SHORT PAPER

J. Chem. Research (S), 2003, 354–355

An efficient solid–phase synthesis of 3-carboxycoumarins based on a scaffold–polymer-bound cyclic malonic ester

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

[a]*Department of Chemistry, Zhejiang University (Campus Xixi), Hangzhou, 310028, P.R. China*

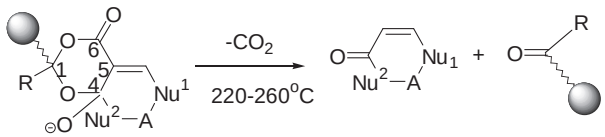
[b]*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, 200032, P.R. China*

The condensation of substituted o-methoxybenzaldehydes or o-hydroxybenzaldehydes with a resin-bound cyclic malonic ester **3** afforded the resin **4** without catalyst. Cyclisation of the resin **4** in sulfuric acid formed 3-carboxycoumarins in good yield and excellent purity.

Keywords: resin-bound cyclic malonic acid ester, o-methoxybenzaldehydes or *o*-hydroxybenzaldehydes, 3-carboxycoumarins.

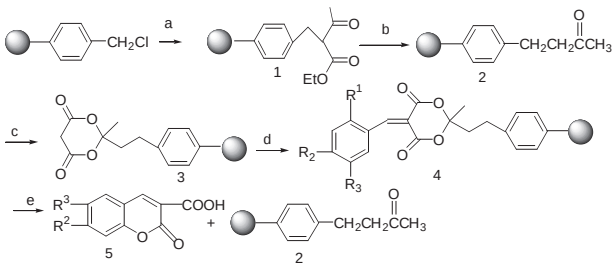
Solid phase synthesis (SPOS) has received attention because it is a powerful method for the rapid discovery of pharmaceutical lead compounds. The products can be easily purified with a simple wash of the resin.[1a–c] Heterocyclic molecules are of biological interest. Coumarins are very well known natural products, which display a broad range of biological activities. They have been prepared in solution phase.[2]

We have previously reported syntheses of a variety of heterocyclic compounds from the derivatives of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) in solution. [3] Recently, we reported the preparation of a resin-bound cyclic malonic ester and the reaction of the resin-bound cyclic malonic acid ester with triethyl orthoformate and subsequent substitution with bidentate nucleophilic reagents, followed by thermal cyclisation at 220–250°C to give a series of heterocyclic compounds.[4]



However, the last cyclisation cleavage step required high temperatures, and this methodology may be limited to thermally stable heterocycles. Meldrum's acid is a versatile intermediate in organic synthesis, arising from electrophilic attack (via the anion) at C-5 and nucleophilic attack at C-4 and C-6 along with its unique ring opening reaction.[5] In view of this, we considered that it can be cleaved by milder methods. In this paper, we described the preparation of 3-carboxycoumarins based on polymer-bound cyclic malonic ester *via* efficient solid-phase synthesis under the mild conditions. The route was outlined as following Scheme 1

Our solid phase synthesis route began with commercially available Merrifield resin loaded with the cyclic malonic ester **3**, which is prepared according to the previous communication.[4] Condensation of the resin-bound malonic ester **3** with *o*-methoxybenzaldehydes or *o*-hydroxybenzaldehydes was performed in DMF without a catalyst. The resin **3** was preswelled in dry DMF, and the *o*-methoxybenzaldehydes or *o*-hydroxybenzaldehydes was then added. The suspension was stirred at 60°C for 10 h to afford the resin **4.** Excess reagents were removed by washing resin with the solvents (H_2O, DMF, EtOH, CH_2Cl_2). Then, concentrated sulfuric acid was added to



Scheme 1 Reagents and conditions (a) sodium ethyl acetoacetate, DMF, 80°C, 16 h. (b) DMSO, NaCl, 140°C, 48h. (c) Malonic acid, acetic anhydride, concentrated H_2SO_4. (d) DMF, o-methoxybenzaldehydes or hydroxybenzaldehydes, 60°C, 10 h. (e) concentrated H_2SO_4, r.t., 5 h.

the resin **4** at 0°C and the mixture was stirred for 5 h at room temperature to afford the 3-carboxycoumarins **5** and resin **2**. The *o*-methoxy group or hydroxy group acted as a nucleophilic group and attacked the carbonyl function readily resulting in the cyclisation reaction. The resin was filtered and washed with AcOEt. The solvent was evaporated to afford the product 3-carboxycoumarins in good yield and excellent purity (Table 1). The regenerated resin **2** can be reused (entry 8, Table 1).

