Chemistry of Heterocyclic Compounds, Vol. 45, No. 5, 2009

REACTION OF ESTERS OF 2-ARYLCYCLO-PROPANECARBOXYLIC ACIDS WITH NITROUS ACID. SYNTHESIS OF ARYL-SUBSTITUTED 3-ETHOXYCARBONYL-4,5-DIHYDROISOXAZOLES AND 3-ETHOXYCARBONYLISOXAZOLES

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Esters of 2-arylcyclopropanecarboxylic acids react with nitrous acid generated in situ with regioselective insertion of the nitrosyl cation into the cyclopropane ring. Depending on the substrate/nitrosylating agent ratio, the reaction proceeds with the formation of either aryl-substituted 3-ethoxycarbonyl-4,5-dihydroisoxazoles or the corresponding isoxazoles. The nature and position of the substituents in the aromatic ring of the starting 2-arylcyclopropanecarboxylic acid esters affect the reaction rate but have no effect on the regioselectivity of the attack by the nitrosyl cation on the three-membered ring. A dependence of the reactivity of isomeric substrates on their stereochemistry and position of the nitro group in the aromatic ring is noted for 2- and 4-nitrophenyl derivatives of esters of cis- and trans-2-arylcyclopropanecarboxylic acids.

Keywords: 5-aryl-3-ethoxycarbonyl-4,5-dihydroisoxazoles, 5-aryl-3-ethoxycarbonylisoxazoles, ethyl esters of 2-arylcyclopropanecarboxylic acids, insertion of the nitrosyl cation into the cyclopropane ring.

The reaction of arylcyclopropanes with nitrosylating agents, which proceeds through insertion of the nitrosyl cation or nitrosyl radical into the cyclopropane ring, may be seen as one of the most efficient methods for the synthesis of aryl-substituted 4,5-dihydroisoxazoles and isoxazoles, which are potential pharmaceutical agents and important precursors for the preparation of biologically-active compounds, including natural products [1-6].

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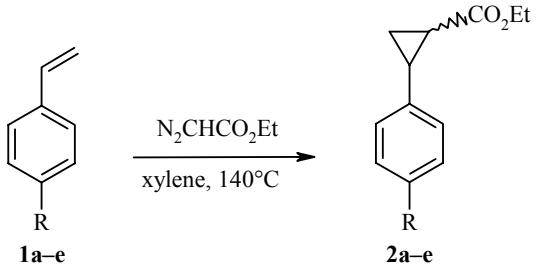
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 753-765, May, 2009. Original article submitted October 6, 2008.

0009-3122/09/4505-0595

The arylcyclopropanes studied in these transformations have been either phenylcyclopropanes [7-9] or benzylcyclopropanes [10] substituted in the aromatic ring or have contained only alkyl and aryl groups [11, 12] or halogen atoms [13, 14] as the second substituent in the cyclopropane ring. Hence, the possible series of substituted 4,5-dihydroisoxazoles and corresponding isoxazoles obtained by this method has been limited to heterocycles with nonfunctional substituents.

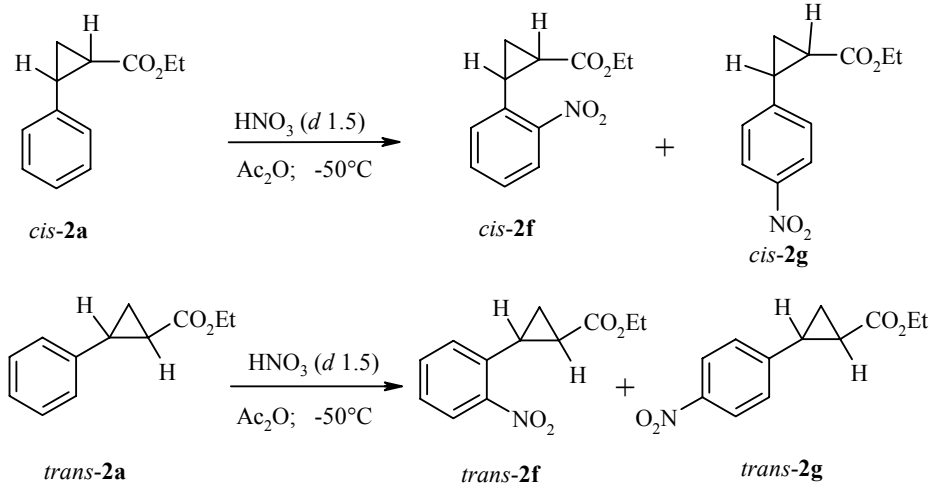
In the present work, we attempted to employ this transformation of arylcyclopropanes in the synthesis of functionally-substituted 4,5-dihydroisoxazoles and isoxazoles. For this purpose, we synthesized a series of ethyl esters of 2-aryl-1-cyclopropanecarboxylic acids and studied their behavior relative to nitrosylation by nitrous acid. The required 2-aryl-1-ethoxycarbonylcyclopropanes were synthesized as mixtures of the *cis* and *trans* isomers by the reaction of ethyl diazoacetate with the corresponding styrenes.



1a–e **2a–e**

a R = H, **b** R = F, **c** R = Cl, **d** R = Me, **e** R = OMe

In order to clarify the effect of the *cis* or *trans* arrangement of the substituents in the small ring on the reactivity of substrates **2a-e**, a mixture of isomeric 1-ethoxycarbonyl-2-phenylcyclopropanes **2a** was separated into pure *cis*-**2a** and *trans*-**2a**. In addition, *cis*- and *trans*-1-ethoxycarbonylcyclo-2-phenylpropanes unsubstituted in the aromatic ring were used in the synthesis of *o*- and *p*-nitro-substituted ethoxycarbonylphenylcyclopropanes *cis*-**2f**, *cis*-**2g**, *trans*-**2f**, and *trans*-**2g.**

