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SYNTHESIS AND SOME ELECTROPHILIC SUBSTITUTION REACTIONS OF 2-PHENYLOXAZOLE

L. I. Belen'kii and M. A. Cheskis

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A new synthesis of 2-phenyloxazole that includes the preparation of 2-phenyloxazoline and aromatization of the latter by the action of nickel peroxide was developed. It was established that under conditions that exclude protonation electrophilic substitution reactions are directed to the oxazole ring of 2-phenyloxazole; the 5 position is considerably more active than the 4 position.

Relatively little study has been devoted to the investigation of electrophilic substitution reactions in the oxazole series, and the studies that have been made have dealt almost exclusively with disubstituted compounds that bear orientators of the I type (see [1-4]). This creates the idea of the low tendency of oxazoles to undergo electrophilic substitution and also hinders an evaluation of the relative activities of the individual positions of the oxazole ring. However, an examination of even the limited literature data provides evidence that the low activity of oxazoles in electrophilic substitution reactions is due not so much to the nature of the oxazole ring, which includes a "pyridine" nitrogen atom, as to deactivation of the heteroring as a consequence of protonation under the reaction conditions. This is confirmed particularly graphically in the case of nitration, attempts to carry out which were either unsuccessful or led, in the case of aryloxazoles, to the introduction of a nitro group into the benzene ring [5]. Nitration of both rings occurs only in the case of activated 2-dimethylamino-4-phenyloxazole, and 2-dimethylamino-5-nitro-4-(p-nitrophenyl)oxazole is formed [6]. At the same time, 2-aryl-4-substituted oxazoles are brominated quite smoothly by bromine in neutral solvents (benzene, carbon disulfide) [7, 8] and acetic acid [9]; bromine enters the 5 position of the oxazole ring. It must be noted that the yields of bromo-substi-

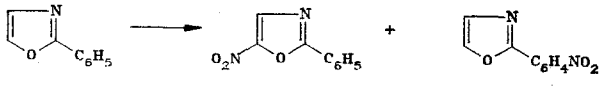
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 881-884, July, 1984. Original article submitted August 2, 1983.

tuted compounds do not exceed 50%, since the hydrogen bromide liberated in the reaction ties up some of the starting oxazole in the form of the hydrobromide, which does not undergo bromination [7]. Acetoxymercuration in the free position of the oxazole ring has been described for three isomeric diphenyloxazoles, as well as for 2-methyl-5-phenyloxazole [10]. The formylation of 5-methyl-2-phenyloxazole in the 4 position of the oxazole ring by the action of dimethylformamide (DMF) and $POCl_3$ has recently been reported [11].

These data undoubtedly indicate the significant potential possibilities of electrophilic substitution reactions in the oxazole ring. The present research was undertaken in order to ascertain such possibilities and, above all, to evaluate the reactivity of the oxazole ring under conditions that exclude or decrease the possibility of its protonation. It is known that the 2 position in the oxazole ring is the least active with respect to electrophilic agents, and it is therefore most expedient to carry out the study of such problems in the case of 2-substituted oxazoles, since this makes it possible to simultaneously evaluate the effect of the substituents. The availability of the starting compounds is of decisive significance for the synthetic utilization of electrophilic substitution in the oxazole series. The existing methods for the preparation of oxazoles usually lead to di- and trisubstituted compounds, which then undergo conversion to oxazole and its monosubstituted derivatives, as in the case of the decarboxylation of the corresponding acids. One of the tasks of the present research was the development of a simple synthesis of 2-substituted oxazoles that are necessary for the study of electrophilic substitution. As the first subject of our investigation we selected 2-phenyloxazole (I); we chose this compound due to the activating effect of the phenyl substituent and the possiblity of observing the change in the direction of electrophilic attack (in the oxazole or benzene ring) on passing from the free compound to a complex with a protic or aprotic acid.

We have developed a synthesis of I that includes the preparation of 2-phenyloxazoline (II) and its aromatization by nickel peroxide, which was recently used for the aromatization of some di- and trisubstituted oxazolines [12]. However, our experiments showed that this method is not a general method and, in particular, does not make it possible to obtain 2-alkyloxazoles. In the case of 2-phenyloxazoline, however, aromatization proceeds relatively readily and leads to oxazole I in 55% yield; starting II is obtained smoothly from ethyl benzoate and monoethanolamine with subsequent cyclization of the resulting N-(2-hydroxyethyl)benzamide. The aromatization of 2-(m-nitrophenyl)oxazoline (IIa), obtained by nitration of II, proceeds similarly.

