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A new and efficient approach to isoxazolines. First synthesis of 3-aryl-5-dichloromethyl-2-isoxazolines

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ABSTRACT

An efficient synthetic method for 3-aryl-5-dichloromethyl-2-isoxazolines has been established. Reactions between anhydrous chloral and acetophenones in hot acetic acid lead to 1-aryl-4,4,4-trichloro-3-hydroxybutan-1-ones (chloralacetophenones), which provided 1-aryl-4,4-dichlorobut-3-en-1-ones (2,2-dichlorovinylacetophenones) by dehydration and subsequent electrochemical reduction. These β,γ-unsaturated enones reacted with hydroxylamine yielding oxime intermediates whose treatment with aqueous sodium hydroxide gave novel 3-aryl-5-dichloromethyl-2-isoxazolines in fair to high yields. The molecular structure of a member of this family of compounds, 5-dichoromethy1-3-(4-methoxyphenyl)-2-isoxazoline, was determined by X-ray crystallography.

1. Introduction

The chemistry of 2-isoxazolines has been excellently reviewed,[1–5] showing that these compounds are of great interest. 2-Isoxazolines have been reported as biologically active compounds with antifungal,[6] antibacterial[7,8] and antidiabetic[9,10] properties. Certain drugs useful against cardiovascular[11] diseases and as anticoagulants[12,13] contain a 2-isoxazoline moiety. A wide range of efficient reactions involving either ring cleavage or ring retention can be selectively promoted from chiral and achiral 2-isoxazolines, evidencing a high value as synthetic intermediates.[1–4,14–26] Therefore, the research on the synthesis of this class of compounds deserves much attention.

The first isolated 2-isoxazoline was obtained in 1895 by the α,β-unsaturated ketone/hydroxylamine reaction[3] that, in general, gives deficient results, mainly due to participation of Michael addition processes. The oximation reaction of conjugated enones is far more complex than one might expect, yielding isoxazolines along with β-hydroxylamino oximes and further products. Serious limitations in purification and yield are usual disadvantages of this procedure since its final result is not easily controllable given that it depends sensitively on several experimental variables, such as pH, nature of solvent and reagent ratio.[27] Nevertheless, it was the most practiced synthetic method until 1,3-dipolar cycloaddition between nitrile oxides and ethylenic double bonds was discovered to be a better preparative procedure.[28–31] However, sometimes the formation of two regioisomers is an unavoidable problem of this alternative methodology.[31]

In an effort to improve the earlier oximation route, the use of nonconjugated β,γ-unsaturated ketones as a substitute of conjugated α,β-unsaturated enones is a highly valuable option since disturbing Michael reactions can be avoided. Nevertheless, unconjugated enones are more difficultly available than conjugated isomers. Besides, they must be prepared with a special care due to its proclivity to isomerise, giving the most stable conjugated compounds. The main synthetic methods for β,γ-unsaturated ketones involve either acylations of allylic organometallics[32–35] or additions of organometallic compounds to aldehydes followed by oxidation of the generated allyl alcohols.[36–39]

In recent years we have worked on developing new approaches to heterocyclic compounds starting from chloral. Chloral is an inexpensive, multipurpose starting material for organic synthesis.[40] It is able to react with amides and acetophenones to yield primary derivatives from which we developed a number of significant synthetic processes on the basis of a conjunction of chemical and electrochemical reactions.[41–49] One of the most advantageous features of this synthetic approach lies in the access to specifically chlorinated compounds. Severe preparative problems of chemical incompatibility with the usual chlorinating reagents can be avoided by using suitable prechlorinated intermediates derived from chloral. A recent report about this purpose was the direct highly efficient electrogeneration of a previously unknown class of β,γ-unsaturated

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enones: 1-aryl-4,4-dichlorobut-3-en-1-ones **4** (2,2-dichlorovinyl acetophenones) by cathodic reduction of 1-aryl-4,4,4-trichlorobut-2-en-1-ones **3** (2,2,2-trichloroethylideneacetophenones) in a protic medium.[47] These unconjugated enones were found to be key intermediates to achieve the first synthesis of 3-aryl-5-dichloromethyl-2-pyrazolines.[49] Given this previous success and the propitious structure of compounds **4** in order to avoid competitive formation of β-hydroxylamino oximes in reactions with hydroxylamine, we recognised the opportunity to attempt an approach to 5-dichloromethyl-2-isoxazolines, which are hitherto unknown compounds of interest in themselves, but as well as being attractive intermediates to investigate the synthesis of a variety of isoxazoline derivatives, including compounds pertinent to fine chemical and pharmaceutical industries.

