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Note

Solid Phase Synthesis of 2-Substituted 1,3-Oxazin-6-ones Using Resin-bound Cyclic Malonic Acid Ester

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A facile solid phase synthesis of 2-substituted 1,3-oxazin-6-ones using polymer-supported Meldrum's acid has been reported. Reaction of the resin-bound cyclic malonic acid ester with triethyl orthoformate and subsequent double substitution with amide, afforded the corresponding polymer-supported acylaminomethylene cyclic malonic acid ester, which upon thermal treatment led to 1, 3-oxazin-6-ones in good yields and with high purity.

Keywords solid phase synthesis, Meldrum's acid, 1,3-oxazin-6-one

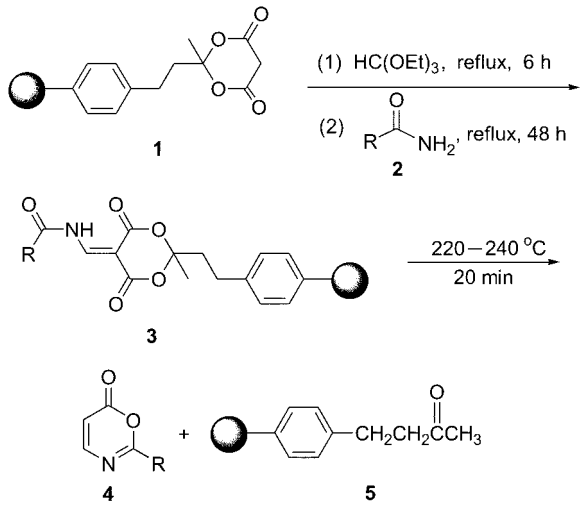
Solid phase organic synthesis is a powerful tool for acceleration of drug discovery, allowing the preparation of highly diverse compound libraries. The solid phase approach makes possible the synthesis of miscellaneous compounds by either parallel or combinatorial methods.[1] 6*H*-1,3-Oxazin-6-ones are important synthetic intermediates as the nitrogen containing dienes of Diels-Alder reactions in the synthesis of heterocyclic compounds.[2]

A number of methods have been reported for synthesis of 6*H*-1,3-oxazin-6-one derivatives via solution phase synthesis.[3-7] But the most convenient one is the thermolysis of acylaminomethylene Meldrum's acids, which have been reported by our group[7] and others.[4-6]

Meldrum's acid is a remarkable reagent for synthesis of the heterocyclic compounds.[8] In our previous paper, we have reported the first application of this chemistry to solid phase synthesis of heterocyclic compounds.[9] Herein we report a facile solid phase synthesis of 6*H*-1,3-oxazin-6-ones using resin-bound cyclic malonic acid ester.

Our solid phase approach to 6*H*-1,3-oxazin-6-ones began with the polymer supported cyclic malonic acid ester **1** (Scheme 1), which was prepared according to our prelimary communication.[9a] The resin **1** was treated with triethyl orthoformate and various amides to give the resin-bound acylaminomethylene cyclic malonic acid ester **3**. Aliphatic and aromatic amides can be used. Excess reagents were removed by filtration before the resin was heated for thermal cyclization. The newly formed resin **3** was thermally cleavaged to give the products **4**. After cleavage, the resin was washed completely with EtOH and acetone. The filtrates were combined to afford the product by evaporation. The product **4** was obtained in good yield and high purity (determined by ^{1}H NMR without further purification) (Table 1).

Scheme 1



For each resin-bound intermediate, the structure was verified by FT-IR spectra. When the resin **1** was transformed to the resin **3**, the carbonyl peak in IR spectra shifted from 1794, 1760 cm^{-1} to 1740, 1690 cm^{-1} (**3a**, R=Ph). Also a new peak appeared at 1590 cm^{-1} (C=C group). After cleavage, the ketone resin **5** was obtained which showed carbonyl peak at 1716 cm^{-1} in IR spectra. The ketone resin **5** can be recovered and reused to prepare the cyclic malonic acid ester resin **1**. The good result was also obtained when the regenerated resin was

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used (Table 1, Entry 9).

