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Simple one-pot synthesis of 5-(chloromethyl)isoxazoles from aldoximes and 2,3-dichloro-1-propene

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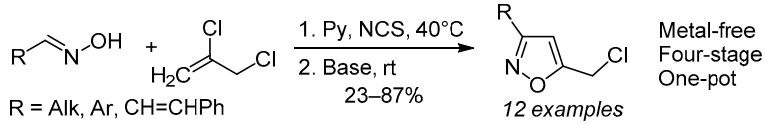


A one-pot synthesis of 3-substituted 5-chloromethylisoxazoles from available starting aldoximes and 2,3-dichloro-1-propene, serving both as a solvent and reagent, is proposed. Excess 2,3-dichloro-1-propene is recovered after the reaction. The synthesis is effective for oximes of both aromatic and aliphatic aldehydes.

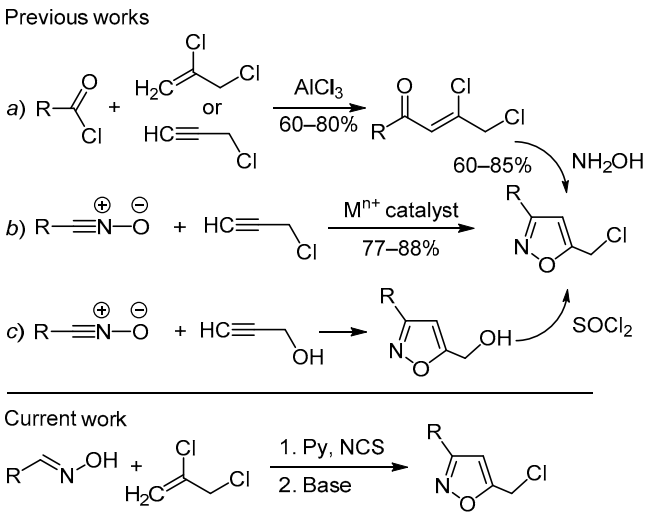
Keywords: 2,3-dichloro-1-propene, isoxazoles, nitrile oxides, oximes, aromatization, 1,3-dipolar cycloaddition, one-pot synthesis.

The isoxazole ring is a constituent of the structures of many medications and is a well-known carrier of pharmacophore properties.[1] In this regard, new methods for the preparation and functionalization of isoxazoles are currently being actively developed.[2] One of the convenient ways of introducing an isoxazole fragment into organic molecules is the reaction of halomethylisoxazoles with O-,[3] N-,[4] S-nucleophiles,[5] including peptides.[5d] Thus, halomethylisoxazoles are in demand as building blocks for the synthesis of isoxazole derivatives, and the development of new methods for their preparation is still relevant.[6]

The existing methods for obtaining 5-(chloromethyl)-isoxazoles are based on the reaction of hydroxylamine with α,β-unsaturated γ-chloro ketones containing a chlorine atom[7] or isothiocyanate fragment[8] at the double bond as a leaving group (Scheme 1, *a*). The method is effective in the synthesis of 3-alkyl-5-(chloromethyl)isoxazoles (75–85% yields) and somewhat less effective in the case of 3-aryl-substituted derivatives (60–73% yields). The starting γ-chloro ketones are obtained from acid chlorides and 2,3-dichloro-1-propene[9] or propargyl chloride.[10]

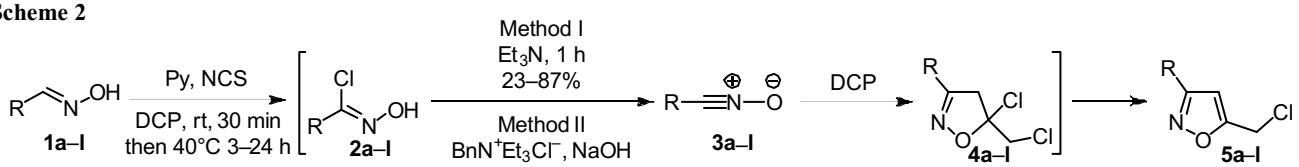
Another approach to the synthesis of 5-(halomethyl)-isoxazoles involves the cycloaddition of nitrile oxides to propargyl halides or propargyl alcohol[11,5a] (Scheme 1, *b*, *c*). In this case, the reactions are accompanied by the formation of furoxans as byproducts and resinification, prevention of which mandates careful selection of the conditions or the use of catalysts based on Cu(II)[12a] or Ce(III)[12b] salts.

