Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 4851–4856

TETRAHEDRON

Solid phase synthesis of benzothiazole and thiophene derivatives based on resin-bound cyclic malonic acid ester

Xian Huang[a,b,*] and Jing Tang[a]

[a]*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou 310028, People's Republic of China*
[b]*Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China*

Received 21 October 2002; revised 2 April 2003; accepted 28 April 2003

Abstract—A new method for the solid phase synthesis of benzothiazoles and 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes is described. Resin bound cyclic malonic acid ester was reacted with aryl isothiocyanates and then with bromine or α-bromoketones, followed by treatment with perchloric acid or sodium methoxide to afford substituted 2-methylbenzothiazoles or 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes, respectively, in high yields and purities. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Combinatorial organic synthesis has developed into an important tool for the generation of libraries of pharmacologically attractive molecules. Solid-phase organic synthesis (SPOS) has been regarded as one of the important new fields in synthetic organic chemistry.[1] SPOS techniques offers a powerful strategy for the discovery and generation of drug lead heterocyclic compounds. In addition, a solid-phase approach is interesting since the reaction can be driven to completion by using excess reagents, which are subsequently removed by simple filtration. The work-up is therefore easy and can be automated.

We have previously reported the synthesis of a variety of heterocyclic compounds from the derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in solution.[2] Recently, we reported the preparation of resin-bound cyclic malonic acid ester and its application in the synthesis of heterocyclic compounds.[3] The reaction of the resin-bound cyclic malonic acid ester with triethyl orthoformate and subsequent double substitution with nucleophilic reagents, followed by thermal cyclization at 220–250°C gave a series of heterocyclic compounds.[3] However, as the last step needs high temperature, this methodology may be limited to thermally stable heterocyclic compounds.

Meldrum's acid is a versatile intermediate in organic synthesis due to nucleophilic on it along with the unique ring-opening reaction.[4] In view of this, it is anticipated that Meldrum's acid derivatives could be cleaved by milder methods. For example, the alkylthiomethylene derivative of Meldrum's acid, which is an important intermediate, can react with various reagents and subsequently cyclise to afford heterocyclic compounds under milder conditions.[5] Meanwhile, benzothiazole derivatives are of particular interest within the realm of medicinal chemistry.[6] For example, many useful therapeutic agents containing the benzothiazole moiety possess selective antitumor activities and antimicrobial properities.[7a–e] Compounds containing a thiophene moiety also possess a wide range of biological activities.[8] As part of our research on the solid-phase synthesis of heterocyclic compounds by resin-bound malonic acid ester, we wish to report in this paper a suitable method for the preparation of resin-bound functionalized alkylthiomethylene cyclic malonic acid esters and their applications in the synthesis of substituted benzothiazoles and multisubstituted thiophenes based on the resin-bound cyclic malonic acid ester under milder cleavage conditions.

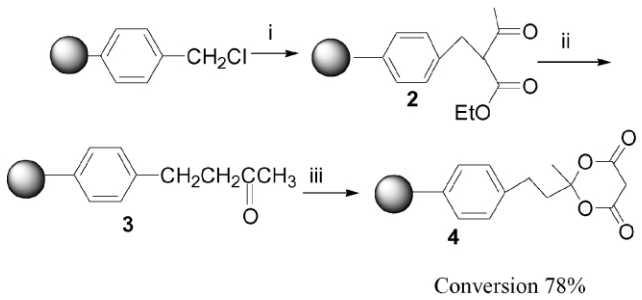
2. Results and discussion

2.1. Preparation of the resin-bound cyclic malonic acid ester 4[3]

The resin-bound cyclic malonic acid ester **4** was prepared from the Merrifield resin, as outlined in Scheme 1. Merrifield resin was reacted with sodium ethyl acetoacetate in DMF to give the β-keto ester resin **2**. Decarboxylation of resin **2** afforded the ketone resin **3**. The resin **3** was reacted with malonic acid and acetic anhydride in the presence of concentrated H_2SO_4 to give the resin-bound cyclic malonic acid ester **4**.

Keywords: benzothiazole; thiophene; resin-bound; cyclic malonic acid ester.
* Corresponding author. Fax: +86-571-88807077;
e-mail: huangx@mail.hz.zj.cn

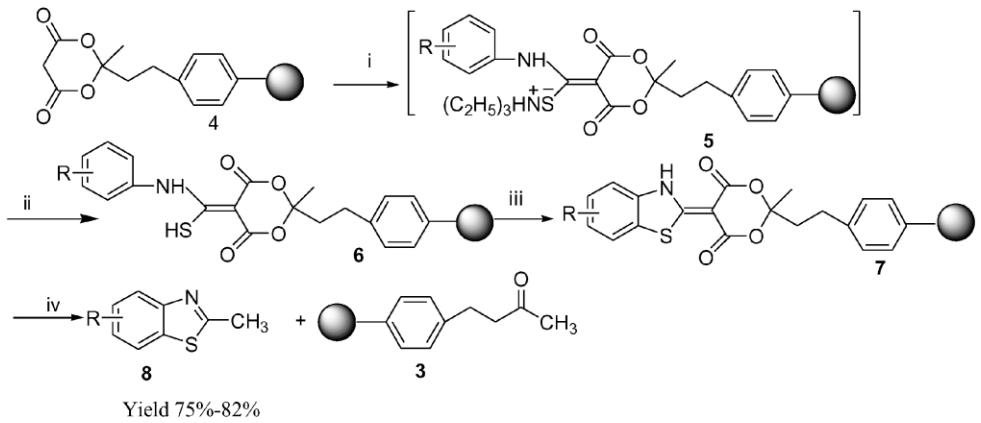
0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4020(03)00688-4