2. Results and discussion

In an effort to obtain a good approach for still unavailable isoxazolines **6** we decided to explore a plausible synthetic route based on our previously developed electrochemical method for the synthesis of dichlorinated β,γ-unsaturated enones,[47] since these compounds could undergo effective oximation reactions followed by internal nucleophilic additions directly yielding the targeted isoxazoline compounds (Scheme 1). Trichloroethylideneacetophenones **3** were efficiently prepared by reaction of acetophenones **1** with anhydrous chloral, leading to chloralacetophenones **2** that were subsequently dehydrated. Intermediates **3** were subjected to electrochemical reduction in a protic medium accordingly to our previously described protocol.[47] Owing to the peculiar mechanism of this reaction[48] the respective 2,2-dichlorovinylacetophenones **4** were selectively generated in high to quantitative yields. The conversion of these compounds into previously undescribed oximes **5** was tested by treatment with hydroxylamine hydrochloride as well as using free hydroxylamine under different experimental conditions. The best results were obtained by carrying out reactions with free hydroxylamine in the presence of equimolecular amounts of glacial acetic acid. In this case clean reactions occurred, providing the expected products in high yields. Given the non-spontaneous cyclization of derivatives **5** into the corresponding isoxazolines **6**, we successfully attempted to promote a closing to the heterocyclic ring by adding a base, since under basic catalysis β,γ-unsaturated oximes **5** are able to isomerise[9] to the corresponding α,β-unsaturated oximes **5′** with a high electrophilic activity so that an intramolecular Michael addition process can occur. Thus, compounds **5** in ethanol solution were treated with aqueous sodium hydroxide (ratio 1:1) for a few minutes. Complete transformations into single products were observed. These were isolated and identified by usual techniques as the corresponding 3-aryl-5-dichloromethyl-2-isoxazolines **6**, a new class of isoxazoline derivatives. Yields were high in all cases. Geometrical characteristics of this class of compounds were determined by single crystal X-ray crystallography of 5-dichloromethyl-3-(4-methoxyphenyl)-2-isoxazoline **6f** (Fig. 1). Selected bond lengths and bond angles for this crystal structure are given in Table 1. The packing shows parallel chains to the **b** axis formed by molecules associated by hydrogen bonds (Fig. 2).

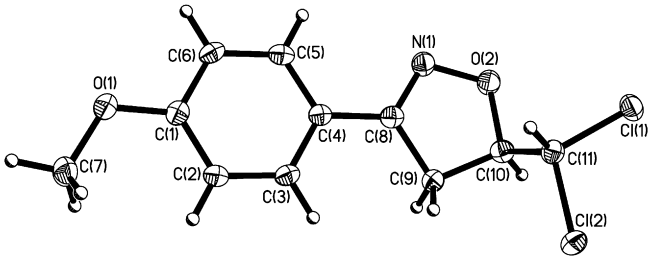
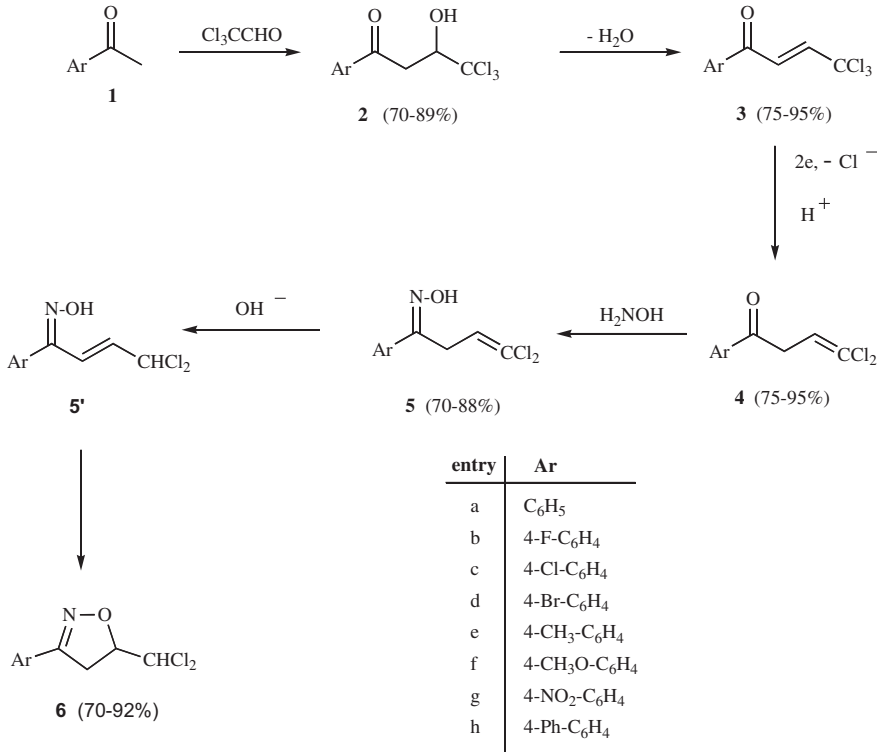


Fig. 1. Thermal ellipsoid plot (50% level) of compound **6f** in the crystal.

