectra were determined in deuteriochloroform, unless otherwise indicated, on the Perkin-Elmer R-32 90 MHz spectrometer with tetramethylsilane as an internal standard. Elemental analyses were performed by Microanalysis, Inc., Wilmington, DE. Most of the starting oximes are known compounds and were prepared following literature methods.

3-Methyl-1-phenyl-2-buten-1-one (*E*)-Oxime (**4b**).

A solution of 16.0 g. (0.1 mole) of 3-methyl-1-phenyl-2-buten-1-one in 75 ml. of 95% ethanol was treated with 7.7 g. (0.11 mole) of hydroxylamine hydrochloride in 25 ml. of water and 1 ml. of concentrated hydrochloric acid and heated under reflux. After 2 hours the ethanol was evaporated, and the residue was treated with 50 ml. of water and extracted with two 50 ml. portions of ether. The ether solutions were washed with saturated sodium chloride dried (sodium sulfate) and evaporated. The residue was purified by chromatography on a 20 × 1000 mm column of silica gel (Woelm, 0.032-0.063 mm). Elution with hexane and then with 5% ether in hexane under 80 psi, with monitoring by thin layer chromatography, gave 5.91 g. of recovered ketone, followed by traces of unidentified material in the intermediate fraction. Further elution gave the desired oxime, 2.59 g. (15%), as a white solid, m.p. 107-114° (13). Recrystallization of the oxime from hexane gave white flakes, m.p. 112-114°; pmr: δ 9.0 (bd s, 1H), 7.25-7.65 (m, 5H), 6.12 (m, fine splitting, 1H), 1.90 (narrow doublet, 3H), 1.43 (narrow doublet, 3H).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.66; H, 7.45; N, 8.09.

Beckmann rearrangement of **4b** with phosphorus pentachloride in ether (8) gave 50% yield of white needles, m.p. 126-128°, which was identical (m.p., mixture m.p., ir spectrum) with an authentic sample of the anilide of 3-methyl-2-butenoic acid (reported m.p. 126-127°) (14), thus

establishing the (*E*) geometry for the oxime.

2-(9'-Fluorenylidene)acetophenone Oxime **10**.

A mixture of 5.65 g. (20 mmoles) of 2-(9-fluorenylidene)acetophenone (15), 2.7 g. (40 mmoles) of hydroxylamine hydrochloride, and 1.2 ml. of concentrated hydrochloric acid in 100 ml. of 95% ethanol was heated under reflux for 8 hours. The solvent was evaporated, and the residue was washed with water and recrystallized from ethanol to give 5.0 g. (85%) of **10** as yellow crystals, m.p. 195-198° (16).

Synthesis of Isoxazoles **2a-2l**. Method A.

A solution of 40 mmoles of the oxime **1** in 150 ml. of benzene was treated over 15-45 minutes with 44 mmoles of *N*-bromosuccinimide at 20-25°. The mixture was stirred at 20-25° until thin layer chromatography indicated completion (generally 15-180 minutes). The mixture was filtered to remove succinimide, and the filtrate was applied to a column of 150 g. of alumina (Alcoa F-20) and eluted rapidly with benzene. The first 200-300 ml. of eluent was collected and evaporated and the residue was recrystallized from ethanol or pentane or distilled under reduced pressure.

Method B.

The procedure used was that reported by Büchi and Vederas (3). The results are reported in Table I.

Synthesis of 4-Bromo-2-isoxazolines **5a-5f**.

The procedure of Method A was used. The products were isolated as described, by rapid chromatography on alumina followed by recrystallization of the solid products or distillation, taking care to avoid heating above 60° for **5a**. Most of the compounds were stable under normal conditions, but **5a** darkened noticably within a few weeks, even when stored in the cold. The results are reported in Table II.

4-Chloro-2-isoxazolines **5g** and **5h**.

Method A was modified by substituting *N*-chlorosuccinimide for NBS. Longer reaction times, 8-24 hours, were required for completion. Results are reported in Table II.

4-Iodo-2-isoxazolines **5i** and **5j**.

Method B was used. The products were recrystallized from dichloromethane-hexane avoiding undue heating. The compounds decomposed on melting. Results are reported in Table II.

4'-Bromo-3'-phenylspiro[9*H*-fluorene-9,5'(4'*H*)isoxazole] (**11**).