Scheme 1. *Reagents and conditions*: (i) sodium ethyl acetoacetate, DMF, 80°C, 16 h; (ii) DMSO, NaCl, 140°C, 48 h; (iii) malonic acid, acetic anhydride, conc. H_2SO_4.

same purity as the first time even after five runs (entry **9**, Table 1).

The multi-step synthesis from resin **4** to final product was monitored by FT-IR. The resin-bound cyclic malonic acid ester **4** showed carbonyl peaks at 1767 and 1794 cm^{-1} in the IR spectrum. When the cyclic malonic acid ester resin was converted into the resins **6**, the IR carbonyl peaks shifted to 1738 and 1684 cm^{-1} with new peaks at 1545 cm^{-1} (C=C) and 2552 cm^{-1} (S–H). Disappearance of the 2552 cm^{-1} indicated complete transformation of resin **6** into resin **7**. After cleavage, the recovered resin possessed the same IR spectrum as that of the resin **3.**



Scheme 2. *Reagents and conditions*: (i) (a) Et_3N, DMF, rt, 1 h; (b) R–C_6H_4NCS, 45°C, 18 h; (ii) 2 M HCl; (iii) Br_2, AcOH, rt, 2 h; (iv) $HClO_4$, CH_3CN, reflux, 4 h.

2.2. Solid-phase synthesis of 2-methyl benzothiazoles 8

Because aryl isothiocyanates are highly reactive towards activated methylene compounds, aryl isothiocyanates can react with resin-bound cyclic malonic ester smoothly (Scheme 2).

Initially, we investigated the synthesis of resin **6** by using various bases. When sodium hydride was used as base at room temperature, the yield and purity of product **8** were unsatisfactory. Due to the stronger acidity of the methylene of resin-bound cyclic malonic acid ester **4**, triethylamine was used to deprotonate the methylene of the resin-bound cyclic malonic acid ester **4** to form the anion at room temperature. The formed anion was reacted with the aryl isothiocyanates in anhydrous DMF at 45°C, and after 18 h, was treated with 2 M HCl to generate resin **6**. Excess reagents were removed by simple washing with solvents (EtOH, CH_2Cl_2). The resin **6** was then treated with bromine at room temperature to give the corresponding resin **7**. We further examined cleavage conditions of the resin **7**, but when 50% TFA/CH_2Cl_2 and 100% TFA were adopted, cleavage did not take place. However, the desired product **8** was obtained in good yield and excellent purity when the resin **7** was treated with perchloric acid (70–72%) in refluxing CH_3CN. The results are summarized in Table 1. Finally, we verified that the released ketone resin **3** was reusable. Resin **4** was thus prepared from the recovered ketone resin **3** and the corresponding reactions were repeated. After cleavage, **8a** was obtained in nearly the

2.3. Solid-phase synthesis of 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes 10

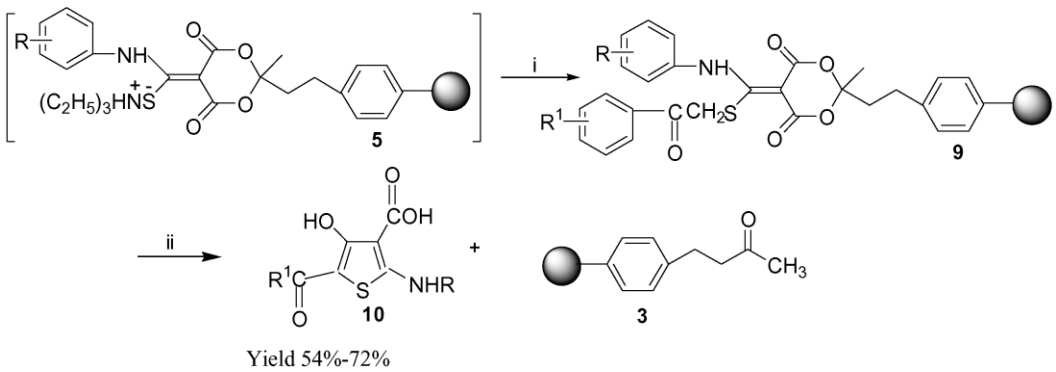
The potential utility of intermediate **5** for the synthesis of other heterocyclic compounds makes the solid-phase approach even more attractive. So, we further investigated the reaction of intermediate **5** with α-bromoketones, which provides an efficient method for the synthesis of 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes (Scheme 3).