Scheme 1



Alternatively, 5-(chloromethyl)isoxazoles can be prepared by cycloaddition of nitrile oxides to 2,3-dichloro-1-propene (DCP), which can be considered the synthetic equivalent of propargyl chloride, followed by dehydrochlorination of the intermediate isoxazoline. The implementation of this approach would avoid the

Scheme 2



DCP = 2,3-dichloro-1-propene
a R = Me, **b** R = *n*-C_7H_{15}, **c** R = Cy, **d** R = Ph, **e** R = 4-$MeOC_6H_4$, **f** R = 4-FC_6H_4, **g** R = 4-ClC_6H_4, **h** R = 2-ClC_6H_4, **i** R = 4-$O_2NC_6H_4$, **j** R = 2-$O_2NC_6H_4$, **k** R = 2-HOC_6H_4, **l** R = PhCH=CH

disadvantages inherent in the reactions of nitrile oxides with acetylenes. On the other hand, DCP is a cheap commercially available reagent obtained from organochlorine chemicals production waste streams.[13] However, to date, only two examples of the use of DCP in the synthesis of 5-(chloromethyl)isoxazoles are presented in the literature. Thus, its reaction with bromonitrile oxide[14] obtained *in situ* and stable 2,6-dichlorophenyl nitrile oxide[15] with the yields of the desired 5-(chloromethyl)-isoxazoles of 81 and 65%, respectively, is described.

Thus, the aim of this work was to develop a simple convenient method for the synthesis of 5-(chloromethyl)-isoxazoles from DCP and aldoximes, to determine the scope and limitations of the method and the characteristics of the process.

Isolation of individual nitrile oxides or their precursors, *N*-hydroxyimidoyl chlorides, presents a certain problem due to the chemical instability of these compounds. For instance, the time for complete dimerization of lower alkyl nitrile oxides into furoxans at 18°C is less than 1 min.[16] To optimize the process of obtaining the desired isoxazoles, we synthesized *N*-hydroxyimidoyl chlorides and then nitrile oxides from them sequentially in one pot without isolation of intermediates.

To carry out the transformations, we proposed the use of DCP as the solvent in the chlorination of oximes **1a**–**l** with *N*-chlorosuccinimide (NCS) and as a reactant in the subsequent 1,3-dipolar cycloaddition reaction (Scheme 2). The synthesis of *N*-hydroxyimidoyl chlorides **2a**–**l** in a DCP solution was carried out similarly to the known methods for the chlorination of aldoximes in CH_2Cl_2 or $CHCl_3$ in the presence of catalytic amounts of pyridine.[17] Under the selected conditions, we did not observe any adverse reactions of chlorination of DCP or the addition of NCS at the C=C double bond of DCP. Chlorination of aliphatic aldoximes was, as a rule, faster than aromatic aldoximes and complete in 3–4 h. The progress of the reaction was monitored by TLC.

Upon subsequent addition of 2 equiv of the base, a cascade of transformations took place, as shown in Scheme 2. In the first step, chloro oximes **2a**–**l** are dehydrochlorinated to nitrile oxides **3a**–**l**, which react with DCP to form isoxazolines **4a**–**l**. The action of the second equivalent of the base brings about aromatization of isoxazolines **4a**–**l** to isoxazoles **5a**–**l**. After the reactions, the excess DCP is distilled off under reduced pressure and can be reused.

We used Et_3N (method I) or an aqueous solution of NaOH (method II) as the base. The yields of the target isoxazoles **5d**,**l** slightly depend on the nature of the base (Table 1). At the same time, the replacement of the organic base with an alkali leads to a significant decrease in the yields of 3-alkylisoxazoles **5a**,**b**, probably due to side reactions involving the active methylene group of nitrile oxide or hydrolysis of chloro oxime **2**.