In conclusion, a proficient and general new method for the synthesis of dichloromethyl-2-isoxazolines involving chloral derivatives is reported. Good yields and easy availability of starting materials are valuable, noteworthy advantages of the method, which allows a privileged access to previously unattainable products. Not



entry	Ar
a	C_6H_5
b	4-F-C_6H_4
c	4-Cl-C_6H_4
d	4-Br-C_6H_4
e	4-CH_3-C_6H_4
f	4-CH_3O-C_6H_4
g	4-NO_2-C_6H_4
h	4-Ph-C_6H_4

Scheme 1.

Table 1
Selected bond lengths and bond angles in crystal structure of **6f**

Bond lengths (Å)			
Cl(1)–C(11)	1.7777(18)	O(2)–C(10)	1.451(2)
Cl(2)–C(11)	1.7862(18)	C(8)–C(9)	1.503(2)
N(1)–C(8)	1.280(2)	C(9)–C(10)	1.524(3)
N(1)–O(2)	1.431(2)	C(10)–C(11)	1.523(3)
Bond angles (°)			
C(8)–N(1)–O(2)	108.86(15)	O(2)–C(10)–C(11)	107.28(15)
N(1)–O(2)–C(10)	108.87(13)	O(2)–C(10)–C(9)	104.74(14)
N(1)–C(8)–C(4)	121.86(17)	C(11)–C(10)–C(9)	111.55(15)
N(1)–C(8)–C(9))	114.12(16)	C(10)–C(11)–Cl(1)	110.55(13)
C(4)–C(8)–C(9)	124.00(16)	C(10)–C(11)–Cl(2)	108.90(13)
C(8)–C(9)–C(10)	100.71(15)	Cl(1)–C(11)–Cl(2)	109.30(10)

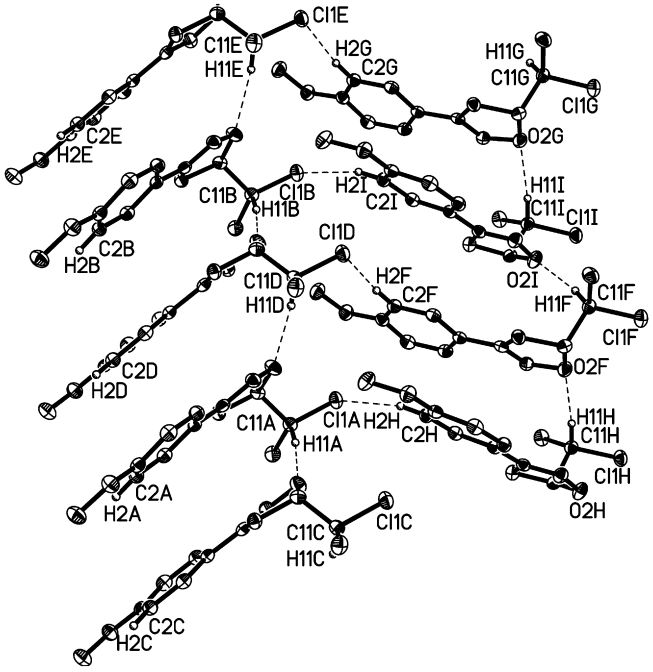


Fig. 2. View of (C11–H11···O2) and (C11–C2···H2) interactions in crystal structure of **6f**.

only are the prepared compounds of interest in themselves, the presence of a dichloromethyl substituent also suggests an attractive synthetic potential through hydrolysis, substitution and elimination reactions, which merits further exploration.

3. Experimental

3.1. General

NMR spectra were determined on Bruker AV-300 or Bruker AV-400 with tetramethylsilane as internal reference. Electron-impact mass spectra were obtained on a Thermoquest trace MS spectrometer under an ionizing voltage of 70 eV. IR spectra (Nujol emulsions) were recorded on a Nicolet Impact 400 Spectrometer. Microanalyses were performed on a Carlo Erba EA-1108 analyzer. Melting points were determined on a Büchi Melting point B-540, and are uncorrected. Compounds **2**–**4** were prepared as previously described.[49]

3.2. Preparation of 2,2-dichlorovinylacetophenone oximes 5

A 50% aqueous solution of hydroxylamine (0.2 mL; 3.6 mmol), water (1 mL) and acetic acid (3.6 mmol) was added to the corresponding enone **4** (3 mmol) dissolved in ethanol (20 mL). The mixture was stirred at room temperature for 9 h. The solvent was removed under reduced pressure. Then, cool water (40 mL) was added and the insoluble solid was collected by filtration and washed with cool chloroform, leaving a small amount of insoluble material that was eliminated by filtration. The chloroform solution was dried over anhydrous magnesium sulfate. After evaporation of solvent the solid residue was crystallised from petroleum ether (60–80 °C). Compound **5g** was previously purified by column chromatography (silica gel/hexane–ethyl ether, ratio 3:1).