The specificity of the nitration of I depends substantially on the reaction conditions. Thus, despite the data in [1], according to which the nitro group always enters the para position of the benzene ring of phenyloxazoles, nitration with a mixture of nitric and sulfuric acids actually gives a mixture of two substances. One of them, which was isolated in individual form, was 2-(p-nitrophenyl)oxazole (IIIa), but we were unable to purify the other; however, according to the results of gas-liquid chromatography (GLC), the latter was 2-(m-nitrophenyl)oxazole (IIIb) (see the data in [9] regarding the nitration of 2-phenyl-4-chloromethyloxazole). In the case of nitration with nitric acid in refluxing dichloroethane, the reaction gives, in addition to products of nitration in the benzene ring, 5-nitro-2-phenyloxazole (IV), which constitutes ~15% of the total amount of nitro-substituted products. Compound IV was obtained as the chief product (90%) by nitration of I under conditions that exclude protonation, viz., by the action of N-nitropicolinium tetrafluoroborate in acetonitrile.



I IV III

The bromination of oxazole I was carried out under conditions similar to those described in [7] for methylphenyl-substituted compounds, viz., by the action of bromine in benzene. The only difference was that triethylamine was added to the reaction mixture, which made it possible to obtain 5-bromo-2-phenyloxazole (V) in 56% yield. 4,5-Dibromo-2-phenyloxazole (VI) is formed in low yields, in addition to oxazole V, when excess bromine is used. Formylation by the action of DMF and $POCl_3$ gives ~60% 2-phenyl-5-formyl-oxazole (VII).

Thus, if protonation is excluded, the oxazole ring in 2-phenyloxazole behaves, with respect to electrophilic agents, in the same way as activated five-ring heteroaromatic systems with one heteroatom, viz., it is formylated via the Vilsmeier reaction, is brominated without a catalyst, and is also nitrated by a mild agent such as N-nitropicolinium tetra-

TABLE 1. PMR Spectra of 2-Phenyloxazole and Its Substituted Derivatives

Compound	Chemical shifts, δ, ppm			Solvent
	4-H	5-H	2-Ar	
I	7,10*	7,53*	7,2—7,4 m (3H) 7,8—8,1 m (2H)	CCl_4
IV	8,02 s	—	7,5—7,7 m (3H) 8,1—8,3 m (2H)	$CDCl_3$
IIIa	7,32*	7,78*	8,25 (4H)	$CDCl_3$
IIIb	7,28*	7,77*	7,6m (1H), 8,3 m (2H), 8,8 m (1H)	$CDCl_3$
V	7,02 s	—	7,2—7,5 m (3H) 7,8—8,1 m (2H)	CCl_4
VI	—	—	7,2—7,5 m (3H) 7,7—8,0 m (2H)	CCl_4
VII	7,80 s	9,75 † s	7,3—7,5 m 7,9—8,2 (2H)	CCl_4

*The signals have the form of singlets; no spin—spin coupling constant (SSCC) [(0.9 Hz for oxazoles [1]] is displayed.
†Signal of the CHO group.

fluoroborate. The individuality of the compounds obtained and their structures were confirmed by GLC data and the PMR spectra (see Table 1).

EXPERIMENTAL

The PMR spectra were recorded with Varian DA-60-IL and Tesla BS-467 (60 MHz) spectrometers. The chromatographic analyses were carried out with LKhM-8M and LKhM-80 chromatographs with a flame-ionization detector and nitrogen as the carrier gas; the feed rate was 20 ml/min, the column temperature was 150-200°C, the column (A) (dimensions 3 by 2000 mm with 7% versamide on Chromaton N-AW treated with KOH, (B) 2 by 2000 mm with 5% SE-30 on Chromaton N-AW-DMCS; (C) 2 by 1500 mm with 15% Carbowax 20M on Chromaton N-AW-DMCS.

2-Phenyloxazoline (II). A 55-g (330 mmole) sample of N-(2-hydroxyethylbenzamide [obtained from ethyl benzoate and ethanolamine, with removal of the ethanol by distillation, bp 218-220°C (8 mm), 77% yield] was added at 0°C to 110 ml (1500 mmole) of $SOCl_2$, and the resulting solution was maintained at 0°C for 1 h. The excess $SOCl_2$ was removed by distillation in vacuo, a solution of 99 g of KOH in 100 ml of water was added, and the mixture was refluxed for 8 h. The solution was cooled and extracted with benzene. The benzene was removed by distillation, and fractional distillation of the residue gave 29.4 (60%) g of II with bp 122-123°C (15 mm) and n_D^{20} 1.5670. See [13] for the literature data.

2-Phenyloxazole (I). A solution of 10 g (68 mmole) of 2-phenyloxazoline in 50 ml of benzene was refluxed with 15 g of nickel peroxide (obtained from $NiSO_4$ and NaOCl by the method in [14]) in a flask with a stirrer and a Dean—Stark trap. After 5 h, 10 g of nickel peroxide was added, and this operation was repeated twice (with monitoring by GLC with column C). The solution was filtered, and the precipitate was washed with benzene. The combined extracts were evaporated by distillation, and the residue [5.6 g (56%)] was identified as oxazole I with bp 98-100°C (10 mm) and n_D^{20} 1.5790. See [15] for the literature data.

