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Diastereoselective cycloadditions of a soluble polymer-supported substituted allyl alcohol derived from Baylis–Hillman reaction with nitrile oxides

Yongjia Shang *, Zhijun Feng, Lili Yuan, Shaowu Wang

Anhui Key Laboratory of Functional Molecular Solids, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, PR China

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ABSTRACT

A diastereoselective cycloaddition of a soluble polymer-supported Baylis–Hillman adduct with nitrile oxides is described. The reaction has shown to proceed with moderate diastereoselectivity, favoring the *syn* isomer of the resulting 3,5-substituted isoxazolines. The stereochemistry of the products has been assigned using ^{1}H NMR studies. The structure of one of the diastereomers has been determined by single-crystal X-ray crystallographic analysis.

1. Introduction

1,3-Dipolar cycloaddition reactions of nitrile oxides to alkenes are widely used in organic synthesis due to the generally high regioselectivity and stereoselectivity of these reactions[1] and the synthetic versatility of the corresponding isoxazolines. The isoxazoline ring system is of particular interest since it is a component of various pharmaceutical agents and also a precursor to useful synthetic intermediates for the construction of a variety of 1,3-difunctionalized compounds, such as β-hydroxycarbonyls and γ-amino alcohols.[2] If a chiral alkene is used as the dipolarophile, two diastereoisomers could be formed by 1,3-dipolar cycloaddition.[3] Control of diastereoselectivity in these cycloadditions is important for economical syntheses of intermediates and natural products.[4] So, cycloaddition of nitrile oxide with chiral alkenes in solution phase have been thoroughly studied.[3,5a–h] Several models, which allow the prediction of the main diastereomer, have been published and theoretical calculations have given insights into the origins of their selectivities.[5] It has been found that diastereoselectivity of the cycloadditions depends mainly upon the nature of dipole and dipolarophile, and electrostatic factors play a major role in controlling the stereoselectivity of these reactions. Furthermore, a number of cycloadditions of nitrile oxides to alkenes carried out on solid supports have also been reported in the last few years.[6] However, few examples of diastereoselective cycloadditions of nitrile oxides to chiral alkenes on soluble solid supports have been reported. Soluble polymer-supported organic synthesis, termed 'liquid-phase' organic synthesis (LPOS), couples the advantages of traditional homogeneous solution chemistry (high reactivity, lack of diffusion phenomena, and ease of analysis) with those of solid phase methods (use of excess reagents, easy isolation, and purification of products).[7] So, the synthetic approaches that utilize soluble polymer have been developed by many workers in the past decades.[7,8] We are interested in the development of the liquid-phase stereoselective strategy for the synthesis of isoxazolines, which can be applied to combinatorial synthesis of small polyfunctional heterocycle libraries.

As mentioned above, coupled with our previous work on the liquid-phase synthesis of isoxazol(in)es through the nitrile oxide cycloaddition,[9] we turn our attention to the substituted allyl alcohols **3** by using Baylis–Hillman reaction[6,10] on the soluble resin. We predicted that the OH group at the allylic stereocenter of the chiral adduct **3** would play an important role in controlling the diastereoselectivity in the cycloaddition of nitrile oxides with the soluble polymer-supported adduct **3**. Our attempts to obtain the diastereoselectivity in these reactions were successful. And they also provide the first examples of the liquid-phase diastereoselective cycloadditions of nitrile oxides to chiral alkenes. Herein, we would like to describe the details of the reactions.

2. Results and discussion

As shown in Scheme 1, we chose to perform our reactions on the soluble poly(ethylene glycol) 4000 (PEG4000). The polymeric acrylate **2** was prepared by treatment of dihydroxyl-PEG4000 (MW=4000 g/mol) **1** with acryloyl chloride in the presence of Et_3N in refluxing dichloromethane. Then the reaction of benzaldehyde with the polymeric acrylate **2** in the presence of a catalytic amount of 3-quinuclidinol in absolute ethanol gave the polymer-supported racemic mixture of Baylis–Hillman adduct **3**. After precipitation with diethyl ether, the resin **3** was treated with 4 equiv of aldoximine **4** and *N*-chlorosuccinimide (NCS) in dichloromethane in a one-pot procedure. Successively, triethylamine was added slowly over a period of

* Corresponding author. Fax: +86 553 3883517.
E-mail address: shyj@mail.ahnu.edu.cn (Y. Shang).