Table 1. Yields of isoxazoles **5a**,**b**,**d**,**l** depending on the nature of the base, %

Base	Compound			
	5a	**5b**	**5d**	**5l**
Et_3N (method I)	62	86	87	57
NaOH (method II)	8	52	77	64

In a dedicated experiment, we determined that DCP is not subjected to dehydrochlorination to propargyl chloride by the action of Et_3N or an aqueous solution of NaOH under the reaction conditions. Consequently, nitrile oxides formed *in situ* enter the cycloaddition reaction precisely with DCP.

Considering the high propensity of nitrile oxides to dimerize into furoxans, the generation of nitrile oxides **3a**–**l** in a DCP solution, that is, under conditions of multiple molar excess of the reactant, favorably affects the conversion of nitrile oxides **3** to isoxazoles **5**. Thus, under optimal conditions, we did not observe the formation of furoxans, unlike existing literature methods for the synthesis of nitrile oxides in organic solvents.

It should be noted that the cycloaddition of nitrile oxides to DCP occurs regioselectively with the formation of only one regioisomer, in this case, 5-(chloromethyl)isoxazoles. The observed fact is consistent with the general reactivity of nitrile oxides with terminal alkenes.[18]

Using the example of isoxazoles **5g**,**k**, we compared the efficacy of methods for the synthesis of heterocycles **5a**–**l** from various precursors: oximes **1** (method I) and chloro oximes **2** (method III). In the synthesis of 3-(4-chlorophenyl)isoxazole **5g**, both methods gave similar results (81 and 84% yields when using methods I and III, respectively). However, the yield of isoxazole **5k** from the preliminarily obtained chloro oxime **2k** (method III) was significantly higher compared to the yield obtained with method I (45% versus 23%). This is obviously due to the low efficiency of obtaining chloro oxime **2k** in DCP solution as compared with $CHCl_3$.

Unfortunately, we were not able to extend this synthesis method to the oximes of furfural and thiophene-2-carbox-

aldehyde. The chlorination of furan-2-carboxaldehyde oxime by NCS in a DCP medium occurs mainly at position 5 of the ring accompanied by extensive resinification and then extremely slowly at the aldoxime group. A similar problem was observed during a reaction in a CH_2Cl_2 solution.[19] Similar chlorination of thiophene-2-carboxaldehyde oxime in DCP by 2 equiv of NCS, after addition of the base, results in a difficult to separate mixture of 3-(thiophen-2-yl)- and 3-(5-chlorothiophen-2-yl)-5-(chloromethyl)isoxazoles and unidentified impurities.

The structure of the obtained compounds **5a**–**l** was proved by NMR spectroscopy and GCMS, while the composition was confirmed by elemental analysis. The ^{1}H NMR spectra contain the characteristic singlet signals of the CH_2Cl group protons at 4.56–4.70 ppm and of the 4-CH proton of the isoxazole ring at 6.14–6.16 ppm (for 3-alkylisoxazoles **5a**–**c**) and 6.45–6.78 ppm (for 3-arylisoxazoles). In the ^{13}C NMR spectra, the signals of C-4 carbon atoms of the isoxazole ring of compounds **5b**,**h**–**l** are observed at 101–105 ppm, while the signals of C-3,5 atoms are evident in the 160–168 ppm region. ^{1}H NMR spectra of the known isoxazoles **5a**,**c**–**g** correspond to the published data.[5d,6]

To conclude, we developed in this work a one-pot method for the synthesis of 3-substituted 5-(chloromethyl)-isoxazoles from the simple and available starting compounds, aldoximes and 2,3-dichloro-1-propene.

Experimental

IR spectra were registered on a Varian 3100 FT-IR spectrometer with the sample in thin film. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker DPX-400 (400 and 100 MHz, respectively) in $CDCl_3$, with TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A mass spectrometer (EI ionization, 70 eV). Elemental analysis was performed on a Thermo Finnigan Flash series 1112 Elemental analyzer. Silica gel (215–400 mesh) was used for column chromatography.

Et_3N and 2,3-dichloro-1-propene were dried before use. Oxime **1a** was commercially available, oximes **1b**–**l**,[20] chloro oximes **2g**[20] and **2k**[17d] were synthesized according to literature methods.