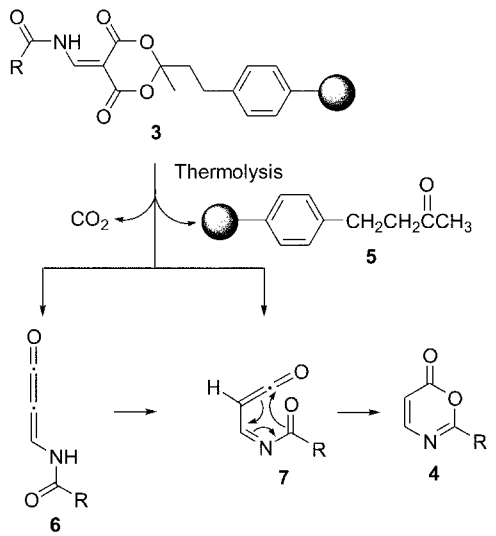
Table 1 Solid phase synthesis of 2-substituted 1,3-oxazin-6-ones

Entry	Product	R	Yield[a]/%	Purity[b]/%
1	**4a**	Ph	87	>95
2	**4b**	4-ClC_6H_4	80	>95
3	**4c**	4-$CH_3C_6H_4$	73	>95
4	**4d**	4-$CH_3OC_6H_4$	65	>95
5	**4e**	4-$NO_2C_6H_4$	67	>95
6	**4f**	3-$NO_2C_6H_4$	86	>95
7	**4g**	4-BrC_6H_4	70	>95
8	**4h**	CH_3	69	>95
9	**4a**[c]	Ph	85	>95

[a] The yields were based on the loading of resin **1**; [b] determined by ^{1}H NMR (400 MHz); [c] using the regenerated resin.

In summary, we have developed a facile method of solid phase synthesis of 6*H*-1,3-oxazin-6-ones. Simple work-up procedures replace the time-consuming isolation and purification steps in the corresponding solution-phase reaction. This study also provides a traceless cleavage solid phase organic synthesis (SPOS)[10] route based on the electrocyclization of an intermediate acylaminomethyleneketene. The mechanism is shown in Scheme 2. Further work is in progress on the solid phase synthesis of heterocyclic compounds via the resin-bound cyclic malonic ester.

Scheme 2



Experimental

The melting points were uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Brucker Avance 400 spectrometer in $CDCl_3$ with TMS as the internal standard. IR spectra were recorded on a Bruker Vector 22 spectrometer. EI-MS was run on an HP 5989B mass spectrometer. DMF (AR), ethanol (AR), amides and Merrifield resin (Cl 1.96 mmol/g) were obtained commercially and used in reactions without any further purification. Triethyl orthoformate was freshly distilled before use.

Solid phase synthesis of 2-substituted 1,3-oxazin-6-ones (4a—4h)

A suspension of resin **1** (500 mg, loading=1.20 mmol/g, 1.0 equiv.) in triethyl orthoformate (50 equiv., 5 mL) was refluxed for 6 h. The amide **2** (5 equiv.) was added. The mixture continued to reflux for 48 h. The resin was filtered and washed with 3×5 mL of EtOH, 3×5 mL of CH_2Cl_2. Then the resin was heated with an oil bath at 220 ℃ for 20 min under N_2 atmosphere and washed with EtOH/acetone in the sintered glass funnel. The filtrates were combined and the solvents were removed *in vacuo* to afford the product.

2-Phenyl-6*H*-1,3-oxazin-6-one (4a) White solid, m.p. 85—87 ℃ (lit.[5] 85—87 ℃). ^{1}H NMR δ: 6.21 (d, J=6.8 Hz, 1H), 7.48—7.52 (m, 2H), 7.55—7.68 (m, 1H), 7.82 (d, J=6.8 Hz, 1H), 8.21 (m, 2H); IR ν: 3085, 1752, 1604, 1579, 1542, 1494, 1246, 1134, 835 cm^{-1}; MS (70 eV) *m/z* (%): 173 (M^+, 42), 145 (26), 105 (100), 77 (44).

2-(4-Chlorophenyl-6*H*-1,3-oxazin-6-one (4b) White solid, m.p. 112—114 ℃ (lit.[5] 112—114 ℃); ^{1}H NMR δ: 6.21 (d, J=6.8Hz, 1H), 7.46—7.48 (dd, J^1=1.88, J^2=6.9 Hz, 2H), 7.80 (d, J=6.8 Hz, 1H), 8.14 (dd, J^1=1.9, J^2=6.9 Hz, 2H); IR ν: 3080, 2926, 1765, 1603, 1570, 1540, 1488, 1239, 1093, 844 cm^{-1}; MS (70 eV) *m/z* (%): 207 (M^+, 35), 209 (M^++2, 12), 179 (24), 181 (7.5) 139 (100), 141 (33), 111 (41), 113 (12).

2-(4-Methylphenyl)-6*H*-1,3-oxazin-6-one (4c) White solid, m.p. 148—150 ℃ (lit.[5] 149—150 ℃); ^{1}H NMR δ: 2.44 (s, 3H), 6.18 (d, J=6.7 Hz, 1H), 7.29 (d, J=8 Hz, 2H), 7.80 (d, J=6.7 Hz, 1H), 8.10 (d, J=8.0 Hz, 2H); IR ν: 3082, 1739, 1611, 1599, 1245, 1188 cm^{-1}; MS (70 eV) *m/z* (%): 187 (M^+, 26), 159 (11), 119 (100), 91 (60), 65 (31).