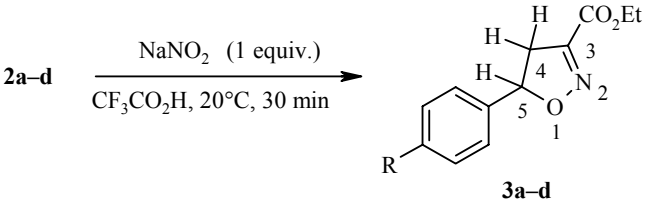


cis-**2a** *cis*-**2f** *cis*-**2g**

trans-**2a** *trans*-**2f** *trans*-**2g**

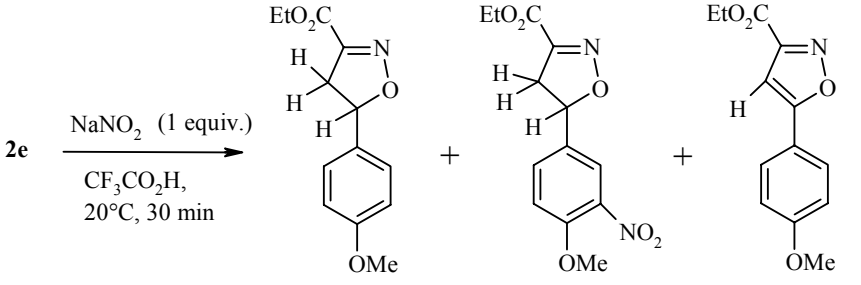
We should note that the steric arrangement of the substituents had no significant effect on the ratio of the *ortho* and *para* nitro isomers in the nitration of pure isomers *cis*-**2a** and *trans*-**2a** under the conditions employed. In each case, the mixture consisted of virtually equal amounts of nitro compounds *cis*-**2f** and *cis*-**2g** (from *cis*-**2a**) as well as *trans*-**2f** and *trans*-**2g** (from *trans*-**2a**).

In principle, polysubstituted ethoxycarbonylcyclopropanes lacking aromatic substituents, which are classified, according to Reissig [15] and Yu [16], as donor-acceptor cyclopropanes, have been used in the synthesis of ethoxycarbonylhydrofurans [17, 18] and ethoxycarbonylpyrroles [19]. Examples have been reported, in which reactions, proceeding with the participation of these ethoxycarbonylcyclopropanes, take place either with insertion of the reagent into the cyclopropane ring and the ethoxycarbonyl fragment is retained in the final reaction product or attack of the reagent directed toward any of the substituents in the cyclopropane ring and termination of the reaction with intramolecular participation of the ethoxycarbonyl group such that the three-membered carbocycle is retained [17, 18]. As shown in this work, monoaryl-substituted ethoxycarbonylcyclopropanes undergo reaction with an equimolar amount of nitrous acid formed *in situ* only with insertion of an N=O group into the cyclopropane fragment and resultant formation of the corresponding 3-ethoxycarbonyl-4,5-dihydroisoxazoles. The reaction proceeds virtually without complication with ethoxycarbonylcyclopropanes **2a-d**, in which the phenyl groups either lack substituents (**2a**) or the phenyl group substituents are weak electron-donor groups or halogen atoms (**2b-d**). In the case of isomeric 1-ethoxycarbonyl-2-phenylcyclopropanes (*cis*-**2a** and *trans*-**2a**), we found that the geometrical structure of the substrates and their stereochemistry do not affect the formation of 3-ethoxycarbonyl-5-phenyl-4,5-dihydroisoxazoles (**3a**, Table 1).



3a–d

Subsequently, we learned that if the *para* position of the benzene ring in 2-arylethoxy-carbonylcyclopropanes is occupied by a substituent capable of stabilizing the nascent benzylic carbenium ion (**2e**), the reaction proceeds to give multiple products although all the compounds formed correspond to insertion of an N=O fragment into the cyclopropane ring.



3e (44%) **3f** (18%) **4e** (21%)

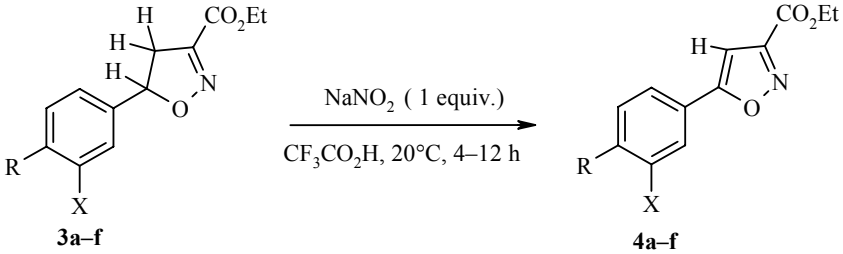
Apparently anomalous reaction products **3f** and **4e** obtained in the reaction of ethoxycarbonylcyclopropane **2e** with nitrous acid, in principle, may be formed as the result of nitration and oxidation of an intermediate, 3-ethoxycarbonyl-4,5-dihydroisoxazole **3e** by nitrous acid, which can be the source of both the $O_2N^{\bullet}$ radical and ON^{+} cation [20]. In order to check this hypothesis, we carried out the reaction of 3-ethoxycarbonyl-5-(4-methoxyphenyl)- 4,5-dihydroisoxazole (**3e**) with an additional equivalent of HNO_2.

