Pergamon

Tetrahedron Letters 42 (2001) 7655–7657

TETRAHEDRON LETTERS

Preparation of a resin-bound cyclic malonic ester and a facile solid-phase synthesis of 4(1*H*)quinolones

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Received 21 June 2001; revised 16 August 2001; accepted 30 August 2001

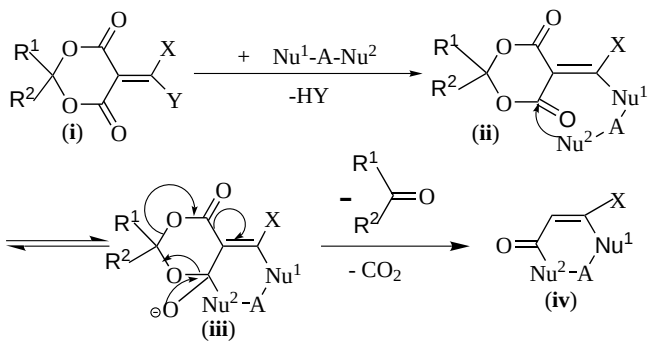
Abstract—A resin-bound cyclic malonic ester has been prepared on Merrifield resin. Reaction of the cyclic malonic ester with triethyl orthoformate and subsequent substitution by an arylamine afforded arylaminomethylene cyclic malonic ester preloaded resin. A series of 4(1*H*)quinolones were prepared by thermal cyclization in moderate yields and high purity. © 2001 Elsevier Science Ltd. All rights reserved.

The solid-phase synthesis of small molecules has been under intensive study recently.[1] Due to the ease of workup and isolation, solid-phase organic synthesis (SPOS) allows rapid synthesis of a large number of structurally diverse molecules in a short period of time which can accelerate the lead generation and lead optimization processes in the pharmaceutical industry. 4(1*H*)Quinolone and its derivatives are found in many naturally occurring alkaloids[2] which exhibit broad biological activities. This ring system has been successfully prepared by the reaction of arylamines with Meldrum's acid derivatives via solution-phase synthesis.[3]

Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) is a remarkable reagent of varied reactivities.[4] The susceptibility to electrophilic attack (via its anion) at C-5 and nucleophilic attack at C-4 and C-6 along with the ring opening reactions makes this reagent useful in organic synthesis. 5-Ethoxymethylene or 5-methylthiomethylene derivatives of Meldrum's acid (Scheme 1, **i**, X=H, Y=OEt; or X=R, SMe, Y=SMe) are new synthetic intermediates of considerable utility. As shown in Scheme 1, compound (**i**) can easily be attacked by doubly nucleophilic reagents (Nu^1-A-Nu^2), followed by loss of the ketone and CO_2 to afford the heterocyclic compound (**iv**).

Our group has reported work on 5-(bismethylthiomethylene)-2,2-dimethyl-1,3-dioxane-4,6-dione in novel synthesis of quinolones,[3b] pyrazolones[5a] and pyrimidine.[5b] However, for the construction of libraries of these heterocyclic compounds, solution-phase strategies are time-consuming and cannot be easily isolated. To the best of our knowledge, the use of this chemistry to prepare combinatorial libraries of small molecules on solid supports has not been explored. In continuation of our work on Meldrum's acid derivatives, we attempted to develop resin-bound cyclic malonic esters and to prepare heterocyclic compounds by solid-phase synthesis. Herein, we describe solid-phase synthesis of 4(1*H*)quinolones from a resin-bound, cyclic, malonic ester. We have also prepared a novel scaffold—a resin-bound cyclic malonic ester.

Our solid-phase synthetic route (Scheme 2) begins with commercially available Merrifield resin. It was reacted



Scheme 1.

Keywords: 4(1*H*)quinolone; solid-phase synthesis; Meldrum's acid; cyclic malonic ester.