The polymer-bound cyclic malonic acid ester **4** was treated with aryl isothiocyanates in the presence of Et_3N in dry DMF at 45°C to afford intermediates **5**, then an

Table 1. Yields and purities of benzothiazoles **8**

Entry	R	Product	Yield[a]	Purity[b]
1	H	**8a**	79	>95
2	5-Cl	**8b**	75	>95
3	4-Br-6-CH_3O	**8c**	80	>95
4	4-CH_3	**8d**	80	>95
5	6-CH_3	**8e**	82	>95
6	6-Cl	**8f**	81	>95
7	6-Br	**8g**	77	>95
8	6-F	**8h**	76	>95
9	H	**8a**	76	>95[c]

[a] The yields are based on the loading of the cyclic malonic acid ester resin **4**.[9]
[b] Determined by ^1H NMR spectroscopy.
[c] The regenerated resin was used (fifth run).



Scheme 3. *Reagents and conditions*: (i) α-bromo-ketones, rt, 6 h; (ii) CH_3OH, CH_3ONa, reflux, 4 h.

α-bromoketone was added and stirred at room temperature for 6 h to provide resin **9**.[5] Excess reagents were removed by simple washing with the solvents (EtOH, CH_2Cl_2). The cyclization cleavage of resin **9** was carried out using CH_3ONa in refluxing methanol. 2-Arylamino-3-carboxyl-4-hydroxyl-5-arylthiophenes was obtained in good yields and excellent purities (Table 2). The multisubstituted thiophenes are potentially useful building blocks for further transformations. Furthermore, the regenerated resin **3** was reusable. This method has attractive features such as the cyclisation with concomitant cleavage from the resin in one-step and under mild reaction conditions. For each resin-bound intermediate, the structure was also verified by FT-IR spectra. When the cyclic malonic acid ester resin **4** was converted into the resin **9**, the IR carbonyl peak shifted to 1738, 1684 cm^{-1} from 1794, 1768 cm^{-1}, respectively, and two new peaks appeared at 1545 cm^{-1} (C═C) and 1680 cm^{-1} (C═O) attributed to the additional ketone carbonyl group. After cleavage, the recovered resin possessed the same IR spectra as that of the resin **3.**

Table 2. Yields and purities of 2-amino-3-carboxyl-4-hydroxy-5-arylthiophenes **10**

Entry	R	R^1	Product	Yield[a]	Purity[b]
1	C_6H_5	C_6H_5	**10a**	68	95
2	C_6H_5	$4\text{-}CH_3C_6H_4$	**10b**	66	92
3	C_6H_5	$4\text{-}ClC_6H_4$	**10c**	72	90
4	$4\text{-}CH_3C_6H_4$	C_6H_5	**10d**	63	91
5	$4\text{-}CH_3C_6H_4$	$4\text{-}ClC_6H_4$	**10e**	60	90
6	$2\text{-}CH_3C_6H_4$	$4\text{-}CH_3C_6H_4$	**10f**	62	93
7	$2\text{-}CH_3C_6H_4$	$4\text{-}ClC_6H_4$	**10g**	71	92
8	$3\text{-}ClC_6H_4$	C_6H_5	**10h**	54	94
9	$3\text{-}CH_3C_6H_4$	$4\text{-}ClC_6H_4$	**10i**	68	90
10	$4\text{-}CH_3OC_6H_4$	$4\text{-}ClC_6H_4$	**10j**	58	88
11	C_6H_5	$4\text{-}CH_3C_6H_4$	**10b**	64	91[c]

[a] The yields were based on the loading of the cyclic malonic acid ester resin **4**.[9]
[b] Determined by ^1H NMR spectroscopy.
[c] The recovered resin was used (third run).

3. Conclusion

In summary, we have developed a new method for the preparation of resin-bound functionalized alkylthiomethylene cyclic malonic acid esters and applied them to the synthesis of substituted 2-methyl-benzothiazoles and 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes using mild cleavage protocols. The distinct advantages of this solid-phase synthetic method include the milder cleavage conditions, the practicality and the excellent yields and purities. Moreover, we have described a new traceless cleavage SPOS route for the synthesis of heterocyclic compounds and the polymer bound ketone could be regenerated easily for reuse after cleavage. We are extending this methodology to the synthesis of other heterocyclic templates, and we will continue to report on this work in future disclosures.

4. Experimental

The melting points were uncorrected. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ with TMS as the internal standard; chemical shifts were quoted in ppm and *J* values were given in Hz. IR spectra were recorded on a Bruker Vector 22 spectrometer. EIMS was run on a HP 5989B mass spectrometer. The resin was prepared according to a literature procedure.[3] Aryl isothiocyanates were prepared according to the standard methodologies.[10] DMF (AR) and methanol (AR) were obtained commercially and dried before used.