TABLE 1. Characteristics of Compounds **3a-h** and **4a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, % (method)
		C	H	N		
3a	$C_{12}H_{13}NO_3$	65.62 / 65.75	6.05 / 5.94	6.18 / 6.39	Oil	94 (A)
3b	$C_{12}H_{12}FNO_3$	60.73 / 60.76	5.10 / 5.06	5.91 / 5.91	Oil	83 (A)
3c	$C_{12}H_{12}ClNO_3$	56.71 / 56.80	4.83 / 4.73	5.82 / 5.51	Oil	81 (A)
3d	$C_{13}H_{15}NO_3$	66.65 / 66.95	6.08 / 6.44	6.18 / 6.01	Oil	79 (A)
3e	$C_{13}H_{15}NO_4$	62.50 / 62.65	6.17 / 6.02	5.48 / 5.62	68-69	51 (A)
3f	$C_{13}H_{14}N_2O_6$	52.91 / 53.06	4.58 / 4.76	9.56 / 9.52	117-118	24 (A)
3g	$C_{12}H_{12}N_2O_5$	54.59 / 54.54	4.74 / 4.54	10.91 / 10.61	Oil	72 (A)
3h	$C_{12}H_{12}N_2O_5$	54.48 / 54.54	4.84 / 4.54	10.57 / 10.61	Oil	54 (A)
4a	$C_{12}H_{11}NO_3$	66.11 / 66.36	5.08 / 5.07	6.26 / 6.47	43-44	88 (A), 71 (B)
4b	$C_{12}H_{10}FNO_3$	61.03 / 61.28	4.36 / 4.26	5.76 / 5.96	98-99	81 (A), 69 (B)
4c	$C_{12}H_{10}ClNO_3$	56.92 / 57.26	4.22 / 3.98	5.68 / 5.57	127-128	78 (A), 74 (B)
4d	$C_{13}H_{13}NO_3$	67.28 / 67.53	5.51 / 5.63	5.86 / 6.06	52-53	94 (A), 68 (B)
4e	$C_{13}H_{13}NO_4$	62.93 / 63.16	5.12 / 5.26	5.28 / 5.67	86-87	86 (A), 34 (B)
4f	$C_{13}H_{12}N_2O_6$	53.15 / 53.42	4.05 / 4.11	9.75 / 9.59	161-162	79 (A), 16 (B)
4g	$C_{12}H_{10}N_2O_5$	54.94 / 54.96	3.71 / 3.82	10.57 / 10.69	178-179	87 (A), 65 (B)

*Recrystallization solvents: chloroform–hexane for **3e** and ethanol for **3f** and **4a-g**

Only 3-ethoxycarbonyl-5-(4-methoxyphenyl)isoxazole (**4e**) is formed in this case. It is interesting that both 4,5-dihydroisoxazole **3f** and 4,5-dihydroisoxazoles **3a-d** are converted upon similar treatment into the corresponding 5-aryl-3-ethoxycarbonylisoxazoles **4a-f** in high yield (Table 1).

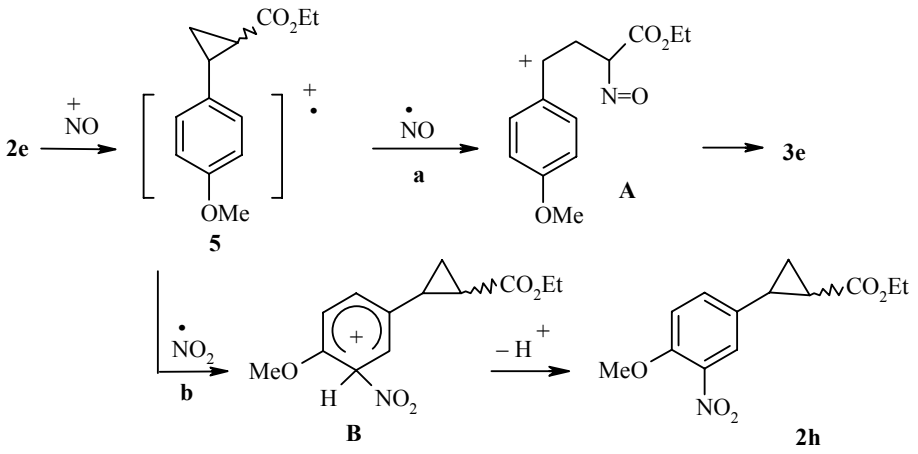


3a–f **4a–f**

4 a–e X = H; **a** R = H, **b** R = F, **c** R = Cl, **d** R = Me, **e** R = OMe,
f X = NO_2, R = OMe

Hence, 5-aryl-3-ethoxycarbonyl-4,5-dihydroisoxazoles **3a-f** may readily be oxidized under nitrosylation conditions and 3-ethoxycarbonyl-5-(4-methoxy-3-nitrophenyl)-4,5-dihydroisoxazole (**3f**) is not formed by nitration of 4,5-dihydroisoxazole **3e**. This latter finding suggests that two processes, namely, the insertion of an

NO fragment into the cyclopropane ring and nitration in the phenyl ring activated by a methoxy group, occur in parallel in the reaction of substrate **2e** with nitrous acid but at different rates. Since the formation of a nitronium cation (NO_2^+) required for the electrophilic nitration of aromatic ring, appears unlikely under the reaction conditions employed, we may assume that both processes in our case occur through the single-electron oxidation of substrate **2e** with subsequent reaction of radical cation **5** with $ON^•$ or $O_2N^•$ radicals.