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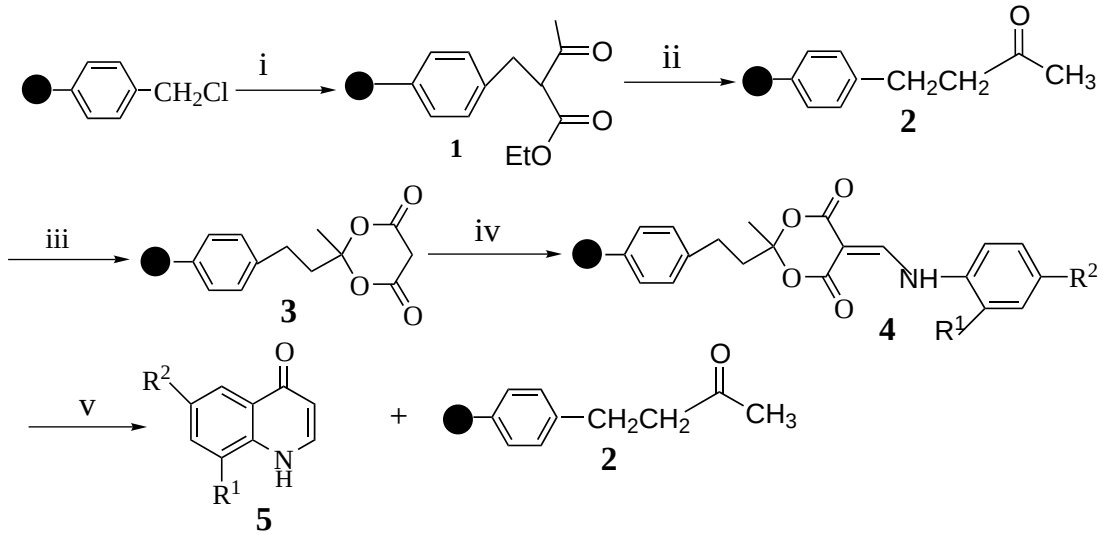
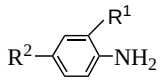
PII: S0040-4039(01)01622-7



Scheme 2. *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; (iv) a. $HC(OEt)_3$, reflux, 6 h, b.  , reflux, 20 h; (v) thermolysis, N_2, 240°C, 30 min.

with sodium ethyl acetoacetate in DMF to give the β-keto ester resin **1**. Decarboxylation of resin **1** in DMSO yielded the ketone resin **2**. The ketone resin **2** was reacted with malonic acid and acetic anhydride under concentrated H_2SO_4 conditions according to Ott's method[6] to give the resin-bound cyclic malonic ester **3**. Resin **3** was treated with triethyl orthoformate and various arylamines to give the resin-bound aryl-aminomethylene, cyclic malonic ester **4**.[3a] Excess reagents were removed by filtering before the resin was heated for thermal cyclization. The resin was washed with solvents after thermal cleavage to give the products. The products generally do not require purification and show good purity (>90%) by ^{1}H NMR analysis (400 MHz).

Table 1 summarizes the yields and purities of a number of 4(1*H*)quinolones that were prepared using this methodology.

The successful formation of resin **1** was supported by a comparative FTIR study of Merrifield resin and a sample of resin **1** (KBr pellets). In the IR spectrum of resin **1**, several characteristic signals were present which confirmed the attachment of the ethyl acetoacetate moiety to the resin. There were two strong bands at 1740 and 1716 cm^{-1}, typical for C=Os of β-keto esters. Also, the peak at 1260 cm^{-1} (CH_2-Cl) had disappeared. The formation of resin **2** was shown by the existence of a single strong carbonyl peak at 1716 cm^{-1}. The cyclic malonic ester was monitored by IR spectroscopy which showed carbonyl peaks at 1767 and 1794 cm^{-1}. There was also a weak peak at 1710 cm^{-1} because the resin **2** was not completely converted into **3**. When the cyclic malonic ester resin was converted to the resin **4**, the IR carbonyl peak shifted to 1738 and 1684 cm^{-1} (**4a**). Also, a new peak appeared at 1625 cm^{-1} (C=C) compared with resin **3**. Resin **4** was cleaved by thermal cyclization. This is a novel traceless cleavage strategy based on the electrocyclization of an intermediate amino ketene.[3c] The recovered resin can be recycled (converted to resin **2**[7]) at the end of the reaction.

