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NOVEL SYNTHESIS OF 2-TRICHLOROMETHYL-4-VINYLOXAZOLINE AND ITS DERIVATIZATION BY RING CLEAVAGE REACTIONS*

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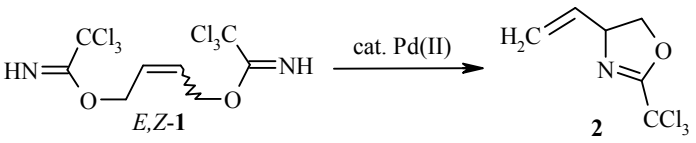
A novel efficient and eco-friendly method for the synthesis of 2-trichloromethyl-4-vinyloxazoline is presented that involves Lewis acid-catalyzed cyclization of bisimidate derived from but-3-ene-1,2-diol. The derivatization potential of 2-trichloromethyl-4-vinyloxazoline is demonstrated by ring opening reactions with water, hydrobromic acid, hydrochloric acid, and acetic acid leading to allylamine derivatives.

Keywords: allyl amine, Lewis acids, oxazoline, trichloroacetimidate, cyclization.

2-Trichloromethyl-4-vinyloxazoline (**2**) is an attractive multifunctional building block with high derivatization potential. The synthesis of 2-trichloromethyl-4-vinyloxazoline (**2**) using Pd(II)-catalyzed cyclization of bistrichloroacetimidate *Z*-**1** derived from (*Z*)-but-2-ene-1,4-diol was first reported by Sabat and Johnson [1]. They have also demonstrated the transformation of vinyloxazoline **2** to protected vinylglycinol, which was further used for the synthesis of unnatural amino acids. Asymmetric synthesis of vinyloxazoline **2** from both bistrichloroacetimidate isomers *E*-**1** and *Z*-**1** catalyzed by cationic Pd(II) complex was later developed in our group [2].



E,Z-**1** **2**

Recently, we reported that vinyloxazolines could also be obtained by Lewis acid (LA)-catalyzed cyclization of bistrichloroacetimidates derived from substituted 1,4-butenediols [3, 4]. Compared to palladium catalysis, this method offers a cheaper and more eco-friendly alternative for the synthesis of vinyloxazolines as amino acid and amino alcohol precursors. Unfortunately, cyclization of the simplest analog – bistrichloroacet-

*Dedicated to professor Ivars Kalvinsh on the occasion of his 65th birthday.

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imidate *E*-**1** – to vinyloxazoline **2** by the use of $FeCl_3$ or $AlCl_3$ as catalysts was problematic due to the formation of side products to a considerable extent (one major unidentified side product >20%, by GC/MS and ^{1}H NMR spectroscopy). In addition, we observed relatively slow formation of product **2** from bistrichloro-