a – ether–hexane, 1:4, **b** – ether–chloroform–petroleum ether (40–70°C), 1:1:3

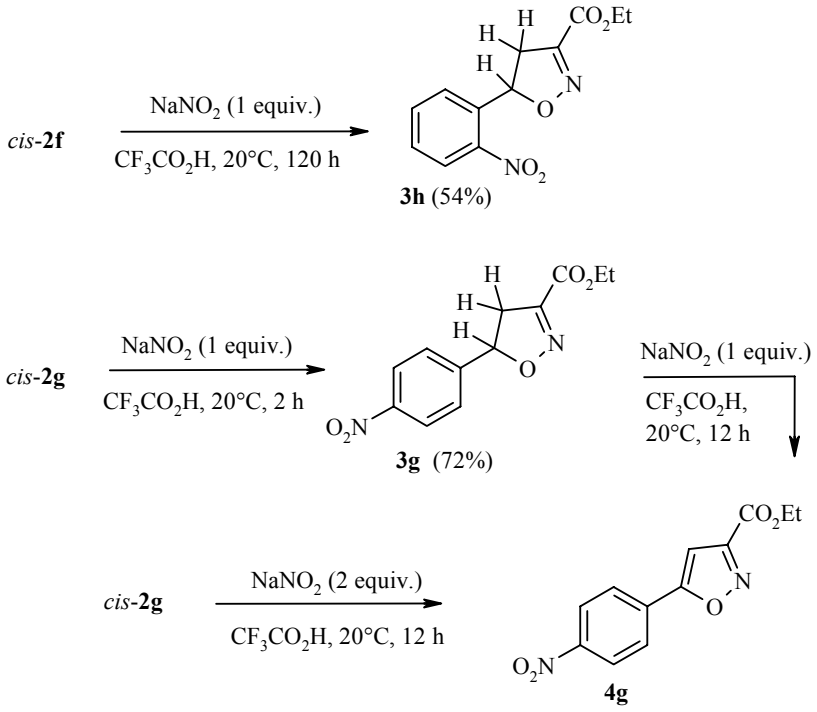
We should note that the proposed scheme for the conversion of ethoxycarbonylcyclopropane **2e** involving the one-electron oxidation of this compound is in accord both with the scheme proposed by Ichinose et al. [11] for the insertion of nitric oxide into the cyclopropane ring of 1,2-diarylcyclopropanes, whose first ionization potential permits oxidation of the starting substrates by the nitrosyl cation to the corresponding radical cations and a scheme involving nitration of arylcyclopropanes by dinitrogen tetroxide through a single-electron transfer (SET) mechanism [8]. Nitroaromatic compound **2h** formed due to the complexing action of the electron-donor and electron-withdrawing substituents apparently may be comparable in their reactivity with unsubstituted 1-ethoxycarbonyl-2-phenylcyclopropane (**2a**), which accounts for its subsequent transformation into nitro-substituted 3-ethoxycarbonyl-4,5-dihydroisoxazole (**3f**) at a rate as far as we can estimate from the yields of reaction products **3e**,**f**, only 2.5 times less than the rate of the conversion of ethoxycarbonylcyclopropane **2e**.

An experiment on the consecutive transformation of 2-aryl-1-ethoxycarbonylcyclopropanes **2a-e** initially by the action of one equivalent of HNO_2 to give the corresponding 5-aryl-3-ethoxy-carbonyl-4,5-dihydroisoxazoles **3a-e** and then by the oxidation of these products by an additional one equivalent of nitrous acid to give the corresponding isoxazoles **4a-f** suggested that the conversion of arylethoxycarbonylcyclopropanes **2a-e** to give substituted 3-ethoxycarbonylisoxazoles may be achieved by a single treatment of the starting substrates with two equivalents of nitrous acid. Indeed, such treatment of **2a-e** gave 5-aryl-3-ethoxycarbonylisoxazoles **4a-f** in high yield (Table 1). As expected, ethoxycarbonyl-cyclopropane **2e** was converted into a 2:1 mixture of two isoxazoles **4e**,**f**.

While 2-aryl-1-ethoxycarbonylcyclopropanes with electron-donor or weakly electron-withdrawing substituents in the benzene ring can be readily converted by the action of a corresponding amount of nitrous acid into either 4,5-dihydroisoxazoles **3a-f** or isoxazoles **4a-f**, the behavior of nitrophenyl derivatives of ethoxy-carbonylcyclopropanes **2f**,**g** under the conditions employed is quite different. We very unexpectedly found that *trans*-etoxycarbonyl(*o*-nitrophenyl)- (*trans*-**2f**) and *trans*-ethoxycarbonyl(*p*-nitrophenyl)cyclopropanes (*trans*-**2g**) do not react either with an equimolar amount of nitrous acid or with a large excess of nitrous acid over a very

prolonged period (240 h). In contrast, *cis*-nitrophenylcyclopropanes (*cis*-**2f** and *cis*-**2g**) are converted quite readily to the corresponding 4,5-dihydroisoxazoles **3g**,**h** by the action of even equimolar amounts of nitrous acid. The reaction with *cis*-1-ethoxycarbonyl-2-(*p*-nitrophenyl)cyclopropane (*cis*-**2g**) proceeds much more rapidly than the reaction with the corresponding *ortho* isomer.

The oxidation of 4,5-dihydroisoxazole **3g** by a second equivalent of HNO_2, as in the case of the reactions of **3a-f**, leads to 3-ethoxycarbonyl-5-(*p*-nitrophenyl)isoxazole (**4g**), which may be obtained directly from ethoxycarbonylcyclopropane *cis*-**2g** using two equivalents of nitrous acid.



It is interesting that the inability of *trans*-ethoxycarbonylnitrophenylcyclopropanes to give any reaction products under the conditions employed indicates that the formation of 4,5-dihydroisoxazoles from the *cis* isomers does not include a step involving single-electron oxidation of the starting substrates by the nitrosyl cation. Apparently, the nitrosyl cation directly attacks the cyclopropane carbon atom attached to the ethoxycarbonyl group.

An important goal in this investigation was to discuss the following. In the case of 2-arylethoxycarbonylcyclopropanes **2a-e**, we showed that both the pure *trans* isomer of **2a** and the *trans* isomers of **2b-e** within the starting isomer mixtures are converted in high yield by the action of HNO_2 into the corresponding 4,5-dihydroisoxazoles **3a-f**. In contrast, *trans*-nitrophenyl derivatives of ethoxycarbonylcyclopropanes *trans*-**2f** and *trans*-**2g** are nevertheless converted to the corresponding nitrophenyl derivatives of 4,5-dihydroisoxazoles **3g**,**h** even though more slowly than the *cis* isomers of **2a-e**. Hence, we may assume that the *cis* isomers of the ethoxycarbonylcyclopropanes studied are significantly more reactive relative to nitrous acid than the corresponding *trans* isomers. We assume that the discrepancy in behavior of *trans*-ethoxycarbonylcyclopropanes (*trans*-**2a-e**) and the nitrophenyl derivatives of *trans*-**2g** and *trans*-**2g** is probably linked to a difference in the mechanism of their reaction with HNO_2.