2-(m-Nitrophenyl)oxazole (IIIb). A solution of 1.92 g (10 mmole) of 2-(m-nitrophenyl)-oxazoline [16] in 60 ml of benzene was refluxed with 15 g of nickel peroxide for 10 h (according to GLC with column A, IIa was absent). The solution was then filtered, and the nickel peroxide was washed with benzene. The extracts were combined and evaporated to give 1 g (53%) of IIIb with mp 95-96°C (from MeOH). See [17] for the literature data.

Nitration of 2-Phenyloxazole. A) A solution of 3 ml (30 mmole) of α-picoline in 7 ml of acetonitrile was added dropwise to a solution of 4 g (30 mmole) of nitronium tetrafluoroborate in 50 ml of acetonitrile at 0-5°C, after which 2.8 g (19 mmole) of oxazole I was added 20°C, and the mixture was maintained at this temperature for 4 h. It was then poured over ice, and the aqueous mixture was extracted with chloroform. The extract was washed with water, the chloroform was removed by distillation, and the resinous residue was extracted with hexane. Removal of the hexane gave 1.8 g of a mixture containing, according to GLC (column A), 5-nitro-2-phenyloxazole (IV), 2-(p-nitrophenyloxazole (IIIa), and 2-(m-nitrophenyl)oxazole

(IIIb) in a ratio of 90:5:5, for an overall yield of ~35%. Recrystallization from hexane and ethanol gave pure 5-nitro-2-phenyloxazole with mp 110-112°C. Found: C 57.4; H 3.1; N 14.8%. $C_9H_6N_2O_3$. Calculated: C 56.8; H 3.2; N 14.7%.

B) A solution of 4 g (27 mmole) of I in 8 ml of fuming HNO_3 was refluxed for 1 h, 15 ml of concentrated H_2SO_4, was added, and the resulting solution was heated at 100°C for 1 h. The reaction mass was cooled, 500 ml of ice with water was added, and the resulting solution was neutralized and extracted with ether. The ether was removed to give 0.6 g of a mixture of two substances (according to GLC, column A), in which product IV was absent. Recrystallization from hexane gave 2-(p-nitrophenyl)oxazole (IIIa) with mp 159-160°C (in agreement with the data in [5]).

C) A 1.6-g (25 mmole) sample of fuming HNO_3 in 5 ml of dichloroethane was added to a heated (to 50°C) solution of 2.9 g (20 mmole) of oxazole I in 15 ml of 1,2-dichloroethane, and the mixture was refluxed for 3 h. It was then poured into 300 ml of water, the organic layer was evaporated and washed with water, and the solvent was removed to give 2.1 g of a liquid containing, according to GLC data (column A) 60% of starting oxazole I, ~30% of products of nitration in the benzene ring, and ~10% of 5-nitro-2-phenyloxazole (IV). Extraction of the aqueous layer with chloroform gave (after removal of the solvent) another 0.5 g of solid product containing 95% of products of nitration in the benzene ring of (III) and 5% IV. Overall, the yield of IV was ~5%, the yield of III was 30%, and I was recovered in 33% yield.

Bromination of 2-Phenyloxazole. A solution of 1.6 g (10 mmole) of bromine in 20 ml of benzene was added to 1.45 g (10 mmole) of oxazole I in 20 ml of benzene, the solution was refluxed for 6 h, 1.5 g of triethylamine was added, and the mixture was refluxed for 1 h. It was then cooled and washed with a solution of sodium sulfite, and the benzene was removed by distillation. The residue was extracted with hexane, the solvent was removed by distillation to give 1.9 g of a mixture that contained, according to GLC data (columns A and B) starting oxazole I and bromide V in a ratio of 3:7. Chromatography of the mixture with a column packed with silica gel (elution with benzene gave 1.26 g (56%) of 5-bromo-2-phenyloxazole (V) with mp 61-63° (from hexane). Found: C 48.1; H 2.7; Br 35.5; N 6.2%. C_9H_6BrNO. Calculated: C 48.2; H 2.7; Br 35.7; N 6.3%. Under similar conditions, but with 4.5 g (27 mmole) of bromine, in addition to oxazole V (54%), we isolated 9% 4,5-dibromo-2-phenyloxazole (VI) with mp 88-89°C (from hexane). Found: C 36.2; H 2.0; N 4.6%. $C_9H_5Br_2NO$. Calculated: C 35.7; H 1.7; N 4.6%.

Formylation of 2-Phenyloxazole. A 15-g sample of $POCl_3$ and 2.5 g of DMF were added to 1.45 g (10 mmole) of oxazole I in 2 ml of DMF, the solution was stirred at 90°C for 4 h, after which it was neutralized with an aqueous solution of NaOH and cooled with ice. The resulting mixture was refluxed for 1 h and extracted with chloroform. The residue that was obtained after removal of the chloroform by distillation was extracted with hot hexane to give 1 g (58%) of 2-phenyl-5-formyloxazole (VII) with mp 72-74°C (from hexane). Found: C 69.1; H 4.2; N 8.1%. $C_{10}H_7NO_2$. Calculated: C 69.4; H 4.1; N 8.1%.

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