Heteroatom Chemistry
Volume 18, Number 4, 2007

Construction of a Combinatorial Library of 2-(4-Oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones by Microwave-Assisted One-Pot Parallel Syntheses

Zhong-Zheng Zhou, Wei Huang, Feng-Qin Ji, Ming-Wu Ding, and Guang-Fu Yang

Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, 430079, P.R. China

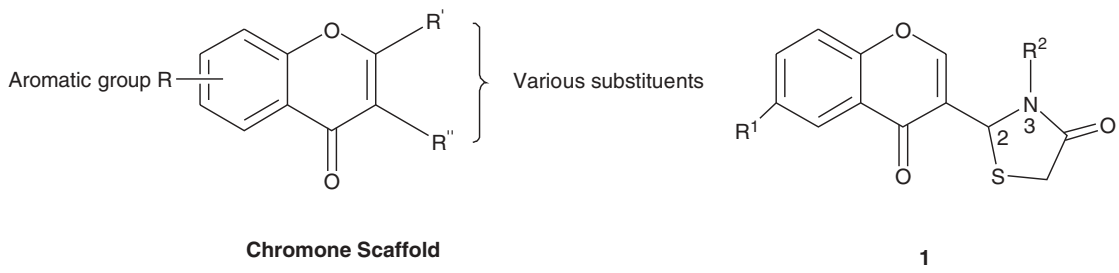
Received 14 March 2006; revised 2 July 2006

ABSTRACT: *A one-pot liquid-phase combinatorial synthesis of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones bearing diverse substituents at the 3-position under microwave irradiation was successfully performed using 3-formyl chromone, primary amine, and mercaptoacetic acid as reactants. Compared to an identical library generated by conventional parallel synthesis, the microwave-assisted parallel synthesis approach dramatically decreased the reaction time from an average of 9 h to 5 min, and substantially increased the product yields. The coupling of microwave technology with liquid-phase combinatorial synthesis constitutes a novel and particularly attractive avenue for the rapid generation of structurally diverse libraries.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:381–389, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20309

Correspondence to: Guang-Fu Yang; gfyang@mail.ccnu.edu.cn.
Contract grant sponsor: National Key Project for Basic Research, National Natural Science Foundation of China.
Contract grant number: 2002CCA00500 and 2003CB114400.
Contract grant sponsor: Program for New Century Excellent Talents in University of China.
Contract grant number: 20432010, 20476036, and 20172017.
Contract grant sponsor: Program for Excellent Research Group of Hubei Province.
Contract grant number: 2004ABC002.

INTRODUCTION

Combinatorial chemistry has emerged as a powerful technique for the generation of structurally diverse drug-like compounds [1]. Research in this area initially focused on the development of solid-phase synthetic methods for mixture libraries, but subsequently shifted to high-throughput parallel synthesis. Although the solid-phase synthesis technique has been successfully applied to the preparation of a large variety of heterocyclic molecules, and a number of review articles have appeared in this area [2], the use of this technique to identify the compound of highest biological activity from among a structurally diverse mixture library is very tedious and time-consuming. In addition, high-throughput parallel synthesis has the advantage that it can produce large amounts of pure compounds for direct bioscreening; however, this strategy is still subject to the same reaction times and yields as for the solid-phase synthesis technique [3]. Hence, the demand for diverse compound libraries for screening in drug discovery and material science is driving the efforts to develop new technologies for rapid



Chromone Scaffold **1**

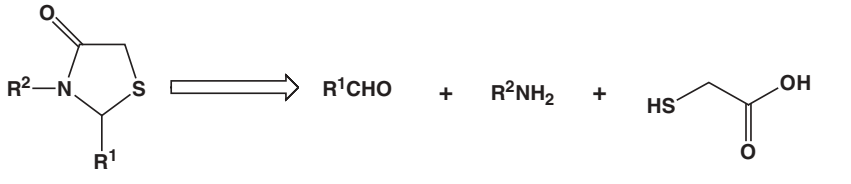
SCHEME 1

parallel and combinatorial synthesis. One promising high-speed technique is microwave-assisted organic synthesis, which has attracted considerable attention in the past few years [4,5]. A recent comprehensive review [6a] highlighted the applications of controlled microwave heating in modern organic synthesis and discussed some of the underlying phenomena and issues. Another recent mini-review described microwave-assisted organic synthesis using ionic liquids [6b]. The main benefits of performing reactions under microwave irradiation are the significant rate enhancements and higher product yields frequently observed under those conditions. Not surprisingly, these features have recently sparked interest in microwave-assisted reactions from drug discovery and medicinal chemistry researchers, for whom reaction speed is of great importance [7]. The combination of microwave irradiation technology and combinatorial chemistry applications therefore seems a logical consequence of the increased speed and effectiveness offered by using microwave irradiation instead of conventional heating methods [4d–h,8].