We have already proposed that the reactions of 2-aryl-1-ethoxycarbonylcyclopropanes **2a-e** with HNO_2 proceed through a SET mechanism. If this is true and the conversion of cyclopropanes **2a-e** to the corresponding 4,5-dihydroisoxazoles **3a-e** is accomplished through a step involving generation of a radical

TABLE 2. IR and Mass Spectra of Compounds **3** and **4**

Compound	IR spectrum, ν, cm^{-1}		Mass spectrum, m/z (I_{rel}, %)
	C=O	NO_2	
3a	1720		219 $[M]^+$ (61.9)
3b	1725		237 $[M]^+$ (52.4), 236 [M–1] (86.3)
3c	1725		253 $[M]^+$ (56.5)
3d	1720		233 $[M]^+$ (27.2)
3e	1720		
3f	1715	1535, 1365	294 $[M]^+$ (16.1)
3g	1725	1545, 1345	
3h	1725	1535, 1375	
4a	1740		217 $[M]^+$ (36.1)
4b	1735		235 $[M]^+$ (68.6)
4c	1730		251 $[M]^+$ (25.2)
4d	1740		231 $[M]^+$ (74.5)
4e	1745		247 $[M]^+$ (28.6)
4f	1725	1535, 1360	292 $[M]^+$ (100)
4g	1745	1555, 1325	262 $[M]^+$ (37.8)

cation **5**, whose analogs, as shown by Mizuno et al. [12], may account for the *cis-trans* isomerization of 1,2-disubstituted cyclopropanes, we may justifiably assume that all the conversions of isomeric ethoxycarbonylcyclopropanes **2a-e** are achieved either through *cis*-ethoxycarbonylcyclopropanes *cis*-**2a-e**, which react rapidly with HNO_2 and whose regeneration in the reaction medium occurs due to isomerization of the *trans* isomers (*trans*-**2a-e**) to the corresponding *cis* species, or that radical cations **5** formed from both *cis*- and *trans*-ethoxycarbonylcyclopropanes upon single-electron oxidation by the nitrosyl cation have identical structures equally capable of undergoing radical cation doubling to give intermediates **A**, which are responsible for the formation of substituted 4,5-dihydroisoxazoles **3a-e**. In all likelihood, ethoxycarbonylnitrophenyl-cyclopropanes **2f** and **2g** are incapable of undergoing oxidation by the nitrosyl cation and form radical cations **5***. The reaction of these compounds should be initiated by direct attack of the nitrosyl cation on the cyclopropane carbon atom attached to the ethoxycarbonyl group, which, in the case of the *trans* isomers (*trans*-**2f** and *trans*-**2g**) is sterically hindered.

The structure of the products and the stereochemistry of the insertion of the N=O fragment into the three-membered carbocycle of the aryl-substituted ethoxycarbonylcyclopropanes under the conditions employed were unequivocally indicated not only by the IR, ^1H NMR, and mass spectra and comparison of the data from these spectra with the data of spectra of reported isomeric ethoxycarbonyl-4,5-isoxazoles [21], but also by studying the structure of the isoxazole obtained by the reaction of 1-ethoxycarbonyl-2-(*p*-tolyl)cyclo-propane (**2d**) with nitrous acid by X-ray diffraction crystallographic analysis, which showed that heterocycle **4d** has the structure of 3-ethoxycarbonyl-5-(*p*-tolyl)isoxazole*[2]. In other words, the insertion of the N=O fragment into the cyclopropane ring of the starting esters is initiated by attack of $ON^{\bullet}$ or ON^+ on the small ring carbon atom attached to the ethoxycarbonyl group.

* The introduction of a nitro group into an organic molecule significantly enhances its first ionization potential [22].

*[2] The X-ray diffraction crystallographic analysis data will be published separately.

