One-pot synthesis of isoxazolines and isoxazoles using soluble polymer-supported aldehyde

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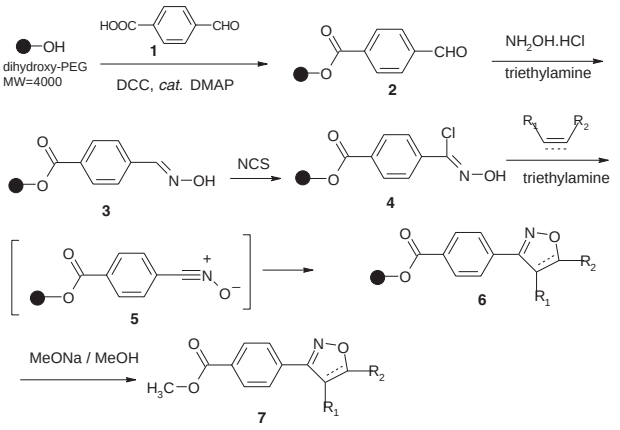
Liquid-phase synthesis of isoxazoles and isoxazolines through a 1,3-dipolar of nitrile oxides is described. Soluble polymer-supported nitrile oxides generated *in situ* react with dipolarophiles to afford isoxazoles and isoxazolines in good yields and purity.

Keywords: liquid-phase synthesis, isoxazol(in)es, 1,3-dipolar cycloaddition

The development of combinatorial chemistry has allowed for a rapid expansion in the number of compound libraries for the investigation of biological activity. Solid-supported organic synthesis has been widely used recently for the synthesis of small organic molecules and non-peptide peptidomimetics.[1] However, emerging problems associated with the heterogeneous nature of the ensuing chemistry and with 'on-bead' spectroscopic characterisation has meant that soluble polymers are being developed as alternative matrices for combinatorial library production[2] and organic synthesis.[3] We performed our reactions on the soluble polymer support[4] poly (ethylene glycol) 4000 (PEG). This polymer is soluble in many solvents, *e.g.*, THF, CH_2Cl_2, or H_2O at room temperature, but can be precipitated and thus purified by addition a solution of diethyl ether, hexane, or 2-propanol.[5] Soluble polymers have several advantages over polystyrene-derived resins. Reactions of soluble polymer bound and the corresponding non polymer-bound substrates generally show the same kinetics, insoluble byproducts or reagents can easily be separated from the polymer solution by filtration and the polymer is significantly less expensive than polystyrene-resins. Furthermore, each reaction can be easily monitored by solution phase ^{1}H NMR of a polymer sample in $CDCl_3$. Hegedus described the use of MeOPEG in a two-phase reaction as advantageous compared to the use of Merrifield resin.[6] Kahn and Blaskovich have successfully demonstrated the optimisation of a multistep sequence using MeOPEG bound substrates.[7]

Isoxazoles and isoxazolines are versatile scaffolds for the synthesis of a wide variety of complex natural products and important pharmacophores in medicinal chemistry.[8] Solution methods for their preparation *via* 1,3-dipolar cycloaddition[9] of an alkyne with a nitrile oxide is well documented. The solid-phase synthesis of isoxazoles has been described earlier using either polymer-supported nitrile oxide precursors[10] or polymer-supported alkynes.[11] In our previous paper,[12] we have described the liquid-phase synthesis of isoxazoles and isoxazolines by trapping the *in situ* generated nitrile oxide with the polymer-supported alkyne. Herein we disclose a practical and efficient liquid-phase synthesis of isoxazoles and isoxazolines using soluble polymer supported nitrile oxides.

As shown in Scheme 1, the aldehyde was attached onto the soluble support by condensation of dihydroxy-PEG_{4000} (MW=4000g/mol) with 4-formyl benzoic acid **1** in the presence of DCC and DMAP. The loading was complete after 12 h at room temperature as determined (~100%) by ^{1}H NMR spectroscopy. After precipitation of the polymeric aldehyde in diethyl ester and recrystallisation from cold ethanol, the aldehyde resin **2** was converted to aldoxime **3** by treating with excess hydroxylamine hydrochloride in the presence of trithylamine in CH_2Cl_2 at room temperature. The reaction



Scheme 1

went to completion over night and gave a high yield of the corresponding aldoxime resin **3**. After precipitation in diethyl ester and recrystallisation from cold ethanol, the aldoxime resin **3** was chlorinated with 2 equiv. N-chlorosuccinimide (NCS) in methylene chloride for 1 h to provide chloro oxime **4**, which is a precursor to the nitrile oxide **5**. To this was added a 4 equiv. of dipolaraphile (olefin/alkyne) as a methylene chloride solution before generating the nitrile oxide **5** by slow addition of 4 equiv. triethylamine over a period of 2 h. The resulting mixture was stirred at room temperature overnight. The resin was precipitated in diethyl ester, washed by 2-propanol and diethyl ester, the isoxazole or isoxazoline **7** was cleaved off the resin **6** under standard conditions sodium methoxide.