*3.2.1. 2,2-Dichlorovinylacetophenone oxime (**5a**).* Yield 80%; crystallisation from petroleum ether gave white prisms; mp 60–62 °C. Found C 52.11; H 3.91; N 6.13. $C_{10}H_9Cl_2NO$ requires: C 52.20; H 3.94; N 6.09; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 3.70 (d, 2H, J=7.2 Hz), 5.99 (t, 1H, J=7.2 Hz), 7.38–7.44 (m, 3H), 7.57–7.62 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 27.66 (CH_2), 122.26 (CCl_2), 124.16 (CH), 126.43 (CH), 128.85 (CH), 129.85 (CH), 134.80 (C), 155.60 (C=N); MS, m/z (%) 231 (M^++2, 5), 229 (M^+, 3), 212 (6), 194 (19), 145 (24), 117 (52), 105 (100), 76 (90); IR (Nujol) 3229, 1619, 1338, 1292, 1083, 943, 867, 757, 689, 647 cm^{-1}.

*3.2.2. 2,2-Dichlorovinyl-4′-fluoroacetophenone oxime (**5b**).* Yield 70%; crystallisation from petroleum ether gave yellow plates; mp 80–82 °C. Found C 48.39; H 3.44; N 5.62. $C_{10}H_8Cl_2FNO$ requires: C 48.41; H 3.25; N 5.65; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.69 (d, 2H, J=7.2 Hz), 5.98 (t, 1H, J=7.2 Hz), 7.11 (m, 2H), 7.60 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 27.63 (CH_2), 115.91 (d, J=21.8 Hz) (CH), 122.45 (CCl_2), 123.91 (CH), 128.34 (d, J=8.3 Hz) (CH), 130.90 (d, J=3.1 Hz) (C), 154.72 (C=N), 163.75 (d, J=255.7 Hz) (C); MS, m/z (%) 249 (M^++2, 4), 247 (M^+, 7), 230 (3), 212 (80), 214 (28), 195 (13), 135 (100), 121 (67), 109 (24), 95 (61), 75 (25); IR (Nujol) 3214, 1599, 1511, 1333, 1158, 1078, 1045, 964, 942, 877, 839, 770, 670 cm^{-1}.

*3.2.3. 2,2-Dichlorovinyl-4′-chloroacetophenone oxime (**5c**).* Yield 85%; crystallisation from petroleum ether gave yellow prisms; mp 86–88 °C (dec). Found C 45.33; H 3.05; N 5.28. $C_{10}H_8Cl_3NO$ requires: C 45.40; H 3.05; N 5.29; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.67 (d, 2H, J=7.2 Hz), 5.96 (t, 1H, J=7.2 Hz), 7.38 (d, 2H, J=8.7 Hz), 7.54 (d, 2H, J=8.7 Hz), 8.45 (br s, 1H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 27.42 (CH_2), 122.59 (CCl_2), 123.75 (CH), 127.72 (CH), 129.08 (CH), 133.15 (C), 135.98 (C), 154.76 (C=N); MS, m/z (%) 265 (M^++2, 2), 263 (M^+, 3), 228 (4), 247 (3), 180 (22), 151 (100), 139 (49), 137 (83), 111 (95), 113 (31), 102 (42), 75 (69); IR (Nujol) 3229, 1619, 1592, 1493, 1331, 1290, 1097, 1054, 1039, 945, 866, 827 cm^{-1}.

*3.2.4. 2,2-Dichlorovinyl-4′-bromoacetophenone oxime (**5d**).* Yield 88%; crystallisation from petroleum ether gave yellow prisms; mp 100–103 °C. Found C 38.58; H 2.56; N 4.50. $C_{10}H_8BrCl_2NO$ requires: C 38.87; H 2.61; N 4.53; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.65 (d, 2H, J=7.2 Hz), 5.94 (t, 1H, J=7.2 Hz), 7.46 (d, 2H, J=8.6 Hz), 7.54 (d, 2H, J=8.6 Hz), 8.95 (br s, 1H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 27.38 (CH_2), 122.58 (CCl_2), 123.74 (CH), 124.26 (C), 127.93 (CH), 132.04 (CH), 133.64 (C), 154.80 (C=N); MS, m/z (%) 309 (M^++2, 7), 307 (M^+, 6), 291 (9), 272 (17), 274 (21), 257 (19), 223 (26), 195 (45), 197 (45), 181 (66), 183 (99), 154 (42), 156 (42), 102 (100), 75 (73); IR (Nujol) 3226, 1629, 1587, 1328, 1186, 1072, 1007, 942, 869, 824 cm^{-1}.

