Reaction of β-Dimethylaminovinyl Ketones with Hydroxylamine: a Simple and Useful Method for Synthesis of 3- and 5-Substituted Isoxazoles

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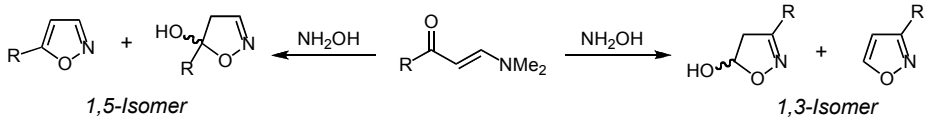

R = Ph, MeO-4-C_6H_4, F-4-C_6H_4, Cl-4-C_6H_4, Br-4-C_6H_4, O_2N-4-C_6H_4, fur-2-yl, thien-2-yl, pyrrol-2-yl, Et, CCl_3

The regioselective synthesis of 3- and 5-substituted-isoxazoles from the reaction of β-dimethylaminovinyl ketones [R-C(O)CH=CH-NMe_2, where R = Ph, MeO-4-C_6H_4, F-4-C_6H_4, Cl-4-C_6H_4, Br-4-C_6H_4, O_2N-4-C_6H_4, fur-2-yl, thien-2-yl, pyrrol-2-yl, Et and CCl_3] and hydroxylamine hydrochloride varying only the reaction conditions (with and without the addition of pyridine) is reported.

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INTRODUCTION

The synthesis of isoxazole and its derivatives has been a subject of continuous interest because of the numerous applications for such heterocycles in the pharmaceutical and agrochemical industry [1]. Recently, these compounds have been found to be an integral part of the selective inhibitors of the transglutaminase human 2 being thus important prototypes for treatment of Huntington's, Alzheimer's, and Parkinson's diseases [2]. Other pharmacological activities of this core involve the potent and selective antagonism of NMDA receptor [3], antagonism of the $GABA_A$ receptor, in the low nanomolar range, [4] and in vitro antiprotozoal activities [5].

Therefore, continuous efforts have been devoted to the development of more general, efficient, and regioselective methods for the synthesis of this class of compounds. The synthesis of isoxazoles is relatively well explored using the so-called [3+2] atom fragments, where β–diketones or α,β–unsaturated ketones are used as 3-atom building blocks, and hydroxylamine is the 2-atom fragment. However, the main limitation with these cyclocondensation reactions is the lack of regioselectivity of the obtained products [6-7]. The use of the unsymmetrical β-dicarbonyl compounds in the cyclocondensation reaction can lead to two possible isomers, and thus, the development of regioselective methods for the synthesis of heterocycle compounds became an important research area. In addition, the regioisomers 3- and 5-substituted-isoxazoles have shown different pharmacological activities in rodent parasite screen demonstrating still that these compounds possibly not acting at a common receptor site [8].

As part of our research program, we have reported the general synthesis of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones, a β-diketone derivative, and demonstrated their usefulness in the preparation of heterocycles by studying the regiochemistry of the ring closure [9]. These studies have shown that a determining factor in establishing the regiochemistry of the heterocyclic ring is the presence of the haloalkyl group (R) in the precursors, because of its great electronic effects, which change the electron-density distribution in the β-diketone derivatives, and consequently, the relative reactivity of the carbonyl group. However, data from the literature have shown that when the R moiety is not of haloalkyl group, the cyclocondensation reaction with hydroxylamine hydrochloride leads to a mixture of 5-substituted-isoxazoles (1,5-isomer) and 3-substituted-isoxazoles (1,3-isomer) (figure 1) [10-14]. In continuation of our work, we report here a practical and systematic methodology for preparation of a series of aryl-, heteroaryl-, -ethyl and trichloromethyl-3-substituted-isoxazoles and/or 5-substituted-isoxazoles from the reaction of β-dimethylaminovinyl ketones and hydroxylamine varying only the reaction conditions (with and without the addition of pyridine).

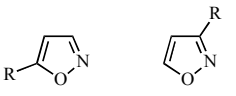
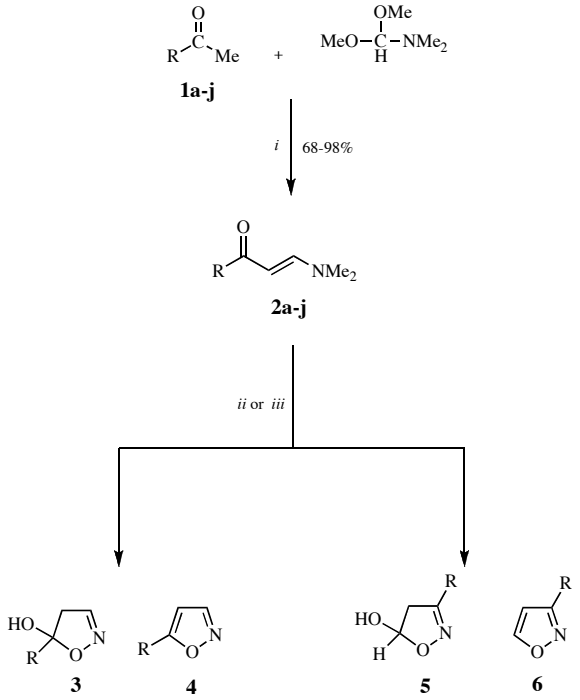


Figure 1

RESULTS AND DISCUSSION

Enaminones are versatile synthons for the synthesis of a variety of heterocycles, and their preparation has been recognized for some time. The convenient synthesis of β-dimethylaminovinyl ketones from the reaction of aryl ketones and formamide acetal has already been described [14-17]. Thus, the β-dimethylaminovinyl ketones **2** were prepared in good yields by the one-step reaction of substituted ketones, *N,N*-dimethylformamide dimethyl acetal and BF_3•OEt_2 in toluene under reflux for 24 hours (Scheme 1). The structures of **2a-j** were confirmed by NMR spectroscopy (^1H and ^{13}C) and MS spectra.