TABLE 3. Spectral Characteristics of Compounds **3a-h** and **4a-g**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
3a	1.26 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 3.15 (1H, dd, J_1 = 18.2, J_2 = 8.2, H-4); 3.68 (1H, dd, J_1 = 18.2, J_2 = 11.4, H-4); 4.26 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 5.82 (1H, dd, J_1 = 11.4, J_2 = 8.2, H-5); 7.38 (5H, m, H arom.)
3b	1.35 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 3.16 (1H, dd, J_1 = 17.6, J_2 = 8.8, H-4); 3.65 (1H, dd, J_1 = 17.6, J_2 = 12.2, H-4); 4.35 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 5.75 (1H, dd, J_1 = 12.2, J_2 = 8.8, H-5); 7.05 (2H, m, H arom.); 7.28 (2H, m, H arom.)
3c	1.37 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 3.18 (1H, dd, J_1 = 18.8, J_2 = 8.2, H-4); 3.65 (1H, dd, J_1 = 18.8, J_2 = 12.3, H-4); 4.36 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 5.76 (1H, dd, J_1 = 12.3, J_2 = 8.2, H-5); 7.25 (2H, d, *J* = 8.2, H arom.); 7.35 (2H, d, *J* = 8.2, H arom.)
3d	1.37 (3H, t, *J* = 7.8, $CH_2C\underline{H}_3$); 2.36 (3H, s, CH_3); 3.21 (1H, dd, J_1 = 18.2, J_2 = 8.8, H-4); 3.62 (1H, dd, J_1 = 18.2, J_2 = 12.4, H-4); 4.38 (2H, q, *J* = 7.8, $C\underline{H}_2CH_3$); 5.75 (1H, dd, J_1 = 12.4, J_2 = 8.8, H-5); 7.19 (2H, d, *J* = 8.0, H arom.); 7.23 (2H, d, *J* = 8.0, H arom.)
3e	1.38 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 3.21 (1H, dd, J_1 = 17.2, J_2 = 8.6, H-4); 3.56 (1H, dd, J_1 = 17.2, J_2 = 12.0, H-4); 3.78 (3H, s, OCH_3); 4.35 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 5.73 (1H, dd, J_1 = 12.0, J_2 = 8.6, H-5); 6.88 (2H, d, *J* = 8.4, H arom.); 7.24 (2H, d, *J* = 8.4, H arom.)
3f	1.41 (3H, t, *J* = 7.7, $CH_2C\underline{H}_3$); 3.21 (1H, dd, J_1 = 18.2, J_2 = 8.8, H-4); 3.68 (1H, dd, J_1 = 18.2, J_2 = 12.2, H-4); 3.95 (3H, s, OCH_3); 4.41 (2H, q, *J* = 7.7, $C\underline{H}_2CH_3$); 5.18 (1H, dd, J_1 = 12.2, J_2 = 8.5, H-5); 7.11 (2H, d, *J* = 8.4, H-5 arom.); 7.51 (2H, dd, J_1 = 8.4, J_2 = 2.4, H-6 arom.); 7.81 (1H, d, J_2 = 2.4, H-2 arom.)
3g	1.28 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 3.15 (1H, dd, J_1 = 17.4, J_2 = 8.6, H-4); 3.75 (1H, dd, J_1 = 17.4, J_2 = 12.4, H-4); 3.95 (3H, s, OCH_3); 4.25 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 6.05 (1H, dd, J_1 = 12.4, J_2 = 8.6, H-5); 7.36 (2H, d, *J* = 8.3, H-2,6 arom.); 8.31 (2H, d, *J* = 8.3, H-3,5 arom.)
3h	1.31 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 3.16 (1H, dd, J_1 = 16.8, J_2 = 8.4, H-4); 3.91 (1H, dd, J_1 = 16.8, J_2 = 12.2, H-4); 4.52 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 6.31 (1H, dd, J_1 = 12.2, J_2 = 8.4, H-5); 7.61 (2H, m, H arom.); 7.79 (1H, m, H arom.); 8.15 (1H, d, *J* = 8.2, H arom.)
4a	1.45 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 4.49 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 6.95 (1H, s, H-4); 7.41 (5H, m, H arom.)
4b	1.47 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 4.48 (2H, q, *J* = 6.8, $C\underline{H}_2CH_3$); 6.88 (1H, s, H-4); 7.19 (2H, m, H arom.); 7.83 (2H, m, H arom.)
4c	1.45 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$); 4.47 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 6.94 (1H, s, H-4); 7.48 (2H, d, *J* = 8.4, H arom.); 7.75 (2H, d, *J* = 8.4, H arom.)
4d	1.47 (3H, t, *J* = 6.6, $CH_2C\underline{H}_3$); 2.42 (3H, s, CH_3); 4.48 (2H, q, *J* = 6.6, $C\underline{H}_2CH_3$); 6.87 (1H, s, H-4); 7.29 (2H, d, *J* = 8.4, H arom.); 7.71 (2H, d, *J* = 8.4, H arom.)
4e	1.44 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 3.87 (3H, s, OCH_3); 4.46 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 6.77 (1H, s, H-4); 6.92 (2H, d, *J* = 8.2, H-3,5 arom.); 7.71 (2H, d, *J* = 8.2, H-2,6 arom.)
4f	1.47 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$); 4.06 (3H, s, OCH_3); 4.49 (2H, q, *J* = 6.9, $C\underline{H}_2CH_3$); 6.94 (1H, s, H-4); 7.24 (1H, d, *J* = 8.6, H-5 arom.); 8.01 (1H, dd, J_1 = 8.6, J_2 = 2.2, H-6 arom.); 8.29 (1H, d, *J* = 2.2, H-2 arom.)
4g	1.37 (3H, t, *J* = 6.4, $CH_2C\underline{H}_3$); 4.41 (2H, q, *J* = 6.4, $C\underline{H}_2CH_3$); 7.71 (1H, s, H-4); 8.27 (2H, d, *J* = 8.3, H arom.); 8.41 (2H, d, *J* = 8.3, H arom.)

EXPERIMENTAL

The ^{1}H NMR spectra were taken on Varian VXR-400 (400 MHz) and Bruker DRX-500 spectrometers (500 MHz) in $CDCl_3$ (**2a-e, 3a-h,** and **4a-f**) and DMSO-d_6 (**4g**) using the residual protons of the deuterated solvent as the standard. The IR spectra were taken on a UR-20 spectrometer in vaseline mull or hexachlorobutadiene. The mass spectra were taken on a Finnigan SSQ-7000 GC/MS using a 30 m capillary

column with DV-1 as the stationary phase, helium as the gas carrier, and temperature programming from 50 to 300°C (10 deg/min). The ionization energy was 70 eV. The purity of the products was monitored on plates or columns packed with Silufol alumina (Brockmann activity II).

Chromatographic monitoring of the purity of **2a-h** was carried out with 1:4 ether–hexane as the eluent, while monitoring for **7a-h** and **8a-h** was carried out with 1:1:3 ether–chloroform–petroleum ether (40-70°C) as the eluent.