With the aim of developing a rapid route to diversely substituted drug-like scaffolds, we have focused on the 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones system. The 3-substituted chromone pharmacophore is an important structural element in medicinal chemistry, and shows a broad spectrum of pharmacological activities [9]. Compounds containing this pharmacophore have been used as antianaphylactic agents for the treatment of asthma for many years [9a], and seem to have great potential as cardioprotective agents in doxorubicin antitumor therapy [9c] and as inhibitors of thymidylate synthase [9d], trypsin [9e], and steroid sulfatase [9f], which may serve to treat a number of diseases including breast cancer. Meanwhile, 4-thiazolidinones have also been reported to possess a wide range of biological activities, including antifungal, antibacterial, antihistaminic, antimicrobial, and anti-inlammatory [10]. Hence, we were curious to explore the family of biheterocyclic compounds that contain both the thiazolidinone and chromone pharmacophores (Scheme 1), with a view to discovering novel lead structures for the development of antifungal and antimicrobial agents. To the best of our knowledge, application of microwave technology to parallel synthesis has not been demonstrated for the 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinone system. Here we report the first microwave-assisted parallel synthesis of a library of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones by the combination of three components in one pot, which can deliver higher yields and purity of products after a few minutes of reaction time.

RESULTS AND DISCUSSION

4-Thiazolidinones are most conveniently made by the three-component condensation of a primary amine, an aldehyde, and a mercaptoacetic acid (Scheme 2), whose reaction mechanism was



4-Thiazolidinone **Aldehydes** **Amines** **Mercaptoacetic Acid**

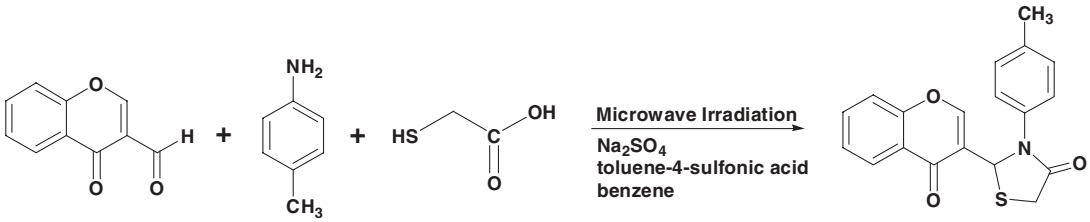
SCHEME 2

TABLE 1 Temperature and Time Optimization of Microwave-Assisted Synthesis

No.	*Temp (°C)**	*Yield† (%)*	*Time (min)‡*	*Yield† (%)*
1	80	6	0.5	50 (42)
2	90	15 (10)	1	65 (59)
3	100	31 (24)	3	74 (68)
4	110	45 (39)	5	81 (75)
5	120	62 (55)	7	81 (74)
6	130	75 (60)	9	80 (72)
7	140	80 (74)	11	80 (72)
8	150	75 (68)	13	79 (70)

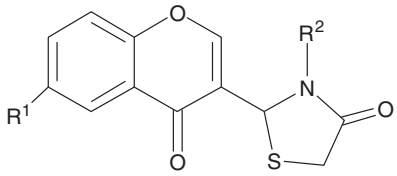
*The reaction time is 10 min.
†Yields were determined by HPLC. The isolated yields are in parentheses.
‡The reaction temperature is 140°C.