Scheme 1



i = BF_3•OEt_2, toluene, reflux, 24 hours
ii = NH_2OH•HCl, pyridine, ethanol, reflux, 16 hours
iii = NH_2OH•HCl, ethanol, reflux, 16 hours

1,2	a	b	c	d	e	f
R	Ph	MeO-4-C_6H_4	F-4-C_6H_4	Cl-4-C_6H_4	Br-4-C_6H_4	O_2N-4-C_6H_4

1,2	g	h	i	j	k
R	fur-2-yl	thien-2-yl	pyrrol-2-yl	Et	CCl_3

Considering that the reaction of 1,1,1-trihalo-4-alkoxy-3-alken-2-ones with hydroxylamine hydrochloride is usually carried out in the presence of pyridine [18,19], we used pyridine in ethanol under reflux for 16 hours in the preliminary investigation. The result obtained for precursors with R = Ph, Cl-4-C_6H_4, thien-2-yl was a mixture of the 3-substituted-4,5-dihydroisoxazoles **5** and 5-substituted-isoxazoles **4**. For precursors with R = MeO-4-C_6H_4, F-4-C_6H_4, Br-4-C_6H_4, Et a mixture of 3-substituted-isoxazoles **6** and 5-substituted-isoxazoles **4** was obtained. These isomeric mixture were easily separate by difference of solubility, the *1,5*-isomer had good solubility in $CHCl_3$ while the *1,3*-isomer, in agreement with the literature [8], did not show solubility in several organic solvents and thus could be easily isolated by filtration. The regioselectivity of the ring closure reaction was observed as follows: for R = O_2N-4-C_6H_4, fur-2-yl, 3-substituted-4,5-dihydro isoxazoles **5** were obtained; for R = pyrrol-2-yl, 5-substituted-isoxazole **4** was obtained, and for R = CCl_3, 5-substituted-4,5-dihydroisoxazoles **3** were obtained. From GC/MS data, the presence of compounds **6a** (R = Ph), **6b** (R = MeO-4-C_6H_4), **6c** (R = F-4-C_6H_4), **6d** (R = Cl-4-C_6H_4), **6e** (R = Br-4-C_6H_4), **6f** (R = O_2N-4-C_6H_4), **6g** (R = fur-2-yl), **6h** (R = thien-2-yl), **6j** (R = Et) in less than 8% yields, was also identified (Scheme 1). From these results, one can observe that the ring closure reaction is regioselective for some precursors (**2f**, **2g**, **2i**, **2k**). Thus, it was not possible to affirm that the regioselectivity depended on the structure of the R moiety in the cases studied.

In a second stage the reaction was carried out using the same reaction conditions, however, without the use of pyridine. Under this condition, a high regioselectivity of the ring closure reaction was observed. Regardless of the structure of the R moiety of the precursors, the cyclocondensation reaction was highly regioselective, furnishing preferentially 5-substituted-isoxazole **4**, in good yields (Scheme 1, Table 1). The structure of **4** was confirmed by X-ray diffraction (Figure 2) [20]. In both methodologies, the product obtained when R = CCl_3 was the 5-trichloromethyl-4,5-dihydroisoxazole, which is in full agreement with the literature [9]. This fact have been attributed to strong electron-withdrawing of the trichloromethyl group which stabilizes the hemi-acetal portion leading to formation of 5-trichloromethyl-4,5-dihydroisoxazole ring exclusively [9].

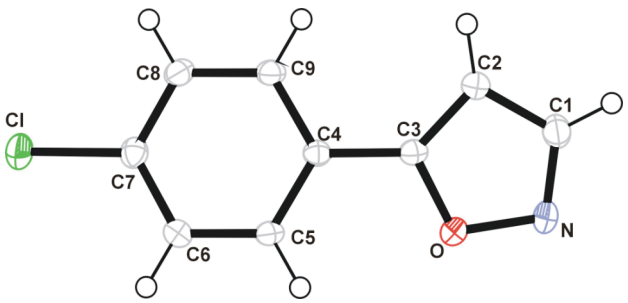


Figure 2. ORTEP of 5-(4-chlorophenyl)-isoxazole **4d**; reaction carried without the use of pyridine.

Table 1

Substituted-isoxazoles obtained from the reaction of β-dimethylaminovinyl ketones with hydroxylamine hydrochloride.

	With pyridine			Without pyridine	
R	Compound	Yield (%)[a]	R	Compound	Yield (%)[a]
Ph	**4a + 5a**	29 : 37	Ph	**4a**	76
MeO-4-C_6H_4	**4b + 6b**	57 : 11	MeO-4-C_6H_4	**4b**	76
F-4-C_6H_4	**4c + 6c**	54 : 9	F-4-C_6H_4	**4c**	70
Cl-4-C_6H_4	**4d + 5d**	17 : 44	Cl-4-C_6H_4	**4d**	81
Br-4-C_6H_4	**4e + 6e**	77 : 4	Br-4-C_6H_4	**4e**	77
O_2N-4-C_6H_4	**5f**	79	O_2N-4-C_6H_4	**4f**	67
Fur-2-yl	**5g**	82	Fur-2-yl	**4g**	53
Thien-2-yl	**4h + 5h**	30 : 35	Thien-2-yl	**4h**	65
Pyrrol-2-yl	**4i**	72	Pyrrol-2-yl	**4i**	74
Et	**4j + 6j**	49 : 8	Et	**4j**	52
CCl_3	**3k**	76	CCl_3	**3k**	81