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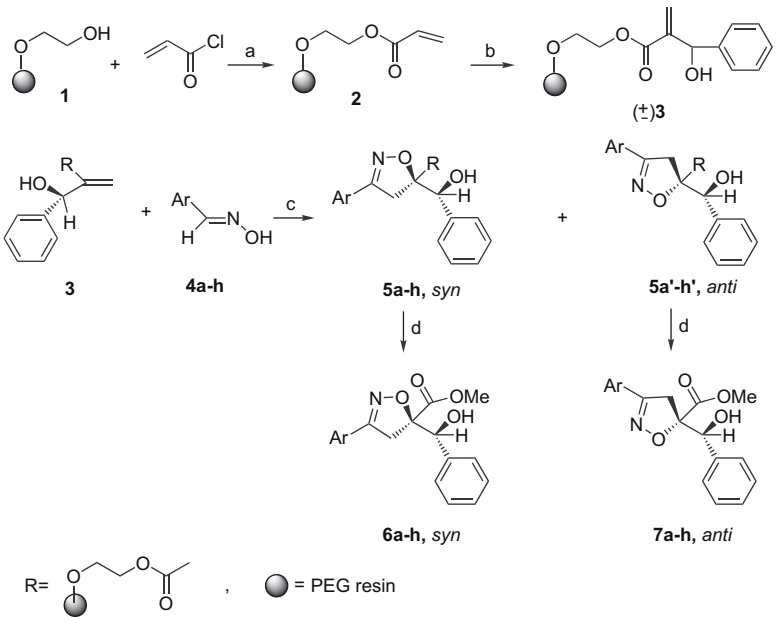
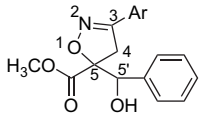


Scheme 1. Reagents and conditions: (a) Et_3N, CH_2Cl_2, 24 h; (b) benzaldehyde, 3-quinuclidinol, absolute ethanol, 50 °C, 96 h; (c) NCS, Et_3N, rt, 16 h; (d) $NaOCH_3$, CH_3OH.

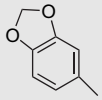
2 h to generate the nitrile oxide and the resulting mixture was stirred at room temperature overnight. The triethylamine hydrochloride was removed by precipitation with benzene. The solution was concentrated and the polymer-supported isoxazolines **5** were precipitated out by adding diethyl ether. Substrate cleavage was accomplished by treating **5** with 5% MeONa in methanol at room temperature. Then, the diastereomeric mixture of cycloproducts **6** and **7** was obtained and purified by flash column chromatography. Yields and diastereoisomeric ratios are summarized in Table 1.

It was observed the *syn*-diastereoisomer was the major product with moderate diastereoselectivity in all cases. The diastereoisomeric ratio of the resulting cycloadducts **6a**–**h**, **7a**–**h** was determined by HPLC and the isomers purified by flash column chromatography. The relative stereochemistry of the major isomer was assigned by examination of the ^1H NMR chemical shifts of the proton attached to C-5′ (see Section 4). In all cases examined above, the chemical shift of the C-5′ proton of the major *syn* isomer occurred at higher field than that of the *anti*, analogous to those reported in the literature.[5b,h]

Table 1
Results of diastereoselective cycloaddition products



Product **6** and **7**

Product	Ar–	Yield[a] (%)	Ratio[b] **6**/**7**
6a, **7a**	4-MePh–	83	72:28
6b, **7b**	Ph–	81	63:37
6c, **7c**	4-MeOPh–	85	79:21
6d, **7d**	3-NO_2Ph–	56	76:24
6e, **7e**	4-ClPh–	62	70:30
6f, **7f**		85	78:22
6g, **7g**	2,4-ClPh–	79	60:40
6h, **7h**	3,4-MeOPh–	74	61:39

[a] Combined yield of both isomers.
[b] Determined by HPLC (silica gel, LC-18; MeOH/H_2O).

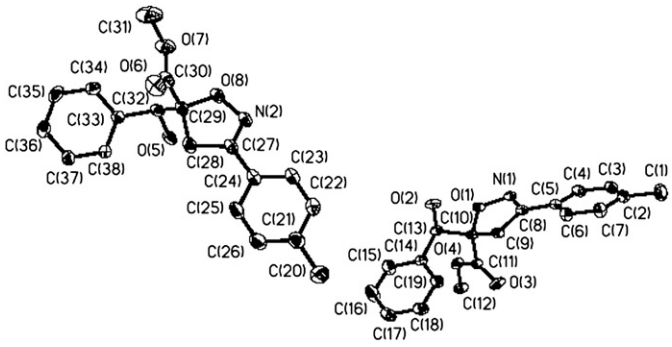


Figure 1. Single-crystal X-ray structure of **6a**.

