J. Iran. Chem. Soc., Vol. 8, No. 4, December 2011, pp. 1036-1042.

JOURNAL OF THE
Iranian
Chemical Society

Efficient Microwave-Assisted Synthesis of 3-Benzothiazolo and 3-Benzothiazolino Coumarin Derivatives Catalyzed by Heteropoly Acids

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(Received 21 January 2011, Accepted 22 April 2011)

Heteropoly acids are reported as efficient catalysts for the microwave-assisted synthesis of 3-benzothiazolo and 3-benzothiazolino coumarin from *o*-aminothiophenol derivatives with 3-acetly and 3-cyanochromen-2-one in good to excellent isolated yields (73-95%). This study suggests new techniques for the synthesis of chromene derivatives using an inexpensive and easily available catalyst, a simple procedure, short reaction time, and good to excellent yields of the products.

Keywords: *o*-Aminothiophenol, 3-Benzothiazolino coumarin, 3-Benzothiazolo coumarin, Heteropoly acid

INTRODUCTION

Benzothiazoline and benzothiazole derivatives have received considerable attention in organic synthesis and pharmaceutical chemistry [1-5]. These heterocycles have varied pharmacological activities such as antibiotic [6], anticancer [7], antiviral [8], antifungal [9], antimicrobial [10] and antiparkinson [11] properties.

On the other hand, several coumarin derivatives have pronounced medicinal value as antibacterial and antifungal agents [12]. Others have varied bioactivity such as anticancer [13], antitumor, antiviral [14] and inhibition of HIV-1 protease [15].

The approach to the preparation of potentially-biologically active compounds today is predominantly based on the combination of different substructures which enhance the biological activity of known active substances. Given the pharmacological importance of the benzothiazoline and benzothiazole ring systems, we have focused on the synthesis of new 3-benzothiazolino and dihydrothiazolino coumarins. For the synthesis of benzothiazoline and benzothiazole moieties several methods have been reported which typically involve the reaction of carboxylic acids [16-18] and their derivatives like orthoesters [19-21], esters [22], nitriles [23-26], amides [27], aldehydes [28-30] and ketones [31] with 2-aminothiophenol in the presence of an acidic catalyst at elevated temperatures.

3-Benzothiazolo coumarins have been synthesized using benzothiazol-2-yl-acetic acid ethyl ester with *o*-hydroxy-benzaldehyde [32]. Recently, a one pot synthesis of 3-benzothiazolo coumarins was reported from salicylaldehydes, ethyl cyanoacetate and *o*-aminothiophenols in the presence of piperidine as a base [33]. Different methods for the synthesis of 3-benzothiazolo coumarins, have been reported, but none of them starts from 3-cyanocoumarin under acidic conditions.

Also, condensation of *o*-aminothiophenol with carbonyl

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compounds has been reported in the presence of alumina [31], *p*-toluenesulfonic acid [34], hydrochloric acid [35] and a Lewis acid such as $Ga(OTf)_3$ [36]. However, heteropoly acid was not used for this condensation.

Due to the interesting properties of coumarin derivatives, and since close attention has been paid to the use of heteropoly acid in the organic reactions for the last decade [37], we thus present our research findings on the synthesis of 3-benzothiazolo coumarin and 3-benzothiazolino coumarin derivatives, using *o*-aminothiophenol with 3-acetly and 3-cyanochromen-2-one catalyzed by heteropoly acids as a new catalyst for this reaction in good to excellent isolated yields (62-97%) under thermal condition and or microwave irradiation.

EXPERIMENTAL

Chemicals were obtained from commercial sources. The 3-cyano and 3-acetylcoumarins were prepared using reported methods [38]. Melting points were measured on a Kofler hot stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker FT-500 spectrometer in $CDCl_3$ or DMSO-d_6, and TMS was used as the internal standard at 500 and 125.7 MHz respectively. Mass spectra were recorded on a Finnigan Mat TSQ-70 spectrometer. Infrared (IR) spectra were acquired on a Nicollet Magna 550-FT spectrometer. The experiments were performed using a microwave oven (ETHOS 1600, Milestone) with a power of 600 W specially designed for an organic synthesis and modified with a condenser and mechanical stirrer. Elemental analyses were carried out with a Perkin-Elmer model 240-C apparatus. The results of elemental analyses (C, H, N) were within ±0.4% of the calculated values.