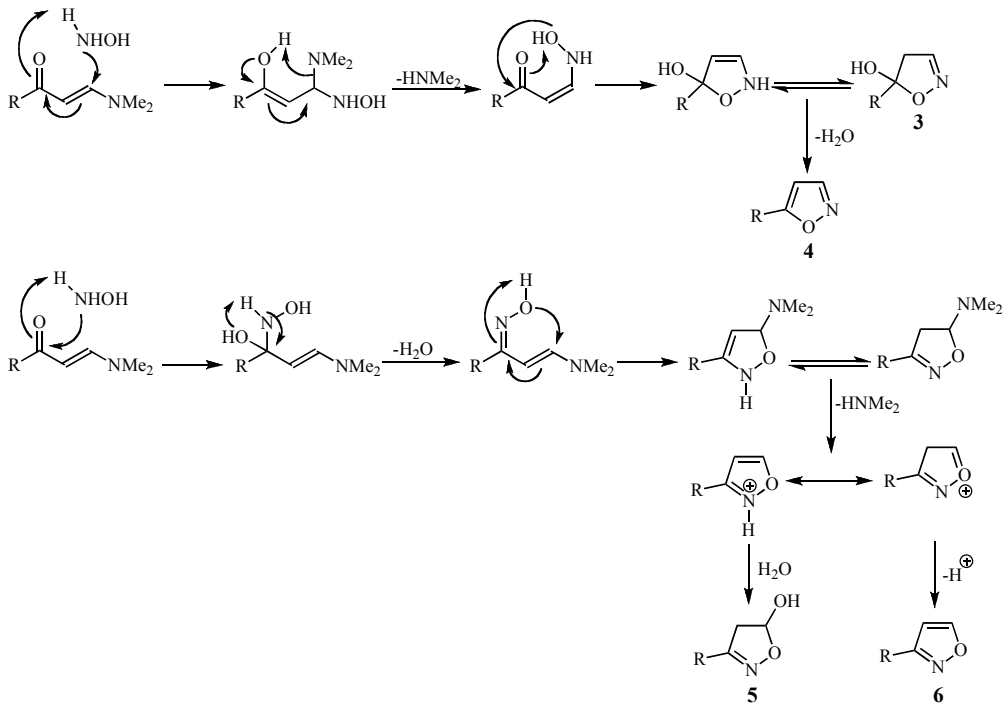
[a] Yield of isolated product or mixture of products.

The regioselectivity observed when the reaction was carried out without pyridine could be explained by the stronger reactivity of the C-β, which was increased as the concentration of HCl, coming from the hydroxylamine hydrochloride, increased.

The presence of HCl in the reaction protonated the carbonyl oxygen, which increased the reactivity of the C-β. As the attack was favored in the C-β, the addition of the NH_2 group on this carbon occurred first, followed by the addition of the OH group to the carbonyl carbon to give the 5-substituted-isoxazole **4** (Scheme 2). Although other methods have been reported for the regioselective synthesis of 5-substituted-isoxazole derivatives from enaminones, *e.g.* Molina's [21] and Lin's [22] methods, they have reported disadvantages, mainly due to their limited scope and the use of more reaction steps than the procedure here showed.

On the other hand, the use of the pyridine conduced to loss of regioselectivity in the reactions as a mixture of isoxazole derivatives were obtained, however, in some cases, this method showed high regioselectivity in the ring closure with the formation of the 3-substituted-isoxazole derivatives as majority product. This finding was obtained when the R = Ph, Cl-4-C_6H_4, O_2N-4-C_6H_4, fur-2-yl, thien-

Scheme 2



2-yl. Noteworthily, when the R = O_2N-4-C_6H_4 and fur-2-yl the products exhibited opposite regioselectivity conducing to formation of compounds **5f** and **5g** exclusively.

This control of the regiochemistry in the closure of isoxazole rings by varying the reaction conditions on the same precursors was later reported by Umada *et al*. [23] however, this report did not use an enaminone but a trifluoracetyl-β-diketone derivative of the 4-homo-adamantone as substrate. The synthesis of the 3-substituted-isoxazole derivatives have been scarcely literature reported, the few methods involve 1,3-dipolar cycloadditions [8,24], use of strong bases as BuLi [25], or the use of the reagents not readily available [26]. These few reports concerned with the synthesis of 3-substituted-isoxazoles do, to the best of our knowledge, of the great part of the 3-substituted-isoxazoles **5** and **6** compounds reported here at first time. The loss of regioselectivity in the reactions with pyridine could be due the C-β was not activated as the pyridine used in stoichiometric amount with the hydroxylamine hydrochloride trapped the hydrochloric acid forming the pyridine hydrochloride and free hydroxylamine which could then allow a nucleophilic attack on both electrophilic centers of the enaminone (carbonyl-carbon and C-β) (Scheme 2). Further investigations are necessary to clarify the effect of pyridine on these cyclocondensation reactions specially with regards to their capacity to control the regiochemistry of ring closure.

In summary, a concise and useful method for the regioselective synthesis of 5-substituted-isoxazoles and, for some substituents, 3-substituted-isoxazoles is described. The method is performed under mild conditions and without the use of expensive reagents or methods of separation. The regioisomers were easily separated by difference in their solubility in organic solvents. Our findings suggests that the increase of the acid medium seemed to play an important role in the regioisomeric formation of the isoxazoles from β-dimethylaminovinyl ketones and that the use of pyridine conduces an interesting result as in some case switching the regiochemistry of ring closure in the isoxazole derivatives.

EXPERIMENTAL

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Yields listed are of isolated compounds. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer (1H at 400.13 MHz and ^{13}C at 100.63 MHz) 298 K, digital resolution of ±0.01ppm, 0.5 *M* in $CDCl_3$ or DMSO-d_6, using TMS as an internal standard. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced by a Pentium PC. Crystallographic data was obtained on a Bruker Kappa APEX-II CCD 3 kW Sealed Tube System diffractometer. Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. IR spectra were obtained with a Bruker Tensor 27 spectrometer using films or KBr pellets of the compounds. The CHN elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer (Federal University of Rio Grande do Sul, UFRGS/ Brazil).