Ethyl Esters of *cis*- and *trans*-2-Arylcyclopropanecarboxylic Acids 2a-e (General Method). A mixture of corresponding styrene (0.17 mol) and ethyl diazoacetate (19.4 g, 0.17 mol) was added with vigorous stirring to 50 ml dry *o*-xylene at reflux and stirred at 135-140°C until no further nitrogen was liberated (~6 h). The mixture was distilled in vacuum. The reaction of styrene (17.7 g, 0.17 mol) by this procedure gave 17 g (52%) of a mixture of ethyl esters of *cis*- and *trans*-2-phenylcyclopropanecarboxylic acid (**2a**); bp 126-127°C (6 mm Hg) [23]. The ratio of the *cis* and *trans* isomers after distillation was 0.74. The mixture of *cis*- and *trans*-**2a** (17 g) was dissolved in 50 ml methanol and maintained for 2 h at -50°C. The crystalline precipitate of the ethyl ester of *trans*-2-phenylcyclopropanecarboxylic acid (*trans*-**2a**) was filtered off and washed with cold methanol to give 8.2 g (48% of the mixture); mp 36-37°C [24, 25]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.19 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 1.34 (1H, m, H *c*-Pr); 1.47 (1H, m, H *c*-Pr); 1.91 (1H, m, H *c*-Pr); 2.43 (1H, m, H *c*-Pr); 4.12 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 7.14 (3H, m, H arom); 7.25 (2H, m, H arom). Methanol was removed from the mother liquor. The residue (8.6 g) was hydrolyzed as described by Burger [23] to give 7.3 g (78%) of a mixture of *cis*- and *trans*-2-phenylcyclopropanecarboxylic acids. Crystallization of this mixture from heptane gave 3.5 g (48%) *cis*-2-phenylcyclopropanecarboxylic acid, mp 105°C [26]. Esterification of this *cis*-acid in absolute ethanol in the presence of concentrated sulfuric acid gave 3.4 g ethyl ester of *cis*-2-phenylcyclopropane-carboxylic acid; bp 121-122°C (8 mm Hg), n_D^{20} 1.5172 [26]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, t, *J* = 7.5, $CH_2C\underline{H}_3$); 1.32 (1H, m, H *c*-Pr); 1.57 (1H, m, H *c*-Pr); 2.09 (1H, m, H *c*-Pr); 2.61 (1H, m, H *c*-Pr); 3.78 (2H, q, *J* = 7.5, $C\underline{H}_2CH_3$); 7.21 (5H, m, H arom).

Ethyl Esters of *cis*- and *trans*-2-(4-Fluorophenyl)cyclopropanecarboxylic Acid (2b). Analogously, *p*-fluorostyrene was used to give 17.3 g (48%) of a mixture of esters **2b**; bp 170-171°C (10 mm Hg), the *cis/trans* ratio was 0.34. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-**2b**: 1.29 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 1,33 (1H, m, H *c*-Pr); 1.58 (1H, m, H *c*-Pr); 1.84 (1H, m, H *c*-Pr); 2.51 (1H, m, H *c*-Pr); 4.19 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 6.95 (2H, m, H arom); 7.11 (2H, m, H arom); *cis*-**2b**: 1.01 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 1.25 (1H, m, H *c*-Pr); 1.67 (1H, m, H *c*-Pr); 2.12 (1H, m, H *c*-Pr); 2.53 (1H, m, H *c*-Pr); 3.89 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 6.98 (2H, m, H arom), 7.24 (2H, m, H *c*-Pr).

Ethyl Esters of *cis*- and *trans*-2-(4-Chlorophenyl)cyclopropanecarboxylic Acid (2c). Analogously, 23.5 g *p*-chlorostyrene gave 19 g (49%) of a mixture of the *cis* and *trans* isomers of this ester; bp 179-181°C (10 mm Hg), the *cis/trans* ratio was 0.28. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-**2c**: 1.24 (3H, t, *J* = 7.2, $CH_2C\underline{H}_3$); 1.32 (1H, m, H *c*-Pr); 1.47 (1H, m, H *c*-Pr); 1.87 (1H, m, H *c*-Pr); 2.42 (1H, m, H *c*-Pr); 4.11 (2H, q, *J* = 7.2, $C\underline{H}_2CH_3$); 7.11 (2H, d, *J* = 8.2, H arom); 7.24 (2H, d, *J* = 8.2, H arom); *cis*-**2c**: 0.99 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 1.28 (1H, m, H *c*-Pr); 1.56 (1H, m, H *c*-Pr); 2.03 (1H, m, H *c*-Pr); 2.51 (1H, m, H *c*-Pr); 4.15 (2H, q, *J* = 7.4, $C\underline{H}_2CH_3$); 7.27 (2H, d, *J* = 8.2, H arom); 7.24 (2H, d, *J* = 8.2, H arom).

Ethyl Esters of *cis*- and *trans*-2-(4-Methylphenyl)cyclopropanecarboxylic Acid (2d) were obtained by the above method from 20.1 g *p*-methylstyrene as a mixture of *cis* and *trans* isomers. The yield of **2d** was 17.7 g (51%); bp 135-137°C (11 mm Hg), the *cis/trans* ratio was 0.48. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-**2d**: 1.32 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 1.37 (1H, m, H *c*-Pr); 1.62 (1H, m, H *c*-Pr); 1.91 (1H, m, H *c*-Pr); 2.53 (1H, m, H *c*-Pr); 2.35 (3H, s, CH_3); 4.21 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 7.01 (2H, d, *J* = 8.4, H arom); 7.08 (2H, d, *J* = 8.4, H arom); *cis*-**2d**: 1.06 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 1.35 (1H, m, H *c*-Pr); 1.72 (1H, m, H *c*-Pr); 2.07 (1H, m, H *c*-Pr); 2.56 (1H, m, H *c*-Pr); 3.92 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 7.16 (2H, d, *J* = 8.4, H arom); 7.19 (2H, d, *J* = 8.4, H arom).

Ethyl Esters of *cis*- and *trans*-2-(4-Methoxyphenyl)cyclopropanecarboxylic Acid (2e). Analogously, 23 g *p*-methoxystyrene gave 20.9 g (56%) of a mixture of the *cis* and *trans* isomers of **2e**; bp 179-181°C (10 mm Hg), the *cis/trans* ratio was 0.36. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): *trans*-**2e**: 1.32 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 1.27 (1H, m, H *c*-Pr); 1.62 (1H, m, H *c*-Pr); 1.85 (1H, m, H *c*-Pr); 2.51 (1H, m, H *c*-Pr); 3.77 (3H, s, OCH_3); 4.19 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 6.81 (2H, d, *J* = 8.2, H arom); 7.05 (2H, d, *J* = 8.2, H arom); *cis*-**2e**: 1.03 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 1.33 (1H, m, H *c*-Pr); 1.65 (1H, m, *c*-Pr); 2.02 (1H, m, H *c*-Pr); 2.52 (1H, m, H *c*-Pr); 3.80 (3H, s, OCH_3); 3.92 (2H, q, $C\underline{H}_2CH_3$); 6.87 (2H, d, *J* = 8.2, H arom); 7.21 (2H, d, *J* = 8.2, H arom).