General Procedure for the Synthesis of 3-Benzothiazolo and 3-Benzothiazolino Coumarin Derivatives

To a mixture of 3-acetylcoumarins **1** (1 mmol) and 2-aminothiophenols **2** (1.2 mmol) was added 3 ml AcOH as solvent and catalyst and the mixture was irradiated with microwaves at 300 W for 7 min under reflux conditions. After completion of the reactions, the mixture was cooled and the precipitated solid was filtered out and washed with Et_2O and water. Further purifications were carried out by crystallization from EtOH. Similar procedure can be performed in the presence of 3 ml absolute EtOH and HPMo (5 mol%, 0.09 g) as the catalyst. The mixture was irradiated for 10 min (5 × 2 min). The reaction mixture, after each 2-minute irradiation was thoroughly mixed outside the microwave oven for 1 min with ultrasound and again irradiated for another 2 min. This cycle was repeated for the total irradiation time. Upon the completion of the reaction monitored by (TLC), the solvent was evaporated and dichloromethane (10 ml) was added to the residue. The catalyst was filtered and washed with dichloromethane (3 × 5 ml) and the solvent was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (n-hexane/ethyl acetate = 8:2) to give the pure product. The same procedure was followed for the synthesis of compound **5**; however, 30 and 15 min were used for the completion of the reaction in the presence of acetic acid or HPMo in ethanol, respectively. All the products were identified by their NMR, IR and Mass spectral data.

3-(2-Methyl-2,3-dihydrobenzo[d]thiazol-2-yl)-2H-chromen-2-one (3a). Yellow solid; Yield: 95%; m.p.: 159-161 °C; IR (KBr, cm^{-1}) ν_{max}: 3344 (NH), 3074, 2988, 1705 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.19 (s, 3H), 5.03 (bs, 1H, NH), 6.76 (m, 2H), 6.95 (t, J = 7.5 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.50 (m, 2H), 8.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.2, 76.9, 111.3, 116.2, 118.9, 121.1, 121.8, 124.5, 125.4, 127.3, 128.4, 131.5, 138.4, 145.1, 153.1, 160.2; Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.74. Found: C, 69.26; H, 4.23; N, 4.62.

Compound **3a** was also prepared in the following way. A mixture of 3-acetylcoumarins **1a** (1 mmol), 2-aminothiophenol **2a** (1.2 mmol) and $H_3PW_{12}O_{40}$ (5 mol%, 0.14 g) in ethanol was stirred for 12 h at room temperature. The solid was filtered and the crude mixture was washed with water to yield pure product **3a**.

3-(6-Chloro-2-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)-2H-chromen-2-one (3b). Yellow solid; Yield: 73%; m.p.: 190-192 °C; IR (KBr, cm^{-1}) ν_{max}: 3334 (NH), 3068, 2987, 1705 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.16 (s, 3H), 5.21 (bs, 1H, NH), 6.69 (m, 2H), 6.92 (d, J = 8.5 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 7.51 (m, 2H), 8.07

(s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.4, 77.8, 110.8, 116.3, 118.8, 120.5, 122.3, 124.6, 125.0, 128.4, 131.0, 131.7, 136.6, 146.3, 153.1, 160.2; Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.67; N, 4.25. Found: C, 61.76; H, 3.83; N, 4.02.

8-Methoxy-3-(2-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)-2H-chromen-2-one (3c). Yellow solid; Yield: 93%; m.p.: 187-189 °C; IR (KBr, cm^{-1}) ν_{max}: 3348 (NH), 3076, 2965, 1700 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.18 (s, 3H), 3.95 (s, 3H), 5.10 (bs, 1H, NH), 6.74 (m, 2H), 6.94 (t, J = 7.5 Hz, 1H), 7.04 (m, 3H), 7.18 (t, J = 8.0 Hz, 1H), 8.08 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 28.3, 56.2, 76.7, 111.1, 113.3, 119.6, 119.8, 120.9, 121.8, 124.3, 125.4, 127.0, 131.7, 138.6, 142.8, 145.2, 146.9, 159.7; Anal. Calcd. for $C_{18}H_{15}NO_3S$: C, 66.44; H, 4.65; N, 4.30. Found: C, 66.36; H, 4.43; N, 4.49.

6-Bromo-3-(2-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)-2H-chromen-2-one (3d). Yellow solid; Yield: 91%; m.p.: 109-111 °C; IR (KBr, cm^{-1}) ν_{max}: 3351 (NH), 3052, 2970, 1697 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.17 (s, 3H), 5.20 (bs, 1H, NH), 6.77 (m, 2H), 6.94 (t, J = 7.5 Hz, 1H),7.04 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 8.5 Hz, 1H), 7.56 (dd, J = 8.5 Hz and J = 2.2, 1H), 7.62 (d, J = 2.2, 1H), 7.98 (s, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.8, 76.5, 111.8, 117.0, 117.9, 120.5, 121.6, 121.8, 125.5, 127.9, 130.6, 132.7, 134.2, 136.9, 144.9, 151.9, 159.6; MS, m/z (%) 375 ($M^{\bullet+}$+2, 17%), 373 ($M^{\bullet+}$, 17%), 360 (100), 358 (89), 251 (17), 150 (20), 109 (17); Anal. Calcd. for $C_{17}H_{12}BrNO_2S$: C, 54.56; H, 3.23; N, 3.74. Found: C, 54.50; H, 3.03; N, 3.86.

