Note

A Facile Solid Phase Synthesis of 2-Alkylthio-4(1*H*)-quinolones

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The resin-bound cyclic malonic acid ester 2 reacted with aryl isothiocyanate and alkyl halides to afford the key intermediate arylthioaminomethylene cyclic malonic ester resin 3. Subsequently, resin 3 proceeded thermal cyclization giving the 2-alkylthio-4(1*H*)-quinolones in good yields and excellent purities.

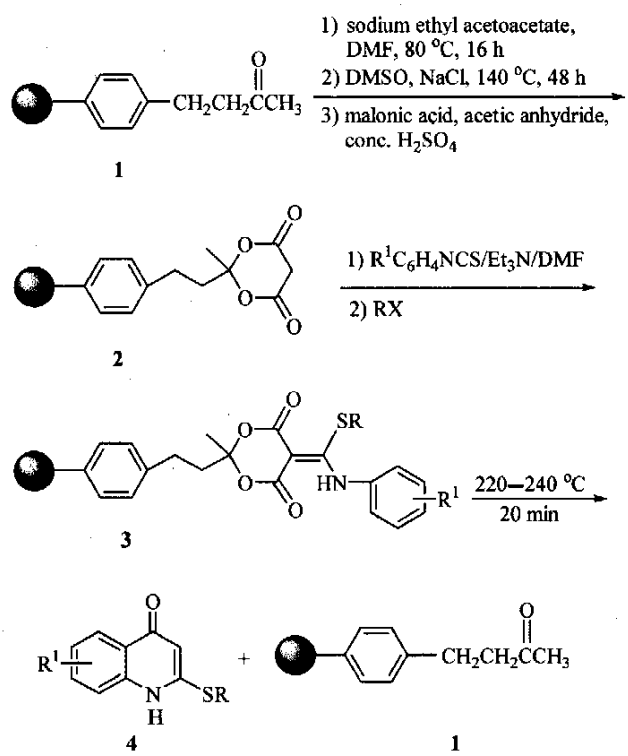
Keywords solid-phase synthesis, resin-bound cyclic malonic acid ester, 2-alkylthio-4(1*H*)-quinolones

Recently, solid phase organic synthesis (SPOS) plays an important role in parallel synthesis and combinatorial libraries, particularly in the area of the discovery of pharmaceutical lead compounds. SPOS enjoys several advantages over the traditional solution-phase synthesis, such as use of excess inexpensive reagents for a complete reaction, and convenience of handling.[1] 4(1*H*)-Quinolones are effective building blocks in the syntheses of some compounds with interesting pharmacological properties.[2] For example, 4-alkylaminoquinoline derivatives are used for treatment of malaria.[3a] Recently, *Arnoamines A* was prepared through 4(1*H*)-quinolones.[3b]

Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, appears to be an attractive reagent in organic synthesis.[4] Due to considerably higher acidity of Meldrum's acid (pK_a = 4.97), it is an active methylene compounds. Meanwhile, isothiocyanate is a functional group that has greater reactivity with activated methylene compounds. Aryl isothiocyanate could react with Meldrum's acid to give the key intermediate alkylthioaminomethylene compounds smoothly. Then the intermediate undergoes alkylation with alkyl agents.[5] In this paper, we wish to report the preparation of the resin-bound alkylthioaminomethylene cyclic malonic acid ester via the reaction of resin **1** with aryl isothiocyanates, and its application to the synthesis of 2-alkylthio-4(1*H*)-quinolones by thermal cyclization conveniently (Scheme 1).

Our solid phase synthesis began with the resin-bound cyclic malonic acid ester resin **2** which was prepared by our previous method.[6] At our first attempt to synthesize the resin **3**, we investigated the reaction conditions. Initially, we attempted to carry out the reaction by using NaH as base at room temperature, but the yield and purity was unsatisfying. Due to the high activity of the methylene of resin-bound cyclic malonic acid ester **2**, triethylamine was then used to form the anion at room temperature for 1 h, and the formed anion reacted with the aryl isothiocyanates in dry dimethyl formamide at 45 ℃. Subsequently, methyl iodide or benzyl chloride was added and stirred for 5 h to give resin **3**. After formation of the resin **3**, excess reagents were removed by washing with the solvents (EtOH, CH_2Cl_2). The resin **3** was cleaved by thermal cyclization at 220—240 ℃ smoothly leading to the heterocyclic compounds **4** and the resin **1**, which can be reused. The cleaved resin was washed with EtOH and acetone to give the products **4**. Products **4** generally did not require

Scheme 1



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purification and showed good purities (>90%) as indicated by the ^{1}H NMR spectra (400 MHz) (Table 1).