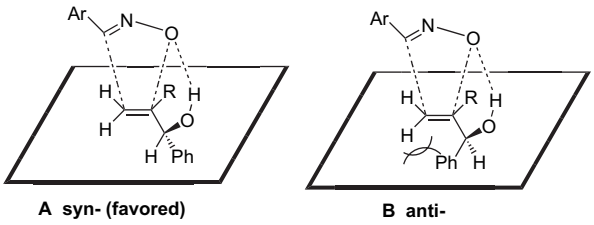


Figure 2. Model for the transition state of the 1,3-DC reaction of nitrile oxides to alkenes.

In addition, the structure of a diastereomer **6a**, which is a racemic mixture, has been determined directly by the single-crystal X-ray diffraction studies (Fig. 1).[11] It could also confirm that **6a** is the *syn* isomer.

The observed *syn* selectivity in these reactions are probably due to hydrogen bonding of OH group with the incoming nitrile oxide oxygen and the steric repulsion between the substituent at the chiral alkene stereocenter and the allylic proton (Fig. 2).[1d] However, the small phenyl group at the allylic stereocenter affects the effect of steric factors; and the electrostatic repulsion due to the negatively charged oxygen of the incoming nitrile oxide determines that the *syn* selectivity is moderate.[5,12] The experimental data also show a dependence of the amount of diastereoselectivity on the nature of the nitrile oxide; in particular, it seems to correlate with the amount of negative charge present on the nitrile oxide oxygen.

3. Conclusion

In summary, we have accomplished the diastereoselective cycloadditions of nitrile oxides to a soluble polymer-supported substituted allyl alcohols derived from the Baylis–Hillman reaction with a moderate diastereoselectivity. Thus, we have provided the liquid-phase diastereoselective synthesis of the 3,5-substituted isoxazolines through 1,3-dipolar cycloaddition of nitrile oxides with chiral alkenes. On the basis of this work, we expect to improve the diastereoselectivity by changing the structures of the Baylis–Hillman adducts and nitrile oxides. Extension of the work is now in progress in our laboratory.

4. Experimental

4.1. General

All chemicals and resin were commercially available and the preparation of the acryloyl chloride and aldoximes was made according to previously described procedures. IR spectra were recorded on KBr pellets on a PTIR-8400S spectrometer. ^{1}H NMR spectra were recorded at 300 MHz on a Bruker Avance DMX300 spectrometer and ^{13}C NMR spectra at 75 MHz on the same spectrometer in deuteriochloroform solutions. All chemical shifts are reported in parts per million from TMS as an internal standard. Mass spectra (EI) were performed on a HP-5989 instrument with ionization energy maintained at 70 eV. Elemental analyses were carried out on an EA-1110 elemental analyzer. Column chromatography was carried out on Merck Kieselgel (particle size 0.300–0.400 mm) and solvents were distilled before use. X-ray crystallographic data were determined on a SMART APEX II X-ray diffractometer. Crystal of **6a** were obtained by slow evaporation of a solution in diethyl ether/hexane. The results of the structural analyses are illustrated in Figure 1.

4.2. General procedure for the synthesis of poly(ethylene glycol)-supported acrylate 2

To a solution of dihydroxy-PEG4000 **1** (10 g, M_W=4000, 2.5 mmol) in CH_2Cl_2 (50 mL) was added triethylamine (2.8 mL) and the mixture was cooled to 0 °C. Subsequently, acryloyl chloride (1.6 mL, 20 mmol) was added dropwise within 30 min. The reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 24 h. Then, a three-fold excess of anhydrous benzene was added to the reaction mixture 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 acrylate **2** in 97% yield.

4.2.1. Compound *2*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.64–3.87 (m, PEG-H), 4.31 (t, 2H, PEGOCH$_2$C*H*$_2$OCO), 5.84 (d, 1H, J=10.1, –COCH=C*H*$_2$), 6.12 (m, 1H, COC*H*=CH$_2$), 6.42 (d, 1H, J=15.9, –COCH=C*H*$_2$).

4.3. General procedure for the synthesis of poly(ethylene glycol)-supported Baylis–Hillman adduct 3

A solution of the polymeric acrylate **2** (10 g, 2.5 mmol), benzaldehyde (25 mmol), and 3-quinuclidinol (2.5 mmol) in 50 mL absolute ethanol was stirred at 50 °C for 96 h. Then, 500 mL Et_2O was added to precipitate the resin, which was then filtered and washed with Et_2O to afford the polymer-supported Baylis–Hillman adduct **3** in 95% yield.

