Chinese Chemical Letters Vol. 13, No. 3, pp 193 – 194, 2002
http://www.imm.ac.cn/journal/ccl.html

Solid Phase Synthesis of 4(1H)Quinolones from Resin-Bound Cyclic Malonic Ester

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Abstract: The solid phase synthesis of 4 (1H) quinolones has been reported.

Keywords: 4 (1H) Quinolone, Meldrum's acid, solid phase synthesis, cyclic malonic ester.

Due to the ease of workup and isolation, solid phase organic synthesis (SPOS) allows rapid synthesis of a large number of structurally diverse molecules[1]. 4 (1H) Quinolone has been successfully prepared by the reaction of arylamine with Meldrum′s acid derivatives *via* solution-phase synthesis[2]. Meldrum's acid is widely used as an interesting reagent for synthesis of heterocyclic compounds[3]. We attempt to develop the resin-bound cyclic malonic ester and prepare heterocyclic compounds.

Our solid phase synthetic route (**Scheme 1**) begins with Merrifield resin (2 g, 1% cross-linked, 200-400 mesh, loading = 1.96 meq Cl/g). It reacted with sodium ethyl acetoacetate (39.2 mmol) to form the β-keto ester resin **1**. The decarboxylation of the resin **1** (2 g) yielded the ketone resin **2** (loading = 1.88 mmol/g, based on C=O). A mixture of malonic acid (38 mmol), concentrated sulfuric acid (0.1 mL) and acetic anhydride (117 mmol) was allowed to stand for 24 hours at room temperature and was then concentrated in vacuum below 40°C. The resin **2** (2 g,) was added to the residue after cooling to 0°C. The mixture was stirred below 20°C for 24 hours. The resin-bound cyclic malonic ester **3** (loading = 1.2 mmol/g) can be obtained. We treated the resin **3** (500 mg, 1.20 mmol/g) with triethyl orthoformate (5 mL) and arylamines (6 mmol) to obtain the resin-bound arylamine methylene cyclic malonic ester **4**. Then the resin **4** was heated with oil-bath at 240°C for 30 minutes under N_2 atmosphere. The resin was washed with EtOH/acetone completely. The products generally do not require purification and show good purity (> 90%) by ^{1}HNMR (**Table 1**).

We have developed a method for preparation of polymer-bound cyclic malonic ester. This is also a novel traceless cleavage strategy to prepare 4 (1H) quinolones. The resin **2** can be recycled.

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Scheme 1

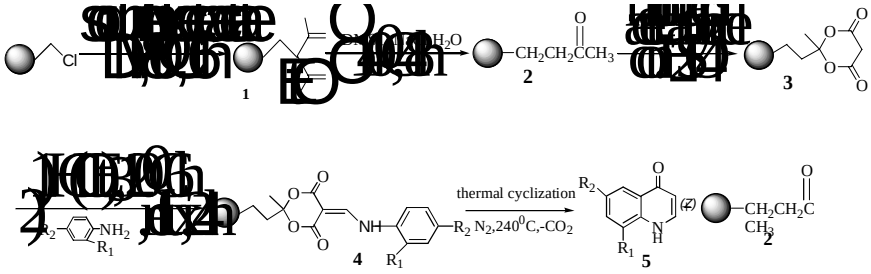

Table 1 Yields and purities of 4(1H)quinolones [a]

Entry	R_1	R_2	Yield[b]	Purity	Entry	R_1	R_2	Yield	Purity
5a	H	H	62%	95%	**5f**	H	OCH_3	57%	91%
5b	CH_3	H	59%	90%	**5g**	H	CH_3	49%	90%
5c	H	$COCH_3$	59%	92%	**5h**	H	Br	58%	93%
5d	H	NO_2	62%	90%	**5i**	Cl	Cl	61%	93%
5e	NO_2	H	47%	94%					

a All compounds are confirmed by ^{1}HNMR, MS, IR. b The yields are based on the resin **3**

Acknowledgment

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

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Received 20 June, 2001