2-(4-Methoxyphenyl)-6*H*-1,3-oxazin-6-one (4d) White solid, m.p. 116—118 ℃; ^{1}H NMR δ: 3.89 (s, 3H), 6.13 (d, J=6.7 Hz, 1H), 6.97—7.00 (m, 2H), 7.78 (d, J=6.7 Hz, 1H), 8.16—8.19 (m, 2H); ^{13}C NMR δ: 55.595, 108.349, 114.345, 118.904, 122.009, 130.762, 155.073, 158.731, 164.049, 164.887; IR ν: 3086, 2925, 1741, 1609, 1572, 1533, 1505, 1424, 1257, 1240, 1137, 837, 761 cm^{-1}; MS (70 eV) *m/z* (%): 203 (M^+, 35), 175 (4), 135 (100), 107 (15), 92 (16), 77 (26). Anal. calcd for $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89; found C 64.96, H 4.52, N 6.96.

2-(4-Nitrophenyl)-6*H*-1,3-oxazin-6-one (4e) White solid, m.p. 162—164 ℃; ^{1}H NMR δ: 6.31 (d, J=6.80 Hz, 1H), 7.87 (d, J=6.80 Hz, 1H), 8.34—8.36 (m, 2H), 8.40—8.42 (m, 2H); ^{13}C NMR δ: 110.987, 124.009, 129.601, 135.081, 150.628, 154.110, 157.305, 162.495; IR ν: 2922, 1757, 1594, 1541, 1353, 1236, 1006 cm^{-1}; MS (70 eV) *m/z* (%): 218 (M^+, 40), 190 (73), 150 (100), 120 (19), 104 (69), 92 (51), 76 (81), 50 (66). Anal. calcd for $C_{10}H_6N_2O_4$: C 55.05, H 2.77, N 12.84; found C 55.14, H 2.75, N 12.96.

2-(3-Nitrophenyl)-6*H*-1,3-oxazin-6-one (4f) White solid, m.p. 68—70 ℃; ^{1}H NMR δ: 6.32 (d, J=6.80 Hz, 1H), 7.67—7.78 (m, 1H), 7.94 (d, J=6.8 Hz, 1H), 8.43—8.46 (m, 1H), 8.53—8.55 (d, J=7.80 Hz, 1H), 9.04 (s, 1H); ^{13}C NMR δ: 110.732, 123.445, 127.579, 130.165, 131.436, 133.849, 148.590, 154.180, 157.299, 163.342; IR ν: 3080, 1762, 1623, 1534, 1352, 1238, 1091 cm^{-1}; MS (70 eV) *m/z* (%): 218 (M^+, 28), 190 (53), 150 (100), 104 (56), 104 (69), 92 (17), 76 (36). Anal. calcd for $C_{10}H_6N_2O_4$: C 55.05, H 2.77, N 12.84; found C 55.21, H 2.83, N 12.68.

2-(4-Bromophenyl)-6*H*-1,3-oxazin-6-one (4g) White solid, m.p. 120—122 ℃; ^{1}H NMR δ: 6.23 (d, J=6.76 Hz, 1H), 7.63 (d, J=8.45 Hz, 2H), 7.81 (d, J=6.76 Hz, 1H), 8.07 (m, J=8.45 Hz, 2H); ^{13}C NMR δ: 109.838, 128.593, 128.804, 129.998, 132.310, 154.567, 158.027, 164.042; IR ν: 3085, 1746, 1607, 1540, 1398, 1482, 1242, 843, 724 cm^{-1}; MS (70 eV) *m/z* (%): 251 (M^+, 30), 253 (30), 223 (23), 225 (22), 183 (100), 185 (98), 155 (45), 157 (43). Anal. calcd for $C_{10}H_6BrNO_2$: C 47.65, H 2.40, N 5.56; found C 47.72, H 2.39, N 5.62.

2-Methyl-6*H*-1,3-oxazin-6-one (4h) Oil,[6] ^{1}H NMR δ: 2.32 (s, 3H), 6.47 (d, J=6.8 Hz, 1H), 7.89 (d, J=6.8 Hz, 1H); IR ν: 3085, 1741 1607, 1540, 1242, 843, 724 cm^{-1}; MS (70 eV) *m/z* (%): 111 (M^+, 31), 96 (19), 86 (33), 69 (17), 43 (100).

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