

# Reactive organogels based on isoxazole esters: alkali metal ions selected gelation and crystallization

Qingxian Jin,<sup>a</sup>Jing Li,<sup>a,b</sup>Li Zhang,<sup>\*b</sup> Shaoming Fang,<sup>a</sup>and Minghua Liu<sup>\*b</sup>

<sup>a</sup>Henan Provincial Key Laboratory of Surface & Interface Science,Zhengzhou University of Light Industry, Zhengzhou, Henan 450002, (P.R. China).

<sup>b</sup>Beijing National Laboratory for Molecular Science, CAS Key Laboratory of Colloid Interface and Chemical Thermodynamics, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190 (P.R. China), E-mail: liumh@iccas.ac.cn, [zhangli@iccas.ac.cn](mailto:zhangli@iccas.ac.cn)

## Experimental Section

### Chemicals

2-acetylthiophene(99%), 3-acetylthiophene(98%), acetophenone(99%), diethyl oxalate(99%), hydroxylamine hydrochloride (98%) were purchased by Beijing InnoChem Science & Technology Co., Ltd. LiOH, NaOH and KOH were purchased by Sinopharm Chemical Reagent Co., Ltd. All solvent were purchased by Beijing Chemical Work. All chemicals were used directly without further purification.

### The synthesis of compound E1

The mixture of 2-acetylthiophene (63.09g, 0.5mol)and diethyl oxalate (73g, 0.5mol) was added to sodiummethoxide (0.5mol) solution in methanol (1000mL) at 0-5 °C, then the resulting solution was stirred for 6 hour at room temperature. After the reaction finished, the reaction was treated with HCl(3mol/L, 150mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was concentrated on a rotary evaporator to afford methyl 2,4-dioxo-4-(thiophen-2-yl) butanoate which could be used in the next step without further purification.

A solution of methyl 2,4-dioxo-4-(thiophen-2-yl)butanoate and hydroxylamine hydrochloride (35g, 0.5mol) in MeOH (700mL)was refluxed for 4 hours, when the reaction

finished, the solvent was concentrated on a rotary evaporator, and the residue was diluted with  $\text{CH}_2\text{Cl}_2$ , the organic layer was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was concentrated again on a rotary evaporator, the residue is recrystallized from MeOH and  $\text{H}_2\text{O}$  to afford compound **E1** as a white solid, (67.4g, 64.49%). MS:[ $\text{M}+\text{H}$ ]<sup>+</sup> 209.9, [ $\text{M}+\text{Na}$ ]<sup>+</sup> 231.9. <sup>1</sup>H NMR(500MHz, $\text{CDCl}_3$ ):  $\delta$ =7.60-7.54(t,1H), 7.53(s,1H), 7.29(s,1H), 6.82(s,1H), 4.03(s,3H).

### **The synthesis of compound E2**

The mixture 3-acetylthiophene (6.31g, 0.05mol) and diethyl oxalate (7.3g, 0.05mol) was added to sodium methoxide (0.05mol) solution in methanol (100mL) at 0-5 °C, and then the resulting solution was stirred for 6 hour at room temperature. After the reaction finished, the mixture was treated with HCl(3mol/L, 15mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was concentrated on a rotary evaporator to afford methyl 2,4-dioxo-4-(thiophen-3-yl)butanoate which could be used in the next step without further purification.

A solution of methyl 2,4-dioxo-4-(thiophen-3-yl)butanoate and hydroxylamine hydrochloride (3.5g, 0.05mol) in MeOH (80mL) was refluxed for 7 hours. After the reaction finished, the solvent was concentrated on a rotary evaporator, and the residue was diluted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was concentrated again on a rotary evaporator, and the residue is recrystallized from MeOH and  $\text{H}_2\text{O}$  to afford compound **E2** as a white solid (7.23g, 69.21%). MS:[ $\text{M}+\text{H}$ ]<sup>+</sup> 210.0, [ $\text{M}+\text{Na}$ ]<sup>+</sup> 231.9; <sup>1</sup>H-NMR(500MHz, $\text{CDCl}_3$ ):  $\delta$ =7.87-7.86,(t,1H); 7.47-7.44(m,2H); 6.80(s,1H); 4.02(s,3H).