6-Hydroxy-3-(2-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)-2H-chromen-2-one (3e). Green solid; Yield: 94%; m.p.: 189-191 °C; IR (KBr, cm^{-1}) ν_{max}: 3442 (OH), 2967, 1726 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.98 (s, 3H), 4.92 (bs, 1H, NH), 6.59 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.89 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 7.6 Hz, 1H), 7.03 (m, 2H), 7.26 (d, J = 7.6 Hz, 1H), 7.92 (s, 1H), 9.79 (s, 1H). Anal. Calcd. for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.35; H, 4.50; N, 4.17.

7-Hydroxy-3-(2-methyl-2,3-dihydrobenzo[d]thiazol-2-yl)-2H-chromen-2-one (3f). Yellow solid; 91%; m.p.: 101-103 °C; IR (KBr, cm^{-1}) ν_{max}: 3343 (OH), 3052, 2912, 1704 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.07 (s, 3H), 4.99 (bs, 1H, NH), 6.57 (t, J = 7.5 Hz, 1H), 6.70 (d, J = 7.7 Hz, 1H), 6.73 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 6.87 (t, J = 7.7 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 10.59 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 19.0, 76.2, 102.1, 110.0, 111.2, 113.9, 119.4, 121.4, 125.6, 126.5, 128.2, 130.5, 137.5, 146.2, 154.9, 160.0, 161.6; MS, m/z (%) 311 ($M^{\bullet+}$, 25%), 296 (100), 150 (8), 109 (7). Anal. Calcd. for $C_{17}H_{13}NO_3S$: C, 65.58; H, 4.21; N, 4.50. Found: C, 65.24; H, 4.58; N, 4.21.

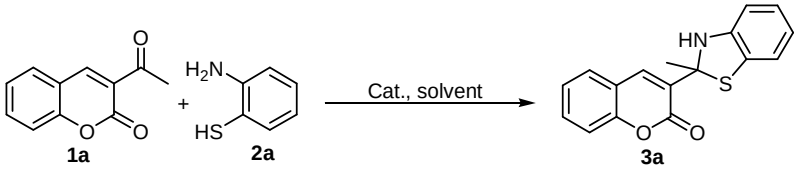
3-(Benzo[d]thiazol-2-yl)-2H-chromen-2-one (5a). Yellow solid; Yield: 88%; m.p.: 215-217 °C; IR (KBr, cm^{-1}) ν_{max}: 3048, 3025, 1716 (C=O), 1607, 1557 (C=N); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.40 (td, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.45-7.47 (m, 2H), 7.55 (td, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.66 (td, J = 8.0 Hz, J = 1.4 Hz, 1H), 7.75 (dd, J = 8.5 Hz, J = 2.4 Hz, 1H), 7.99 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 9.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 116.7, 118.6, 120.3, 121,7, 122.9, 125.2, 125.4, 126.5, 129.3, 133.2, 136.8, 141.4, 152.4, 153.8, 159.8, 159.9; Anal. Calcd. for $C_{16}H_9NO_2S$: C, 68.80; H, 3.25; N, 5.01. Found: C, 68.75; H, 3.49; N, 4.82.

3-(Benzo[d]thiazol-2-yl)-8-hydroxy-2H-chromen-2-one (5b). Orange solid; Yield: 68%; m.p.: 284-286 °C; IR (KBr, cm^{-1}) ν_{max}: 3429 (OH), 1745 (C=O), 1553 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.24 (m, 2H), 7.48 (m, 2H), 7.58 (t, J = 8.4 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 9.19 (s, 1H), 10.41 (s, 1H); Anal. Calcd. for $C_{16}H_9NO_3S$: C, 65.07; H, 3.07; N, 4.74. Found: C, 65.33; H, 2.83; N, 4.39.