Table 1 Yields and purities of substituted 3-carboxycoumarins **5**

Entry	Product	R^1	R^2	R^3	Yield/%[a]	Purity/%[b]
1	**5a**	Methoxy	H	H	65	>95
2	**5b**	Hydroxy	H	H	64	>95
3	**5c**	Methoxy	Methoxy	H	68	>95
4	**5d**	Methoxy	H	Methoxy	71	>95
5	**5e**	Methoxy	H	Br	73	>95
6	**5f**	Methoxy	H	Cl	70	>95
7	**5g**	Hydroxy	H	Cl	65	>95
8	**5h**	Hydroxy	H	H	63	>95 [c]

[a] Crude yields are based on the loading of the cyclic malonic ester resin **2**.
[b] Determined by ^1H NMR.
[c] The regenerated resin was used.

In summary, we have developed a solid phase synthesis method for the preparation of 3-carboxycoumarins. The solid-phase synthesis enjoys several advantages over the traditional solution-phase synthesis, since the intermediates and the products can be easily purified by washing the resin. However, in the solution phase each product must be isolated. Meanwhile, the mild conditions of the reaction and convenient handling suggest that the solid phase synthesis can be automated in combinatorial chemistry. Moreover, the regenerated resin can be recycled.

* To receive any correspondence. E-mail: huangx@zju.edu.cn
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400MHz instrument as DMSO-d_6 solutions using TMS as an internal standard. Chemical shifts (δ) are reported in ppm and coupling constants *J* is given in Hz. IR spectra were recorded using KBr disks with a Bruker Vector-22 infrared spectrometer. All solvents were purchased from commercial sources and used without further purification.

Procedure for the preparation of the resin bound cyclic malonic acid ester **2**:[4]

To the solution of sodium ethyl acetoacetate (39.2 mmol, 5.96 g) in 30 ml DMF was added Merrifield resin (2 g, 1% cross-linked, 200–400 mesh, loading = 1.96 mequiv Cl/g) and the mixture was stirred at 80°C for 16 h. After the mixture had been washed with DMF, EtOH and CH_2Cl_2, the keto ester resin **1** was obtained. The keto ester resin (2 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 then washed with water, DMF, EtOH and CH_2Cl_2, and ketone resin **2** (loading = 1.88 mmol/g, based on C=O) was obtained. A mixture of malonic acid (38 mmol), concentrated sulfuric acid (0.1 ml) and acetic anhydride (117 mmol) was allowed to stand for 24 h at room temperature and was then concentrated at 40°C under reduced pressure. The ketone resin **2** (2 g, pre-swelled in dry CH_2Cl_2) was added to the residue at 0°C. Then dry CH_2Cl_2 (2ml) was added to the mixture and the mixture was stirred at 15°C for 24 h. The resin was then washed with H_2O, EtOH and CH_2Cl_2. The cyclic malonic ester resin **3** (loading=1.10 mmol/g) was obtained. The loading of resin **3** was determined by reversed titration with hydrochloride acid after saponification with excess NaOH in EtOH.

General procedure for the solid-phase synthesis of 3-Carboxycoumarins **4**:

The resin-bound cyclic melonic acid ester **3** (500 mg, 1.10 mmol/g) was pre-swelled in 5 ml dry DMF for 5h, and the aldehyde(5 eqiv, 2.75mmol) was added and stirred at 60°C for 10 h. Then the suspension was cooled to room temperature; the resin was filtered and washed with H_2O, DMF, CH_3CH_2OH, CH_2Cl_2 successively. The resin **4** was obtained. The resin **4** was dried in vacuum and was preswelled in CH_2Cl_2, (5 ml) and concentrated sulfuric acid (1 ml) was added to the resin **4** at 0°C. The mixture was stirred for 5 h at room temperature, then excess H_2O was added to the mixture and stirred for 20 minutes. The product was precipitated along with the resin. The mixture was filtered and washed with H_2O. Then, the mixture was washed with AcOEt. The organic layer was collected, and dried with $MgSO_4$. The solvent was evaporated under reduced pressure to give the products **5**.

Compound **5a** *2-oxo-2H-1-benzopyran-3-carboxylic acid*: m.p.191–192°C (lit [6] 191-192°C). ^{1}H NMR (DMSO-d_6) δ 7.49–7.51(m, 2H), 7.76–7.80 (m, 1H), 7.82 (d, 1H, *J*=8.0Hz, ArH), 8.95 (s, 1H, HC=CH). MS *m/z* (relative intensity), 190 (M^+, 31), 146 (100), 118 (78), 89 (55), 63 (56). IR ν_{max} (cm^{-1}) 1745, 1683, 1613, 1568, 1419, 1227, 1207, 1024

Compound **5b** *2-oxo-2H-1-benzopyran-3-carboxylic acid*: m.p.191–192°C (lit [6] 191–192°C). ^{1}H NMR (DMSO- d_6) δ 7.47–7.51(m, 2H,), 7.74–7.80 (m, 1H,), 7.82 (d, 1H, *J*=8.0Hz, ArH), 8.93 (s, 1H, HC=CH). MS *m/z* (relative intensity), 190 (M^+, 31), 146 (100), 118 (78), 89 (55), 63 (56). IR ν_{max} (cm^{-1}) 1745, 1683, 1613, 1568, 1419, 1227, 1207, 1024.

