A cleavage reaction of benzothiazole with cyclic 1,3-dicarbonyls in the presence of potassium dihydrogen phosphate

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A facile and convenient synthesis of phenothiazine derivatives has been achieved by condensation reaction of benzothiazole derivatives with 1,3-dicarbonyls in the presence of potassium dihydrogen phosphate (KH_2PO_4) in moderate to good yields under mild conditions.

Keywords: potassium dihydrogen phosphate, benzothiazoles, 1,3-dicarbonyls, phenothiazines, cleavage reaction

Phenothiazine derivatives exhibit a variety of biological activities and are widely used in medicine.[1-9] These compounds possess a wide spectrum of biological and pharmacological activities due to the presence of nitrogen and sulfur groups, which are considered to be one of the structural features that impart their activities.[10-13] Modifications of the phenothiazine ring system produce different activities, such as neuroleptics, tranquilisers, antihistaminic, anticholinergic, anthelmintic, antibacterial and antiallergics.[14-21]

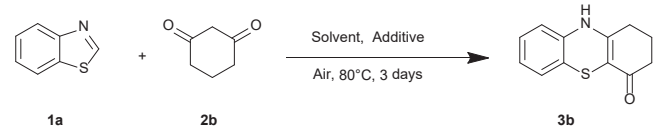
The synthesis of potential drug-delivery systems from maleic anhydride copolymers and phenothiazine derivatives has been reported.[22,23] Munde and coworkers[24] reported an *in-situ* synthesis of 1,4-benzothiazines without solvent from 2-aminobenzenethiol and acyclic 1,3-dicarbonyls under oxidative conditions involving the formation of dimer of 2-aminobenzenethiols. Sheibani[25] reported the synthesis of 1,4-benzothazines by using acyclic 1,3-bielectorphiles and binucleophiles such as 1,3-dicarbonyl, enaminones and 2,2'-disulfanediyldianiline.[25] Also, he obtained 2,3-disubstituted 1,4-benzothiazines at ambient temperature and in aqueous media from 2-aminobenzenethiol and 1,3-dicarbonyls by oxidative cyclocondensation.[12]

Another method for phenothiazine synthesis has been developed by Jain through the condensation of *o*-aminobenzenethiol with 1,3-dicarbonyls in dimethyl sulfoxide.[26] Our efforts are continuing into studying the cleavage reaction of dicarbonyls without a non-transition metal.[27,28] We now report a facile synthetic method obtaining 1,4-benzothiazines from the cleavage reaction of benzothiazole with 1,3-dicarbonyls under mild conditions.

Results and discussion

Initially, potassium phosphate was employed in the reaction of benzothiazole **1a** and cyclohexane-1,3-dione **2b** in dimethyl sulfoxide (DMSO) at 80 ºC under air for 3 days (Table 1, entry 1). Only a modest yield 15% was obtained under these conditions. Interestingly, when potassium phosphate was changed to sodium acetate, the reaction result was enhanced (50% yield) (Table 1, entry 2). However, neither alkali nor organic bases could enhance the reactivity of this reaction (Table 1, entries 2–5). It seems that the base had less effect on

Table 1 Screening of optimal conditions in the formation of **3b**[a]



1a **2b** **3b**

Entry	Solvent	Additive	Yield/%[b]
1	DMSO	K_3PO_4	15
2	DMSO	NaOAc	50
3	DMSO	Cs_2CO_3	20
4	DMSO	Triethylamine	20
5	DMSO	KOH	Trace
6	DMSO	NH_4Cl	50[c]
7	DMSO	K_2HPO_4	58
8	DMSO	KH_2PO_4	70
9	DMF	KH_2PO_4	Trace
10	DMAc	KH_2PO_4	50[c]
11	EtOH	KH_2PO_4	10
12	DMSO/H_2O (5/1)	KH_2PO_4	70
13	DMSO/H_2O (2/1)	KH_2PO_4	80
14	DMSO/H_2O (1/1)	KH_2PO_4	86
15	DMSO/H_2O (1/2)	KH_2PO_4	75
16	DMAc/H_2O (1/1)	KH_2PO_4	65[d]

[a] Reaction conditions: benzothiazole (0.5 mmol), 1,3-cyclohexanedione (1 mmol), base (1 mmol), solvent (2.0 mL), 80 °C, stirred for 3 days under air.
[b]Yields obtained after column chromatography.
[c]Reaction time of 6 days.
[d]Reaction time of 7 days.