4.1. General procedure for the preparation of the resin bound cyclic malonic acid ester 4

To a solution of sodium ethyl acetoacetate (39.2 mmol, 5.96 g) in 30 mL of DMF was added Merrifield resin (2.0 g, 1% cross-linked, 200–400 mesh, loading=1.96 mequiv. Cl/g) and the mixture was stirred at 80°C for 16 h and filtered. After washing successively with DMF, EtOH and CH_2Cl_2, the β-keto ester resin **2** was obtained (IR 1749, 1715 cm^{-1}). The β-keto ester resin **2** (2.0 g) was suspended in a mixture of DMSO (30 mL), NaCl (40 mmol) and H_2O (120 mmol) and the mixture was refluxed for 48 h. The mixture was filtered and washed with H_2O, DMF, EtOH and CH_2Cl_2, The ketone resin **3** (IR, 1717 cm^{-1}) was obtained (loading=1.88 mmol/g, the loading of resin **3** was determined by titration with sodium hydroxide after the reaction of resin **3** with hydroxylamine hydrochloride.[3,11]). A solution of malonic acid (38 mmol, 3.95 g), concentrated sulfuric acid (0.1 mL) and acetic anhydride (117 mmol, 11.90 g) was allowed to stand for 24 h at room temperature and was then concentrated at 40°C under reduced pressure. The resin **3** (2 g, pre-swelled in 17 mL dry CH_2Cl_2 for 12 h) was added to the residue at 0°C. Then the mixture was stirred at 15°C for 24 h and filtered. After washing with

H_2O, EtOH and CH_2Cl_2. The cyclic malonic acid ester resin **4** (loading=1.11 mmol/g, IR, 1794, 1767, 1290 cm^{-1}) was obtained. The loading of resin **4** was determined by reversed titration with hydrochloric acid after saponification with excess NaOH in EtOH.[3]

4.2. General procedure for the syntheses of 2-methylbenzothiazoles 8

Resin-bound cyclic malonic acid ester **4** (500 mg, 1.11 mmol/g) was pre-swelled in dry DMF (5 mL) for 5 h, triethylamine (5.55 mmol, 0.77 mL) was added and then stirred at room temperature for 1 h, the aryl isothiocyanate (2.78 mmol) was added dropwise to the suspension. The mixture was warmed to 45°C and stirred for 18 h, cooled to room temperature, then 2 M HCl solution was added to the reaction mixture and stirred for 30 min to afford the resin **6** (IR 2552, 1738, 1684, 1545 cm^{-1}) after washing with H_2O (3×10 mL), EtOH (3×10 mL), CH_2Cl_2 (3×10 mL) and drying under vacuum. Bromine (0.55 mmol, 89 mg) was added to a suspension of resin **6** in acetic acid and stirred for 2 h at room temperature and filtered. After washing successively with H_2O (3×10 mL), EtOH (3×10 mL), CH_2Cl_2 (3×10 mL) and drying under vacuum, the resin **7** was obtained. The resin **7** was swelled in acetonitrile (5 mL), then treated with 70–72% perchloric acid (0.5 mL) and heated to reflux for 4 h. When the mixture was cooled to room temperature, the resin was filtered and washed thoroughly with water. The filtrates were combined and neutralized with 2 M NaOH to pH=7 and extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with water and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give the products **8**.

4.2.1. 2-Methylbenzothiazole 8a. Yield: 65.3 mg (79%); white solid; mp 12–14°C (lit [12] picrate salt 151–152°C); ^1H NMR ($CDCl_3$) δ 2.83 (3H, s), 7.26–7.36 (1H, m), 7.42–7.46 (1H, m), 7.82 (1H, d, J=8.0 Hz), 7.96 (1H, d, J=7.2 Hz); MS *m/z* (relative intensity) 149 (M^+, 100), 117 (15), 104 (4); IR ν_{max} (cm^{-1}) 1558, 1523, 1456, 1312, 1238.

4.2.2. 5-Chloro-2-methylbenzothiazole 8b. Yield: 76.1 mg (75%); white solid; mp 68–69°C (lit [13] 67–69°C); ^1H NMR ($CDCl_3$) δ 2.82 (3H, s), 7.38–7.41 (1H, dd, J_1=2.0 Hz, J_2=8.6 Hz), 7.79 (1H, s), 7.83 (1H, d, J=8.6Hz); MS *m/z* (relative intensity) 185 (M^+, ^{37}Cl, 37), 183 (M^+, ^{35}Cl, 100), 148 (39), 116 (20), 103 (21); IR ν_{max} (cm^{-1}) 1546, 1523, 1446, 1305, 1271.

4.2.3. 4-Bromo-6-methoxy-2-methylbenzothiazole 8c. Yield: 114.9 mg (80%); white solid; mp 104–106°C; ^1H NMR ($CDCl_3$) δ 2.79 (3H, s), 3.95 (3H, s), 7.29 (1H, s), 8.11 (1H, s); Elemental analysis Calcd for C_9H_8BrNOS, C 41.88%; H 3.12%; N 5.43% Found C 41.87%, H 3.14%, N 5.40%; MS *m/z* (relative intensity) 259 (M^+, ^{81}Br, 98), 257 (M^+, ^{79}Br, 100), 242 (64), 212 (32), 133 (15); IR ν_{max} (cm^{-1}) 1604, 1558, 1530, 1452, 1306, 1245, 1203.