Trapping *in situ* generated nitrile oxides with appropriate olefins or acetylenes in a practical and efficient one-pot operation thus generated a library of isoxazoles and isoxazolines. As shown in Table 1, the yields were satisfactory (85–92%), and the purity of recovered compounds after cleavage was greater than 95%, as shown in Table 1.

In summary, a facile method for the synthesis of isoxazoles and isoxazolines has been developed. The liquid-phase 1,3-dipoar cycloaddition reaction is useful for building a library of isoxazoles and isoxazolines for pharmaceutical drug discovery.

Experimental

All chemicals and resin were obtained from commercial suppliers and used without further purification. IR spectra were recorded on a Perkin-Elmer 983 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Bruker Avance DMX 500 instrument. GC–MS analyses were performed on a HP-5973 spectrometer. Elemental analyses were carried out on an EA-1110 elemental analyzer.

Yields and purity determination of PEG-supported compounds: The yields of the PEG-supported compounds were determined by weight with the assumption that MW is 4000 Da for the PEG

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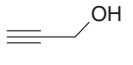
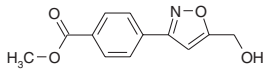
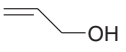
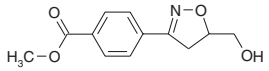
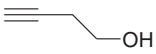
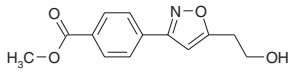
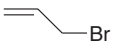
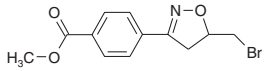
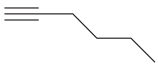
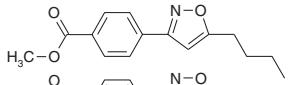
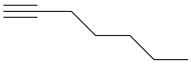
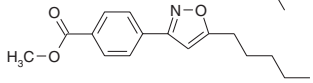
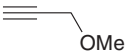
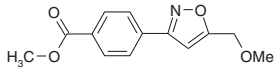
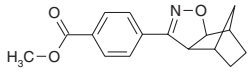
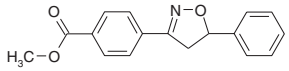
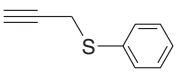
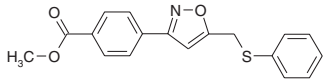
Table 1 Liquid-phase synthesis of isoxazoles and isoxazolines

Entry	alkyne/alkene	Isoxazole	Yield/%[a]	Purity/%[b]
a			91	99
b			86	100
c			85	98
d			89	100
e			87	96
f			88	99
g			89	97
h			89	96
i			92	100
j			90	95

[a]Yields by gravimetric analysis based on isolated material following cleavage from support. [b]Purities based on GC/MS analysis of cleaved samples. GC/MS purity was consistent with purity by ^{1}H NMR.

fragment. The MW actually ranged from 3500 to 4500. The indicated yields were for pure compounds. The purity of these compounds was determined by ^{1}H NMR analysis in $CDCl_3$ at 500 MHz (with pre-saturation of the CH_2 signals of the polymer), exploiting the PEGOCO–CH_2CH_2–CO_2R signal at σ= 4.25ppm as internal standard. The estimated integration error is ±7%.

General procedure for the synthesis of polymer-supported aldehyde **2**: To a solution of HO–PEG–OH (20.00 g, 5.00 mmol) in dichloromethane (100 ml) were added 4-formyl benzoic acid **1** (3.0g.20.00mmol), DCC (2.06g, 10.00mmol) and a catalytic amount of DMAP, and the mixture was stirred at r.t. for 16 h. The polymer was precipitated by addition of diethyl ether (1.5 l). For completion of the precipitation, the suspension was left at 0 °C for another 30 min. The polymer was filtered, rinsed with 0.5 l of diethyl ether, and dried for 5 h at 0.5 torr *in vacuo*. Thus, the polymer-supported aldehyde was obtained as a colourless powder: TLC (EtOAc–hexane, 1:2) showed that the solid did not contain free 4-formyl benzoic acid.