*3.2.5. 2,2-Dichlorovinyl-4′-methylacetophenone oxime (**5e**).* Yield 75%; crystallisation from petroleum ether gave yellow prisms; mp 86–88 °C. Found C 54.47; H 4.64; N 5.76. $C_{11}H_{11}Cl_2NO$ requires: C 54.12; H 4.54; N 5.74; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 2.38 (s, 3H), 3.68 (d, 2H, J=7.2 Hz), 5.98 (t, 1H, J=7.2 Hz), 7.21 (d, 2H, J=8.0 Hz), 7.49 (d, 2H, J=8.0 Hz), 8.90 (br s, 1H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 21.39 (CH_3), 27.56 (CH_2), 122.08 (CCl_2), 124.31 (CH), 126.30 (CH),

129.55 (CH), 131.89 (C), 140.01 (C), 155.44 (C=N); MS, *m*/*z* (%) 245 (M^++2, 64), 243 (M^+, 81), 226 (8), 208 (98), 210 (64), 191 (31), 157 (19), 132 (71), 134 (100), 116 (84), 117 (52), 118 (63), 109 (69), 89 (55), 91 (50), 73 (30), 65 (73); IR (Nujol) 3222, 1619, 1238, 1293, 1189, 1080, 1040, 966, 938, 867, 818 cm^{-1}.

*3.2.6. 2,2-Dichlorovinyl-4′-methoxyacetophenone oxime (**5f**).* Yield 81%; crystallisation from petroleum ether gave yellow prisms; mp 87–89 °C. Found C 50.80; H 4.23; N 5.29. $C_{11}H_{11}Cl_2NO_2$ requires: C 50.79; H 4.26; N 5.38; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.67 (d, 2H, *J*=7.2 Hz), 3.84 (s, 3H), 5.98 (t, 1H, *J*=7.2 Hz), 6.93 (d, 2H, *J*=8.9 Hz), 7.56 (d, 2H, *J*=8.9 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz): 27.55 (CH_2), 55.50 (CH_3), 114.28 (CH), 122.12 (CCl_2), 124.30 (CH), 126.92 (C), 127.90 (CH), 155.25 (C=N), 161.01 (C); MS, *m*/*z* (%) 261 (M^++2, 16), 259 (M^+, 26), 242 (6), 224 (22), 226 (7), 207 (13), 192 (7), 147 (69), 133 (100), 109 (18), 90 (21), 77 (15), 63 (15); IR (Nujol) 3243, 1602, 1514, 1338, 1302, 1258, 1179, 1029, 939, 879, 833 cm^{-1}.

*3.2.7. 2,2-Dichlorovinyl-4′-nitroacetophenone oxime (**5g**).* Yield 72%; crystallisation from petroleum ether gave yellow plates; mp 104–106 °C. Found C 43.75; H 2.88; N 10.17. $C_{10}H_8Cl_2N_2O_3$ requires: C 43.66; H 2.93; N 10.18; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.72 (d, 2H, *J*=7.3 Hz), 5.96 (t, 1H, *J*=7.3 Hz), 7.80 (d, 2H, *J*=9.0 Hz), 8.26 (d, 2H, *J*=9.0 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 27.14 (CH_2), 123.11 (CCl_2), 123.22 (CH), 124.01 (CH), 127.25 (CH), 140.87 (C), 148.45 (C), 153.99 (C=N); MS, *m*/*z* (%) 276 (M^++2, 1), 274 (M^+, 2); 256 (8), 239 (8), 241 (27), 210 (10), 162 (100), 148 (14), 119 (68), 102 (42), 76 (47), 75 (47), 63 (15), 50 (23); IR (Nujol) 3200, 1623, 1595, 1517, 1338, 1189, 1108, 1083, 1041, 941, 856, 846, 693, 655 cm^{-1}.