4.2.4. 2,4-Dimethylbenzothiazole 8d. Yield: 72.3 mg (80%); white solid; mp 33–34°C (lit[14] mp 33–34°C); ^1H NMR ($CDCl_3$) δ 2.64 (3H, s), 2.75 (3H, s), 7.13–7.17 (2H, m), 7.54–7.57 (1H, m); MS *m/z* (relative intensity) 163 (M^+, 100), 148 (10), 130 (8), 121 (52); IR ν_{max} (cm^{-1}) 1604, 1558, 1530, 1452, 1306, 1245.

4.2.5. 2,6-Dimethylbenzothiazole 8e. Yield: 74.1 mg (82%); oil (lit[15]); ^1H NMR ($CDCl_3$) δ 2.41 (3H, s), 2.76 (3H, s), 7.21 (1H, d, J=8.2 Hz), 7.53 (1H, s), 7.81 (1H, d, J=8.3 Hz); MS *m/z* (relative intensity) 163 (M^+, 100), 148 (10), 133 (8); IR ν_{max} (cm^{-1}) 1604, 1558, 1530, 1452, 1306, 1245.

4.2.6. 6-Chloro-2-methylbenzothiazole 8f. Yield: 82.2 mg (81%); white solid; mp 84–86°C (lit [13] 84–86°C); ^1H NMR ($CDCl_3$) δ 2.82 (3H, s), 7.38–7.41 (1H, dd, J_1=2.0 Hz, J_2=8.6 Hz), 7.79 (1H, d, J=8.5 Hz), 7.83 (1H, s); MS *m/z* (relative intensity) 185 (M^+, ^{37}Cl, 37), 183 (M^+, ^{35}Cl, 100), 148 (39), 116 (21); IR ν_{max} (cm^{-1}) 1548, 1523, 1446, 1305, 1271.

4.2.7. 6-Bromo-2-methylbenzothiazole 8g. Yield: 97.8 mg (77%); white solid; mp 87–88°C (lit [16] 85–87°C); ^1H NMR ($CDCl_3$) δ 2.82 (1H, s), 7.52 (1H, dd, J_1=2.0 Hz, J_2=8.6 Hz), 7.78 (1H, d, J=8.6 Hz), 7.95 (1H, s); MS *m/z* (relative intensity) 229 (M^+, ^{81}Br, 100), 227 (M^+, ^{79}Br, 98), 148 (40), 133 (40); IR ν_{max} (cm^{-1}) 1587, 1517, 1440, 1303, 1268.

4.2.8. 6-Flouro-2-methyl-benzothiazole 8h. Yield: 70.4 mg (76%); white solid; mp 112–114°C; ^1H NMR ($CDCl_3$) δ 2.80 (1H, s), 7.14–7.19 (1H, m), 7.47–7.50 (1H, dd, J_1=2.5 Hz, J_2=8.1 Hz), 7.85–7.89 (1H, m); ^{13}C NMR 19.4, 107.0 (J=26.2), 113.8 (J=24.4), 122.6 (J=9.3), 136.0 (J=10.9), 149.4, 159.6 (J=243.2), 166.0 (J=24.4); Elemental analysis. Calcd for C_8H_6FNS, C 57.47%; H 3.62%; N 8.38% Found C 57.33%, H 3.66%, N 8.36%; MS *m/z* (relative intensity) 167 (M^+, 100), 148 (20), 133 (7), 101 (2); IR ν_{max} (cm^{-1}) 1603, 1567, 1528, 1453, 1311, 1254.

4.3. General procedure for the syntheses of 2-arylamino-3-carboxyl-4-hydroxy-5-arylthiophenes 10

Resin-bound cyclic malonic acid ester **4** (500 mg, 1.11 mmol) was pre-swelled in dry DMF (5 mL) for 5 h, triethylamine (5.55 mmol, 0.77 mL) was added and then stirred at room temperature for 1 h, the aryl isothiocyanate (2.78 mmol) was added dropwise to the suspension, the mixture was allowed to warm 45°C and stirred for 18 h. The suspension was then cooled to room temperature, α-bromoketone (2.78 mmol) was added and the mixture was stirred for 6 h to afford the resin **9** (IR 1738, 1684, 1680, 1545 cm^{-1}) after washing with H_2O (3×10 mL), EtOH (3×5 mL), CH_2Cl_2 (3×5 mL) and then drying under vacuum for 24 h. The resin **9** and sodium methoxide (2.78 mmol) in methanol (15 mL) were refluxing for 4 h. Then solvent was evaporation under reduced pressure. Water was added to the residual, the resin was filtered and washed with water (3×10 mL). The filtrates were combined and neutralized with 1 M HCl to pH=5 to produce the precipitated. After filtered, washed with water (3×5 mL) and dried under vacuum, the products **10** were obtained.