### **The synthesis of compound E3**

The mixture of acetophenone (12g, 0.1mol) and diethyl oxalate (14.6g, 0.1mol) was added to the prepared sodium methoxide (0.1mol) solution in methanol (200mL) at 0-5 °C, and then the resulting solution was stirred for 6 hour at room temperature. After the reaction finished, the mixture was treated with HCl(3mol/L, 30mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ), the solvent was concentrated on a rotary evaporator to afford methyl 2,4-dioxo-4-phenylbutanoate.

A solution of methyl 2,4-dioxo-4-phenylbutanoate and hydroxylamine hydrochloride (7g, 1mol) in MeOH (150mL) was refluxed for 6 hours, when the reaction finished, the solvent was concentrated on a rotary evaporator, and the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was concentrated again on a rotary evaporator, and the residue is recrystallized from MeOH and H<sub>2</sub>O to afford compound **E3** as a white solid (15.14g, 74.6%). MS:[M+H]<sup>+</sup> 204.1, [M+Na]<sup>+</sup> 225.9. <sup>1</sup>H-NMR(500MHz,CDCl<sub>3</sub>): δ=7.79-7.78(m,2H); 7.48-7.45(m,3H); 6.92(s,1H); 3.99(s, 3H).

#### The synthesis of compound **E4**

The mixture of acetone (24g, 0.5mol) and diethyl oxalate(73g, 0.5mol) was added slowly to sodiummethoxide (0.5mol) solution in methanol (800mL) at 0-5 °C, and then the resulting solution was stirred for 6 hour at room temperature. After the reaction finished, the mixture was treated with HCl(3mol/L, 150mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was concentrated on a rotary evaporator to afford methyl 2,4-dioxopentanoate.

A solution of methyl 2,4-dioxopentanoate and hydroxylamine hydrochloride(3.5g, 0.5mol) in MeOH (150 mL)was refluxed for 4 hours, when the reaction finished, the solvent was concentrated on a rotary evaporator, and the residue was diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layer was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), the solvent was concentrated again on a rotary evaporator, and the residue is recrystallized from MeOH and H<sub>2</sub>O to afford compound **E4** as a white solid (59.36g, 84.2%). MS:[M+H]<sup>+</sup> 142.1 ; [M+Na]<sup>+</sup> 164.0; <sup>1</sup>H-NMR(400MHz,CDCl<sub>3</sub>):δ=6.43-6.42 (d,1H) ; 3.97(s,3H); 2.51-2.50(d,3H).

#### The synthesis of acid (**H1**) of compound **E1**

Compound **E1** (20.9g, 0.1mol) was dissolved in methanol (100mL), LiOH(8.2g, 0.2mol) was added and then the reaction mixture was stirred for 3h at room temperature. When the reaction finished, the precipitate was filtered and the filter cake was dissolved in water. After the aqueous solution was acidified with HCl (6mol/L) to pH 6, the aqueous was extracted with ethylacetate two times, then the ethylacetate was removed by rotavapor to afford **H1** (17.78g, 91.2%). MS:[M+H]<sup>+</sup> 196.0 ; [M+Na]<sup>+</sup> 217.9; <sup>1</sup>H

NMR(500MHz,DMSO):  $\delta$ =14.12(s,1H); 7.88-7.89(d,1H), 7.82(d,1H), 7.31(s,1H),7.25-7.28(m,1H).

### The synthesis of compound E5-E10

A series of 5-(thiophen-2-yl)isoxazole-3-carboxylatederivatives containing different alcohol moiety were synthesized with the same method, as shown in Table 1. We describe the synthesis of compound **E5** as a sample. Particularly, the purification of compound 6 is a bit different.

