RESEARCH IN THE ISOXAZOLE SERIES

XXVI.* CHLORINATION OF ARYLISOXAZOLES

S. D. Sokolov and I. M. Yudintseva

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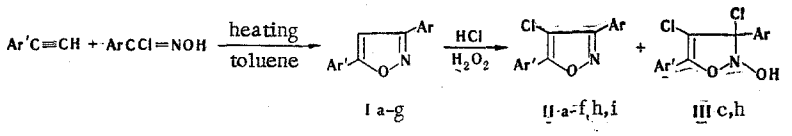
3,5-Diarylisoxazoles in acetic acid are smoothly converted to 4-chloro derivatives by the action of chlorine in situ. A side reaction is subsequent addition of hypochlorous acid, which proceeds under the influence of excess chlorine. It is convenient to use tert-butyl hypochlorite for the chlorination of more reactive arylisoxazoles.

The bromination and iodination of isoxazoles have been studied in quite some detail [2, 3]. There is much less information on the chlorination of these compounds. Liquid alkylisoxazoles react smoothly with chlorine to give 4-chloro derivatives [2, 4]. However, the chlorination of arylisoxazoles requires the use of solvents and has its own limitations.

A 4-chloro derivative was obtained in low yield as a result of the reaction of 3,5-diphenylisoxazole with sulfuryl chloride [5]. The action of chlorine in situ proved to be more effective. When acetic acid solutions of reactive 3,5-disubstituted isoxazoles are used, one observed not only substitution but also addition of hypochlorous acid to the heterocyclic ring [6], while only the 3,4-dichloro derivative is obtained from the less active 3-chloro-5-phenylisoxazole [7]. We have investigated this reaction in greater detail since, in contrast to the action of gaseous chlorine, it provides a possibility for accurate measuring out of the chlorinating mixture.

3,5-Diarylisoxazoles (Ia-g) containing electron-acceptor substituents (Cl, Br, NO_2) in the p-positions of the benzene rings were synthesized by reaction of arylacetylenes with α-chloroaldoximes [8] (Table 1). Chlorination of them in acetic acid with chlorine in situ gives 4-chloroisoxazoles IIa-f (Table 1).



I a-g II a-f,h,i III c,h

a Ar=*p*-ClC_6H_4, Ar'=C_6H_5; b Ar=C_6H_5, Ar'=*p*-ClC_6H_4; c Ar=Ar'=*p*-ClC_6H_4; d Ar=*p*-ClC_6H_4, Ar'=*p*-BrC_6H_4; e Ar=*p*-BrC_6H_4, Ar'=*p*-ClC_6H_4; f Ar=*p*-$O_2NC_6H_4$, Ar'=*p*-ClC_6H_4; g Ar=*p*-ClC_6H_4, Ar'=*p*-$O_2NC_6H_4$; h Ar=Ar'=C_6H_5; i Ar=C_6H_5, Ar'=*m*-$O_2NC_6H_4$.

The formation of chloro derivatives II as the only reaction products is due to the reduced nucleophilicity of the heterocyclic ring in starting substances Ia-f and in IIa-f themselves as compared with unsubstituted analogs Ih and IIh.

Using a 30% excess of hydrochloric acid, we have previously obtained 3,5-diphenyl-4-chloroisoxazole (IIh) in 45% yield [6]. It was found that a further increase in the excess of acid (up to 70%) promotes the addition of hypochlorous acid: the yield of IIh is not raised, whereas considerable amounts of 2-hydroxy-3,4-dichloro-3,5-diphenyl-4-isoxazoline (IIIh) are formed. Substances III are formed by the action of a 10-fold amount of chlorinating mixture on haloarylisoxazoles; thus, 2-hydroxy-3,4-dichloro-3,5-di(p-chlorophenyl)-4-isoxazoline (IIIc) is obtained in 63% yield.

*See [1] for communication XXV.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow.

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TABLE 1. 3,5-Diarylisoxazoles (Ic-g) and Aryl-4-chloroisoxazoles (IIa-f, h-k)