4.3.1. 5-Benzoyl-4-hydroxy-2-phenylamino-3-thiophenecarboxylic acid 10a. Yield: 127.9 mg (68%); yellow solid;

mp 169–170°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.38 (3H, m), 7.46–7.55 (5H, m), 7.79 (2H, d, J=6.9 Hz), 11.07 (1H, s, NH), 12.33 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 99.2, 102.3, 123.0, 127.9, 128.2, 129.4, 130.4, 132.6, 133.6, 137.5, 166.6, 169.3, 172.4, 187.3; Elemental analysis. Calcd for $C_{18}H_{13}NO_4S$, C 63.71%; H 3.86%; N 4.13% Found C 63.53%, H 3.77%, N 4.36%; MS m/z (relative intensity), 339 (M^+, 24), 321 (23), 295 (23), 105 (35), 77 (100); IR ν_{max} (cm^{-1}) 3337, 1715, 1680, 1593, 1549, 1493, 1462, 1438, 1363, 1080.

4.3.2. 5-(4-Methylbenzoyl)-4-hydroxy-2-phenylamino-3-thiophenecarboxylic acid 10b. Yield: 129.3 mg (66%); yellow solid; mp 218–220°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (3H, s), 7.29–7.38 (5H, m), 7.45 (2H, d, J=7.8 Hz), 7.69 (2H, d, J=8.1 Hz), 11.04 (1H, s, NH), 12.40 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 21.1, 98.3, 100.8, 122.0, 126.9, 127.3, 129.2, 129.4, 129.9, 136.6, 142.6, 165.7, 168.8, 171.2, 186.2; Elemental analysis. Calcd for $C_{19}H_{15}NO_4S$, C 64.58%; H 4.28%; N 3.96% Found C 64.36%, H 4.11%, N 4.03%; MS m/z (relative intensity) 353 (M^+, 50), 335 (38), 309 (33), 91 (100), 77 (93); IR ν_{max} (cm^{-1}) 3400, 1707, 1677, 1591, 1569, 1544, 1458, 1076.

4.3.3. 5-(4-Chlorobenzoyl)-4-hydroxy-2-phenylamino-3-thiophenecarboxylic acid 10c. Yield: 149.0 mg (72%); yellow solid; mp 221–222°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.36 (2H, m), 7.49–7.58 (5H, m), 7.79 (2H, d, J=8.3 Hz), 11.07 (1H, s, NH), 12.45 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 99.8, 102.2, 123.0, 127.3, 128.2, 129.2, 130.5, 133.9, 137.6, 141.8, 166.3, 169.5, 171.9, 187.3; Elemental analysis. Calcd for $C_{18}H_{12}ClNO_4S$, C 57.84%; H 3.24%; N 3.75% Found C 57.54%; H 3.40%; N 3.98%; MS m/z (relative intensity) 373 (M^+, ^{35}Cl, 50), 375 (M^+, ^{37}Cl, 20), 355 (38), 329 (33), 292 (36), 91 (100), 77 (93); IR ν_{max} (cm^{-1}) 3380, 1715, 1678, 1593, 1549, 1462, 1438, 1080.

4.3.4. 5-Benzoyl-4-hydroxy-2-(4-methylphenylamino)-3-thiophenecarboxylic acid 10d. Yield: 123.4 mg (63%); yellow solid; mp 194–196°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s), 7.13–7.26 (3H, m), 7.44–7.54 (4H, m), 7.77 (2H, d, J=6.9 Hz), 10.86 (1H, s, NH), 12.41 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.2, 98.5, 100.9, 123.2, 127.1, 128.1, 129.4, 129.6, 129.8, 130.4, 142.8, 166.3, 169.1, 171.3, 187.2; Elemental analysis. Calcd for $C_{19}H_{15}NO_4S$, C 64.58%; H 4.28%; N 3.96% Found 64.59%, H 4.59%, N 4.01%; MS m/z (relative intensity) 353 (M^+, 51), 335 (30), 309 (25), 91 (100), 77 (68); IR ν_{max} (cm^{-1}) 3400, 1707, 1680, 1591, 1569, 1544, 1442, 1076.

4.3.5. 5-(4-Chlorobenzoyl)-4-hydroxy-2-(4-methylphenylamino)-3-thiophenecarboxylic acid 10e. Yield: 128.8 mg (60%); yellow solid; mp 214–216°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 7.44 (4H, m), 7.71 (2H, d, J=8.5 Hz), 8.02 (2H, d, J=8.4 Hz), 10.94 (1H, s, NH), 12.21 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.1, 98.5, 101.9, 123.5, 127.4, 128.5, 129.2, 131.7, 134.6, 135.6, 137.8, 166.8, 168.3, 171.4, 187.5; Elemental analysis. Calcd for $C_{19}H_{14}ClNO_4S$, C 58.84%; H 3.64%; N 3.61% Found C 59.01%, H 3.55%, N 3.79%; MS m/z (relative intensity 387 (M^+, ^{35}Cl, 28), 389 (M^+, ^{37}Cl, 11), 369 (29), 343 (50), 306 (26), 91 (100); IR ν_{max} (cm^{-1}) 3345, 1717, 1678, 1604, 1592, 1574, 1550, 1448, 1424, 1092.