^{1}H NMR (500MHz, $CDCl_3$): δ 10.11(s, 1H, –C**H**O), 8.22 (d, 2H, Ar**H**), 7.95 (d, 2H, A**rH**), 4.48(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78 (m, PEG) ppm.

General procedure for the synthesis of polymer-supported oxime **3**: Hydroxylamine hydrochloride (1.34g, 20.00mmol) and triethylamine (2.8ml, 20.00mmol) were added to polymer-supported aldehyde **2** (20.00 g, 5.00 mmol) in dichloromethane. The mixture was stirred at room temperature over night. The precipitate was removed by filtration and the filtrate was diluted with Et_2O. The precipitate was collected, washed with Et_2O and dried affording the polymer-supported oxime.

^{1}H NMR (500MHz, $CDCl_3$): δ 8.13 (s, 1H, –C**H**=N), 8.05 (d, 2H, Ar**H**), 7.64 (d, 2H, A**rH**), 4.48 (t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78 (m, PEG) ppm.

General procedure for the synthesis of polymer-supported isoxazol(in)es **6a-6j**: To a solution of N-chlorosuccinimide (267 mg, 2 mmol) in CH_2Cl_2 (5 ml) was added the polymer-supported oxime **3** (0.5 mmol). The mixture stirred at 30°C for *ca* 30 min. After the chlorination was over, dipolarophile (olefin/alkyne) (0.5mmol) was added in one portion. The reaction mixture was stirred at r.t. for *ca* 30 min, and then Et_3N (0.14 ml) in CH_2Cl_2 (2 ml) was added dropwise over *ca* 2 h and the mixture was stirred overnight at r.t. Then, a five-fold excess of anhydrous benzene was added to remove the triethylamine hydrochloride formed. The mixture was filtered and the filtrate was concentrated. Addition of Et_2O to the residue precipitated the resin, which was then filtered and washed with Et_2O to afford the polymer-supported isoxazol(in)es **6a**–**j**.

6a: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.14 (d, 2H, Ar**H**), 7.89 (d, 2H, A**rH**), 6.61 (s, 1H, C=C**H**), 4.84 (s, 2H, C**H**$_2$), 4.48(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG) ppm.

6b: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.04 (d, 2H, Ar**H**), 7.70 (d, 2H, A**rH**), 4.92 (m, 1H), 4.45(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG), 3.40(dd, 1H, C**H**$_2$), 3.34(dd, 1H, C**H**$_2$) ppm.

6c: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.13 (d, 2H, Ar**H**), 7.88 (d, 2H, A**rH**), 6.52 (s, 1H, C=C**H**), 4.50(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 4.04 (t, 2H, C**H**$_2$), 3.50–3.78(m, PEG), 3.11 (t, 2H, C**H**$_2$) ppm.

6d: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.08 (d, 2H, Ar**H**), 7.73 (d, 2H, A**rH**), 5.08 (m, 1H), 4.48(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG), 3.42(dd, 1H, C**H**$_2$), 3.32(dd, 1H, C**H**$_2$) ppm.

6e: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.12 (d, 2H, Ar**H**), 7.87 (d, 2H, A**rH**), 6.35(s, 1H, C=C**H**), 4.49(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78 (m, PEG), 2.82(t, 2H, C**H**$_2$CH$_2$), 1.74(m, 2H, CH$_2$C**H**$_2$CH$_2$), 1.44(m, 2H, CH$_2$C**H**$_2$CH$_2$), 0.97(s, 3H, C**H**$_3$) ppm.

6f: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.13 (d, 2H, Ar**H**), 7.87 (d, 2H, A**rH**), 6.34 (s, 1H, C=C**H**), 4.48(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG), 2.81(t, 2H, C**H**$_2$CH$_2$), 1.76(m, 2H, CH$_2$C**H**$_2$CH$_2$), 1.38(m, 4H, CH$_2$C**H**$_2$C**H**$_2$CH$_2$), 0.92(s, 3H, C**H**$_3$) ppm.

6g: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.14 (d, 2H, Ar**H**), 7.88 (d, 2H, A**rH**), 6.62(s, 1H, C=C**H**), 4.62(s, 2H,C**H**$_2$), 4.49(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG), 3.48(s, 3H, OC**H**$_3$) ppm.