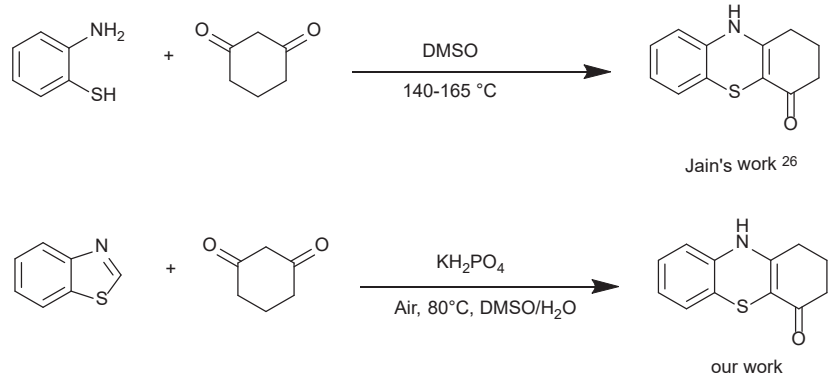


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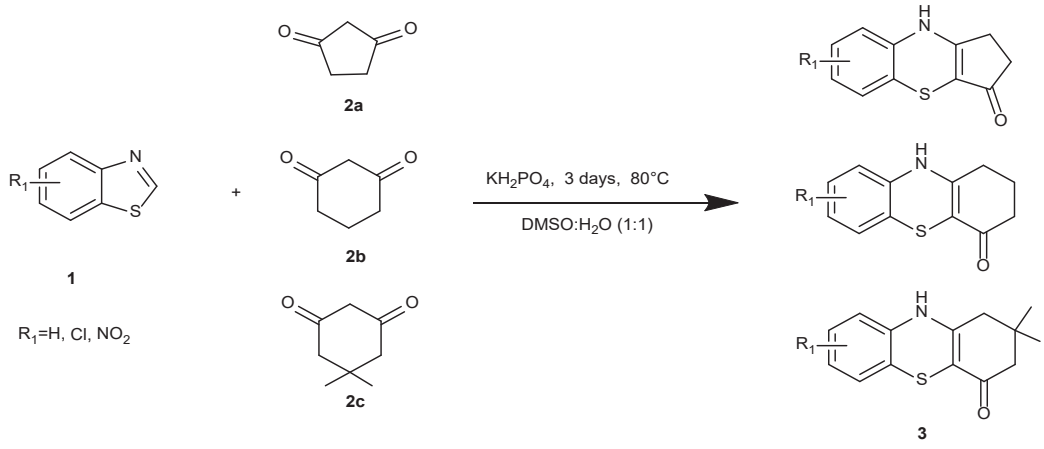
Table 2 Condensation reaction of benzothiazoles (**1**) and 1,3-dicarbonyls (**2**)[a]



Entry	R_1	Dicarbonyls	Product	Yield/%[b]	M.p./°C	Lit. m.p./°C
1	H	**2a**	**3a**	60	216–218	–
2	H	**2b**	**3b**	86	216–220	202–208[26]
3	H	**2c**	**3c**	80	238–240	212–214[25]
4	NO_2	**2a**	**3d**	60	288–290	–
5	NO_2	**2b**	**3e**	72	278–280	–
6	NO_2	**2c**	**3f**	82	296–298	–
7	Cl	**2a**	**3g**	40	290–292	–
8	Cl	**2b**	**3h**	70	285–287	–
9	Cl	**2c**	**3i**	85	205–208	–

[a] Reaction conditions: a mixture of 1 (0.5 mmol), 2 (1 mmol), KH_2PO_4 (1 mmol), DMSO (2 mL) and water (2 mL) were placed in a 15 mL flask, stirred for 3 days at 80 °C.
[b] Yields obtained after column chromatography.

the reaction and the high pKa value of the additives could not promote the formation of the product.

Encouraged by these results, we investigated the influences of different additives on the reaction (Table 1, entries 6–8). Among these additives, potassium dihydrogen phosphate (KH_2PO_4) is generally the best additive in this reaction. The acceptable yield of product could be achieved using KH_2PO_4 in DMSO (Table 1, entry 8). Next, several solvents were also screened for the reaction, such as DMF, *N*, *N*-dimethylacetamide (DMAc), and ethanol (Table 1, entries 9–11), but they could not give satisfactory results in comparison with DMSO. The best yield of the corresponding product **3b** (86%) was achieved when DMSO was mixed with water in the ratio 1:1 (Table 1, entry 14).