4.3.6. 5-(4-Methylbenzoyl)-4-hydroxy-2-(2-methylphenylamino)-3-thiophenecarboxylic acid 10f. Yield: 126.2 mg (62%); yellow solid; mp 204–206°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 2.40 (3H, s), 7.28–7.33 (5H, m), 7.39–7.41 (1H, m), 7.68 (2H, d, J=8.1 Hz), 10.80 (1H, s, NH), 12.34 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.5, 22.1, 99.7, 101.7, 121.0, 123.1, 127.9, 128.3, 130.2, 130.7, 131.4, 136.1, 138.7, 143.8, 166.6, 170.4, 171.2, 187.0; Elemental analysis. Calcd for $C_{20}H_{17}NO_4S$, C 65.38%; H 4.66%; N 3.81% Found C 65.38%, H 4.33%, N 3.79%; MS m/z (relative intensity) 367 (M^+, 17), 349 (12), 323 (21), 308 (41), 293 (27), 91 (100), 77 (16); IR ν_{max} (cm^{-1}) 3400, 1710, 1677, 1609, 1588, 1543, 1440, 1077.

4.3.7. 5-(4-Chlorobenzoyl)-4-hydroxy-2-(2-methylphenylamino)-3-thiophenecarboxylic acid 10g. Yield: 152.4 mg (71%); yellow solid; mp 186–188°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 7.26–7.34 (3H, m), 7.38–7.41 (1H, m), 7.44 (2H, d, J=8.5 Hz), 7.69 (2H, d, J=8.6 Hz), 10.84 (1H, s, NH), 12.21 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.2, 98.5, 102.2, 123.8, 127.4, 128.6, 129.1, 129.3, 131.7, 131.8, 133.2, 135.7, 138.4, 166.1, 167.1, 173.4, 187.1; Elemental analysis. Calcd for $C_{19}H_{14}ClNO_4S$, C 58.84%; H 3.64%; N 3.61% Found C 58.54%; H 3.31%; N 3.77%; MS m/z (relative intensity) 387 (M^+, ^{35}Cl, 22), 389 (M^+, ^{37}Cl, 8), 369 (27), 343 (42), 306 (65), 91 (65), 77 (30); IR ν_{max} (cm^{-1}) 3385, 1713, 1680, 1592, 1586, 1544, 1441, 1073.

4.3.8. 5-Benzoyl-4-hydroxy-2-(3-chlorophenylamino)-3-thiophenecarboxylic acid 10h. Yield: 111.7 mg (54%); yellow solid; mp 197–198°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.33 (2H, m), 7.39–7.43 (2H, m), 7.51–7.57 (3H, m), 7.80 (2H, d, J=7.0 Hz), 11.09 (1H, s, NH), 12.29 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 99.6, 102.2, 123.2, 127.1, 128.3, 129.4, 130.5, 131.7, 132.2, 133.4, 135.7, 138.1, 166.8, 169.2, 173.3, 187.1; Elemental analysis. Calcd for $C_{18}H_{12}ClNO_4S$, C 57.84%; H 3.24%; N 3.75% Found C 57.93%; H 3.29%; N 4.01%; MS m/z (relative intensity) 373 (M^+, ^{35}Cl, 15), 375 (M^+, ^{37}Cl, 5), 355 (21), 329 (12), 77 (100); IR ν_{max} (cm^{-1}) 3388, 1711, 1682, 1606, 1588, 1543, 1440, 1077.

4.3.9. 5-(4-Chlorobenzoyl)-4-hydroxy-2-(3-methylphenylamino)-3-thiophenecarboxylic acid 10i. Yield: 146.0 mg (68%); yellow solid; mp 190–192°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 7.27–7.29 (3H, m), 7.40–7.44 (3H, m), 7.61 (2H, d, J=8.6 Hz, ArH), 10.92 (1H, s, NH), 12.30 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.4, 99.2, 101.8, 120.6, 122.8, 127.6, 127.8, 129.1, 131.0, 132.4, 133.1, 135.7, 138.2, 166.1, 169.7, 171.7, 186.7; Elemental analysis. Calcd for $C_{19}H_{14}ClNO_4S$, C 58.84%; H 3.64%; N 3.61% Found C 59.05%; H 3.88%; N 3.88%; MS m/z (relative intensity), 387 (M^+, ^{35}Cl, 18), 389 (M^+, ^{37}Cl, 6), 349 (12), 323 (21), 91(100); IR ν_{max} (cm^{-1}) 3400, 1712, 1680, 1609, 1588, 1543, 1440, 1077.