investigated by Bolognese et al. [11]. Usually, the reaction proceeds through the intermediate imine, and the mercaptoacetic acid is always added into the reaction solution after the imine has formed. In this reaction, azeotropic removal of water is a key procedure. In addition, the stepwise assembly of 4-thiazolidinones has been reported [12] and there have also been reports describing the solid-phase synthesis of 4-thiazolidinones [13] and several reports [14] in which the nitrogen of this heterocycle originates from an α-amino acid, with the carboxylic function serving as the site of attachment to the support. Although microwave-assisted syntheses of 4-thiazolidinones have been reported by Dandia et al. [15a] and Bolognese et al. [11], the former authors developed a two-step microwave irradiation procedure whereas the latter developed a method that is not economical because it requires 2 equivalents of aldehyde and 3 equivalents of mercaptoacetic acid. Recently, Bazureau et al. [16] reported the use of a task-specific ionic liquid as the synthetic equivalent of an ionic liquid-phase matrix for the preparation of a small library of 4-thiazolidinones, in which the synthesis of the ionic liquid-phase–bound 4-thiazolidinones was performed by a one-pot three-component condensation under microwave dielectric heating, without azeotropic removal of water. In this method, however, a functional group must be reserved to graft the aromatic aldehyde component onto the pre-prepared [PEG1imm][BF4]-ionic liquid by construction of an ester linker, and the cleavage of the ionic liquid-phase–bound thiazolidinones by



SCHEME 3

TABLE 2 Confirmation of Reaction Condition for Microwave-Assisted Synthesis



No.	R_1	R_2	*Time (min)*	*Temperature (°C)*	*Power (W)*	*Yield (%)**
1	H	4-CH_3—C_6H_4—	5	140	90–150	81 (75)
2	H	4-CH_3—C_6H_4—	11	140	90–150	80 (73)
3	H	4-Cl—C_6H_4—	5	140	90–150	74 (68)
4	H	4-Cl—C_6H_4—	11	140	90–150	67 (61)
5	Cl	4-Cl—C_6H_4—	5	140	90–150	65 (58)
6	Cl	4-Cl—C_6H_4—	11	140	90–150	51 (44)
7	Cl	4-F—C_6H_4—	5	140	90–150	54 (49)
8	Cl	4-F—C_6H_4—	11	140	90–150	46 (40)

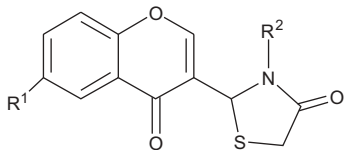
*Yields were determined by HPLC. The isolated yields are in parentheses.

ester aminolysis lead to low product yields, limiting the practical utility of this method. This shortcoming prompted us to develop an economical one-pot three-component liquid-phase synthesis of the 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinone system under microwave irradiation without any polymer support and without azeotropic removal of water.

Under conventional conditions, we first examined the practicality of performing a one-pot three-component synthesis of the title compounds. When the mixture of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde, *p*-tolylamine, and 5 equivalents of mercaptoacetic acid in the presence of a catalytic amount of toluene-4-sulfonic acid was refluxed in dry benzene for 9 h (Scheme 1, $R^1 = 4$-oxo-4*H*-1-benzopyran-3-yl, $R^2 = 4{-}CH_3{-}C_6H_4$, $R^3 = H$), only 30% yield of 4-thiazolidinone could be obtained. Then, microwave irradiation was applied to improve the yields and shorten the reaction time.

To determine the optimal reaction conditions for the microwave-assisted syntheses, we carried out the reaction of 4-oxo-4*H*-1-benzopyran-3-carbaldehyde, *p*-tolylamine, and mercaptoacetic acid under a range of conditions (Scheme 3). During these experiments, we closely monitored the temperature and reaction time. All reactions were carried out at an adjustable