Using the best conditions, different cyclic 1,3-dicarbonyls **2** were reacted with the substituted benzothiazoles **1** to test the reaction scope (Table 2). Fortunately, most substrates could react well under the optimal conditions. 5,5-Dimethylcyclo-1,3-dione **2c** reacted with the substituted benzothiazoles in better yield due to the high reactivity of this 1,3-dicarbonyl. When benzothiazole **1a** reacted with **2c** in the presence of KH_2PO_4, the corresponding product **3c** could be generated in 80% yield. Meanwhile, cyclopentane-1,3-dione **2a** showed fewer reactivity in comparison with **2b** and **2c**, while it was treated with different benzothiazoles under the same conditions. The nitro group and the chloro group in the phenyl ring of benzothiazole decreased the yields of the reaction. The structure of the product **3g** has been shown in Fig. 1, and the details of the crystal were shown in Table 3. However, the reaction of benzothiazole with noncyclic1,3-dicarbonyls could not be carried out easily.

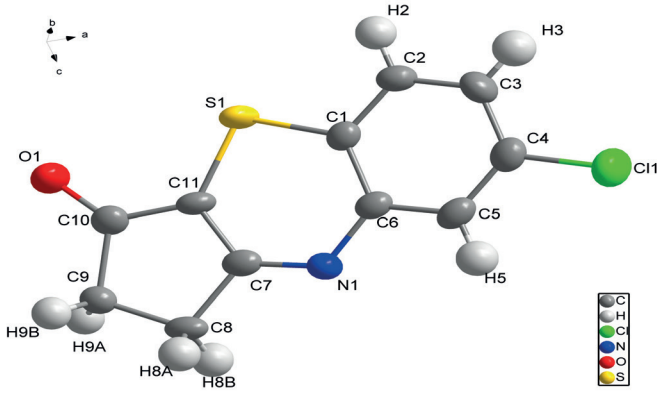


Fig. 1 X-ray crystal structure of product **3g**.

Table 3 Crystallographic data and structure refinement details for **3g**

Empirical formula	$C_{11}H_8ClNOSNa$
Formula mass	236.69
Crystal system	Orthorhombic
Space group	P c a 21
a/Å	17.659(4)
b/Å	4.6932(10)
c/Å	12.051(2)
α/°	90
β/°	90
γ/°	90
V/Å^3	998.8(4)
Z	4
d_{calcd}/g cm^{-3}	1.574
F(000)	484.0
Reflections collected	2097/1491
$R_{(int)}$	0.0655
R^1, wR^2 [I > 2σ(I)]	0.1025, 0.0580
R^1, wR^2 (all data)	0.1096, 0.0977
CCDC reference number	1426308

Experimental

All commercial reagents and solvents were used as received without further purification unless specified, and reaction solvents were distilled. Melting points were determined in capillaries and the thermometer is uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AVANCE 600 spectrometer in DMSO-d_6. IR spectra were recorded with a Bruker Tensor 27 FT-IR spectrophotometer using KBr pellets. GC-MS was performed on a Finnigan Trace DSQ chromatograph. High-resolution mass spectra were obtained on UHR-TOF MAXis.

Synthesis of **3***; general procedure*

A mixture of benzothiazole **1a** (67.5 mg, 0.5 mmol), cyclohexane-1,3-dione **2b** (112 mg, 1 mmol), KH_2PO_4 (136 mg, 1 mmol), DMSO (2 mL) and water (2 mL) were placed into a 15 mL flask under air. The reaction mixture was stirred in oil bath for 3 days at 80 ºC. The progress of the reaction was monitored by TLC.

When the reaction was complete, it was neutralised with a saturated $KHCO_3$ aqueous solution, and extracted with ethyl acetate (3 × 10 mL). The extract was washed with water (3 × 5 mL) and dried over anhydrous Na_2SO_4. After drying, it was concentrated under reduced pressure to give the crude product, which was further purified by silica-gel column chromatography to afford 2,3-dihydro-10*H*-phenothiazin-4 (1*H*)-ones **3b** (93.2 mg, yield: 86%).