Compound **5c** *7-methoxy-2-oxo-2H-1-benzopyran-3-carboxylic acid*: 192–193°C (lit [7] 192–194°C). ^{1}H NMR (DMSO- d_6) 3.88 (s, 3H, OCH_3), 6.78(s, 1H), 6.98–7.01 (m., 1H,), 7.78–7.80 (d, 1H, *J*=7.8Hz, ArH), 8.75 (s, 1H, HC=CH). MS *m/z* (relative intensity), 220 (M^+, 100), 176 (32), 148 (36), 133 (38), 105 (27), 77 (72). IR ν_{max} (cm^{-1}) 1759, 1706, 1674, 1574, 1494, 1404, 1286, 1240, 1104, 871.

Compound **5d** *6-methoxy-2-oxo-2H-1-benzopyran-3-carboxylic acid***:** 179–180°C (lit [2] 179–180°C). ^{1}H NMR (DMSO- d_6) 3.81 (s, 3H, OCH_3), 7.33–7.35 (d, 1H, *J*=8.0Hz, ArH), 7.38–7.40 (m, 1H), 7.47–7.48 (s, 1H), 8.69 (s, 1H, HC=CH). MS *m/z* (relative intensity) 220 (M^+, 100), 176 (30), 148 (39), 133 (40), 105(20), 77 (79). IR ν_{max} (cm^{-1}) 1756, 1704, 1664, 1570, 1496, 1404, 1286, 1240, 1104, 871.

Compound **5e** *6-bromo-2-oxo-2H-1-benzopyran-3-carboxylic acid***:** 195–196°C (lit [6] 199°C). ^{1}H NMR (DMSO- d_6), 7.46–7.48 (d, 1H, *J*=8.0Hz, ArH), 7.71–7.73 (m, 1H), 7.86–7.89 (s, 1H), 8.86 (s, 1H, HC=CH), MS *m/z* (relative intensity) 268 (M^+, ^{79}Br, 42), 270(M^+, ^{81}Br, 46), 224 (91), 196 (64), 173 (28), 117 (52), 89 (100). IR ν_{max} (cm^{-1}) 1763, 1675, 1611, 1597, 1559, 1367, 1248,

Compound **5f** *6-chloro-2-oxo-2H-1-benzopyran-3-carboxylic acid*: 198–199°C (lit [8] 198–199°C). ^{1}H NMR (DMSO- d_6), 7.41–7.43 (d, 1H, *J*=8.0Hz, ArH), 7.61–7.63(m, 1H), 7.86–7.89 (s, 1H), 8.86 (s, 1H, HC=CH). MS *m/z* (relative intensity), 224(M^+, ^{35}Cl, 100), 226(M^+, ^{37}Cl, 36), 180 (90), 152 (40), IR ν_{max} (cm^{-1}) 1760, 1684, 1600, 1574, 1494, 1404, 1286, 1240, 1104, 880

Project.20072032 was supported by the National Nature Science Foundation of China

Received 20 October 2002; accepted 8 January 2003
Paper 02/1638

References

1 Review on SPOS: (a). F. Guillier, D. Orain and M. Bradley, *Chem. Rev*., 2000, **100**, 2091; (b). B.A. Lorsbach and M.J. Kurth. *Chem. Rev*., 1999, **99**, 1541; (c) I.W. James. *Tetrahedron*, 1999, **55**, 4855-4946.

2 V. Armstrong, O. Soto, J.A. Valderrama and R. Tapia. *Synth. Commun*., 1988, **18**, 717

3 (a) B.C. Chen, X. Huang and J.Wang, *Synthesis*, 1987, 482; (b) B.C. Chen, X. Huang and S.M. Ma, *Synth. Commun*., 1987, **17**, 1519; (c) F.C. Ye, B.C. Chen and X. Huang, *Synthesis*, 1989, **4**, 317; (d) X. Huang, B.C. Chen, G.Y. Wu and H.B. Chen, *Synth. Commun.*, 1991, **21**, 1213.

4 (a) Z.X. Liu and X. Huang, *Tetrahedron. Lett.*, 2001, **42**, 7655; (b) Z.X. Liu and X. Huang, *J. Org. Chem*. (In press).

5 (a) H. McNab, *Chem. Soc. Rev.*, 1978, **7**, 345; (b) B.C. Chen, *Heterocycles*, 1991, **32**, 529.

6 R.O. Clinton and S.C. Laskowski, *J. Am. Chem. Soc*., 1949, **71**, 3602

7 T. Hogberg, M. Vora, S.D. Drake, L.A. Mitscherm and D.T.W. Ohem, *Acta. Chem. Scand., B.* 1984**, 38**, 359

8 B. Leonardo, C. Filippo, M, M. Anna and S. Daniela, *J. Heterocy. Chem.*, 1995**, 32**, 573