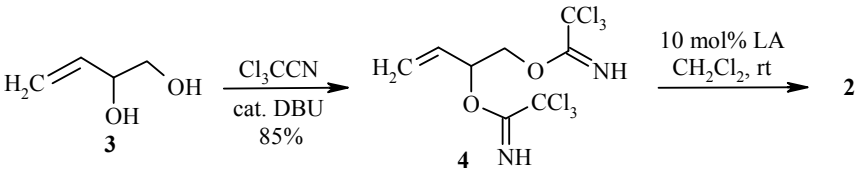


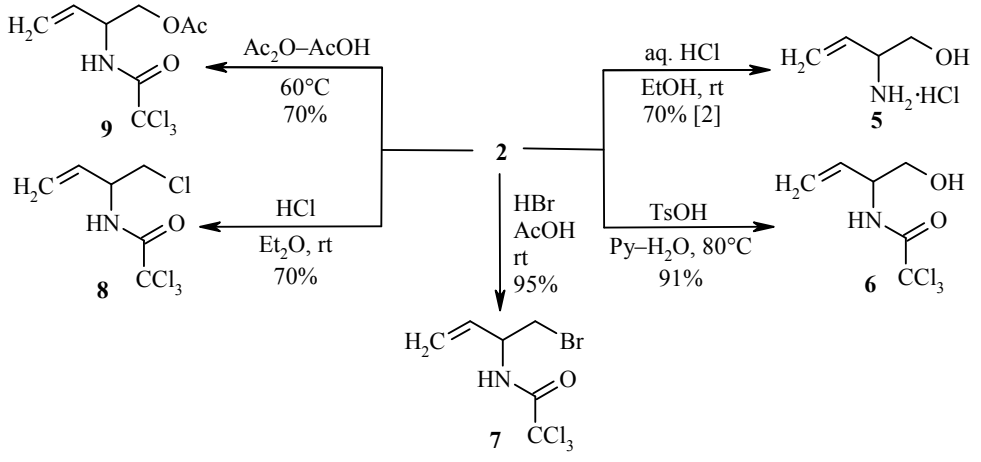
TABLE 1. Yield of Vinyloxazoline **2** in Lewis Acid-catalyzed Cyclization of Bistrichloroacetimidate **4**

Entry	Catalyst	Time, min	Yield, %
1	$AlCl_3$	5	95
2	$FeCl_3$	10	94
3	$BF_3 \cdot OEt_2$	1	96
4	TMSOTf	1	93

acetimidate *E*-**1** compared to its higher homologs [3, 4]. A reason for that could be slower ionization of acid-complexed imidate derived from primary alcohol in compound *E*-**1** to give carbenium ion, which is the proposed reactive intermediate for this reaction type [3, 4].

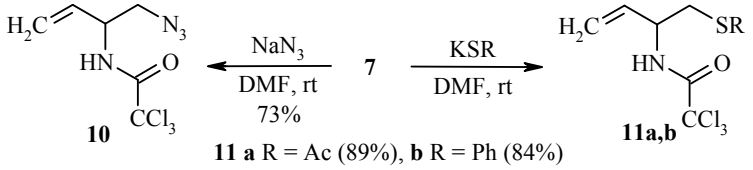
We anticipated that clean and efficient synthesis of the vinyloxazoline **2** could be achieved from bistrichloroacetimidate **4** as the starting material, since the more facile ionization of the secondary imidate group in compound **4** would lead to fast formation of the allylic cation intermediate and thus side reactions would be diminished. Indeed, bistrichloroacetimidate **4**, regioisomeric to compound **1**, derived from commercially available but-3-ene-1,2-diol (**3**) underwent rapid cyclization when exposed to Lewis acid catalysts. The reaction provided the desired vinyloxazoline **2** in excellent yields with all the catalysts studied (Table 1).

To expand the utility of vinyloxazoline **2**, its ring cleavage reactions were investigated. As reported previously, hydrolysis of vinyloxazoline **2** under strongly acidic conditions leads to vinylglycinol **5** [1, 2, 5]. Partial hydrolysis of vinyloxazoline **2** was achieved by literature protocol using TsOH in aqueous pyridine to give *N*-trichloroacetyl glycinol **6** in excellent yield [6-8]. There are several literature precedents demonstrating that protonation of the oxazoline ring makes it susceptible for ring cleavage with nucleophiles [9-12]. Based on this, we explored ring cleavage of vinyloxazoline **2** with acids containing a nucleophilic counterion. The reaction of vinyloxazoline **2** with HBr and HCl provided allyl amine derivatives **7** and **8** in good yields. In a similar way, heating of oxazoline **2** in a mixture of acetic acid and acetic anhydride gave *O*-acylated



vinylglycinol **9**. Next, we demonstrated that acidic conditions can be used also for cleavage of chiral vinyloxazoline **2** without inducing racemization. For this purpose, the enantiomerically enriched substrate (*R*)-**2** [2] (*ee* 82%) was transformed to bromide (*R*)-**7** according to previously established conditions. Bromide (*R*)-**7** was then subjected to K_2CO_3 which regenerated vinyloxazoline (*R*)-**2** (*ee* 82%) with complete conservation of enantiomeric purity.

