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Convenient Solid-phase Synthesis of Benzothiazole Derivatives

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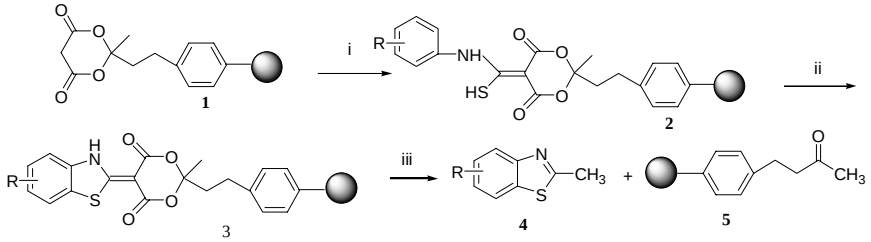
Abstract: Resin-bound cyclic malonic ester **1** reacted with aryl isothiocynate, then was treated with bromine, followed by cleavage from the resin under perchloric acid to give benzothiazoles **4**.

Keywords: Solid-phase, resin-bound cyclic malonic acid ester, benzothiazole derivires.

Meldrum's acid is a kind of versatile intermediate in organic synthesis and it is susceptible to nucleophilic attack at C-4 and C-6 along with the unique ring openning reaction which make it exhibit versatile reactivity[1]. In view of this, we built up the resin-bound cyclic malonic ester[2]. Meanwhile, the benzothiazole nucleus is of particular interest especially within the realm of medicinal chemistry[3]. Although there are many publications on the synthesis of benzothiazole derivatives in solution-phase[4], there have been only a few reports on solid-phase synthesis of these compounds.

Inspired by the solution-phase strategy[5], we report here the novel solid-phase synthesis of a series of substituted 2-methylbenzothiazoles *via* resin-bound cyclic malonic ester **1** conveniently. The synthetic route was outlined in **Scheme 1**.

Scheme 1



Reagents and conditions: i (a) Et_3N, DMF, rt, 1 h. (b) R-C_6H_4NCS, 45℃, 18 h. (c) 2mol/L HCl. ii) Br_2, AcOH, rt, 2 h. iii) $HClO_4$, CH_3CN, reflux, 4 h

Due to the high reactivity of the methylene of resin-bound cyclic malonic acid ester **1**, triethylamine was used to form the anion at room temperature for 1 hour, the formed

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anion reacted with the aryl isothiocyanates in dry dimethyl formamide at 45℃, and subsequently treated with 2mol/L HCl to transform into resin **2**. Excess reagents were removed by simple washing with the solvents (EtOH, CH_2Cl_2). Then resin **2** reacted with bromine at room temperature to give the corresponding resin **3**. Resin **3** was treated with perchloric acid in refluxing CH_3CN, the expected product **4** was obtained cleanly in good yield and excellent purity (**Table 1**). The recovered resin **5** can be reused.

The procedures from resin **1** to final products were monitored by FT-IR. The resin **1** showed carbonyl peaks at 1767 cm^{-1} and 1794 cm^{-1}, when the resin **1** was converted to the resin **2**, the IR carbonyl peaks shifted to 1738 cm^{-1} and 1684 cm^{-1} respectively, with appearing the new peaks at 1545 cm^{-1} (C=C) and 2552 cm^{-1} (S-H). Disappearance of the peak at 2552 cm^{-1} indicated complete transformation of the compound **2** to afford resin **3**. After cleavage, the ketone resin **5** showed carbonyl peak at 1717 cm^{-1} and it can be reused to form the resin-bound cyclic malonic ester **1**.

Table 1 Yields and purities of benzothiazoles[a]

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

a. The crude yields were based on the loading of the cyclic malonic acid ester resin **1**
b. Determined by ^{1}H NMR. c. The regenerated resin was used (the 3 rd run)

In summary, a novel and convenient method was achieved for the solid-phase synthesis of benzothiazole derivatives under the mild conditions. Moreover, the present strategy described the new traceless cleavage SPOS route.

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