Synthesis of compounds 5a–l (General procedure). Method I. A drop of pyridine and then NCS (294 mg, 2.2 mmol) with stirring were added to a suspension of oxime **1** (2 mmol) in DCP (5 ml). Dissolution of the NCS took place, followed by precipitation of succinimide. The mixture was stirred at room temperature for 30 min, then heated to 40°C for 3–24 h (TLC control). A solution of Et_3N (455 mg, 4.5 mmol) in DCP (1 ml) was added with vigorous stirring to the mixture at room temperature. Heating of the mixture and precipitation occurred. The reaction mixture was stirred for 1 h, DCP was distilled off under reduced pressure, and the target compound was isolated by flash chromatography on silica gel, eluent CH_2Cl_2 or $CHCl_3$, R_f 0.6–0.8.

Method II. Benzyltriethylammonium chloride (22 mg, 0.1 mmol) was added to a solution of *in situ* prepared chloro oxime **2** in DCP (method I), then a solution of NaOH (200 mg) in H_2O (3 ml) was added with vigorous stirring. The reaction mixture was stirred for 2 h, H_2O (20 ml) and CH_2Cl_2 (25 ml) were added, the organic phase was separated, dried over $MgSO_4$, and the solvents were distilled off under reduced pressure. In order to recover DCP, the distilled solvent mixture was fractionated. An analytically pure sample was obtained by flash chromatography (the same as in method I).

Method III. Chloro oxime **2** (2 mmol) prepared by a published procedure was dissolved in DCP (5 ml). A solution of Et_3N (455 mg, 4.5 mmol) in DCP (1 ml) was added with vigorous stirring to the mixture at room temperature. Heating of the mixture and precipitation occurred. The reaction mixture was stirred for 1 h, DCP was distilled off under reduced pressure, and the target compound was isolated by flash chromatography (the same as in method I).

5-(Chloromethyl)-3-methylisoxazole (5a). A drop of pyridine was added and then a solution of acetaldoxime (237 mg, 4 mmol) in DCP (2 ml) was added dropwise to a suspension of NCS (560 mg, 4.2 mmol) in DCP (5 ml). A slight heating, dissolution, and precipitation were observed. After 3 h, a solution of Et_3N (910 mg, 9 mmol) in DCP (2 ml) was added with vigorous stirring, resulting in heating and formation of a large volume of precipitate. Stirring was continued at room temperature for 1 h, the reaction mixture was diluted with pentane (20 ml), the precipitate was filtered off, and the filtrate was evaporated. The residue was purified by flash chromatography on silica gel, eluent CH_2Cl_2. Yield 327 mg (62%, method I), 42 mg (8%, method II), colorless oil. ^{1}H NMR spectrum, δ, ppm: 2.27 (3H, s, CH_3); 4.55 (2H, s, CH_2Cl); 6.14 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 11.4; 34.5; 104.4; 160.1; 167.2. Analytical data match those published previously.[5d]

5-(Chloromethyl)-3-heptylisoxazole (5b). Yield 370 mg (86%, method I), 228 mg (52%, method II), colorless oil. IR spectrum, ν, cm^{-1}: 734 (C–Cl), 1005, 1139, 1271, 1427, 1460, 1608 (C=C, C=N), 2858 (CH Alk), 2927 (CH Alk), 3131 (CH Het). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.86–0.89 (3H, m, CH_3); 1.28–1.33 (8H, m, $4CH_2$); 1.62–1.69 (2H, m, CH_2); 2.65 (2H, t, *J* = 7.7, CH_2); 4.58 (2H, s, CH_2Cl); 6.16 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 14.1; 22.6; 26.0; 28.2; 29.0; 29.2; 31.7; 34.6; 103.4; 164.4; 167.1. Mass spectrum, *m/z* (I_{rel}, %): 215 $[M]^+$ (1), 186 $[M–C_2H_5]^+$ (6), 172 $[M–C_3H_7]^+$ (9), 166 $[M–CH_2Cl]^+$ (28), 144 $[M–C_5H_{11}]^+$ (35), 131 $[M–C_6H_{12}]^+$ (100), 96 (19), 41 (56). Found: %: C 61.17; H 8.71; N 6.72. $C_{11}H_{18}ClNO$. Calculated, %: C 61.25; H 8.41; N 6.49.