4.3.1. Compound *3*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.39–3.86 (m, PEG-H), 4.25 (t, 2H, PEGOCH$_2$C*H*$_2$OCO), 5.58 (s, 1H, –C*H*OH), 5.83 (s, 1H, =C*H*$_2$), 6.36 (s, 1H, =C*H*$_2$), 7.28–7.36 (m, 5H, Ar*H*).

4.4. General procedure for the synthesis of poly(ethylene glycol)-supported isoxazolines 5

To a solution of *N*-chlorosuccinimide (NCS, 2 mmol) in 5 mL dry CH_2Cl_2 was added the aldoxime (2 mmol). After the chlorination was over, the polymer-supported Baylis–Hillman adduct **3** (0.5 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 30 min, and then Et_3N (2 mmol) in 4 mL CH_2Cl_2 was added dropwise over 2 h and the mixture was stirred overnight at room temperature. Then, a three-fold excess of dry 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 isoxazolines **5**.

4.4.1. Compounds *5a*, *5a′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, C*H*$_3$), 3.48–3.78 (m, PEG-H), 4.28 (t, 2H, J=4.7, PEGOCH$_2$C*H*$_2$OCO), 5.25 (d, 1H, J=5.8, C*H*OH), 5.36 (d, 1H, J=3.5, C*H*OH), 7.15 (d, 2H, J=7.7, Ar*H*), 7.27–7.35 (m, 5H, Ar*H*), 7.49 (d, 2H, J=7.7, Ar*H*). Yield: 95%.

4.4.2. Compounds *5b*, *5b′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45–3.78 (m, PEG-H), 4.34 (t, 2H, J=4.7, PEGOCH$_2$C*H*$_2$OCO), 5.18 (d, 1H, J=6.3, C*H*OH), 5.31 (d, 1H, J=3.9, C*H*OH), 7.22–7.31 (m, 8H, Ar*H*), 7.60 (m, 2H, Ar*H*). Yield: 97%.

4.4.3. Compounds *5c*, *5c′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48–3.80 (m, PEG-H), 4.35 (t, 2H, J=4.8, PEGOCH$_2$C*H*$_2$OCO), 5.23 (d, 1H, J=6.5, C*H*OH), 5.35 (s, 1H, C*H*OH), 6.91 (d, 2H, J=8.7, Ar*H*), 7.27–7.51 (m, 5H, Ar*H*), 7.60 (d, 2H, J=8.7, Ar*H*). Yield: 95%.

4.4.4. Compounds *5d*, *5d′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45–3.85 (m, PEG-H), 4.34 (t, 2H, J=4.7, PEGOCH$_2$C*H*$_2$OCO), 5.42 (d, 1H, J=3.6, C*H*OH), 5.43 (d, 1H, J=3.8, C*H*OH), 7.27–7.39 (m, 5H, Ar*H*), 7.60 (m, 1H, Ar*H*), 8.10 (d, 1H, J=7.2, Ar*H*), 8.23 (d, 1H, J=7.8, Ar*H*), 8.59 (s, 1H, Ar*H*). Yield: 96%.

4.4.5. Compounds *5e*, *5e′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48–3.82 (m, PEG-H), 4.32 (t, 2H, J=4.8, PEGOCH$_2$C*H*$_2$OCO), 5.18 (d, 1H, J=3.8, C*H*OH), 5.37 (d, 1H, J=3.8, C*H*OH), 7.27–7.38 (m, 5H, Ar*H*), 7.43 (d, 2H, J=8.5, Ar*H*), 7.65 (d, 2H, J=8.5, Ar*H*). Yield: 96%.

4.4.6. Compounds *5f*, *5f′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45–3.85 (m, PEG-H), 4.34 (t, 2H, J=4.8, PEGOCH$_2$C*H*$_2$OCO), 5.22 (d, 1H, J=6.3, C*H*OH), 5.35 (d, 1H, J=3.8, C*H*OH), 5.99 (s, 2H, OC*H*$_2$O), 6.80 (d, 1H, J=8.0, Ar*H*), 7.03 (d, 1H, J=8.0, Ar*H*), 7.12–7.48 (m, 6H, Ar*H*). Yield: 95%.

4.4.7. Compounds *5g*, *5g′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.48–3.80 (m, PEG-H), 4.25 (t, 2H, J=4.7, PEGOCH$_2$C*H*$_2$OCO), 5.26 (d, 1H, J=5.3, C*H*OH), 5.32 (s, 1H, C*H*OH), 7.08–7.50 (m, 8H, Ar*H*). Yield: 95%.