General Synthesis of β-dimethylaminovinyl ketones. A mixture of compound (**1**) (20 mmol), dimethylformamide dimethyl acetal (2.38 g, 24 mmol) and BF_3•OEt_2 (3 drops) in toluene (10 mL) was heated at 110°C for 24 hours. The mixture was then evaporated under reduced pressure to give a solid. The solid was washed with hexane and collected by filtration, and finally dried. The final products are solids.

(*E*)-3-Dimethylamino-1-phenyl-2-propen-1-one (**2a**). Yield 13.60 mmol (68%); mp 89-90 °C (from hexane); IR (KBr) 3454, 3010, 2807, 1639, 1584 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.90 (s, 3H, N-Me), 3.12 (s, 3H, N-Me), 5.71 (d, 1H, J = 12 Hz, H-2), 7.41-7.89 (m, 5H, Ph) 7.79 (d, 1H, J = 12 Hz, H-3); ^{13}C NMR (DMSO-d_6) δ 36.9 (N-Me), 44.3 (N-Me), 92.0 (C-2), 127.2, 127.9, 130.6, 140.3 (Ph), 154.0 (C-3), 188.3 (C-1); MS m/z (%) 175 (M+, 43), 158 (100), 143 (5), 131 (10), 98 (90). *Anal*. Calcd for $C_{11}H_{13}NO$: C 75.40; H, 7.48; N, 7.99. Found: C 75.22; H 7.19; N 7.70.

(*E*)-3-Dimethylamino-1-(4-methoxyphenyl)-2-propen-1-one (**2b**). Yield 16.20 mmol (81%); mp 85-87 °C (from hexane); IR (KBr) 3430, 3060, 2980, 1674, 1600 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.85 (s, 3H, O-Me), 2.89 (s, 3H, N-Me), 3.11 (s, 3H, N-Me), 5.71 (d, 1H, *J* = 12 Hz, H-2), 6.91 (d, 2H, Ph), 7.79 (d, 1H, *J* = 12 Hz, H-3), 7.90 (d, 2H, Ph); ^{13}C NMR (DMSO-d_6) δ 36.4 (N-Me), 44.0 (N-Me), 55.9 (O-Me), 91.3 (C-2), 114.2, 130.0, 133.1, 162.3 (Ph), 155.3 (C-3) 186.8 (C-1); MS *m/z* (%) 205 (M^+, 38), 188 (100), 162 (10), 135 (38), 98 (48). *Anal*. Calcd for $C_{12}H_{15}NO_2$: C 70.22; H 7.37; N 6.82. Found: C 70.09; H 7.11; N 6.71.

(*E*)-3-Dimethylamino-1-(4-fluorophenyl)-2-propen-1-one (**2c**). Yield 14.00 mmol (70%); mp 94-96 °C (from hexane); IR (KBr) 3418, 3070, 2926, 1644, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3H, N-Me), 3.12 (s, 3H, N-Me), 5.66 (d, 1H, *J* = 12 Hz, H-2), 7.07-7.91 (m, 4H, Ph), 7.79 (d, 1H, *J* = 12 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 37.0, (N-Me), 44.8 (N-Me), 91.3 (C-2), 114.7, 129.5, 136.5, 164.2 (Ph), 154.1 (C-3), 186.9 (C-1); MS *m/z* (%) 193 (M^+, 38), 176 (100), 161 (5), 149 (7), 123 (30), 109 (16), 98 (52). *Anal*. Calcd for $C_{11}H_{12}FNO$: C 68.38; H 6.26; N 7.25. Found: C 68.30; H 6.12; N 6.97.

(*E*)-3-Dimethylamino-1-(4-chlorophenyl)-2-propen-1-one (**2d**). Yield 16.00 mmol (80%); mp 85-87 °C (from hexane); IR (KBr) 3340, 3070, 2970, 1646, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.94 (s, 3H, N-Me), 3.14 (s, 3H, N-Me), 5.66 (d, 1H, *J* = 12 Hz, H-2), 7.37 (d, 2H, Ph), 7.79 (d, 1H, *J* = 12 Hz, H-3), 7.84 (d, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 36.5 (N-Me), 44.3 (N-Me), 90.8 (C-2), 127.5, 128.2, 136.0, 138.2 (Ph), 153.8 (C-3), 185.8 (C-1); MS *m/z* (%) 209 (M^+, 30), 192 (90), 174 (5), 157 (10), 139 (30), 98 (100). *Anal*. Calcd for $C_{11}H_{12}ClNO$: C 63.01; H 5.77; N 6.68. Found: C 62.68; H 5.61; N 6.28.

(*E*)-3-Dimethylamino-1-(4-bromophenyl)-2-propen-1-one (**2e**). Yield 14.40 mmol (72%); mp 70-72 °C (from hexane); IR (KBr) 3416, 2908, 2808, 1640, 1575; ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 3H, N-Me), 3.15 (s, 3H, N-Me), 5.65 (d, 1H, *J* = 12 Hz, H-2), 7.81 (d, 1H, *J* = 12 Hz, H-3), 7.53 (d, 2H, Ph), 7.76 (d, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 37.2 (N-Me), 44.9 (N-Me), 91.5 (C-2), 125.3, 129.0, 131.1, 139.1 (Ph) 154.4 (C-3), 187.0 (C-1); MS *m/z* (%) 253 (M^+, 37), 238 (100), 183 (19), 169 (9), 157 (34),

131 (11), 98 (97). *Anal.* Calcd for $C_{11}H_{12}BrNO$: C 51.99; H 4.76; N 5.51. Found: C 51.88; H 4.63; N 5.79.