*2,9-Dihydro-1*H*-cyclopenta[*b*][1,4]benzothiazin-3-one* **(3a):** Yield 60%; yellow solid; m.p. 216–218 ºC; IR (KBr) cm^{-1} : 3348, 2907, 1596, 1568, 1530, 1472, 1432, 1288, 1286, 750; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 9.47 (s, 1H), 6.90 (t, *J* = 7.3Hz, 1H), 6.73–6.77 (m, 2H), 6.54 (d, *J* = 7.9Hz, 1H), 2.47 (t, *J* = 4.5Hz, 2H), 2.27(t, *J* = 4.2Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 195.2, 166.6, 136.6, 127.5, 127.2, 124.7, 117.3, 116.6 , 99.9, 32.5 , 25.6 ; MS (EI): *m/z* = 203 [M]$^+$. HRMS-(ESI) (m/z) (M+Na)$^+$ calcd for $C_{11}H_9NOSNa$ 226.0297; found: 226.0291.

*2,3-Dihydro-1*H*-phenothiazin-4(10*H*)-one* **(3b):**[26] Yield 86%; yellow solid; m.p. 216–220 ºC (lit.[26] 202–208 ºC), IR (KBr) cm^{-1}: 3347, 3016, 2906, 1564, 1515, 1468, 1431, 1353, 1294, 1564, 1515, 1294, 746; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 8.91 (s, 1H), 6.86 (t, *J* = 6.4 Hz, 1H), 6.79-6.69 (m, 2H), 6.54 (d, *J* = 7.7 Hz, 1H), 2.32 (t, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 6.0 Hz, 2H), 1.87-1.76 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 189.0, 156.0, 136.6, 126.8, 126.4, 124.5, 119.9, 115.6, 97.8, 36.1, 28.0, 20.1; MS (EI): *m/z* = 217 [M]$^+$.

*2,2-Dimethyl-2,3-dihydro-1*H*-phenothiazin-4(10*H*)-one* **(3c):**[25] Yield 80%; orange solid; m.p. 238–240 ºC (lit.[25] 212-214 ºC), IR (KBr) cm^{-1} : 3432, 3066, 3025, 2957, 2870, 1574, 1519, 1472, 1427, 1355, 1306, 748; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 8.86 (s, 1H), 6.86 (t, *J* = 5.9 Hz, 1H), 6.74 (m, 2H), 6.54 (d, *J* = 7.6 Hz, 1H), 2.28 (s, 2H), 2.23(s, 2H), 0.99 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 188.4, 153.9, 136.6, 126.8, 126.4, 124.4, 119.8, 115.6, 96.5, 49.6, 41.2, 31.4, 27.5; MS (EI): *m/z* = 245 [M]$^+$.

*6-Nitro-2,9-dihydro-1*H*-cyclopenta[*b*][1,4]benzothiazin-3-one* **(3d):** Yield 60%; purple solid; m.p. 288–290 ºC; IR (KBr) cm^{-1} : 3439, 3233, 3052, 1665, 1595, 1534, 1500, 1473, 1338, 1303, 1252, 886, 824; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 10.02 (s, 1H), 7.77 (d, *J* = 8.4Hz, 1H), 7.60 (s, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 2.48 (t, *J* = 4.2 Hz, 2H), 2.32 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 195.9, 165.8, 143.6, 143.4, 124.4, 122.0, 119.7, 115.9, 101.6, 32.8, 25.6; MS (EI): *m/z* = 248 [M]$^+$. HRMS-(ESI) (*m/z*) (M+Na)$^+$ calcd for $C_{11}H_8N_2O_3SNa$ 271.0148; found: 271.0141.

*7-Nitro-2,3-dihydro-1*H*-phenothiazin-4(10*H*)-one* **(3e):** Yield 72%; yellow solid; m.p. 278–280 ºC; IR (KBr) cm^{-1} : 3445, 2961, 1594, 1465, 1418, 1388, 1310, 1262, 1095, 1023, 808, 881; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 9.46 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.55 (s, 1H), 6.62 (d, *J* = 8.7 Hz, 1H), 2.32 (t, *J* = 5.8 Hz, 2H), 2.28 (t, *J* = 6.3 Hz, 2H), 1.86-1.81 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 190.2, 155.0, 143.8, 143.5 , 124.2, 122.3 , 121.5, 115.3, 100.0, 36.3, 28.0, 20.2; MS (EI): *m/z* = 262 [M]$^+$. HRMS-(ESI) (*m/z*) (M+Na)$^+$ calcd for $C_{12}H_{10}N_2O_3SNa$ 285.0304; found: 285.0296.