4.4.8. Compounds *5h*, *5h′*

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45–3.85 (m, PEG-H), 4.34 (t, 2H, J=4.7, PEGOCH$_2$C*H*$_2$OCO), 5.24 (d, 1H, J=5.8, C*H*OH), 5.31 (d, 1H, J=3.8, C*H*OH), 6.82 (s, 1H, Ar*H*), 7.06 (s, 1H, Ar*H*), 7.28–7.39 (m, 6H, Ar*H*). Yield: 97%.

4.5. General procedure for the synthesis of isoxazolines 6 and 7

The cleavage of the polymer support was accomplished by treating **5** with CH_3ONa in CH_3OH at room temperature for 8 h. Et_2O was added to the mixture and the organic phase was separated. Removal of Et_2O gave the desired isoxazolines **6** and **7**, which were separated by the column chromatography on silica gel (EtOAc/hexane).

4.5.1. 3-(4-Methylphenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6a**: white solid. IR (KBr): ν_{max} 3308, 1736, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.38 (s, 3H, CH_3), 3.02 (d, 1H, J=3.5, CHOH), 3.66 (s, 2H, N=CCH_2), 3.79 (s, 3H, OCH_3), 5.36 (d, 1H, J=3.4, CHOH), 7.19 (d, 2H, J=7.7, ArH), 7.27–7.37 (m, 5H, ArH), 7.55 (d, 2H, J=7.7, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21 (CH_3), 37 (N=CCH_2), 53 (OCH_3), 73 (CHOH), 93 (CH_2CON), 125, 126, 127, 128, 129, 137 and 140 (C_6H_5 and C_6H_4), 157 (N=CCH_2), 170 (COOCH_3). EIMS m/z=326 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}O_4N$: C, 70.15; H, 5.85; N, 4.31. Found: C, 70.37; H, 5.90; N, 4.52.

Compound **7a**: white solid. IR (KBr): ν_{max} 3308, 1736, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.87 (d, 1H, J=5.8, CHOH), 3.65 (d, 1H, J=17.5, N=CCH_2), 3.74 (s, 3H, OCH_3), 3.78 (d, 1H, J=17.5, N=CCH_2), 5.24 (d, 1H, J=5.8, CHOH), 7.16 (d, 2H, J=7.8, ArH), 7.28–7.35 (m, 5H, ArH), 7.49 (d, 2H, J=7.8, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21 (CH_3), 40 (N=CCH_2), 53 (OCH_3), 74 (CHOH), 91 (CH_2CON), 125, 126, 127, 128, 129, 137 and 140 (C_6H_5 and C_6H_4), 156 (N=CCH_2), 170 (COOCH_3). EIMS m/z=326 $[M+H]^+$. Anal. Calcd for $C_{19}H_{19}O_4N$: C, 70.15; H, 5.85; N, 4.31. Found: C, 70.37; H, 5.90; N, 4.52.

4.5.2. 3-Phenyl-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6b**: white solid. IR (KBr): ν_{max} 3482, 1740, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.17 (d, 1H, J=3.8, CHOH), 3.59 (s, 2H, N=CCH_2), 3.68 (s, 3H, OCH_3), 5.28 (d, 1H, J=3.8, CHOH), 7.22–7.31 (m, 8H, ArH), 7.56 (d, 2H, J=7.5, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40 (N=CCH_2), 53 (OCH_3), 74 (CHOH), 91 (CH_2CON), 126, 127, 128, 129, 130 and 137 (C_6H_5 and C_6H_4), 156 (N=CCH_2), 170 (COOCH_3). EIMS m/z=312 $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}O_4N$: C, 69.45; H, 5.47; N, 4.50. Found: C, 69.74; H, 5.73; N, 4.84.

Compound **7b**: white solid. IR (KBr): ν_{max} 3482, 1740, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.82 (d, 1H, J=6.3, CHOH), 3.57 (d, 1H, J=15.6, N=CCH_2), 3.64 (s, 3H, OCH_3), 3.70 (d, 1H, J=15.6, N=CCH_2), 5.17 (d, 1H, J=6.3, CHOH), 7.17–7.30 (m, 6H, ArH), 7.38–7.46 (m, 4H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42 (N=CCH_2), 53 (OCH_3), 74 (CHOH), 91 (CH_2CON), 126, 127, 128, 129, 130 and 137 (C_6H_5 and C_6H_4), 156 (N=CCH_2), 170 (COOCH_3). EIMS m/z=312 $[M+H]^+$. Anal. Calcd for $C_{18}H_{17}O_4N$: C, 69.45; H, 5.47; N, 4.50. Found: C, 69.74; H, 5.73; N, 4.84.