(*E*)-3-Dimethylamino-1-(4-nitrophenyl)-2-propen-1-one (**2f**). Yield 19.60 mmol (98%); mp 139-141 °C (from hexane); IR (KBr) 3458, 2947, 2862, 1642, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (s, 3H, N-Me), 3.20 (s, 3H, N-Me), 5.68 (d, 1H, J = 12 Hz, H-2), 7.86 (d, 1H, J = 12 Hz, H-3), 8.01 (d, 2H, Ph), 8.25 (d, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 37.3 (N-Me), 45.1 (N-Me), 91.8 (C-2), 123.2, 128.2, 145.9, 148.8 (Ph), 155.1 (C-3), 185.8 (C-1); MS *m/z* (%) 220 (M^+, 30), 203 (92), 157 (15), 130 (6), 98 (100). *Anal.* Calcd for $C_{11}H_{12}N_2O_3$: C 60.00; H 5.49; N 12.72. Found: C 60.06; H 5.30; N 12.90.

(*E*)-3-Dimethylamino-1-(fur-2-yl)-2-propen-1-one (**2g**). Yield 14.80 mmol (74%); mp 84-86 °C (from hexane); IR (KBr) 3417, 2921, 2807, 1639, 1577 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (s, 3H, N-Me), 3.14 (s, 3H, N-Me), 5.68 (d, 1H, J = 12 Hz, H-2), 6.48 (dd, 1H, Furyl), 7.06 (d, 1H, Furyl), 7.49 (d, 1H, Furyl), 7.80 (d, 1H, J = 12 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 37.2 (N-Me), 44.9 (N-Me), 91.3 (C-2), 111.7, 113.2, 144.0, 154.6 (Furyl), 153.4 (C-3) 177.3 (C-1); MS *m/z* (%) 165 (M^+, 64), 150 (10), 136 (100), 120 (11), 98 (59). *Anal.* Calcd for $C_9H_{11}NO_2$: C 65.44; H 6.71; N 8.48. Found: C 65.15; H 6.38; N 8.10.

(*E*)-3-Dimethylamino-1-(thien-2-yl)-2-propen-1-one (**2h**). Yield 15.60 mmol (78%); mp 113-115 °C (from hexane); IR (KBr) 3453, 2998, 2804, 1636, 1546 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.83 (s, 3H, N-Me), 3.01 (s, 3H, N-Me), 5.60 (d, 1H, J = 12 Hz, H-2), 7.04 (dd, 1H, Thienyl), 7.44 (d, 1H, Thienyl), 7.60 (d, 1H, Thienyl), 7.71 (d, 1H, J = 12 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 36.5 (N-Me), 44.3 (N-Me), 90.9 (C-2), 127.1, 127.7, 129.6, 147.0 (Thienyl), 152.9 (C-3), 179.9 (C-1); MS *m/z* (%) 181 (M^+, 71), 164 (95), 148 (100), 131 (33), 111 (91), 98 (83). *Anal.* Calcd for $C_9H_{11}NOS$: C 59.64; H 6.12; N 7.73. Found: C 59.44; H 5.88; N 7.92.

(*E*)-3-Dimethylamino-1-(pyrrol-2-yl)-2-propen-1-one (**2i**). Yield 16.40 mmol (82%); mp 191-193 °C (from hexane); IR (KBr) 3391, 2931, 2802, 1627, 1524 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.94 (s, 6H, N-$(Me)_2$), 5.63 (d, 1H, J = 12 Hz, H-2), 6.10 (dd, 1H, Pyrrolyl), 6.78 (d, 1H, Pyrrolyl), 6.88 (d, 1H, Pyrrolyl), 7.58 (d, 1H, J = 12 Hz, H-3); ^{13}C NMR (DMSO-d_6) δ 37.0 (N-Me), 44.0 (N-Me), 91.3 (C-2), 108.8, 111.7, 122.0, 133.6 (Pyrrolyl), 151.7 (C-3), 177.7 (C-1); MS *m/z* (%) 164 (M^+, 100), 147 (43), 136 (4), 120 (10), 98 (30). *Anal.* Calcd for $C_9H_{12}N_2O$: C 65.83; H 7.37; N 17.06. Found: C 65.78; H 6.91; N 16.69.

(*E*)-5-Dimethylamino-4-peten-3-one (**2j**). Yield 16.40 mmol (82%); oil ; IR (KBr) 3422, 2,972, 1665, 1620, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (t, 3H, Me), 2.88 (s, 3H, N-Me), 2.27 (q, 2H, CH_2), 2.96 (s, 3H, N-Me), 5.00 (d, 1H, J = 12 Hz, H-2), 7.44 (d, 1H, J = 12 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 12.0 (Me), 28.5 (CH_2), 35.9 (N-Me), 42.1 (N-Me), 95.9 (C-4), 154.8 (C-5), 190.5 (C-3); MS *m/z* (%) 127 (M^+, 13), 98 (100), 70 (8), 55 (44). *Anal.* Calcd for $C_7H_{13}NO$: C 66.11; H 10.30; N 11.01. Found: C 66.04; H 10.35; N 11.22.

(E)-4-Dimethylamino-1,1,1-trichloro-3-buten-2-one (**2k**). Yield 13.60 mmol (68%); mp 47-49 °C (from hexane); IR (KBr) 3452, 2812, 1660, 1587 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97 (s, 3H, N-Me), 3.21 (s, 3H, N-Me), 5.59 (d, 1H, J = 12 Hz, H-2), 7.80 (d, 1H, J = 12 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 37.4 (N-Me), 45.4 (N-Me), 84.9 (C-2), 98.0 (CCl_3), 157.2 (C-3), 180.4 (C-1); MS *m/z* (%) 215 (M^+, 5), 152 (10), 98 (100). *Anal.* Calcd for $C_6H_8Cl_3NO$: C 33.29; H 3.72; N 6.47. Found: C 33.01; H 4.18; N 6.85.

General synthesis of isoxazoles using pyridine. A mixture of compound **2** (1 mmol), hydroxylamine hydrochloride (0.139 g, 2 mmol) and pyridine (0.158 g, 2 mmol) in ethanol (15 mL) was stirred for 16 hours at 78°C. After completion of the reaction, the ethanol was evaporated on a rotary evaporator and the residue was diluted with $CHCl_3$ (15 mL). Because of the poor solubility in $CHCl_3$ of the compounds assigned as 1,3-isomers, these were collected by filtration. The organic layer was them washed with water (3×30 mL), dried over magnesium sulfate and the solvent evaporated on a rotary evaporator to afforded the compounds assignment as 1,5-isomers. When necessary, both 1,3- and 1,5-isomers were purified by recrystallization from hot hexane.