3-(6-Chlorobenzo[d]thiazol-2-yl)-2H-chromen-2-one (5c). Yellow solid; Yield: 62%; m.p.: 269-271 °C; IR (KBr, cm^{-1}) ν_{max}: 1711 (C=O), 1548 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (m, 2H), 7.50 (d, J = 8.5 Hz, 1H), 7.69 (t, J = 8.5 Hz, 1H), 7.69 (t, J = 8.5 Hz, 1H), 7.82 (d, J = 7.7 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 9.23 (s, 1H); Anal. Calcd. for $C_{16}H_8ClNO_2S$: C, 61.25; H, 2.57; N, 4.46. Found: C, 61.41; H, 2.22; N, 4.73.

3-(Benzo[d]thiazol-2-yl)-6-bromo-2H-chromen-2-one (5d). Yellow solid; Yield: 84%; m.p.: 276-278 °C; IR (KBr, cm^{-1}) ν_{max}: 1725 (C=O), 1569 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.52 (m, 2H), 7.59 (t, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 8.35 (s, 1H), 9.23 (s, 1H); Anal. Calcd. for $C_{16}H_8BrNO_2S$: C, 53.65; H, 2.25; N, 3.91. Found: C, 53.83; H, 2.42; N, 3.76.

3-(Benzo[d]thiazol-2-yl)-7-hydroxy-2H-chromen-2-one (5e). Red solid; Yield: 87%; m.p.: 293-295 °C; IR (KBr, cm^{-1})



Sheme 1. Model reaction for catalyst screening under thermal and microwave irradiation

Table 1. Screening of some Acidic Catalysts for Model Reaction under Thermal and Microwave Irradiation[a]

Entry	Catalyst	Conditions	Solvent	Time (min)	Yield (%)[b]
1	*p*-TsOH (30 mol%)	Reflux	Benzene	360	90
2	Al_2O_3 (1 g)	80 °C	-	300	40
3	HPW (5 mol%)	r.t.	EtOH	720	97
4	HPW (5 mol%)	Reflux	EtOH	360	94
5	HPMo (5 mol%)	Reflux	EtOH	360	72
6	AcOH (3 cc)	Reflux	-	720	94
7	HPMo (5 mol%)	Reflux	DMSO	360	10
8	HPW (5 mol%)	Reflux	DMSO	360	20
9	-	MW	CH_3CN	30	No reaction
10	Al_2O_3 (1 g)	MW	-	10	30
11	$AlCl_3$ (10 mol%)	MW	CH_3CN	10	10
12	*p*-TsOH (1 mmol)	MW	CH_3CN	10	20
13	$HClO_4$-SiO_2 (10 mol%)[c]	MW	CH_3CN	10	46
14	SSA (10 mol%)[d]	MW	CH_3CN	10	32
15	HPW (5 mol%)	MW	CH_3CN	10	57
16	HPMo (5 mol%)	MW	CH_3CN	10	93
17	HSiW (5 mol%)[e]	MW	CH_3CN	10	72
18	$ZnCl_2$ (5 mol%)	MW	CH_3CN	10	37
19	AcOH (3 cc)	MW	-	5	83
20	AcOH (3 cc)	MW	-	7	95
21	HPMo (3 mol%)	MW	EtOH	10	87
22	HPMo (5 mol%)	MW	EtOH	10	95
23	HPMo (7 mol%)	MW	EtOH	10	95
24	HPW (5 mol%)	MW	EtOH	10	53

[a]Reaction condition: 3-acetylcoumarins, 1 mmol; *o*-aminothiophenol, 1.2 mmol; Cat.; solvent, 3 cc. The experiments were performed using a modified microwave oven (ETHOS 1600, Milestone with a power of 600 W specially designed for organic synthesis) which modified with condenser and mechanical stirrer at 300 W. [b]Isolated yield. [c]The catalyst $HClO_4$-SiO_2 was prepared according to the reported procedure [40] in which 1 g of silica gel contains 0.37 mmol $HClO_4$. [d]SSA (silica sulfuric acid) was prepared following the reported procedure [41]. [e]HSiW ($H_4SiW_{12}O_{40}$).

ν_{max}: 3421 (OH), 1722 (C=O), 1565 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.84 (s, 1H), 6.91 (d, J = 8.4 Hz, 1H), 7.44 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 9.12 (s, 1H), 11.01 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 101.9, 111.3, 114.3, 114.4, 121.9, 122.0, 124.8, 126.3, 131.8, 135.5, 142.5, 151.9, 155.6, 159.6, 160.2, 163.4; Anal. Calcd. for $C_{16}H_9NO_3S$: C, 65.07; H, 3.07; N, 4.74. Found: C, 65.32; H, 3.36; N, 4.51.