4.5.3. 3-(4-Methoxyphenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6c**: white solid. IR (KBr): ν_{max} 3418, 1726, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.19 (br s, 1H, CHOH), 3.70 (s, 2H, N=CCH_2), 3.77 (s, 3H, COOCH_3), 3.82 (s, 3H, PhOCH_3), 5.35 (s, 1H, CHOH), 6.90 (d, 2H, J=8.7, ArH), 7.33–7.36 (m, 5H, ArH), 7.56 (d, 2H, J=8.7, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37 (N=CCH_2), 53 (COOCH_3), 55 (PhOCH_3), 74 (CHOH), 93 (CH_2CON), 114, 120, 126, 128, 137 and 161 (C_6H_5 and C_6H_4), 156 (N=CCH_2), 170 (COOCH_3). EIMS m/z=342 $[M]^+$. Anal. Calcd for $C_{19}H_{19}O_5N$: C, 66.86; H, 5.57; N, 4.11. Found: C, 66.98; H, 5.81; N, 4.36.

Compound **7c**: white solid. IR (KBr): ν_{max} 3418, 1726, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.90 (d, 1H, J=6.5, CHOH), 3.69 (d, 1H, J=17.3, N=CCH_2), 3.72 (s, 3H, COOCH_3), 3.82 (d, 1H, J=17.3, N=CCH_2), 3.92 (s, 3H, PhOCH_3), 5.23 (d, 1H, J=6.5, CHOH), 6.85 (d, 2H, J=8.8, ArH), 7.26–7.36 (m, 5H, ArH), 7.48 (d, 2H, J=8.8, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39 (N=CCH_2), 53 (COOCH_3), 55 (PhOCH_3), 75 (CHOH), 91 (CH_2CON), 114, 120, 126, 128, 137 and 161 (C_6H_5 and C_6H_4), 156 (N=CCH_2), 170 (COOCH_3). EIMS m/z=342 $[M]^+$. Anal. Calcd for $C_{19}H_{19}O_5N$: C, 66.86; H, 5.57; N, 4.11. Found: C, 66.98; H, 5.81; N, 4.36.

4.5.4. 3-(3-Nitrophenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6d**: pale yellow solid. IR (KBr): ν_{max} 3509, 1728, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (d, 1H, J=3.8, CHOH), 3.77 (s, 2H, N=CCH_2), 3.83 (s, 3H, OCH_3), 5.43 (d, 1H, J=3.8, CHOH), 7.25–7.39 (m, 5H, ArH), 7.64 (t, 1H, ArH), 8.05 (d, 1H, J=7.8, ArH), 8.29 (d, 1H, J=7.1, ArH), 8.44 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39 (N=CCH_2), 53 (OCH_3), 74 (CHOH), 93 (CH_2CON), 124, 126, 128, 130, 131, 132, 137 and 148 (C_6H_5 and C_6H_4), 156 (CH_2C=NO), 171 (COOCH_3). EIMS m/z=357 $[M]^+$. Anal. Calcd for $C_{18}H_{16}O_6N_2$: C, 60.67; H, 4.49; N, 7.87. Found: C, 60.91; H, 4.70; N, 7.96.

Compound **7d**: pale yellow solid. IR (KBr): ν_{max} 3509, 1728, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.88 (d, 1H, J=3.9, CHOH), 3.72 (d, 1H, J=9.0, N=CCH_2), 3.81 (d, 1H, J=9.0, N=CCH_2), 3.84 (s, 3H, OCH_3), 5.42 (d, 1H, J=3.6, CHOH), 7.27–7.39 (m, 5H, ArH), 7.63 (t, 1H, ArH), 8.05 (d, 1H, J=7.2, ArH), 8.28 (d, 1H, J=7.8, ArH), 8.43 (s, 1H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40 (N=CCH_2), 53 (OCH_3), 75 (CHOH), 92 (CH_2CON), 124, 126, 128, 130, 131, 132, 137 and 148 (C_6H_5 and C_6H_4), 156 (CH_2C=NO), 171 (COOCH_3). EIMS m/z=357 $[M]^+$. Anal. Calcd for $C_{18}H_{16}O_6N_2$: C, 60.67; H, 4.49; N, 7.87. Found: C, 60.91; H, 4.70; N, 7.96.