*3.2.8. 2,2-Dichlorovinyl-4′-phenylacetophenone oxime (**5h**).* Yield 84%; crystallisation from petroleum ether gave pale yellow powder; mp 109–112 °C. Found C 62.80; H 4.25; N 4.62. $C_{16}H_{13}Cl_2NO$ requires: C 62.76; H 4.28; N 4.57; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.73 (d, 2H, *J*=7.2 Hz), 6.02 (t, 1H, *J*=7.2 Hz), 7.37 (tt, 1H, *J*=7.3, 1.2 Hz), 7.46 (t, 2H, *J*=7.7 Hz), 7.61–7.65 (m, 4H), 7.70 (d, 2H, *J*=8.5 Hz), 8.30 (br s, 1H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 27.55 (CH_2), 122.27 (CCl_2), 124.19 (CH), 126.81 (CH), 127.13 (CH), 127.49 (CH), 127.84 (CH), 128.97 (CH), 133.57 (C), 140.21 (C), 142.57 (C), 155.23 (C=N); MS, *m*/*z* (%) 307 (M^++2, 11), 305 (M^+, 16), 289 (2), 270 (20), 272 (6), 252 (12), 192 (51), 193 (44), 178 (100), 179 (57), 150 (30), 152 (31), 108 (6), 76 (7); IR (Nujol) 3246, 1613, 1329, 1256, 1081, 959, 935, 869, 836, 764, 735, 696, 674 cm^{-1}.

3.3. Preparation of 3-aryl-5-dichloromethyl-2-isoxazolines 6

A sodium hydroxide solution (1.5 mmol) in water (1.5 mL) was added to a solution of the corresponding 2,2-dichlorovinyl-acetophenone oxime **5** (1.5 mmol) in ethanol (10 mL). The mixture was stirred at room temperature for 10–30 min (the course of reactions can be checked by TLC; silica gel/dichloromethane–hexane, ratio 4:1). After elimination of solvent under reduced pressure, water (40 mL) was added. The residue was collected by filtration and crystallised from petroleum ether (60–80 °C) or extracted with dichloromethane (2×25 mL), which was dried over anhydrous magnesium sulfate and evaporated to dryness. The crude compounds obtained were purified by column chromatography (silica gel/dichloromethane–hexane, ratio 4:1) and crystallised from petroleum ether. Chromatography of product **6a** was performed with ethyl acetate–hexane, ratio 1:3.

*3.3.1. 5-Dichloromethyl-3-phenyl-2-isoxazoline (**6a**).* Yield 73%; crystallisation from petroleum ether gave yellow plates; mp 120–121 °C. Found C 52.17; H 3.90; N 6.08. $C_{10}H_9Cl_2NO$ requires: C 52.20; H 3.94; N 6.09; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 3.56 (dd, 1H, *J*=17.4, 9.9 Hz), 3.62 (dd, 1H, *J*=17.4, 7.2 Hz), 5.11 (ddd, 1H, *J*=9.9, 7.2, 4.1 Hz), 5.87 (d, 1H, *J*=4.1 Hz), 7.39–7.46 (m, 3H), 7.67–7.72 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 37.10 (CH_2), 71.93 (CH), 83.75 (CH), 126.95 (CH), 128.50 (C), 128.90 (CH), 130.68 (CH), 156.29 (C=N); MS, *m*/*z* (%) 231 (M^++2, 28), 229 (M^+, 45), 194 (5), 146 (74), 127 (24), 118 (100), 91 (47), 77 (83), 51 (37); IR (Nujol) 1602, 1569, 1357, 1253, 1226, 1169, 1076, 951, 894, 862, 763, 694 cm^{-1}.

*3.3.2. 5-Dichloromethyl-3-(4′-fluorophenyl)-2-isoxazoline (**6b**).* Yield 87%; crystallisation from petroleum ether gave yellow plates; mp 100–101 °C. Found C 48.26; H 3.20; N 5.70. $C_{10}H_8Cl_2FNO$ requires: C 48.41; H 3.25; N 5.65; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.54 (dd, 1H, *J*=17.5, 9.7 Hz), 3.60 (dd, 1H, *J*=17.5, 7.3 Hz), 5.12 (ddd, 1H, *J*=9.7, 7.3, 4.1 Hz), 5.87 (d, 1H, *J*=4.1 Hz), 7.12 (m, 2H), 7.69 (m, 2H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 37.13 (CH_2), 71.86 (CH), 83.83 (CH), 116.10 (d, *J*=22.0 Hz) (CH), 124.77 (d, *J*=3.3 Hz) (C), 128.96 (d, *J*=8.6 Hz) (CH), 155.33 (C=N), 164.12 (d, *J*=251.4 Hz) (C); MS, *m*/*z* (%) 249 (M^++2, 12), 247 (M^+, 18), 212 (1), 164 (60), 136 (100), 121 (15), 109 (39), 95 (65), 75 (43); IR (Nujol) 1654, 1600, 1514, 1351, 1239, 1221, 1163, 943, 886, 869, 841, 771 cm^{-1}.