To a solution of compound **E5** (1.95g, 0.01mol) in toluene (100mL), SOCl<sub>2</sub> (5.95g, 0.05mol) was added, and the reaction mixture was refluxed for 4 hours, during this process, 3-5 drops DMF was added. When the reaction finished, the solvent was removed *in vacuum* to afford to a solid. The obtained solid was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5mL), then ethanol (2mL) was added dropwise slowly. After the resulting solution was stirred for 4h at room temperature, water (10mL) was added, the aqueous solution was extracted with CH<sub>2</sub>Cl<sub>2</sub> two times, and the organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>. the solvent was concentrated again on a rotary evaporator to afford the crude product, which was purified by column chromatography, eluting with ethylacetate:petroleum ether =1:15. Compound **E7** was purified by recrystallization from methanol.

Tab.1 Compound E5-E10 and their correspond materials.

| E5      | E6        | E7      | E8       | E9      | E10    |
|---------|-----------|---------|----------|---------|--------|
| Ethanol | Isopropyl | Butyl   | Tertiary | Benzyl  | Phenol |
|         | alcohol   | alcohol | butyl    | alcohol |        |
|         |           |         | alcohol  |         |        |

Compound **E5**: MS:[M+H]<sup>+</sup> 224.0; [M+Na]<sup>+</sup>246.0; [2M+Na]<sup>+</sup>469.1. Compound **E6**: MS: [M+H]<sup>+</sup>238.1; [M+Na]<sup>+</sup>260.0; [2M+Na]<sup>+</sup>497.2. Compound **E7**: MS: [M+H]<sup>+</sup> 252.0; [M+Na]<sup>+</sup>274.1; [2M+Na]<sup>+</sup> 525.0. Compound **E8**: [M+Na]<sup>+</sup>274.1; [2M+Na]<sup>+</sup>525.1. Compound **E9**: MS: [M+H]<sup>+</sup>286.0; [M+Na]<sup>+</sup>308.0; [2M+Na]<sup>+</sup>593.0. Compound **E10**: MS: [M+H]<sup>+</sup>272.1; [M+Na]<sup>+</sup>294.1; [2M+Na]<sup>+</sup> 565.1.

### **Control experiment**

Reactive experiment with alkali base were carried out in a single methanol (MeOH) solvent, the mole of isoxazole molecules and LiOH、NaOH、KOH are both 0.1mmol, the amount of MeOH solvent is 1mL. The molecules (0.1mmol) were dissolved in methanol (0.5mL) for the later use, and then adding them to the prepared methanol solution of alkali base. The dosages of these three inorganic alkalis methanol solution is 0.5mL. All of the above experimental were carried out at room temperature.

### **Characterization**

<sup>1</sup>H NMR spectra were recorded on a BrukerAV400 spectrometer. The MS spectra were measured by FT-ICR (Bruker Daltonics Inc. APEXII). The morphology of assemblies was investigated by a field emission scanning electron microscope (FE-SEM, Hitachi, S-4800). The samples were dried for 24h before the SEM measurement. The accelerating voltage was 10-15 kV and the emission current was 10 μA. The Fourier transform infrared spectroscopy (FTIR) spectra were taken by Bruker Tensor 27 FTIR spectrometer. The FTIR spectra were measured by dropping the sample on the surface of silicon pallets, and then the samples were dried for 24h. Samples were cast on glass substrates and vacuum-dried for X-ray diffraction (XRD) measurements, which was achieved on a Rigaku D/Max-2500 X-ray diffractometer (Japan) with Cu/Kα radiation ( $\lambda = 1.5406 \text{ \AA}$ ), operating at 45 kV, 100mA. The rheological properties of the gel were measured at  $25 \pm 0.05 \text{ }^\circ\text{C}$  with a Thermo Haake RS300 rheometer (cone and plate geometry of 40 mm in diameter).