Bromomethylallyl amine **7** could be potentially used as alkylating agent by replacement of bromine with nucleophiles. We found that this transformation is limited to very good nucleophiles, such as azide ion, thioacetate, and phenylthiolate, to give azide **10** and thiol derivatives **11a**,**b**. An attempt to achieve the alkylation with other nucleophiles such as phenoxide, alkoxide, potassium phthalimide malonate anion, or Meldrum's acid anion resulted in cyclization regenerating vinyloxazoline **2**.



11 a R = Ac (89%), **b** R = Ph (84%)

In summary, we have developed a new synthesis of vinyloxazoline by Lewis acid-catalyzed cyclization of bisimidate derived from but-3-ene-1,2-diol. This constitutes an efficient and environmentally friendly method for the synthesis of a multifunctional building block. Ring cleavage reactions of vinyloxazoline were studied and it was shown that these can provide access to a variety of vinylamine derivatives. We believe that our research presented in this article will enable the use of vinyloxazoline as intermediate for the synthesis of pharmaceutically relevant compounds and natural products.

EXPERIMENTAL

The IR spectrum was recorded on a Shimadzu IR Prestige 21 spectrometer in nujol. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using the residual solvent signal as internal standard (δ_H 7.26 and δ_C 77.2 ppm). HRMS were obtained using a *Q*-TOF *micro* high resolution mass spectrometer with ESI. Optical rotation was measured on a Perkin Elmer 141 polarimeter. Chiral gas chromatography was performed on an Agilent Technologies 6890N Network GC System chromatograph, chiral stationary phase, column: 6-TBDMS-2,3-Me-β-CD 50%, 25 m; program 60°C, 5 min, then 60–210°C, 8°C/min; injection: split less 250°C; injection volume 1 μl; sample concentration 1 mg/ml, FID detector. Melting points were determined on an OptiMelt Automated Melting Point System. Flash chromatography was carried out using Merck Kieselgel (230-400 mesh). Thin-layer chromatography was performed on silica gel and was visualized by staining with $KMnO_4$. Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80°C was used.

But-1-ene-3,4-diylbis(trichloroacetimidate) (4). 4 Å Molecular sieves were added to a solution of but-3-ene-1,2-diol (**3**) (0.25 g, 2.84 mmol) in CH_2Cl_2 (25 ml). The reaction mixture was cooled to 0°C and then DBU (0.09 ml, 0.57 mmol, 20 mol %) was added. The solution was stirred at 0°C for 30 min. Then trichloroacetonitrile (1.13 ml, 11.30 mmol) was added, and the reaction mixture was stirred until TLC showed complete conversion (0.5 h). The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using petroleum ether–EtOAc, 8:1, as an eluent to give compound **4**. Yield 0.90 g (85%). Colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.47 (1H, dd, *J* = 11.7, *J* = 7.4) and 4.56 (1H, dd, *J* = 11.7, *J* = 3.5, CH_2O); 5.38 (1H, d, *J* = 11.0) and 5.54 (1H, d, *J* = 17.2, C$\underline{H}_2$=CH); 5.79–5.84 (1H, m, HCO); 5.94 (1H, ddd, *J* = 17.2, *J* = 11.0, *J* = 6.7, CH_2=C$\underline{H}$); 8.36 (1H, br. s, NH); 8.42 (1H, br. s, NH). ^{13}C NMR spectrum, δ,

ppm: 69.0 (CH_2O); 76.0 (HCO); 91.0 (CCl_3); 91.3 (CCl_3); 119.3 ($\underline{C}H_2$=C); 131.1 (C=$\underline{C}$H); 161.6 (C=NH); 162.5 (C=NH). Unstable in conditions for high-resolution mass spectrum.