*3.3.3. 5-Dichloromethyl-3-(4′-chlorophenyl)-2-isoxazoline (**6c**).* Yield 72%; crystallisation from petroleum ether gave white needles; mp 97–98 °C. Found C 45.48; H 2.89; N 5.33. $C_{10}H_8Cl_3NO$ requires: C 45.40; H 3.05; N 5.29; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 3.53 (dd, 1H, *J*=17.4, 9.7 Hz), 3.59 (dd, 1H, *J*=17.4, 7.2 Hz), 5.13 (ddd, 1H, *J*=9.7, 7.2, 4.2 Hz), 5.87 (d, 1H, *J*=4.2 Hz), 7.40 (d, 2H, *J*=8.7 Hz), 7.62 (d, 2H, *J*=8.7 Hz); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 36.91 (CH_2), 71.80 (CH), 83.93 (CH), 126.99 (C), 128.17 (CH), 129.20 (CH), 136.73 (C), 155.40 (C=N); MS, *m*/*z* (%) 265 (M^++2, 9), 263 (M^+, 10), 228 (1), 180 (41), 182 (13), 152 (100), 125 (32), 111 (58), 75 (63); IR (Nujol) 1598, 1493, 1406, 1363, 1252, 1212, 1091, 1010, 971, 896, 865, 842, 824, 754, 689 cm^{-1}.

*3.3.4. 3-(4′-Bromophenyl)-5-dichloromethyl-2-isoxazoline (**6d**).* Yield 74%; crystallisation from petroleum ether gave yellow prisms; mp 100–101 °C. Found C 38.88; H 2.57; N 4.50. $C_{10}H_8BrCl_2NO$ requires: C 38.87; H 2.61; N 4.53; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.55 (dd, 1H, *J*=17.4, 9.9 Hz), 3.59 (dd, 1H, *J*=17.4, 7.1 Hz), 5.13 (ddd, 1H, *J*=9.9, 7.1, 4.1 Hz), 5.87 (d, 1H, *J*=4.1 Hz), 7.55 (s, 4H); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 36.82 (CH_2), 71.78 (CH), 83.90 (CH), 125.05 (C), 127.37 (C), 128.36 (CH), 132.14 (CH), 155.51 (C=N); MS, *m*/*z* (%) 309 (M^++2, 54), 307 (M^+, 32), 311 (20), 272 (1), 224 (81), 226 (78), 196 (100), 198 (98), 154 (32), 127 (12), 117 (62), 102 (58), 90 (24), 75 (90); IR (Nujol) 1599, 1568, 1362, 1308, 1252, 1226, 1168, 1076, 950, 894, 862, 763, 734, 693 cm^{-1}.

*3.3.5. 5-Dichloromethyl-3-(4′-methylphenyl)-2-isoxazoline (**6e**).* Yield 85%; crystallisation from petroleum ether gave yellow prisms; mp 99–100 °C. Found C 54.15; H 5.43; N 5.70. $C_{11}H_{11}Cl_2NO$ requires: C 54.12; H 4.54; N 5.74; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 2.39 (s, 3H), 3.53 (d, 1H, *J*=14.7, 9.7 Hz), 3.60 (d, 1H, *J*=17.4, 7.2 Hz), 5.09 (ddd, 1H, *J*=9.7, 7.2, 4.2 Hz), 5.85 (d, 1H, *J*=4.2 Hz), 7.23 (d, 2H, *J*=8.4 Hz), 7.58 (d, 2H, *J*=8.4 Hz); ^{13}C NMR δ ($CDCl_3$, 75.4 MHz) 21.54 (CH_3), 37.24 (CH_2), 72.00 (CH), 83.62 (CH), 125.67 (C), 126.90 (CH), 129.59 (CH), 141.03 (C), 156.22 (C=N); MS, *m*/*z* (%) 245 (M^++2, 13), 243 (M^+, 19), 208 (2), 160 (54), 132 (100), 117 (17), 105 (36), 91 (79), 77 (11), 65 (27), 51 (8); IR (Nujol) 1610, 1354, 1222, 1112, 900, 824, 772 cm^{-1}.

*3.3.6. 5-Dichloromethyl-3-(4-methoxyphenyl)-2-isoxazoline (**6f**).* Yield 90%; crystallisation from petroleum ether gave yellow plates; mp 98–99 °C. Found C 51.87; H 4.40; N 5.43. $C_{11}H_{11}Cl_2NO_2$ requires: C 50.79; H 4.26; N 5.38; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.53 (d, 1H, *J*=17.3, 9.9 Hz), 3.58 (d, 1H, *J*=17.3, 7.0 Hz), 3.84 (s, 3H), 5.07 (ddd, 1H, *J*=9.9, 7.0, 4.3 Hz), 5.85 (d, 1H, *J*=4.25 Hz), 6.93 (d, 2H, *J*=8.8 Hz),

7.63 (d, 2H, J=8.8 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 37.36 (CH_2), 55.47 (CH_3), 72.04 (CH), 83.55 (CH), 114.32 (CH), 121.00 (C), 128.53 (CH), 155.82 (C=N), 161.53 (C); MS, m/z (%) 261 (M^++2, 53), 259 (M^+, 72), 224 (3), 176 (100), 148 (74), 133 (41), 121 (94), 115 (21), 91 (11), 77 (70), 63 (30); IR (Nujol) 1607, 1516, 1421, 1310, 1252, 1179, 1040, 1020, 893, 863, 833, 772 cm^{-1}.