Procedure for the preparation of the resin bound cyclic malonic ester

To a solution of sodium ethyl acetoacetate (39.2 mmol, 5.96 g) in 30 ml DMF, Merrifield resin (2 g, 1% cross-linked, 200–400 mesh, loading = 1.96 meq Cl/g) was added and the mixture was stirred at 80°C for 16 h. After being washed with DMF, EtOH and CH_2Cl_2, the β-keto ester resin **1** was obtained. The β-keto ester resin **1** (2 g) was suspended in a mixture of DMSO (30 ml), NaCl (40 mmol) and H_2O (120 mmol) and the mixture refluxed for 48 h. After washing with water, DMF, EtOH and CH_2Cl_2, the ketone resin **2** (loading = 1.88 mmol/g, based on C=O) was obtained. A solution of malonic acid (38 mmol), concentrated sulfuric acid (0.1

Table 1. Yields and purities of 4(1*H*)quinolones[a]

4(1*H*)Quinolone	R^1	R^2	Yield (%)[b]	Purity (%)
5a	H	H	62	95
5b	CH_3	H	59	90
5c	H	$COCH_3$	59	92
5d	H	NO_2	62	90
5e	NO_2	H	47	94
5f	H	OCH_3	57	91
5g	H	CH_3	49	90
5h	H	Br	58	93
5i	Cl	Cl	61	93

[a] All compounds are determined by ^{1}H NMR, MS, IR.
[b] The yields are based on the loading of the cyclic malonic ester resin **3**.

ml) and acetic anhydride (117 mmol) was allowed to stand for 24 h at rt and was then concentrated in vacuum below 40°C. The resin **2** (2 g, pre-swelled in dry CH_2Cl_2) was added to the residue after cooling to 0°C. Then 2 ml dry CH_2Cl_2 was added to the mixture. The mixture was stirred below 20°C for 24 h. The resin was then washed with water, EtOH and CH_2Cl_2. The cyclic malonic ester resin **3** (loading = 1.20 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 4(1*H*)quinolones: Resin **3** (500 mg, 1.20 mmol/g) was added to triethyl orthoformate (50 equiv., 5 ml) and then refluxed for 6 h. The arylamine (10 equiv.) was added and the mixture was heated under reflux for 20 h. The resin was filtered and washed with EtOH and CH_2Cl_2. Then the resin was heated in an oil bath at 240°C for 30 min under a N_2 atmosphere. The resin was then washed with EtOH/acetone thoroughly in a sintered glass funnel. The filtrates were combined and the solvents removed in vacuo to afford the product.

In conclusion, we have developed a method for the preparation of polymer-bound cyclic malonic ester. A series of 4(1*H*)quinolones were synthesized by thermal cyclization based cleavage providing a SPOS route. The resin-bound cyclic malonic ester can be considered to be an appropriate scaffold for solid-phase synthesis. Further work is in progress on the solid-phase synthesis of heterocyclic compounds via the resin-bound cyclic malonic ester.

Acknowledgements

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

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. Proc. Int.* **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. Reitsema, R. H. *Chem. Rev.* **1948**, *43*, 43–68.
3. (a) Cassis, R.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* **1985**, *15*, 125–133; (b) Chen, B. C.; Huang, X.; Wang, J. *Synthesis* **1987**, 482–483; (c) Gordon, H. J.; Martin, J. C.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1983**, 957–958.
4. (a) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345–358; (b) Chen, B. C. *Heterocycles* **1991**, *32*, 529–597.
5. (a) Chen, B. C.; Huang, X.; Ma, S. M. *Synth. Commun.* **1987**, *17*, 1519–1522; (b) Ye, F. C.; Chen, B. C.; Huang, X. *Synthesis* **1989**, *4*, 317–320.
6. (a) Ott, E. *Annals* **1913**, *401*, 159–177; (b) Michael, A.; Weiner, N. *J. Am. Chem. Soc.* **1936**, *58*, 680–685.
7. The IR spectroscopy of the recovered resin showed a single strong carbonyl peak at 1716 cm^{-1}. (identical to resin **2**). The loading of this resin is 1.80 mmol/g (based on C=O group). The cyclic malonic resin **3** (loading = 1.06 mmol/g) can be prepared from the recovered resin.