4.5.5. 3-(4-Chlorophenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6e**: white solid. IR (KBr): ν_{max} 3503, 1741, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.94 (d, 1H, J=3.8, CHOH), 3.64 (s, 2H, N=CCH_2), 3.80 (s, 3H, OCH_3), 5.38 (d, 1H, J=3.8, CHOH), 7.26–7.38 (m, 5H, ArH), 7.40 (d, 2H, J=8.5, ArH), 7.60 (d, 2H, J=8.5, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37 (N=CCH_2), 53 (OCH_3), 74 (CHOH), 93 (CH_2CON), 126, 127, 128, 130, 132, 136 and 138 (C_6H_5 and C_6H_4), 156 (CH_2C=NO), 170 (COOCH_3). EIMS m/z=346 $[M]^+$. Anal. Calcd for $C_{18}H_{16}O_4NCl$: C, 62.52; H, 4.63; N, 4.05. Found: C, 62.81; H, 4.94; N, 4.36.

Compound **7e**: white solid. IR (KBr): ν_{max} 3503, 1741, 1599 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.89 (d, 1H, J=3.8, CHOH), 3.67 (s, 2H, N=CCH_2), 3.74 (s, 3H, OCH_3), 5.20 (d, 1H, J=3.8, CHOH), 7.33–7.38 (m, 5H, ArH), 7.47 (d, 2H, J=8.5, ArH), 7.58 (d, 2H, J=8.5, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39 (N=CCH_2), 53 (OCH_3), 75 (CHOH), 91 (CH_2CON), 126, 127, 128, 130, 132, 136 and 138 (C_6H_5 and C_6H_4), 156 (CH_2C=NO), 170 (COOCH_3). EIMS m/z=346 $[M]^+$. Anal. Calcd for $C_{18}H_{16}O_4NCl$: C, 62.52; H, 4.63; N, 4.05. Found: C, 62.81; H, 4.94; N, 4.36.

4.5.6. 3-(3,4-(Methylenedioxy)phenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6f**: pale yellow solid. IR (KBr): ν_{max} 3242, 1738, 1633 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.91 (d, 1H, J=3.9, CHOH), 3.66 (s, 2H, N=CCH_2), 3.78 (s, 3H, OCH_3), 5.34 (d, 1H, J=3.9, CHOH), 5.99 (s, 2H, OCH_2O), 6.80 (d, 1H, J=8.0, ArH), 7.03 (d, 1H, J=8.0, ArH), 7.11 (s, 1H, ArH), 7.21–7.48 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38 (N=CCH_2), 53 (OCH_3), 74 (CHOH), 93 (CH_2CON), 101, 114, 115, 122, 126, 127, 128, 129, 136, 149 and 151 (C_6H_5 and C_6H_3), 156 (CH_2C=NO), 170 (COOCH_3). EIMS m/z=356 $[M]^+$. Anal. Calcd for $C_{19}H_{17}O_6N$: C, 64.23; H, 4.79; N, 3.94. Found: C, 64.55; H, 4.91; N, 4.11.

Compound **7f**: pale yellow solid. IR (KBr): ν_{max} 3242, 1738, 1633 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.80 (d, 1H, J=6.4, CHOH), 3.66 (s, 2H, N=CCH_2), 3.80 (s, 3H, OCH_3), 5.23 (d, 1H, J=6.4, CHOH), 5.99 (s, 2H, OCH_2O), 6.79 (d, 1H, J=8.0, ArH), 7.05 (d, 1H, J=8.0, ArH),

7.10 (s, 1H, Ar*H*), 7.23–7.50 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 40 (N=C*C*H$_2$), 53 (O*C*H$_3$), 75 (*C*HOH), 92 (CH$_2$*C*ON), 101, 114, 115, 122, 126, 127, 128, 129, 136, 149 and 151 (C_6H_5 and C_6H_3), 156 (CH$_2$*C*=NO), 170 (*C*OOCH$_3$). EIMS m/z=356 [M]$^+$. Anal. Calcd for $C_{19}H_{17}O_6N$: C, 64.23; H, 4.79; N, 3.94. Found: C, 64.55; H, 4.91; N, 4.11.