6h: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.07 (d, 2H, Ar**H**), 7.76 (d, 2H, A**rH**), 4.68 (d, 1H, C**H**), 4.48(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG), 3.48 (d, 1H, C**H**), 2.68(m, 1H, C**H**), 2.51(m, 1H, C**H**), 1.60(m, 2H, CH$_2$C**H**$_2$), 1.38–1.49(m, 2H, C**H**$_2$), 1.20(m, 2H, CH$_2$C**H**$_2$) ppm.

6i: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.08 (d, 2H, Ar**H**), 7.77 (d, 2H, A**rH**), 7.39(m, 5H, Ar**H**), 5.79 (m, 1H, C**H**), 4.48(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 3.50–3.78(m, PEG), 3.79(dd, 1H, CHC**H**$_2$), 3.39(dd, 1H, CHC**H**$_2$) ppm.

6j: ^{1}H NMR (500MHz, $CDCl_3$): δ 8.09 (d, 2H, Ar**H**), 7.81 (d, 2H, A**rH**), 7.31–7.35(m, 5H, Ar**H**), 6.41 (s, 1H, C=C**H**), 4.50(t, 2H, –PEGOCH$_2$C**H**$_2$OCO), 4.20(s, 2H, CH$_2$), 3.50–3.78(m, PEG) ppm.

General procedure for the synthesis isoxazol(in)es **7a–7j**: The cleavage of the PEG support was accomplished by treating **6a–6j** with 5% MeONa in methanol at room temperature and monitored for the disappearance of the polymeric oxadiazolines by TLC. Water and Et_2O was added to the reaction mixture and the organic phase was separated. Removal of Et_2O gave the desired isoxazol(in)es **7a–7j**. Analytical samples were prepared by column chromatography on silica gel (EtOAc–hexane, 1:1).

3-(4-methoxylcarbonylphenyl)-5-hydroxymethyl-isoxazole **(7a)**: m.p. = 134–135 °C. IR (KBr): 3345 (OH), 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.11 (d, 2H, Ar**H**), 7.87 (d, 2H, A**r**H), 6.61 (s, 1H, C=C**H**), 4.84 (s, 2H, C$\mathbf{H}_2$), 3.94(s, 3H, OC$\mathbf{H}_3$) ppm. EIMS: *m/z* 233 (M^+), 202 (100%). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.86; H, 4.78; N, 6.03.

3-(4-methoxylcarbonylphenyl)-5-hydoxymethyl-isoxazoline **(7b)**: m.p. = 96–98°C .IR (KBr): 3347 (OH), 1731(C=O), 1609(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.06 (d, 2H, Ar**H**), 7.73 (d, 2H, A**r**H), 4.92 (m, 1H), 3.94(s, 3H, OC$\mathbf{H}_3$), 3.89(dd, 1H, C$\mathbf{H}_2$), 3.70(dd, 1H, C$\mathbf{H}_2$), 3.40(dd, 1H, C$\mathbf{H}_2$), 3.34(dd, 1H, C$\mathbf{H}_2$) ppm. EIMS: *m/z* 235 (M^+), 204 (100%), 176. Anal. Calcd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.38; H, 5.58; N, 6.03.

3-(4-methoxylcarbonylphenyl)-5-(2-hydroxyethyl)-isoxazole **(7c)**: m.p. = 95–96°C. IR (KBr): 3348 (OH), 1736(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.11 (d, 2H, Ar**H**), 7.87 (d, 2H, A**r**H), 6.48 (s, 1H, C=C**H**), 4.04 (t, 2H, C$\mathbf{H}_2$), 3.94(s, 3H, OC$\mathbf{H}_3$), 3.11 (t, 2H, C$\mathbf{H}_2$) ppm. EIMS: *m/z* 247 (M^+), 217, 202 (100%). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.17; H, 5.34; N, 5.64.

3-(4-methoxylcarbonylphenyl)-5-bromomethyl-isoxazoline **(7d)**: m.p. = 128–130°C. IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.09 (d, 2H, Ar**H**), 7.74 (d, 2H, A**r**H), 5.08 (m, 1H), 3.94(s, 3H, OC$\mathbf{H}_3$), 3.60(dd, 1H, C$\mathbf{H}_2$), 3.53(dd, 1H, C$\mathbf{H}_2$), 3.42(dd, 1H, C$\mathbf{H}_2$), 3.32(dd, 1H, C$\mathbf{H}_2$) ppm. EIMS: *m/z* 299(M+2), 297 (M^+), 204 (100%), 176. Anal. Calcd for $C_{12}H_{12}BrNO_3$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.42; H, 4.08; N, 4.75.