5-Chloromethyl-3-(cyclohexyl)isoxazole (5c).[6] Yield 343 mg (86%, method I), colorless oil. ^{1}H NMR spectrum, δ, ppm: 1.25–1.46 (5H, m, CH_2); 1.72–1.98 (5H, m, CH_2); 2.69–2.75 (1H, m, CH); 4.56 (2H, s, CH_2Cl); 6.14 (1H, s, H-4).

5-(Chloromethyl)-3-phenylisoxazole (5d). Yield 337 mg (87%, method I), 298 mg (77%, method II), white powder, mp 68–69 °C (mp 69–70 °C[11c], 63–65 °C[6]). ^{1}H NMR spectrum, δ, ppm: 4.67 (2H, s, CH_2Cl); 6.65 (1H, s, H-4); 7.47–7.49 (3H, m, H Ph); 7.80–7.83 (2H, m, H Ph).

5-(Chloromethyl)-3-(4-methoxyphenyl)isoxazole (5e). Yield 349 mg (78%, method I), white powder, mp 78–79°C

(mp 75–77°C[6]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.87 (3H, s, OCH_3); 4.65 (2H, s, CH_2Cl); 6.59 (1H, s, H-4); 6.97–7.00 (2H, d, *J* = 8.0, H Ar); 7.75 (2H, d, *J* = 8.0, H Ar).

5-(Chloromethyl)-3-(4-fluorophenyl)isoxazole (5f). Yield 322 mg (76%, method I), white powder, mp 63–64°C (mp 62–63°C[6]). ^{1}H NMR spectrum, δ, ppm: 4.66 (2H, s, CH_2Cl); 6.61 (1H, s, H-4); 7.13–7.18 (2H, m, H Ar); 7.77–7.81 (2H, m, H Ar).

5-(Chloromethyl)-3-(4-chlorophenyl)isoxazole (5g). Yield 370 mg (81%, method I), 383 mg (84%, method III), white powder, mp 104°C (mp 105°C[12a], 96–98°C[6]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.67 (2H, s, CH_2Cl); 6.62 (1H, s, H-4); 7.45 (2H, d, *J* = 8.0, H Ar); 7.74 (2H, d, *J* = 8.0, H Ar).

5-(Chloromethyl)-3-(2-chlorophenyl)isoxazole (5h). Eluent Et_2O–hexane, 1:5. Yield 339 mg (74%, method I), colorless oil. IR spectrum, ν, cm^{-1}: 737 (C–Cl), 945, 1048, 1265, 1401, 1447, 1605 (C=C, C=N), 2966–3063 (CH Ar), 3141 (CH Het). ^{1}H NMR spectrum, δ, ppm: 4.69 (2H, s, CH_2Cl); 6.81 (1H, s, H-4); 7.34–7.42 (2H, m, H Ar); 7.48–7.51 (1H, m, H Ar); 7.73–7.75 (1H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 34.5 (CH_2Cl); 105.2; 127.3; 128.0; 130.6; 131.1; 131.2; 133.0; 161.4; 167.3. Mass spectrum, *m*/*z* (I_{rel}, %): 229 $[M]^+$ (14), 227 $[M]^+$ (21), 192 $[M–Cl]^+$ (6), 178 $[M–CH_2Cl]^+$ (100), 150 (30), 75 (29). Found, %: C 52.78; H 3.07; N 5.99. $C_{10}H_7Cl_2NO$. Calculated, %: C 52.66; H 3.09; N 6.14.

5-(Chloromethyl)-3-(4-nitrophenyl)isoxazole (5i). Before the addition of NCS, DMF (0.3 ml) was added to the reaction mixture for homogenization. Eluent EtOAc–hexane, 1:3. Yield 248 mg (52%, method I), white powder, mp 120–122 °C (mp 204–206 °C[12b]). IR spectrum, ν, cm^{-1}: 698, 731 (C–Cl), 855, 945, 1344 (NO_2), 1432, 1512 (NO_2), 1600 (C=C, C=N), 3034 (CH Ar), 3082 (CH Ar), 3124 (CH Het). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.70 (2H, s, CH_2Cl); 6.73 (1H, s, H-4); 7.99 (2H, d, *J* = 8.0, H Ar); 8.33 (2H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 34.4 (CH_2Cl); 102.0; 124.3 (2C); 127.8 (2C); 134.7; 148.9; 161.0; 169.3. Found, %: C 50.38; H 2.92; N 11.64. $C_{10}H_7ClN_2O_3$. Calculated, %: C 50.33; H 2.96; N 11.74.