2-Trichloromethyl-4-vinyloxazoline (2). 4 Å Molecular sieves and Lewis acid catalyst (0.053 mmol, 10 mol%) were added to a stirred solution of but-1-ene-3,4-diyl(bistrichloroacetimidate) (**4**) (0.200 g, 0.53 mmol) in CH_2Cl_2 (10 ml) at room temperature. After the reaction was complete (TLC control in the first minute of the reaction), Et_3N (50 mol%, 37 μl, 0.27 mmol) was added to the reaction mixture and then the solvent was removed under reduced pressure. The residue was purified by chromatography on a short silica gel column using petroleum ether–EtOAc, 8:1, as an eluent to give compound **2** as a colorless oil (see Table 1). Spectroscopic characterization matched with literature data [1, 2].

***N*-[1-(Hydroxymethyl)prop-2-en-1-yl]trichloroacetamide (6)**. *p*-TsOH·H_2O (2.18 g, 11.5 mmol) was added to a solution of 2-trichloromethyl-4-vinyloxazoline (**2**) (2.24 g, 10.4 mmol) in a mixture of pyridine and water (4:1, 150 ml). The mixture was heated at 80°C for 2.5 h and then cooled to room temperature. Pyridine was removed *in vacuo* and the residue partitioned between EtOAc (100 ml) and 5% aq. $KHSO_4$ (100 ml). The aqueous phase was separated and extracted repeatedly with EtOAc (2×100 ml). The combined organic phase was washed with brine (100 ml) and dried over Na_2SO_4. The extract was filtered and the solvent was removed *in vacuo* to give compound **6**. Yield 2.21 g (91%). Colorless crystalline material. Physicochemical and spectral data of the obtained compound matched with literature data [13].

***N*-(1-Bromobut-3-en-2-yl)trichloroacetamide (7)**. HBr (33%) in AcOH (2.5 ml) was added to a solution of 2-trichloromethyl-4-vinyloxazoline (**2**) (1.03 g, 4.8 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred at room temperature for 4 h and then poured into saturated aq. $NaHCO_3$ (30 ml). The mixture was extracted with EtOAc (3×40 ml), the combined organic phase was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. The residue was purified on silica gel column (eluent EtOAc–light petroleum ether, gradient 1:8 to 1:3) to give compound **7**. Yield 1.34 g (95%). Colorless crystalline material; mp 58-60°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.53 (1H, dd, *J* = 10.6, *J* = 4.5) and 3.67 (1H, dd, *J* = 10.6, *J* = 4.3, CH_2Br); 4.77 (1H, m, CHN); 5.30-5.42 (2H, m, C$\underline{H}_2$=CH); 5.86 (1H, ddd, *J* = 15.7, *J* = 10.2, *J* = 5.1, CH_2=C$\underline{H}$); 6.96 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 35.6 (CH_2Br); 52.8 (CHN); 92.3 (CCl_3); 118.7 (CH=$\underline{C}H_2$); 133.6 ($\underline{C}$H=CH_2); 161.3 (C=O). Found, *m*/*z*: 293.8853 $[M+H]^+$. $C_6H_8BrCl_3NO$. Calculated, *m*/*z*: 293.8855.

Enantiomerically enriched (*R*)-*N*-(1-bromobut-3-en-2-yl)trichloroacetamide *R*-(**7**) was prepared from (*R*)-2-trichloromethyl-4-vinyloxazoline *R*-(**2**) [2] (*ee* 82%, chiral GC). $[\alpha]_D^{20}$ +26.98° (*c* 5.5, CH_2Cl_2).

Anhydrous K_2CO_3 (25.5 mg, 0.185 mmol) was added to a solution of compound *R*-(**7**) (11.0 mg, 0.037 mmol) in DMF (1 ml). The reaction mixture was stirred at room temperature overnight and then poured into saturated aq. NaCl (25 ml). The mixture was extracted with EtOAc (3×25 ml), the combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed *in vacuo* to give compound (*R*)-**2** (*ee* 82%) as colorless oil.