*3.3.7. 5-Dichloromethyl-3-(4′-nitrophenyl)-2-isoxazoline (**6g**).* Yield 86%; crystallisation from petroleum ether gave yellow plates; mp 141–142 °C. Found C 43.73; H 2.98; N 10.15. $C_{10}H_8Cl_2N_2O_3$ requires C 43.66; H 2.93; N 10.18; ^{1}H NMR δ ($CDCl_3$, 400 MHz) 3.59 (dd, 1H, J=17.4, 10.5 Hz), 3.66 (dd, 1H, J=17.4, 6.9 Hz), 5.22 (ddd, 1H, J=10.5, 6.9, 3.9 Hz), 5.92 (d, 1H, J=3.9 Hz), 7.87 (d, 2H, 9.0 Hz), 8.29 (d, 2H, J=9.0 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 36.45 (CH_2), 71.53 (CH), 84.53 (CH), 124.20 (CH), 127.75 (CH), 134.51 (C), 148.91 (C), 154.87 (C=N); MS, m/z (%) 276 (M^++2, 5), 274 (M^+, 8); 191 (74), 163 (100), 117 (68), 89 (14), 76 (31); IR (Nujol) 1583, 1518, 1346, 1319, 1251, 1153, 1107, 899, 848, 752 cm^{-1}.

*3.3.8. 3-(4′-Biphenylil)-5-dichloromethyl-2-isoxazoline (**6h**).* Yield 72%; crystallisation from petroleum ether gave white prisms; mp 188–190 °C. Found C 62.87; H 4.35; N 4.55. $C_{16}H_{13}Cl_2NO$ requires C 62.76; H 4.28; N 4.57; ^{1}H NMR δ ($CDCl_3$, 300 MHz) 3.59 (dd, 1H, J=17.5, 9.9 Hz), 3.66 (dd, 1H, J=17.5, 7.1 Hz), 5.14 (ddd, 1H, J=9.9, 7.1, 4.2 Hz), 5.89 (d, 1H, J=4.2 Hz), 7.35–7.41 (m 1H), 7.47 (tt, 2H, J=8.7, 1.3 Hz), 7.59–7.68 (m, 4H), 7.77 (d, 2H, J=8.7 Hz); ^{13}C NMR δ ($CDCl_3$, 100.8 MHz) 37.12 (CH_2), 71.95 (CH), 83.78 (CH), 126.16 (CH), 127.30 (C), 127.43 (CH), 127.56 (CH), 128.04 (CH), 129.02 (CH), 140.09 (C), 143.47 (C), 156.07 (C=N); MS, m/z (%) 307 (M^++2, 37), 305 (M^+, 57), 270 (1), 222 (93), 194 (66), 179 (23), 167 (75), 152 (100), 139 (9), 127 (14), 97 (10), 83 (10), 75 (21), 51 (11); IR (Nujol) 1601, 1487, 1409, 1254, 1228, 1077, 951, 896, 845, 767, 693 cm^{-1}.

3.4. X-ray structure determination of compound 6f

Crystal data: $C_{11}H_{11}Cl_2NO_2$, M_r=260.11, orthorhombic, space group *bca*, a=7.9158(4), b=19.9817(9), c=30.1266(14) Å, U=4526.7(14) Å^3 at −173 °C; Z=16, D_x=1.527 g cm^{-3}, F (000)=2144, μ=0.56 mm^{-1}. *Data collection*: A colourless block 0.34×0.21×0.14 mm^3 was mounted in inert oil on a glass fibre and transferred to the cold gas stream of the diffractometer (Bruker SMART APEX CCD). Data were collected using monochromated Mo Kα radiation in w-scan. Absorption correction was applied on the basis of multi-scans (Program SADABS). Of 46,949 measured reflections, 4622 were unique (R_{int}=0.026) and were used for all calculations. *Structure refinement*: The structures were refined anisotropically against F^2 (program SHELXL-97).[50] The hydrogen atoms were refined using rigid methyl groups or a riding model. The final $wR2$ value was 0.092 for all reflections and 291 parameters, with $R1$ 0.0358 for reflections with $I>2\sigma(I)$; max. Δρ 0.72 e/Å^3, S 1.140.

Complete crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre under the number CCDC 815039. Copies may be requested free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, England (e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

X-ray structural data of compound **6f**; NMR spectra of compounds **5** and **6**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.05.110.

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