Comp.	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	Cl	C	H	Cl	
Ic	194—195	$C_{15}H_9Cl_2NO$	62,5	3,4	—	62,1	3,1	—	52
Id	201,5—202,5	$C_{15}H_9BrClNO$	53,9	2,7	—	53,8	2,7	—	41
Ie	190—191	$C_{15}H_9BrClNO$	54,0	2,8	—	53,8	2,7	—	38
If	221—222*	$C_{15}H_9ClN_2O_3$	59,7	3,1	—	59,9	3,0	—	68
Ig	197—198*	$C_{15}H_9ClN_2O_3$	59,8	3,0	—	59,9	3,0	—	61
IIa	93—94	$C_{15}H_9Cl_2NO$	62,4	3,1	24,8	62,1	3,1	24,4	74
IIb	105,5—106,5	$C_{15}H_9Cl_2NO$	62,4	3,5	24,3	62,1	3,1	24,4	83
IIc	152—153	$C_{15}H_8Cl_3NO$	—	—	32,7	—	—	32,8	74
IId	152—153	$C_{15}H_8BrCl_2NO$	48,6	2,0	—	48,8	2,2	—	82
IIe	142—144	$C_{15}H_8BrCl_2NO$	48,8	2,2	—	48,8	2,2	—	75
IIf	168—170	$C_{15}H_8Cl_2N_2O_3$	53,9	2,7	—	53,8	2,4	—	90
IIh	8†[9]	—	—	—	—	—	—	—	86
IIi	141	$C_{15}H_9ClN_2O_3$	60,0	3,1	—	59,9	3,0	—	83
IIj	43‡	C_9H_6ClNO	60,4	3,4	—	60,2	3,4	—	80
IIk	135	$C_{11}H_9ClN_2O_2$	55,9	3,8	12,2 (N)	55,8	3,8	11,8 (N)	71

*Lower melting points in open capillaries are presented in [10].

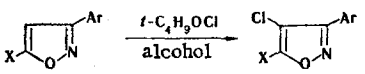
† According to [9], this compound has mp 84°.

‡ The substance was purified by vacuum distillation and had bp 73-75° (0.7 mm).

A nitro group in one of the benzene rings markedly lowers the electron density in the heterocyclic ring, such that only substitution occurs even under severe conditions. The −I effect of the NO_2 group plays the primary role here, as follows from the behavior of 3-phenyl-5-(m-nitrophenyl)isoxazole (Ii), from which a 4-chloro derivative (IIi) is formed in high yield. 5-Phenylisoxazole (Ij) reacts similarly, but is also less active than Ih [3] [4-chloro-5-phenylisoxazole (IIj) is obtained in 80% yield]. Its isomer – 3-phenylisoxazole – has even less nucleophilicity [3], and chlorination does not go to completion under the indicated conditions;* contaminating starting compound cannot be separated by either vacuum fractionation or column chromatography. The action of chlorine in situ on 5-substituted 3-phenylisoxazoles (methyl and amino derivatives) leads to cleavage of the heterocyclic ring to give benzonitrile and other chlorine-free substances, which were not investigated in detail.

Thus the use of chlorine in situ makes it possible to obtain 4-chloro derivatives only from arylisoxazoles of "moderate" activity.

For more reactive compounds we attempted to use a mild chlorinating agent – tert-butyl hypochlorite. In the case of 3,5-diphenylisoxazole (Ih), we selected the optimum conditions using a 1.5-fold excess of the reagent. It was found that the reaction proceeds smoothly on heating in ethanol but not in methanol or benzene. The worst results were obtained in the chlorination of the less active 3,5-di(p-chlorophenyl)isoxazole (Ic) under these conditions. On the other hand, the highly reactive 3-phenyl-5-acetamidoisoxazole (Ik) is chlorinated instantaneously at ~10° with an equivalent amount of reagent to give the 4-chloro derivative (IIk) in ~70% yield. When the reaction mixture is heated, the heterocyclic ring decomposes. 3-Phenyl-4-chloro-5-methoxyisoxazole is much less stable. Although it is also formed under similar conditions [according to thin-layer chromatography (TLC)], it gradually decomposes to give benzonitrile on attempts to purify it by crystallization or column chromatography.



Ih,k IIh,k

I, II k X = CH_3CONH

EXPERIMENTAL

The melting points of all of the compounds were determined in sealed capillaries. The IR spectra of mineral oil suspensions were obtained with a Perkin Elmer 457 spectrophotometer. The PMR spectrum was obtained with a Perkin Elmer R-12 spectrometer with hexamethyldisiloxane as the internal standard.

*The formation of the 4-chloro derivative was proved by the presence of a 5-H singlet at δ 8.93 ppm (acetone) in the PMR spectrum of the reaction mixture.

3,5-Diarylisoxazoles (Ia-g). An equimolar mixture of the appropriate arylacetylene and chlorooxime (0.01 mole each) in toluene (10-20 ml) was refluxed until hydrogen chloride evolution ceased (8-12 h). The mixture was cooled, and the precipitate was removed by filtration and crystallized from alcohol or toluene–petroleum ether (2:1). Data on the compounds obtained for the first time (Ic-g) are presented in Table 1.