Ethyl Esters of *cis*- and *trans*-2-(*o*-Nitrophenyl)cyclopropanecarboxylic Acid (2f) and *cis*- and *trans*-2-(*p*-Nitrophenyl)cyclopropanecarboxylic Acid (2g) were obtained by the nitration of *cis*-**2a** in 27% yield as described in our previous work [27]. The ratio of the *ortho* and *para* isomers was 0.98. Column chromatography of 4.5 g of the mixture of product isomers led to the isolation of *cis*-**2f** and *cis*-**2g**.

Ethyl Ester of *cis*-2-(*o*-Nitrophenyl)cyclopropanecarboxylic Acid (*cis*-2f) was obtained as a viscous oil. The yield was 2.3 g (51% of the mixture). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 1.48 (1H, m, H *c*-Pr); 1.65 (1H, m, H *c*-Pr); 2.52 (1H, m, H *c*-Pr); 2.93 (1H, m, H *c*-Pr); 3.91 (2H, q, *J* = 6.8, $C\underline{H}_2CH_3$); 7.37 (1H, t, *J* = 8.2, H-4 arom); 7.48 (1H, d, *J* = 8.2, H-6 arom); 7.55 (1H, t, *J* = 8.2, H-5 arom); 7.91 (1H, d, *J* = 8.2, H-3 arom); M^+ 235. Found, %: C 61.19; H 5.62; N 5.81. $C_{12}H_{13}NO_4$. Calculated, %: C 61.27; H 5.57; N 5.96.

Ethyl Ester of *cis*-2-(*p*-Nitrophenyl)cyclopropanecarboxylic Acid (*cis*-2g) was obtained as a viscous oil. The yield was 2.07 g (46% of the mixture). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (3H, t, *J* = 6.8, $CH_2C\underline{H}_3$); 1.48 (1H, m, H *c*-Pr); 1.75 (1H, m, H *c*-Pr); 2.21 (1H, m, H *c*-Pr); 2.61 (1H, m, H *c*-Pr); 3.90 (2H, q, *J* = 6.8, $C\underline{H}_2CH_3$); 7.45 (2H, d, *J* = 8.6, H-2,6 arom); 8.12 (2H, d, *J* = 8.6, H-3,5 arom). M^+ 235. Found, %: C 61.42; H 5.34; N 5.71. $C_{12}H_{13}NO_4$. Calculated, %: C 61.27; H 5.57; N 5.96.

Ethyl Esters of *trans*-(*o*-Nitrophenyl)cyclopropanecarboxylic Acid (*trans*-2f) and *trans*-2-(*p*-Nitrophenyl)cyclopropanecarboxylic Acid (*trans*-2g) were obtained in 72% yield analogously by the nitration of *trans*-**2a**. The ratio of the *ortho* and *para* nitro isomers was 1.02. Chromatography on an alumina column yielded 3 g of isomers *trans*-**2f** and *trans*-**2g**.

Ethyl Ester of *trans*-2-(*o*-Nitrophenyl)cyclopropanecarboxylic Acid (*trans*-2f) was obtained as a viscous oil. The yield was 1.45 g (48% of the mixture of isomers *trans*-**2f** and *trans*-**2g**). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 1.35 (1H, m, H *c*-Pr); 1.67 (1H, m, H *c*-Pr); 1.85 (1H, m, H *c*-Pr); 2.97 (1H, m, H *c*-Pr); 4.21 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 7.24 (1H, d, *J* = 8.4, H-6 arom); 7.38 (1H, t, *J* = 8.4, H-4 arom); 7.55 (1H, t, *J* = 8.4, H-5 arom); 7.93 (1H, d, *J* = 8.4, H-3 arom). M^+ 235. Found, %: C 60.91; H 5.64; N 6.04. $C_{12}H_{13}NO_4$. Calculated, %: C 61.27; H 5.57; N 5.96.

Ethyl Ester of *trans*-2-(*p*-Nitrophenyl)cyclopropanecarboxylic Acid (*trans*-2g) was obtained as a viscous oil. The yield was 1.32 g (44% of mixture). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.6, $CH_2C\underline{H}_3$); 1.38 (1H, m, H *c*-Pr); 1.71 (1H, m, H *c*-Pr); 2.01 (1H, m, H *c*-Pr); 2.59 (1H, m, H *c*-Pr); 4.18 (2H, q, *J* = 7.6, $C\underline{H}_2CH_3$); 7.19 (2H, d, *J* = 9.6, H-2,6 arom); 8.12 (2H, d, *J* = 9.6, H-3,5 arom). M^+ 235. Found, %: C 61.06; H 5.71; N 6.08. $C_{12}H_{13}NO_4$. Calculated, %: C 61.27; H 5.57; N 5.96.

Reaction of 2-Arylcyclopropanecarboxylic Acid Esters 2a-h with HNO_2 (General Method). A sample of $NaNO_2$ was added in portions over 10 min with stirring to a solution of ethyl ester of 2-arylcyclopropanecarboxylic acid (0.01 mol) in trifluoroacetic acid (8 ml, 0.01 mol) at 20°C. In Method A, $NaNO_2$ (0.01 mol) was added and stirring was continued for 30 min. In Method B, $NaNO_2$ (0.02 mol) was added and stirring was continued for 6-12 h. The reaction mixture was then poured into 60 ml water and extracted with two 15 ml chloroform portions. The extracts were washed with 2 N aq. Na_2CO_3 and dried over $CaCl_2$. The solvent was distilled off and the residue was subjected to chromatography on an alumina column to give 5-aryl-3-ethoxycarbonyl-4,5-dihydroisoxazoles **3a-h** or 5-aryl-3-ethoxycarbonyl-4,5-isoxazoles **4a-h** (Tables 1 and 2).

This work was carried out with the financial support of a grant to the Leading Scientific School of Academician N. S. Zefirov.

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