5-(Chloromethyl)-3-(2-nitrophenyl)isoxazole (5j). Yield 320 mg (73%, method I), yellow oil. IR spectrum, ν, cm^{-1}: 743 (C–Cl), 948, 1354 (NO_2), 1405, 1531 (NO_2), 1606 (C=C, C=N), 2924, 3136 (CH Het). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.66 (2H, s, CH_2Cl); 6.45 (1H, s, H-4); 7.61–7.72 (3H, m, H Ar); 7.99 (1H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 34.4 (CH_2Cl); 104.2; 124.0; 124.8; 131.0; 131.8; 133.2; 148.6; 160.3; 168.0. Mass spectrum, *m*/*z* (I_{rel}, %): 238 $[M]^+$ (1), 203 $[M–Cl]^+$ (2), 159 (4), 132 (100), 121 (13), 102 (25), 76 (35), 69 (50). Found, %: C 50.32; H 3.27; N 11.92. $C_{10}H_7ClN_2O_3$. Calculated, %: C 50.33; H 2.96; N 11.74.

2-[5-(Chloromethyl)isoxazol-3-yl]phenol (5k). Yield 96 mg (23%, method I), 190 mg (45%, method III), light-yellow powder, mp 59–60°C. IR spectrum, ν, cm^{-1}: 736 (C–Cl), 827, 961, 1166, 1243, 1286, 1405, 1462, 1582, 1616, 3032 (CH Ar), 3130 (CH Het), 3216 (OH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.67 (2H, s, CH_2Cl); 6.72 (1H, s, H-4); 6.94 (1H, t, *J* = 8.0, H Ar); 7.06 (1H, d, *J* = 8.0, H Ar); 7.34 (1H, t, *J* = 8.0, H Ar); 7.43–7.45 (1H, m, H Ar); 9.22 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 34.2 (CH_2Cl); 101.5; 112.8; 117.6; 119.9; 128.0; 132.0; 156.6; 162.7; 167.2. Mass spectrum, *m*/*z* (I_{rel}, %): 211 $[M]^+$ (18), 209 $[M]^+$ (55), 174 $[M–Cl]^+$ (18), 160 $[M–CH_2Cl]^+$ (100), 132 (45), 104 (26), 91 (21), 77 (32). Found, %: C 57.16; H 3.87; N 6.40. $C_{10}H_8ClNO_2$. Calculated, %: C 57.30; H 3.85; N 6.68.

5-(Chloromethyl)-3-((*E*)-2-phenylethenyl)isoxazole (5l). Yield 245 mg (57%, method I), 279 mg (64%, method II), white powder, mp 77–78°C. IR spectrum, ν, cm^{-1}: 696, 731, 809, 967, 1288, 1438, 1605 (C=C, C=N), 1644, 3037 (CH Ph), 3123 (CH Het). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.63 (2H, s, CH_2Cl); 6.57 (1H, s, H-4); 7.12 (1H, d, *J* = 16.5, CH); 7.19 (H, d, *J* = 16.5, CH); 7.34–7.43 (3H, m, H Ph); 7.52–7.55 (2H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 34.5 (CH_2Cl); 100.9; 115.6; 127.1 (2C); 128.9 (2C); 129.1; 135.6; 136.5; 162.0; 167.4. Mass spectrum, *m*/*z* (I_{rel}, %): 221 $[M]^+$ (10), 220 $[M–H]^+$ (27), 219 $[M]^+$ (30), 218 $[M–H]^+$ (65), 190 (59), 170 $[M–CH_2Cl]$ (41), 142 (76), 128 (25), 115 (71), 103 (55), 77 (100). Found, %: C 65.40; H 4.43; N 6.29. $C_{12}H_{10}ClNO$. Calculated, %: C 65.61; H 4.59; N 6.38.

Supplementary information file containing IR, ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

Spectral and analytical data were obtained using the equipment of the Baikal Analytical Center for Collective Use of Irkutsk Institute of Chemistry of the Siberian Branch of the Russian Academy of Sciences.

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