***N*-(1-Chlorobut-3-en-2-yl)trichloroacetamide (8)**. HCl (2.5 M) in Et_2O (2.5 ml) was added to a solution of 2-trichloromethyl-4-vinyloxazoline (**2**) (0.30 g, 1.4 mmol) in CH_2Cl_2 (5 ml). The reaction mixture was stirred at room temperature for 4 h and poured into saturated aq. $NaHCO_3$ (15 ml). The mixture was extracted with EtOAc (3×15 ml), combined organic phase was washed with brine, dried over Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent EtOAc–light petroleum ether, gradient 1:8 to 1:3) to give compound **8**. Yield 0.25 g (70%). White crystalline material, mp 56-57°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.72 (1H, dd, *J* = 10.6, *J* = 4.5) and 3.81 (1H, dd, *J* = 10.6, *J* = 4.3, CH_2Cl); 4.79 (1H, m, CHN); 5.32–5.44 (2H, m, C$\underline{H}_2$=CH); 5.89 (1H, ddd, *J* = 15.8, *J* = 10.6, *J* = 5.5, CH_2=C$\underline{H}$); 6.97 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 46.5 (CH_2Cl); 53.4 (CHN); 92.3 (CCl_3); 118.8 (CH=$\underline{C}H_2$); 132.9 ($\underline{C}$H=CH_2); 161.4 (C=O). Found, *m*/*z*: 249.9416 $[M+H]^+$. $C_6H_8Cl_4NO$. Calculated, *m*/*z*: 249.9360.

2-[(Trichloroacetyl)amino]but-3-en-1-yl Acetate (9). AcOH (1 ml) was mixed with Ac_2O (1 ml) and kept at room temperature for 2 h. In this mixture, 2-trichloromethyl-4-vinyloxazoline (**2**) (0.30 g, 1.4 mmol) was

dissolved. The mixture was heated at 60°C for 2 h and then cooled to room temperature. The reaction mixture was poured into saturated aq. $NaHCO_3$ (25 ml) and agitated for 30 min, then extracted with EtOAc (3×20 ml). The combined organic phase was washed with brine and dried over Na_2SO_4. The extract was filtered, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (eluent EtOAc–light petroleum ether, gradient 1:8 to 1:3) to give compound **9**. Yield 0.27 g (70%). Colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.05 (3H, s, CH_3); 3.42 (1H, dd, *J* = 11.0, *J* = 4.7) and 4.47 (1H, dd, *J* = 11.0, *J* = 5.1, C<u>H</u>$_2$OAc); 4.93 (1H, m, CHN); 5.21-5.44 (2H, m, C<u>H</u>$_2$=CH); 5.75 (1H, s, NH); 5.83 (1H, ddd, *J* = 16.2, *J* = 10.6, *J* = 5.9, CH_2=C<u>H</u>). ^{13}C NMR spectrum, δ, ppm: 23.2 (<u>C</u>H_3C=O); 50.3 (CHN); 69.4 (CH_2OAc); 92.9 (CCl_3); 118.3 (CH=<u>C</u>H_2); 132.9 (<u>C</u>H=CH_2); 161.9 (CCl_3<u>C</u>=O); 170.1 (CH_3<u>C</u>=O). Found, *m/z*: 273.9807 $[M+H]^+$. $C_8H_{11}Cl_3NO_3$. Calculated, *m*/*z*: 273.9805.

***N*-(1-Azidobut-3-en-2-yl)trichloroacetamide (10)**. NaN_3 (0.195 g, 3 mmol) was added to a solution of *N*-(1-bromobut-3-en-2-yl)trichloroacetamide (**7**) (0.300 g, 1 mmol) in DMF (3 ml). The reaction mixture was stirred at room temperature for 12 h and then poured into water (30 ml). The mixture was extracted with EtOAc (60 ml), and the organic phase was washed with brine and dried over Na_2SO_4. The extract was filtered, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (eluent EtOAc–light petroleum ether, gradient 1:8 to 1:3) to give compound **10**. Yield 0.192 g (73%). Colorless oil. IR spectrum, ν, cm^{-1}: 2103 (N_3), 1696 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.56 (1H, dd, *J* = 12.5, *J* = 4.7) and 3.62 (1H, dd, *J* = 12.5, *J* = 4.7, CH_2N_3); 4.61 (1H, m, CHN); 5.34-5.44 (2H, m, CH=C<u>H</u>$_2$); 5.86 (1H, ddd, *J* = 15.7, *J* = 10.2, *J* = 5.5, C<u>H</u>=CH_2); 6.83 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 52.7 (CH_2N_3); 53.8 (CHN); 92.3 (CCl_3); 118.6 (CH=<u>C</u>H_2); 133.2 (<u>C</u>H=CH_2); 161.4 (C=O).