A solution of 2.97 g. (10 mmoles) of **10** in 40 ml. of tetrahydrofuran (the oxime was only very sparingly soluble in benzene) was stirred at room temperature and treated over 30 minutes with 1.96 g. (11 mmoles) of NBS. After stirring overnight, the solution was concentrated to one half its volume and applied to a column of 100 g. of alumina. Elution with 250 ml. of benzene gave, after evaporation and recrystallization from ethanol, 1.24 g. (33%) of **11**, m.p. 168-169°; pmr: δ 8.0 (m, 2H), 7.20-7.75 (m, 11H), 5.75 (s, 1H).

Anal. Calcd. for $C_{21}H_{14}BrNO$: C, 67.02; H, 3.72; N, 3.72. Found: C, 67.02; H, 4.02; N, 4.02.

Silver Ion-assisted Rearrangement of 4-Bromo-2-isoxazolines. Method C.

A mixture of 1 mmole of the 4-bromoisoxazoline in 10 ml. of 95% ethanol was treated with a solution of 1 mmole of silver nitrate in 5 ml. of 95% ethanol. The mixture was heated for 15-30 minutes on a steam bath and filtered while hot. The solid was washed with acetone and the combined filtrate and wash solutions were diluted with 75 ml. of water and cooled. The isoxazole was collected by filtration and recrystallized. Rearrangement of **5e** gave 88% of **2a**, while **5d** gave 72% of **2e**. Reaction of **3** gave 74% of 3,5-diphenylisoxazole **6**.

Rearrangement of **5c** gave 92% of white crystals of 3,4-diphenyl-5-methylisoxazole **7** (R_1 = Me; R_3 = Ph), m.p. 95-97°; pmr: δ 7.05-7.55 (m, 10H), 2.38 (s, 3H).

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.56; N, 5.95. Found: C, 81.65; H, 5.60; N, 5.89.

Similar results were observed using silver acetate in acetic acid (see Method D, below).

4-Acetoxy-5,5-dimethyl-3-phenyl-2-isoxazoline (**13b**). Method D.

A mixture of 1 mmole of **5b** and 2 mmoles of silver acetate in 2 ml. of acetic acid was heated on a steam bath for 15 minutes, filtered, diluted to 20 ml. with water and extracted with 25 ml. and then 10 ml. of ether. The ether solution was washed with five 10 ml. portions of water and with two 10 ml. portions of 10% sodium bicarbonate, dried (sodium sulfate) and evaporated to yield 0.22 g. (95%) of **13b**, which seemed to be pure by pmr analysis. An analytical sample was prepared by evaporative distillation at 100° and 0.2 torr; pmr: δ 7.66 (m, 2H), 7.37 (m, 3H), 6.13 (s, 1H), 2.07 (s, 3H) 1.39 (s, 6H); ir: 1740 cm^{-1}.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.01. Found: C, 66.85; H, 6.76; N, 6.28.

4-Acetoxy-3,3,5-trimethyl-2-isoxazoline (**13a**).

Using Method D, **5a** gave 63% of **13a**, a faintly yellow liquid, b.p. 44° at 0.15 torr; pmr: δ 5.51 (s, 1H), 2.10 (s, 3H), 1.97 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H); ir: 1740 cm^{-1}.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 55.80; H, 7.59; N, 8.08.

3-Phenylphenanthro[9,10-*d*]isoxazole (**12**).

Reaction of 1.9 g. (5 mmoles) of **11** with silver nitrate by Method C, with heating for 2 hours gave, after recrystallization from acetone, 1.05 g. (71%) of white crystals, m.p. 152-153°; pmr (acetone d_6): δ 8.92 (m, 2H), 8.53 (m, 1H), 7.45-8.05 (m, 10H).

Anal. Calcd. for $C_{21}H_{13}NO$: C, 85.42; H, 4.41; N, 4.75. Found: C, 85.69; H, 4.75; N, 4.55.

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(4) The intermediate in the preparation of **2b** was relatively long-lived, and efforts were directed toward its isolation. By running the reaction at lower temperature in carbon tetrachloride, filtration to remove succinimide, and evaporation of the filtrate without heating, a crude mixture of **2b** and the intermediate was obtained. However, all attempts to separate these components, either chromatographically or by recrystallization without heating led to complete conversion of **2b**, with evolution of hydrogen bromide being observed.

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(12) Although this mixture was not separated, and thus positive identification was not possible, a mixture of a nitrate ester and an ethyl ether was suggested by the spectral evidence, which could have been formed in a manner analogous to **13** by nucleophilic substitution at C-4 involving competition between ethanol and nitrate ion.

(13) It has been reported [T. M. Chau, C. Beaute, S. Cornuel, and N. Thoai, *Tetrahedron Letters*, 4313 (1971)] that this ketone reacts with hydroxylamine under basic conditions to give a complex mixture of products with none of the oxime.

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