General synthesis of isoxazoles without use of pyridine. A mixture of compound **2** (1 mmol) and hydroxylamine hydrochloride (0.139 g, 2 mmol) in ethanol (15 mL) was stirred for 16 hours at 78°C. After completion of the reaction, the ethanol was evaporated on a rotary evaporator and the residue was extracted with $CHCl_3$, washed with water (3×30 mL), dried over magnesium sulfate and again the solvent evaporated on a rotatory evaporator. The residue was then purified by recrystallization from hot hexane, affording the pure 5-substituted-isoxazoles.

5-Phenylisoxazole (**4a**). Oil; IR (film) 3063, 1615, 1590, 1459, 764, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (d, 1H, J = 1.7 Hz, H-4), 7.41-7.76 (m, 5H, Ph), 8.25 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 98.5 (C-4), 125.6, 127.1, 128.8, 130.0 (Ph), 150.6 (C-3), 169.1 (C-5); MS *m/z* (%) 145 (M^+, 100), 105 (75), 90 (15), 77 (61). *Anal.* Calcd for C_9H_7NO: C 74.47; H 4.86; N 9.65. Found: C 74.08; H 4.84; N 9.60.

3-Phenyl-5-hydroxy-4,5-dihydroisoxazole (**5a**). mp 120-121 °C (from hexane); IR (KBr) 3413, 3046, 1446, 1364, 766, 692 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.48 (dd, 1H, $J_{Ha\text{-}Hb}$ = 17 Hz, $J_{Ha\text{-}H5}$ = 5 Hz, Ha-4), 3.50 (dd, 1H, $J_{Hb\text{-}Ha}$ = 17 Hz, $J_{Hb\text{-}H5}$ = 9 Hz, Hb-4), 5.81 (dd, 1H, $J_{H5\text{-}Ha}$ = 5 Hz, $J_{H5\text{-}Hb}$ = 9 Hz, H-5), 7.53-7.66 (m, 5H, Ph); ^{13}C NMR (DMSO-d_6) δ 35.9 (C-4), 93.1 (C-5), 129.3, 129.8, 130.0, 130.2 (Ph), 156.2 (C-3); MS *m/z* (%) 145 (M^+, -H_2O, 76), 119 (10), 105 (58), 77 (100). *Anal.* Calcd for $C_9H_9NO_2$: C 66.25; H 5.56; N 8.58. Found: C 65.88; H 5.52; N 8.57.

3-Phenylisoxazole (**6a**). (compound not isolated) MS *m/z* (%) 145 (M^+, 96), 144 (100), 116 (24), 103 (8), 89 (27), 77 (84).

5-(4-Methoxyphenyl)isoxazole (**4b**). mp 61-63 °C (from hexane); IR (KBr) 3007, 2938, 2840, 1615, 1595, 1463, 832, 731, 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H, O-Me), 6.36 (d, 1H, J = 1.7 Hz, H-4), 6.93 (d, 2H, Ph), 7.68 (d, 2H, Ph), 8.22 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 55.1 (O-Me), 97.1 (C-4), 114.2, 119.9, 127.2, 160.9 (Ph), 150.6 (C-3), 169.1 (C-5); MS *m/z* (%) 175 (M^+, 100), 160 (12), 135 (61), 92 (52), 77 (66). *Anal.* Calcd for $C_{10}H_9NO_2$: C 68.56; H 5.18; N 8.00. Found: C 68.19; H 5.15; N 7.93.

3-(4-Methoxy phenyl)isoxazole (**6b**). (compound not isolated) MS *m/z* (%) 175 (M^+, 100), 160 (22), 146 (49), 132 (86), 77 (61), 63 (77).

5-(4-Fluorophenyl)isoxazole (**4c**). mp 51-53 °C (from hexane); IR (KBr) 3120, 3091, 1614, 1598, 1462, 915, 804 cm^{-1}; ^1H NMR ($CDCl_3$) □6.45 (d, 1H, J = 1.7 Hz, H-4), 7.12-7.74 (m, 4H, Ph), 8.26 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 98.3 (C-4), 115.9, 123.5, 127.7, 163.5 (Ph), 150.7 (C-3), 168.1 (C-5); MS *m/z* (%) 163 (M^+, 100), 123 (86), 95 (65), 75 (38). *Anal.* Calcd for C_9H_6FNO: C 66.26; H 3.71; N 8.59. Found: C 65.91; H 3.69; N 8.52.

3-(4-Fluorophenyl) isoxazole (**6c**). (compound not isolated) MS *m/z* (%) 163 (M^+, 8), 162 (7), 153 (82), 136 (23), 121 (36), 107 (7), 95 (100), 75 (38), 68 (9).

5-(4-Chlorophenyl)isoxazole (**4d**). mp 82-84 °C (from hexane); IR (KBr) 3128, 1609, 1491, 1458, 833, 803 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (d, 1H, J = 1.7 Hz, H-4), 7.41 (d, 2H, Ph), 7.70 (d, 2H, Ph), 8.28 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 98.9 (C-4), 125.6, 127.0, 129.1, 136,1 (Ph), 150.7 (C-3), 168.1 (C-5); MS *m/z* (%) 179 (M^+, 100), 139 (94), 111 (57), 89 (28), 75 (38). *Anal*. Calcd for C_9H_6ClNO: C 60.19; H 3.37; N 7.80. Found: C 59.86; H 3.35; N 7.76.