3,5-Diaryl-4-chloroisoxazoles (IIa-f,i,j). A. Concentrated HCl and 26% hydrogen peroxide (0.015-0.02 mole of each) were added all at once to a hot solution of 0.01 mole of 3,5-diarylisoxazole in 50-150 ml of acetic acid, and the mixture was heated at 100° for 30 min. It was then cooled and diluted with water to twice its volume, and the precipitate was removed by filtration and crystallized from alcohol (IIf was crystallized from alcohol–toluene); IIa-f were obtained by this method.

B. The chlorination of arylisoxazoles Ii,j was carried out similarly with 10 g-equiv of hydrogen peroxide and concentrated HCl added in four portions. Data on the 4-chloroisoxazoles obtained are presented in Table 1.

Chlorination of 3,5-Diphenylisoxazole (Ih) with Chlorine in situ. A 1.02 ml (8.5 mmole) sample of 26% hydrogen peroxide and 0.77 ml (8.5 mmole) of concentrated HCl were added in two portions to a hot solution of 1.1 g (5 mmole) of isoxazole Ih in 15 ml of acetic acid, and the mixture was heated at 100° for 1 h and diluted with water. The precipitate was removed by filtration, dried, and crystallized from heptane–benzene to give 0.5 g (33%) of isoxazoline IIIh with mp 136-137° [6]. The mother liquor was evaporated, and the residue was recrystallized from aqueous alcohol to give 0.64 g (50%) of 4-chloro derivative IIh with mp 83-84° [9].

2-Hydroxy-3,4-dichloro-3,5-di(p-chlorophenyl)-4-isoxazoline (IIIc). A 0.8 g (2.8 mmole) sample of isoxazole Ic was similarly chlorinated with 3.3 ml (28 mmole) of hydrogen peroxide and 2.5 ml (28 mmole) of concentrated HCl. Crystallization of the products from alcohol gave 0.18 g (20%) of 4-chloroisoxazole IIc with mp 153°; the mother liquor yielded 0.65 g (63%) of isoxazoline IIIc with mp 180-181°. Found,%: Cl 37.0. $C_{15}H_9Cl_4NO_2$. Calculated,%: Cl 37.6. The IR spectrum contains a broad absorption band at 3200-3300 cm^{-1}, the same band that is present in the spectrum of analog IIIh but absent in the spectra of 4-chloroisoxazoles (hydrogen bonds).

3,5-Diphenyl-4-chloroisoxazole (IIh). A 1 ml (8 mmole) sample of tert-butyl hypochlorite was added dropwise to a solution of 1.1 g (5 mmole) of isoxazole Ih in 15 ml of alcohol, after which the mixture was refluxed for 1 h. The solvents were evaporated, and the residue was worked up to give IIh, data on which are presented in Table 1.

3-Phenyl-4-chloro-5-acetamidoisoxazole (IIk). A solution of 0.6 ml (5 mmole) of tert-butyl hypochlorite in 3 ml of alcohol was added dropwise at about 10° to a solution of 1 g (5 mmole) of amide Ik in 30 ml of alcohol, after which the mixture was vacuum evaporated without heating, and the residue was crystallized from benzene. Data on IIk are presented in Table 1.

LITERATURE CITED

1. I. B. Mazheika, I. S. Yankovska, S. D. Sokolov, and I. M. Yudintseva, Khim. Geterotsikl. Soed., 460 (1972).
2. A. Quilico and R. Justoni, Rend. Ist Lombardo Sci., Pt. I, 69, 587 (1936); Chem. Zentrallblat, I, 1424 (1937).
3. N. K. Kochetkov, S. D. Sokolov, and N. M. Vagurtova, Zh. Obshch. Khim., 31, 2326 (1961).
4. A. Quilico, R. Fusco, and V. Rosnati, Gazz. Chim. Ital., 76, 87 (1946).
5. N. K. Kochetkov, S. D. Sokolov, and N. M. Vagurtova, Zh. Obshch. Khim., 32, 325 (1962).
6. S. D. Sokolov and N. K. Kochetkov, Dokl. Akad. Nauk SSSR, 156, 1391 (1964).
7. A. N. Nesmeyanov, L. V. Rybin, M. I. Rybinskaya, and S. D. Sokolov, Khim. Geterotsikl. Soed., 800 (1967).
8. M. Arbasino and P. Grünanger, Ric. Sci., 34, (P-A), 561 (1964).
9. N. K. Kochetkov, S. D. Sokolov, N. M. Vagurtova, and É. E. Nifant'ev, Dokl. Akad. Nauk SSSR, 133, 598 (1960).
10. T. A. Babushkina, G. K. Semin, S. D. Sokolov, and I. M. Yudintseva, Izv. Akad. Nauk SSSR, Ser. Khim., 2376 (1970).