4.3.10. 5-(4-Chlorobenzoyl)-4-hydroxy-2-(4-methoxylphenylamino)-3-thiophenecarboxylic acid 10j. Yield: 129.7 mg (58%); yellow solid; mp 199–201°C; ^{1}H NMR

(400 MHz, $CDCl_3$) δ 3.85 (3H, s), 6.69 (2H, d, J=8.7 Hz), 7.43–7.46 (2H, m), 7.70 (2H, d, J=8.5 Hz), 8.01 (2H, d, J=8.3 Hz), 10.96 (1H, s, NH), 12.22 (1H, br, COOH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 51.5, 100.8, 102.0, 121.7, 123.2, 126.7, 129.2, 132.1, 134.6, 136.8, 140.9, 166.0, 167.7, 171.2, 180.5; Elemental analysis. Calcd for $C_{19}H_{14}ClNO_5S$, C 56.51%; H 3.49%; N 3.47% Found C 56.76%; H 3.27%; N 3.68%; MS *m/z* (relative intensity) 403 (M^+, ^{35}Cl, 100), 405 (M^+, ^{37}Cl, 37), 387 (21), 361 (12), 324 (36), 77 (100); IR ν_{max} (cm^{-1}) 3400, 1717, 1680, 1609, 1588, 1543, 1440, 1077.

Acknowledgements

We are grateful to the Natural Science Foundation of China (Project No.20072032).

References

1. Recent reviews on SPOS, see: (a) Brown, R. C. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293–3320. (b) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385–15443. (c) James, I. W. *Tetrahedron* **1999**, *55*, 4855–4946. (d) Corbett, J. W. *Org. Prep. Proced.* **1998**, *30*, 491–550. (e) Lorsbach, B. A.; Kurth, M. *J. Chem. Rev.* **1999**, *99*, 1549–1581. (f) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091–2157.
2. (a) Chen, B. C.; Huang, X.; Wang, J. *Synthesis* **1987**, 482–483. (b) Chen, B. C.; Huang, X.; Ma, S. M. *Synth. Commun.* **1987**, *17*, 1519–1522. (c) Ye, F. C.; Chen, B. C.; Huang, X. *Synthesis* **1989**, *4*, 317–320. (d) Huang, X.; Chen, B. C.; Wu, G. Y.; Chen, H. B. *Synth. Commun.* **1991**, *21*, 1213–1221.
3. (a) Huang, X.; Liu, Z. X. *Tetrahedron Lett.* **2001**, *42*, 7655–7657. (b) Huang, X.; Liu, Z. X. *J. Org. Chem.* **2002**, *67*, 6731–6737.
4. For reviews on Meldrum's acid, see: (a) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358. (b) Chen, B. C. *Heterocycles* **1991**, *32*, 529–597. (c) Gaberm, A. M.; McNab, H. *Synthesis* **2001**, 2059–2074.
5. Augustin, M.; Guenther, E.; Wiss, Z. *Martin-Luther-Univ. Halle-Wittenberg, Math-Naturwiss.Reihe* **1989**, *38*(3), 27–36.
6. (a) Bock, M. G.; Dipardo, R. M.; Evans, B. E.; Rittl, K. E.; Whittner, W. L.; Veber, D. F.; Anderson, P. S.; Freidiger, R. M. *J. Med. Chem.* **1989**, *13*, 16. (b) Kantoci, D.; Murray, E. D.; Quiggle, D. D.; Wechter, W. J. *J. Med. Chem.* **1996**, *39*, 1196.
7. (a) Nahed, K. Can. Pat. Appl. CA 2030159/1991 cited in *Chem. Abstr.* **1991**, *115*, 198515f. (b) Nahed, K. Can. Pat, EP 430036/1991 cited in *Chem. Abstr.* **1992**, *116*, 717c. (c) Geoffrey, W.; Tracey, D. B.; Patrizia, D.; Angela, S.; Dong, F. S.; Andrew, D. W.; Malcolm, F. G. S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 513. (d) Pamler, P. J.; Trigg, R. B.; Warrington, J. V. *J. Med. Chem.* **1971**, *14*, 248. (e) Chaffma, M.; Brogden, R. N. *Drugs* **1985**, *29*, 387.
8. (a) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Barzi, A.; Nocentini, G.; Yong, H. Y.; Oconner, A.; Jayaram, H. N.; Carrell, C.; Goldstein, B. M. *J. Med. Chem.* **1995**, *38*(19), 3829. (b) Gromowitz, S.; Hoernfeldt, A. B. *Chem. Heterocycl. Comp.* **1991**, *44*, 1–294.
9. The loading of resin **4** was determined by reversed titration with hydrochloric acid after saponification with excess NaOH in EtOH.
10. Vittenet, H. E. A. *Bull. Soc. Chim. Jpn.* **1899**, *21*, 955.
11. Sidney, S. Quantitative Organic Analysis via Functional Group, **1963**, 3rd, 73.
12. Belsteins Handbuch der Organischen Chemie 27, 46.
13. Spitulmik, M. J. *Synthesis* **1976**, 730.
14. *Chem. Abstr.* 52, 9091fg.
15. Belsteins Handbuch der Organischen Chemie 27, 49.
16. Paramasivam, R.; Ramakrsishnan, V. T.; Indian, *J. Chem. Sect. B* **1987**, *7*, 930.