3-(4-Chlorophenyl)-5-hydroxy-4,5-dihydroisoxazole (**5d**). mp 76-48 °C (from hexane); IR (KBr) 3395, 2924, 1598, 1497, 826 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.42 (dd, 1H, $J_{Ha\text{-}Hb}$ = 17 Hz, $J_{Ha\text{-}H5}$ = 5 Hz, Ha-4), 3.50 (dd, 1H, $J_{Hb\text{-}Ha}$ = 17 Hz, $J_{Hb\text{-}H5}$ = 9 Hz, Hb-4), 5.83 (dd, 1H, $J_{H5\text{-}Ha}$ = 5 Hz, $J_{H5\text{-}Hb}$ = 9 Hz, H-5), 7.51 (d, 2H, Ph), 7.67 (d, 2H, Ph); ^{13}C NMR (DMSO-d_6) δ 35.7 (C-4), 93.4 (C-5), 128.0, 128.8, 129.2, 134.4 (Ph), 155.4 (C-3); MS *m/z* (%) 179 (M^+, -H_2O, 98), 139 (77), 111 (81), 75 (100). *Anal*. Calcd for $C_9H_8ClNO_2$: C 54.70; H 4.08; N 7.09. Found: C 54.31; H 4.05; N 7.02.

3-(4-Chlorophenyl) isoxazole (**6d**). (compound not isolated) MS *m/z* (%) 179 (M^+, 100), 178 (99), 150 (32), 137 (10), 123 (17), 111 (47), 89 (30), 75 (59).

5-(4-Bromophenyl)isoxazole (**4e**). mp 114-115 °C (from hexane); IR (KBr) 3127, 1606, 1489, 1402, 803, 494 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52 (d, 1H, J = 1.7 Hz, H-4), 7.63 (m, 4H, Ph), 8.29 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 99.0 (C-4), 124.4, 126.0, 127.1, 132.1 (Ph), 150.7 (C-3), 168.1 (C-5); MS *m/z* (%) 223 (M^+, 100), 183 (77), 155 (41), 89 (43), 75 (36). *Anal*. Calcd for C_9H_6BrNO: C 48.25; H 2.70; N 6.25. Found: C 47.90; H 2.65; N 6.19.

3-(4-Bromo phenyl)isoxazole (**6e**). (compound not isolated) MS *m/z* (%) 223 (M^+, 100), 213 (39), 196 (34), 184 (33), 155 (70), 116 (42), 102 (50), 89 (57), 75 (98).

5-(4-Nitrophenyl)isoxazole (**4f**). mp 163-165 °C (from hexane); IR (KBr) 3105, 1605, 1577, 1517, 1334, 852, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (d, 1H, J = 1.7 Hz, H-4), 7.98 (d, 2H, Ph), 8.35 (d, 2H, Ph), 8.38 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 101.3 (C-4), 124.4, 126.6, 132.6, 148.5 (Ph), 151.0 (C-3), 168.8 (C-5); MS *m/z* (%) 190 (M^+, 100), 160 (25), 150 (30), 104 (29), 89 (76). *Anal*. Calcd for $C_9H_6N_2O_3$: C 56.85; H 3.18; N 14.73. Found: C 56.46; H 3.17; N 14.63.

3-(4-Nitrophenyl)-5-hydroxy-4,5-dihydroisoxazole (**5f**). mp 136-137 °C (from hexane); IR (KBr) 3522, 3089, 1598, 1582, 1516, 1343, 854, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.50 (dd, 1H, $J_{Ha\text{-}Hb}$ = 17 Hz, $J_{Ha\text{-}H5}$ = 5 Hz, Ha-4), 3.56 (dd, 1H, $J_{Hb\text{-}Ha}$ = 17 Hz, $J_{Hb\text{-}H5}$ = 9 Hz, Hb-4), 5.96 (dd, 1H, $J_{H5\text{-}Ha}$ = 5 Hz, $J_{H5\text{-}Hb}$ = 9 Hz, H-5), 7.92 (d, 2H, Ph), 8.28 (d, 2H, Ph); ^{13}C NMR (DMSO-d_6) δ 35.2 (C-4), 94.3 (C-5), 123.9, 127.4, 135.3, 147.8 (Ph), 155.4 (C-3); MS *m/z* (%) 190 (M^+, -H_2O, 82), 160 (8), 143 (27), 116 (16), 89 (100). *Anal*. Calcd for $C_9H_8N_2O_4$: C 51.93; H 3.87; N 13.46. Found: C 51.63; H 3.84; N 13.37.

3-(4-Nitrophenyl) isoxazole (**6f**). (compound not isolated) MS *m/z* (%) 190 (M^+, 100), 189 (86), 174 (8), 160 (9), 143(21), 132 (7), 116 (12), 89 (67), 76 (26).

5-(Fur-2-yl)isoxazole (**4g**). oil; IR (film) 3133, 1670, 1641, 1195, 1012, 789 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.44 (d, 1H, J = 1.7 Hz, H-4), 6.52 (dd, 1H, Furyl), 6.90 (d, 1H, Furyl), 7.53 (d, 1H, Furyl), 8.26 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 98.1 (C-4), 110.3, 111.7, 143.0, 143.9 (Furyl), 150.2 (C-3), 160,9 (C-5); MS *m/z* (%) 135 (M^+, 100), 95 (81), 68 (9,7). *Anal*. Calcd for $C_7H_5NO_2$: C 62.23; H 3.73; N 10.37. Found: C 61.90; H 3.69; N 10.28.