Table 1 Syntheses of 2-alkylthio-4-(1*H*)-quinolones

Entry	Product	R^1	R	Yield[a] (%)	Purity[b] (%)
1	**4a**	H	SCH_3	81	95
2	**4b**	6-Br	SCH_3	73	93
3	**4c**	6-CH_3	SCH_3	86	95
4	**4d**	6-CH_3O	SCH_3	60	90
5	**4e**	8-CH_3	SCH_3	62	91
6	**4f**	6-Cl	SCH_3	71	92
7	**4g**	H	SCH_2Ph	75	95
8	**4h**	6-Cl	SCH_2Ph	70	91
9	**4a**	H	SCH_3	81[c]	94[c]

[a] Yield based on the loading of the resin **2**. [b] Determined by ^{1}H NMR (400 MHz) spectra. [c] The regenerated resin was used.

The reaction was monitored by FT-IR. The resin-bound cyclic malonic acid ester **1** showed carbonyl peaks at 1767 cm^{-1} and 1794 cm^{-1}. When the cyclic malonic acid ester resin was converted into the resin **2**, the IR carbonyl peaks shifted to 1738 cm^{-1} and 1684 cm^{-1} with a new peak appeared at 1545 cm^{-1} (C=C). The resin **3** was cleaved by thermal cyclization. The regenerated resin possessed the strong carbonyl peak at 1717 cm^{-1}, which can be reused.

Attractive features of this solid phase synthesis of 2-alkylthio-4(1*H*)-quinolones include (a) the final products are obtained by cyclization cleavage from the resin in one step; (b) the efficient introduction of alkylthio group gives potential access to higher diversity by further functionalization of the 2-alkylthio-4(1*H*)-quinolones.

In summary, we have developed a facile solid-phase method for the preparation of 2-alkylthio-4(1*H*)-quinolones by thermal cyclization cleavage. The present strategy described a traceless cleavage SPOS route based on the eletrocyclization of an intermediate aminoketene. Furthermore, it should be noted that the polymer bound ketone **1** could be easily regenerated for reuse after cleavage.

Experimental

General

The melting points were uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in DMSO-d_6 with TMS as the internal standard; chemical shifts were quoted and *J* values were given in Hz. IR spectra were recorded on a Bruker Vector 22 spectrometer. EI-MS was run on an HP 5989B mass spectrometer.

General procedure for the solid phase synthesis of 2-alkylthio-4(1H)-quinolones

A suspension of resin **1** (500 mg, 1.11 mmol/g[7]) in dry DMF (5 mL) was treated with Et_3N (5.55 mmol, 0.772 mL) and stirred for 1 h at room temperature. Then aryl isothiocyanate (2.77 mmol) was added and the mixture was stirred at 45 ℃ for 16 h. After cooling to room temperature, the alkyl halide (2.775 mmol) was added, the mixture was continued to stirr for 5 h at room temperature. Then, the resin was filtrated, washed with 3×5 mL EtOH, 3×5 mL CH_2Cl_2, dried under vacuo for 24 h. Subsequently, thermal cyclization was conducted at 220—240 ℃ for 20 min under N_2 atmosphere. The mixture was washed with EtOH/acetone completely in the sintered glass funnel, and the filtrates were combined to afford the products by evaporation.

2-Methylthio-4-(1H)-quinolone (**4a**) M.p. 221—222 ℃ (lit.[3] 220—222 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.57 (s, 3H), 5.97 (s, 1H), 7.27—7.29 (m, 1H), 7.43—7.45 (m, 1H), 7.61—7.63 (m, 1H), 8.00 (d, J=7.72 Hz, 1H); 11.84 (s, 1H); IR (KBr) ν: 3280, 1640, 1585 cm^{-1}; MS (70 eV) *m/z* (%): 191 (M^+, 100), 145 (25), 105 (15).