3-(4-methoxylcarbonylphenyl)-5-n-butyl-isoxazole **(7e)**: m.p. = 64–65°C.IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.12 (d, 2H, Ar**H**), 7.87 (d, 2H, A**r**H), 6.34(s, 1H, C=C**H**), 3.94(s, 3H, OC$\mathbf{H}_3$), 2.82(t, 2H, C$\mathbf{H}_2$CH$_2$), 1.74(m, 2H, CH$_2$C$\mathbf{H}_2$CH$_2$), 1.44(m, 2H, CH$_2$C$\mathbf{H}_2$CH$_2$), 0.97(s, 3H, C$\mathbf{H}_3$) ppm. EIMS: *m/z* 259 (M^+), 228, 202 (100%). Anal. Calcd for $C_{15}H_{17}NO_3$: C, 69.50; H, 6.56; N, 5.41. Found: C, 69.83; H, 6.59; N, 5.39.

3-(4-methoxylcarbonylphenyl)-5-n-pentyl-isoxazole **(7f)** m.p. = 98–100°C. IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.13 (d, 2H, Ar**H**), 7.87 (d, 2H, A**r**H), 6.34 (s, 1H, C=C**H**), 3.94(s, 3H, OC$\mathbf{H}_3$), 2.81(t, 2H, C$\mathbf{H}_2$CH$_2$), 1.76(m, 2H, CH$_2$C$\mathbf{H}_2$CH$_2$), 1.38(m, 4H, CH$_2$C$\mathbf{H}_2$C$\mathbf{H}_2$CH$_2$), 0.92 (s, 3H, C$\mathbf{H}_3$) ppm. EIMS: *m/z* 273 (M^+), 202 (100%). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.32; H, 6.96; N, 5.12. Found: C, 70.59; H, 7.02; N, 5.05.

3-(4-methoxylcarbonylphenyl)-5-methoxylmethyl-isoxazole **(7g)**: m.p. = 98–100°C. IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.14 (d, 2H, Ar**H**), 7.88 (d, 2H, A**r**H), 6.63(s, 1H, C=C**H**), 4.61(s, 2H,C$\mathbf{H}_2$), 3.95(s, 3H, OC$\mathbf{H}_3$), 3.48(s, 3H, OC$\mathbf{H}_3$) ppm. EIMS: *m/z* 247 (M^+), 202 (100%). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.23; H, 5.36; N, 5.69.

3-(4-methoxylcarbonylphenyl)-4, 5-norbornane-isoxazoline **(7h)**: m.p. = 130–132°C. IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.05 (d, 2H, Ar**H**), 7.77 (d, 2H, A**r**H), 4.68 (d, 1H, C**H**), 3.93(s, 3H, OC$\mathbf{H}_3$), 3.48 (d, 1H, C**H**), 2.64(m, 1H, C**H**), 2.51(m, 1H, C**H**), 1.60(m, 2H, CH$_2$C$\mathbf{H}_2$), 1.38–1.49(m, 2H, C$\mathbf{H}_2$), 1.20(m, 2H, CH$_2$C$\mathbf{H}_2$) ppm. EIMS: *m/z* 271 (M^+, 100%), 215, 175. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.63; H, 6.32; N, 5.16.

3-(4-methoxylcarbonylphenyl)-5-phenyl-isoxazoline **(7i)**: m.p. = 118–120°C.IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.06 (d, 2H, Ar**H**), 7.76(d, 2H, A**r**H), 7.39(m, 5H, Ar**H**), 5.79 (m, 1H, C**H**), 3.94(s, 3H, OC$\mathbf{H}_3$), 3.79(dd, 1H, CHC$\mathbf{H}_2$), 3.36(dd, 1H, CHC$\mathbf{H}_2$) ppm. EIMS: *m/z* 281 (M^+), 104(100%). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.57; N, 5.95. Found: C, 72.54; H, 5.60; N, 5.90.

3-(4-methoxylcarbonylphenyl)-5-phenylthiomethyl-isoxazole **(7j)**: m.p. = 92–94°C. IR (KBr): 1734(C=O), 1612(C=N) cm^{-1}. ^1H NMR (500MHz, $CDCl_3$): δ 8.09 (d, 2H, Ar**H**), 7.81 (d, 2H, A**r**H), 7.31–7.35(m, 5H, Ar**H**), 6.41 (s, 1H, C=C**H**), 4.20(s, 2H, CH_2), 3.94(s, 3H, OC$\mathbf{H}_3$) ppm. EIMS: *m/z* 325 (M^+), 105(100%). Anal. Calcd for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.49; H, 4.68; N, 4.59.

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