*2,2-Dimethyl-7-nitro-2,3-dihydro-1*H*-phenothiazin-4(10*H*)-one* **(3f):** Yield 82%; purple solid; m.p. 296–298 ºC; IR (KBr) cm^{-1}: 3445, 3270, 2961, 2873, 1590, 1481, 1386, 1328, 1254, 1145, 881, 827; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 9.39 (s, 1H), 7.75 (d, *J* = 8.4Hz, 1H), 7.55 (s, 1H), 6.63 (d, *J* = 8.8 Hz, 1H), 2.21 (s, 2H), 2.19 (s, 2H), 1.00 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 189.5, 152.6, 143.6, 143.3, 124.0, 121.9, 121.3, 115.1, 98.5, 49.6, 40.9, 31.6, 27.5; MS (EI): *m/z* = 290 [M]$^+$. HRMS-(ESI) (*m/z*) (M+Na)$^+$ calcd for $C_{14}H_{14}N_2O_3SNa$ 313.0617; found: 313.0610.

*7-Chloro-2,9-dihydro-1*H*-cyclopenta[*b*][1,4]benzothiazin-3-one* **(3g):** Yield 40%; orange solid; m.p. 290–292 ºC; IR (KBr) cm^{-1}: 3447, 3225, 2920, 1658, 1593, 1523, 1467, 1305, 896, 859, 799; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 9.59 (s, 1H), 6.77–6.84, (m, 2H), 6.56 (s, 1H), 2.47 (t, *J* = 4.2 Hz, 2H), 2.27 (t, *J* = 4.2 Hz, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 195.3, 166.2, 138.4, 131.3, 128.4, 124.0, 116.6, 115.8, 100.4, 32.6, 25.6; MS (EI): *m/z* = 237 [M]$^+$. HRMS-(ESI) (*m/z*) (M+Na)$^+$ calcd for $C_{11}H_8ClNOSNa$ 259.9907; found: 259.9916.

*8-Chloro-2,3-dihydro-1*H*-phenothiazin-4(10*H*)-one* **(3h):** Yield 70%; orange solid; m.p. 285–287 ºC; IR (KBr) cm^{-1}: 3444, 3253, 2943, 1714, 1636, 1574, 1502, 1462, 1330, 1291, 927, 878, 804; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 8.99 (s, 1H), 6.51–6.97 (m, 2H), 6.56 (s, 1H), 2.32 (t, *J* = 6.0 Hz, 2H), 2.26 (t, *J* = 6.0 Hz, 2H), 1.80–1.88 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 189.3, 155.5, 138.3, 130.7, 127.6, 123.8, 119.1, 115.0, 100.3, 36.1, 27.9, 20.0; MS (EI): *m/z* = 251 [M]$^+$. HRMS-(ESI) (*m/z*) (M+Na)$^+$ calcd for $C_{12}H_{10}ClNOSNa$ 274.0064; found: 274.0057.

*8-Chloro-2,2-dimethyl-2,3-dihydro-1*H*-phenothiazin-4(10*H*)-one* **(3i):** Yield 85%; orange solid; m.p. 205–208 ºC; IR (KBr) cm^{-1}: 3447, 3276, 2958, 2928, 2867, 1728, 1570, 1508, 1467, 1384, 1273, 934, 861, 805; ^{1}H NMR (600 MHz, DMSO-d_6, ppm): 8.94 (s, 1H), 6.71–6.80 (m, 2H), 6.54 (s, 1H), 2.18 (s, 2H), 2.15 (s, 2H), 0.98 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6, ppm): 188.9, 153.5, 138.4, 130.7, 127.7, 123.8, 119.1, 115.0, 97.2, 49.7, 41.2, 31.5, 27.5; MS (EI): *m/z* = 279 [M]$^+$. HRMS-(ESI) (*m/z*) (M+Na)$^+$ calcd for $C_{14}H_{14}ClNOSNa$ 302.0377; found: 302.0369.

Conclusion

We developed a new approach to synthesise the 2,3-dihydro-1*H*-phenothiazin-4(10*H*)-ones and the cyclopenta[*b*][1,4] benzothiazines under a mild and environment benign conditions. This reaction could be carried out without any transition metals with good to moderate yield.

Electronic Supplementary Information

The ESI including ^{1}H and ^{13}C NMR spectra of the compounds is available through stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

This work was supported by the Priority Academic Program Development of Jiangsu Higher Education Institutions.

Received 23 July 2015; accepted 5 October 2015
Paper 1503507 doi: 10.3184/174751915X14449331711796
Published online: 1 November 2015

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