2-Methylthio-6-bromo-4-(1H)-quinolone (**4b**) M.p. 273—276 ℃ (lit.[3] 274—276 ℃), ^{1}H NMR (DMSO-d_6) δ: 2.58 (s, 3H), 5.97 (s, 1H), 7.39 (d, J=9.21 Hz, 1H), 7.77 (dd, J_1=9.31 Hz, J_2=2.62 Hz, 1H), 8.04 (d, J=2.7 Hz, 1H), 11.99 (s, 1H); IR (KBr) ν: 3280, 1640, 1580 cm^{-1}; MS (70 eV) *m/z* (%): 269 (M^+, 100), 271 (M^++2, 97), 225 (40), 183 (26), 116 (22), 88 (28).

2-Methylthio-6-methyl-4-(1H)-quinolone (**4c**) M.p. 224—227 ℃ (lit.[3] 224—226 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.33 (s, 3H), 2.57 (s, 3H), 5.95 (s, 1H), 7.42—7.57 (m, 2H), 7.93 (s, 1H), 11.80 (s, 1H); IR (KBr) ν: 3280, 1641, 1580 cm^{-1}; MS (70 eV) *m/z* (%): 205 (M^+, 100), 159 (22), 86 (45), 77 (12).

2-Methylthio-6-methoxy-4-(1H)-quinolone (**4d**) M.p. 230—232 ℃ (lit.[3] 230—233 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.58 (s, 3H), 3.84 (s, 3H), 5.94 (s, 1H), 7.24 (dd, J_1=9.63 Hz, J_2=4.32 Hz, 1H), 7.44 (d, J=4.24 Hz, 1H), 7.59 (d, J=9.52 Hz, 1H), 11.81 (s, 1H); IR (KBr) ν: 3240, 1640, 1580 cm^{-1}; MS (70 eV) *m/z* (%): 221 (M^+, 100), 188 (19), 15 (26), 135 (15), 105 (12).

2-Methylthio-8-methyl-4-(1H)-quinolone (**4e**) M.p. 192—193 ℃ (lit.[3] 192—193 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.04 (s, 3H), 2.55 (s, 3H), 6.50 (s, 1H), 7.19—7.98 (m, 3H), 10.90 (s, 1H); IR (KBr) ν: 3280, 1640, 1572 cm^{-1}; MS (70 eV) *m/z* (%): 205 (M^+, 100), 159 (22), 86 (45), 77 (12).

2-Methylthio-6-chloro-4-(1H)-quinolone (**4f**) M.p. 255—257 ℃ (lit.[3] 255—257 ℃); ^{1}H NMR (DMSO-d_6) δ: 2.55 (s, 3H), 5.94 (s, 1H), 7.36 (d, J=8.88 Hz, 1H), 7.41 (dd, J_1=8.91 Hz, J_2=2.73 Hz, 1H), 7.45 (d, J=2.68 Hz, 1H), 11.78 (s, 1H); IR (KBr) ν: 3265, 1643, 1580 cm^{-1}; MS (70 eV) *m/z* (%): 225 (M^+, 100), 227 (M^++2, 38), 179 (46), 139 (34),

123 (19).

2-Benzylthio-4-(1H)-quinolone (**4g**) M.p. 197—199 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.33 (s, 2H), 6.28 (s, 1H), 7.20—8.05 (m, 9H), 11.80 (s, 1H); IR (KBr) ν: 3331, 1630, 1577 cm^{-1}; MS (70 eV) *m/z* (%): 267 (M^+, 37), 234 (24), 190 (8), 91 (100), 77 (15). Anal. calcd for $C_{16}H_{13}NOS$: C 71.91, H 4.87, N 5.24; found C 72.01, H 4.99, N 5.04.

2-Benzylthio-6-chloro-4-(1H)-quinolone (**4h**) M.p. 226—228 ℃; ^{1}H NMR (DMSO-d_6) δ: 4.31 (s, 2H), 6.30 (s, 1H), 7.20 (d, J = 9.33 Hz, 1H), 7.52 (dd, J_1 = 9.42 Hz, J_2 = 2.47 Hz, 1H), 8.05—8.23 (m, 6H), 11.68 (s, 1H); IR (KBr) ν: 3280, 1638, 1567 cm^{-1}; MS (70 eV) *m/z* (%): 301 (M^+, 21), 303 (M^+ + 2, 38), 268 (18), 224 (7), 91 (100), 77 (15). Anal. calcd for $C_{16}H_{12}ClNOS$: C 63.68, H 3.98, N 4.64; found C 63.99, H 4.02, N 4.30.

References and note

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7 The loading of resin **2** was determined by reversed titration with hydrochloride acid after saponification with excess NaOH in EtOH (loading = 1.11 mmol/g).

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