3-(Fur-2-yl)-5-hydroxy-4,5-dihydroisoxazole (**5g**). mp 157-159 °C (from hexane); IR (KBr) 3286, 2916, 1598, 1493, 893 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.38 (dd, 1H, $J_{Ha\text{-}Hb}$ = 17 Hz, $J_{Ha\text{-}H5}$ = 5 Hz, Ha-4), 3.40 (dd, 1H, $J_{Hb\text{-}Ha}$ = 17 Hz, $J_{Hb\text{-}H5}$ = 9 Hz, Hb-4), 5.68 (dd, 1H, $J_{H5\text{-}Ha}$ = 5 Hz, $J_{H5\text{-}Hb}$ = 9 Hz, H-5), 6.47 (dd, 1H, Furyl), 6.73 (d, 1H, Furyl), 7.49 (d, 1H, Furyl); ^{13}C NMR (DMSO-d_6) δ 35.8 (C-4), 92.7 (C-5), 111.8, 112.4, 144.2, 144.9 (Ph), 148.3 (C-3); MS *m/z* (%) 135 (M^+, -H_2O, 100), 95 (55), 68 (21), 52 (77). *Anal*. Calcd for $C_7H_7NO_3$: C 54.91; H 4.61; N 9.15. Found: C 54.66; H 4.59; N 9.09.

3-(Fur-2-yl)isoxazole (**6g**). (compound not isolated) MS *m/z* (%) 135 (M^+, 100), 107 (46), 93 (5), 78 (23), 68 (4).

5-(Thien-2-yl)isoxazole (**4h**). oil; IR (film) 3109, 1611, 1592, 1467, 708 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.37 (d, 1H, , J = 1.7 Hz, H-4), 7.09 (dd, 1H, Thienyl), 7.42 (d, 1H, Thienyl), 7.49 (d, 1H, Thienyl), 8.23 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 98.2 (C-4), 126.8, 127.8, 127.9, 140.3 (Ph), 150.5 (C-3), 164.1 (C-5); MS *m/z* (%) 151 (M^+, 100), 111 (98), 96 (34), 69 (12). *Anal*. Calcd for C_7H_5NOS: C 55.61, H 3.33; N 9.26. Found: C 55.37; H 3.30; N 9.21.

3-(Thien-2-yl)-5-hydroxy-4,5-dihydroisoxazole (**5h**). mp 133-135 °C (from hexane); IR (KBr) 3261, 3099, 1612, 1467, 1352, 713 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.46 (dd, 1H, $J_{Ha\text{-}Hb}$ = 17 Hz, $J_{Ha\text{-}H5}$ = 5 Hz, Ha-4), 3.49 (dd, 1H, $J_{Hb\text{-}Ha}$ = 17 Hz, $J_{Hb\text{-}H5}$ = 9 Hz, Hb-4), 5.80 (dd, 1H, $J_{H5\text{-}Ha}$ = 5 Hz, $J_{H5\text{-}Hb}$ = 9 Hz, H-5), 7.13 (dd, 1H, Thienyl), 7.38 (d, 1H, Thienyl), 7.65 (d, 1H, Thienyl); ^{13}C NMR (DMSO-d_6) δ 36.5 (C-4), 93.3 (C-5), 127.6, 128.5, 129.3, 131.3 (Thienyl), 152.2 (C-3); MS *m/z* (%) 151 (M^+, -H_2O, 100), 131 (14), 111 (53), 96 (48), 69 (43). *Anal*. Calcd for $C_7H_7NO_2S$: C 49.69; H 4.17; N 8.28. Found: C 49.33; H 4.14; N 8.22.

3-(Thien-2-yl)isoxazole (**6h**). (compound not isolated) MS *m/z* (%) 151 (M^+, 100), 122 (42), 109 (4), 96 (4), 69 (22).

5-(Pyrrol-2-yl)isoxazole (**4i**). mp 88-90 °C (from hexane); IR (KBr) 2936, 1623, 1535, 1474, 865, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.23 (d, 1H, J = 1.7 Hz, H-4), 6.30 (dd, 1H, Pyrrolyl), 6.67 (d, 1H, Pyrrolyl), 6.92 (d, 1H, Pyrrolyl), 8.20 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 95.7 (C-4), 109.9, 110.3, 120.0, 121.1 (Pyrrolyl), 150.6 (C-3), 163.1 (C-5); MS *m/z* (%) 134 (M^+, 100), 94 (67), 79 (38), 66 (36). *Anal*. Calcd for $C_7H_6N_2O$: C 62.68; H 4.51; N 20.88. Found: C 62.32; H 4.47; N 20.77.

5-Ethylisoxazole (**4j**). oil; IR (film) 2960, 1684, 1595, 1469, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, Me), 2.73 (q, 2H, CH_2), 5.97 (d, 1H, J = 1.7 Hz, H-4), 8.04 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 12.7 (Me), 27.4 (CH_2), 93.2 (C-4), 148.9 (C-3), 184.5 (C-5); MS *m/z* (%) 97 (M^+, 76), 68 (100), 55 (27); *Anal*. Calcd for C_5H_7NO: C 61.84, H 7.27, N 14.42. Found: C 61.62; H 7.24; N 14.37.

3-Ethylisoxazole (**6j**). (compound not isolated) MS *m/z* (%) 97 (M^+, 72), 82 (18), 54 (100).

5-Trichloromethyl-5-hydroxy-4,5-dihydroisoxazole (**3k**). mp 100-102 °C (from hexane); IR (KBr) 3326, 2846, 1623, 1296, 1081, 845, 797 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (dd, 1H, $J_{Ha\text{-}Hb}$ = 17 Hz, $J_{Ha\text{-}H3}$ = 1.7 Hz, Ha-4), 3.68 (dd, 1H, $J_{Hb\text{-}Ha}$ = 17 Hz, $J_{Hb\text{-}H3}$ = 1.7 Hz, Hb-4), 7.32 (d, 1H, J = 1.7 Hz, H-3); ^{13}C NMR ($CDCl_3$) δ 44.8 (C-4), 100.8 (CCl_3), 109.6 (C-5), 147.2 (C-3); MS *m/z* (%) 186 (MH^+, - H_2O, 1), 86 (100), 68 (34). *Anal*. Calcd for $C_4H_4Cl_3NO_2$: C 23.50; H 1.97; N 6.85. Found: C 23.23; H 1.93; N 6.77.

The presence of compounds **6a-h,j** was detected only by mass spectrometry. Because their low yields, these compounds were not isolated and characterized by others analyses methods.

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