***S*-{2-[(Trichloroacetyl)amino]but-3-en-1-yl} Thioacetate (11a)**. Potassium thioacetate (0.34 g, 3 mmol) was added to a solution of *N*-(1-bromobut-3-en-2-yl)trichloroacetamide (**7**) (0.30 g, 1 mmol) in DMF (3 ml). The reaction mixture was stirred at room temperature for 12 h and then poured into water (30 ml). The mixture was extracted with EtOAc (60 ml), and the organic phase was washed with brine and dried over Na_2SO_4. The extract was filtered, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (eluent EtOAc–light petroleum ether, gradient 1:8 to 1:3) to give compound **11a**. Yield 0.26 g (89%). Colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.37 (3H, s, CH_3C=O); 3.10 (1H, dd, *J* = 14.5, *J* = 9.0) and 3.25 (1H, dd, *J* = 14.5, *J* = 4.3, CH_2S); 4.56 (1H, m, CHN); 5.27 (1H, dt, *J* = 10.2, *J* = 0.8) and 5.31 (1H, dt, *J* = 16.0, *J* = 0.8, CH=C<u>H</u>$_2$); 5.81 (1H, ddd, *J* = 16.0, *J* = 10.2, *J* = 5.5, C<u>H</u>=CH_2); 7.05 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 30.5 (<u>C</u>H_3C=O); 32.3 (CH_2S); 54.1 (CHN); 92.4 (CCl_3); 117.5 (CH=<u>C</u>H_2); 134.6 (<u>C</u>H=CH_2); 161.6 (CCl_3<u>C</u>=O); 196.8 (CH_3<u>C</u>=O). Found, *m/z*: 289.9490 $[M+H]^+$. $C_8H_{11}Cl_3NO_2S$. Calculated, *m*/*z*: 289.9576.

***N*-[1-(Phenylsulfanyl)but-3-en-2-yl]trichloroacetamide (11b)**. Thiophenol (0.330 g, 0.31 ml, 3 mmol) and K_2CO_3 (0.138 g, 1 mmol) were added to a solution of *N*-(1-bromobut-3-en-2-yl)trichloroacetamide (**7**) (0.300 g, 1 mmol) in DMF (3 ml). The reaction mixture was stirred at room temperature for 4 h and then poured into water (30 ml). The mixture was extracted with EtOAc (60 ml), and the organic phase was washed with brine (6×40 ml). The extract was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel (eluent EtOAc–light petroleum ether, gradient 1:20 to 1:8) to give compound **11b**. Yield 0.280 g (84%). Colorless oil. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.21 (2H, m, CH_2S); 4.62 (1H, m, CHN); 5.32-5.45 (2H, m, CH=C<u>H</u>$_2$); 5.85 (1H, ddd, *J* = 15.5, *J* = 10.2, *J* = 5.5, C<u>H</u>=CH_2); 6.92 (1H, s, NH); 7.15-7.35 (3H, m, H Ph); 7.40 (2H; m, H Ph). ^{13}C NMR spectrum, δ, ppm: 38.5 (CH_2S); 52.8 (CHN); 92.4 (CCl_3); 117.5 (CH=<u>C</u>H_2); 127.1 (Ph); 129.3 (Ph); 130.5 (C Ph); 134.7 (<u>C</u>H=CH_2); 134.7 (C Ph); 161.2 (C=O). Found, *m/z*: 323.9778 $[M+H]^+$. $C_{12}H_{13}NOSCl_3$. Calculated, *m*/*z*: 323.9783.

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