4.5.7. 3-(2,4-Dichlorophenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6g**: white solid. IR (KBr): ν_{max} 3374, 1741, 1641 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98 (br s, 1H, CHO*H*), 3.76 (s, 2H, N=CC*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 5.32 (s, 1H, C*H*OH), 7.22–7.44 (m, 8H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42 (N=C*C*H$_2$), 53 (O*C*H$_3$), 73 (*C*HOH), 91 (CH$_2$*C*ON), 126, 127, 128, 129, 130, 133, 136 and 138 (C_6H_5 and C_6H_3), 156 (CH$_2$*C*=NO), 171 (*C*OOCH$_3$). EIMS m/z=380 [M]$^+$. Anal. Calcd for $C_{18}H_{15}O_4NCl_2$: C, 56.84; H, 3.95; N, 3.68. Found: C, 56.98; H, 4.25; N, 3.97.

Compound **7g**: white solid. IR (KBr): ν_{max} 3374, 1741, 1641 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.84 (d, 1H, J=5.4, CHO*H*), 3.74 (d, 1H, J=18.0, N=CC*H*$_2$), 3.81 (s, 3H, OC*H*$_3$), 3.95 (d, 1H, J=18.0, N=CC*H*$_2$), 5.27 (d, 1H, J=5.4, C*H*OH), 7.08–7.50 (m, 8H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43 (N=C*C*H$_2$), 53 (O*C*H$_3$), 74 (*C*HOH), 90 (CH$_2$*C*ON), 126, 127, 128, 129, 130, 133, 136 and 138 (C_6H_5 and C_6H_3), 156 (CH$_2$*C*=NO), 171 (*C*OOCH$_3$). EIMS m/z=380 [M]$^+$. Anal. Calcd for $C_{18}H_{15}O_4NCl_2$: C, 56.84; H, 3.95; N, 3.68. Found: C, 56.98; H, 4.25; N, 3.97.

4.5.8. 3-(3,4-Dimethoxyphenyl)-5-(1-phenyl-hydroxymethyl)-5-methoxycarbonyl isoxazoline

Compound **6h**: white solid. IR (KBr): ν_{max} 3466, 1719, 1601 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92 (d, 1H, J=3.8, CHO*H*), 3.82 (s, 3H, OC*H*$_3$), 3.86 (s, 2H, N=CC*H*$_2$), 3.89 (s, 6H, PhOC*H*$_3$), 5.31 (d, 1H, J=3.8, C*H*OH), 6.84 (d, 1H, J=8.2, Ar*H*), 7.06 (d, 1H, J=8.2, Ar*H*), 7.27 (s, 1H, Ar*H*), 7.34–7.40 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37 (N=C*C*H$_2$), 53 (COO*C*H$_3$), 56 (PhO*C*H$_3$), 74 (*C*HOH), 93 (CH$_2$*C*ON), 112, 115, 120, 126, 127, 128, 129, 137, 150 and 152 (C_6H_5 and C_6H_3), 156 (CH$_2$*C*=NO), 171 (*C*OOCH$_3$). EIMS m/z=372 [M]$^+$. Anal. Calcd for $C_{20}H_{21}O_6N$: C, 64.69; H, 5.66; N, 3.77. Found: C, 64.85; H, 5.93; N, 3.92.

Compound **7h**: white solid. IR (KBr): ν_{max} 3466, 1719, 1601 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.04 (d, 1H, J=5.8, CHO*H*), 3.82 (s, 3H, OC*H*$_3$), 3.86 (s, 2H, N=CC*H*$_2$), 3.89 (s, 6H, PhOC*H*$_3$), 5.25 (d, 1H, J=5.8, C*H*OH), 6.84 (d, 1H, J=8.2, Ar*H*), 7.06 (d, 1H, J=8.2, Ar*H*), 7.27 (s, 1H, Ar*H*), 7.34–7.40 (m, 5H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 39 (N=C*C*H$_2$), 53 (COO*C*H$_3$), 56 (PhO*C*H$_3$), 75 (*C*HOH), 92 (CH$_2$*C*ON), 112, 115, 120, 126, 127, 128, 129, 137, 150 and 152 (C_6H_5 and C_6H_3), 156 (CH$_2$*C*=NO), 171 (*C*OOCH$_3$). EIMS m/z=372 [M]$^+$. Anal. Calcd for $C_{20}H_{21}O_6N$: C, 64.69; H, 5.66; N, 3.77. Found: C, 64.85; H, 5.93; N, 3.92.

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11. Crystallographic data for **6a**: space group *P*-1, a=8.5400(3) Å, b=10.5119(4) Å, c=20.8093(8) Å, α=84.800(2)°, β=88.209(2)°, γ=67.405(2)°, V=1717.59(11) Å^3, T=293(2) K, Z=4. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre [CCDC 672089] for compound **6a**. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).
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