RESULTS AND DISCUSSION

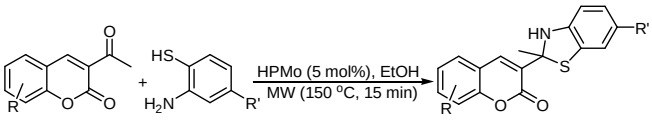
In this work, we extended our previous study [39] concerning the synthesis of novel derivatives of 3-benzothiazolino coumarin. In order to get the best reaction conditions, the efficiency of a variety of solvents and catalysts in the reaction of 3-acetylcoumarin **1a** and 2-aminothiophenol **2a** as a model reaction was studied (Scheme 1).

Based on the previous reports for the condensation of *o*-aminothiophenol with carbonyl compounds in the presence of alumina and *p*-TsOH as best reaction conditions [31,34], and the use of heteropolyacids as environmentally benign catalysts with strong acidity [37], initially we examined the applicability of these catalysts in a model reaction under thermal conditions.

As shown in Table 1, under thermal conditions, the best results in terms of yield and temperature were achieved by using HPW ($H_3PW_{12}O_{40}$) in ethanol (Table 1, entry 3) as compared with the literature procedure [31,34] (Table 1, entries 1 and 2). Also the use of acetic acid under reflux condition was excellent (Table 1, entry 6). The use of other catalysts or solvents did not yield satisfactory results (Table 1, entries 5, 7 and 8). In order to reduce the reaction time, the same procedure was adopted under microwave irradiation (Table 1, entries 9 and 24).

Under this condition, the time was reduced significantly from 6 h to 7-10 min. As indicated in Table 1, acetic acid and HPMo (5 mol%) in ethanol (3 ml) were preferred to other acidic catalysts for this reaction (Table 1, entries 20 and 22). The applicability of the present method to a large scale process was also examined with 50 mmol of 3-acetylcoumarin and 55 mmol of *o*-aminothiophenol which gave **3a** in 92% yield. In order to extend the scope of this reaction, the same procedure was followed for the reaction of 3-acetylcoumarins **1** with *o*-aminothiophenol derivatives **2** (Table 2).

Table 2. MW-Assisted Synthesis of 3-Benzothiazolino Coumarin Derivatives



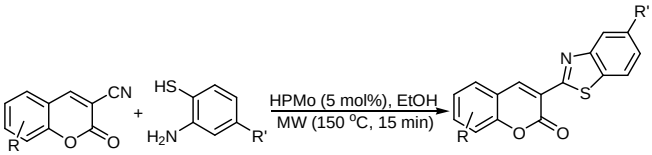
1 **2** **3**

Entry	Product **3**	R	R'	Yield (%)[a]
1	3a	H	H	95
2	3b	H	Cl	73
3	3c	8-OMe	H	93
4	3d	6-Br	H	91
5	3e	6-OH	H	94
6	3f	7-OH	H	91

[a]Isolated yield.

It was found that the introduction of Cl substituent to *o*-aminothiophenol **2** resulted in the decrease of the yields of the reactions. The same reaction was caused by the replacement of 3-cyanocoumarins derivatives **5** with *o*-aminothiophenols **2** which resulted in the formation of 3-benzothiazolo coumarin derivatives in good to moderate yields (Table 3).

Table 3. MW-assisted Synthesis of 3-Benzothiazolo Coumarin Derivatives



6 **2** **7**

Entry	Product **5**	R	R'	Yield (%)[a]
1	5a	H	H	88
2	5b	8-OH	H	68
3	5c	H	Cl	62
4	5d	6-Br	H	84
5	5e	7-OH	H	87

[a]Isolated yield.

No drastic change in yields was observed in comparison with the previous reactions. Similar to the reaction explained previously, slight decrease in yield was observed by the introduction of Cl substituent to *o*-aminothiophenol **2**. Finally, no predictable change in yields was observed by the replacement of the substituent in coumarin derivatives in all reactions. The acceleration of the reaction under microwave irradiation may be rationalized on the basis of the high polarity of the reaction mixtures. The results obtained show that HPMo (5 mol%) or AcOH provide excellent media for this reaction under microwave irradiation.

CONCLUSIONS

In summary, we have developed and introduced a rapid, simple and convenient microwave-assisted method for the synthesis of 3-substituted coumarin derivatives from the reaction of 3-acetyl and 3-cyanocoumarins with *o*-aminothiophenol derivatives in the presence of acetic acid or catalytic amount of the HPMo (5 mol%). This procedure offers several advantages including generality, simplicity, easy work up, clean reactions, scale up and improved yields.

ACKNOWLEDGEMENTS

This work was financially supported by grants from the Research Council of Tehran University of Medical Sciences and INSF (Iran National Science Foundation).

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