TABLE 3 Comparison of conventional and microwave-assisted syntheses



			Conventional		*Microwave-assisted*	
Compound	R^1	R^2	*Time (h)*	*Yield (%)**	*Time (min)*	*Yield (%)†*
1	H	4-CH_3—C_6H_4—	9	36	5	81 (75)
2	H	4-Cl—C_6H_4—	9	27	5	74 (68)
3	H	4-CH_3O—C_6H_4—	9	37	5	79 (71)
4	H	C_6H_5—	9	30	5	78 (72)
5	H	4-Br—C_6H_4—	9	25	5	75 (68)
6	H	3-CH_3—C_6H_4—	9	28	5	75 (68)
7	CH_3	4-CH_3—C_6H_4—	9	42	5	73 (68)
8	CH_3	4-Cl—C_6H_4—	9	48	5	78 (73)
9	CH_3	4-CH_3O—C_6H_4—	9	58	5	72 (65)
10	CH_3	C_6H_5—	9	30	5	79 (72)
11	CH_3	4-Br—C_6H_4—	9	48	5	66 (59)
12	CH_3	3-CH_3—C_6H_4—	9	30	5	65 (60)
13	Cl	4-CH_3—C_6H_4—	9	36	5	65 (58)
14	Cl	4-Cl—C_6H_4—	9	14	5	65 (59)
15	Cl	4-CH_3O—C_6H_4—	9	45	5	62 (55)
16	Cl	C_6H_5—	9	22	5	61 (54)
17	Cl	4-Br—C_6H_4—	9	21	5	66 (59)
18	Cl	3-CH_3—C_6H_4—	9	26	5	69 (63)
19	H	*n*-C_4H_9—	9	47	5	88 (81)
20	H	2-C_4H_3O—CH_2—	9	37	5	84 (78)
21	H	*n*-C_3H_7—	9	48	5	87 (81)
22	CH_3	*n*-C_4H_9—	9	65	5	86 (81)
23	CH_3	2-C_4H_3O—CH_2—	9	63	5	82 (75)
24	CH_3	*n*-C_3H_7—	9	66	5	84 (76)
25	Cl	*n*-C_4H_9—	9	57	5	82 (75)
26	Cl	2-C_4H_3O—CH_2—	9	31	5	87 (81)
27	Cl	*n*-C_3H_7—	9	57	5	90 (83)
28	H	4-F—C_6H_4—	9	38	5	70 (64)
29	Cl	4-F—C_6H_4—	9	31	5	54 (49)
30	Cl	2-F—C_6H_4—	39	26	5	36 (31)
31	H	5-methyl-[1,3,4]thiadiazol-2-yl	9	77	5	98 (92)
32	Me	5-methyl-[1,3,4]thiadiazol-2-yl	9	76	5	94 (90)

*Isolated yields.
†Yields were determined by HPLC. The isolated yields are in parentheses.

TABLE 4 The Elemental Analysis, MS, ^{1}H NMR and mp Data of **1–32** in Table 3

Compound	*Anal., %, (Calc.)*	*MS (m/z, %)*	*^{1}H NMR ($CDCl_3$, δ)*	*mp (°C)*
1	C, 67.84 (67.64); H, 4.13 (4.48); N, 4.14 (4.15)	337 (M^+)	2.28 (s, 3H), 3.77 (d, $J = 15.2$ Hz, 1H), 4.10 (d, $J = 15.2$ Hz, 1H), 6.10 (s, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.19 (d, $J = 8.8$ Hz, 2H), 7.39–7.44 (m, 2H), 7.65–7.67 (m, 2H), 7.77 (s, 1H), 8.21 (dd, $J = 8$, 1.2 Hz, 1H)	181–182
2	C, 60.34 (60.42); H, 3.39 (3.38); N, 3.80 (3.91)	357 (M^+)	3.78 (d, $J = 15.6$ Hz, 1H), 4.11 (d, $J = 15.6$ Hz, 1H), 6.08 (s, 1H), 7.26–7.31 (m, 4H), 7.41–7.45 (m, 2H), 7.66–7.70 (m, 1H), 7.76 (s, 1H), 8.21 (dd, $J = 7.8$ Hz, $J = 1.4$ Hz, 1H)	178–179
3	C, 64.47 (64.58); H, 4.30 (4.28); N, 3.91 (3.96)	353 (M^+)	3.74 (s, 3H), 3.81 (d, $J = 15.6$ Hz, 1H), 4.16 (d, $J = 15.6$ Hz, 1H), 6.01 (s, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.19 (d, $J = 9.2$ Hz, 2H), 7.40–7.44 (m, 2H), 7.65–7.67 (m, 1H), 7.77 (s, 1H), 8.21 (d, $J = 7.6$ Hz, 1H)	171–172
4	C, 66.65 (66.86); H, 4.11 (4.05); N, 4.24 (4.33)	323 (M^+)	3.78 (d, $J = 15.2$ Hz, 1H), 4.10 (d, $J = 15.2$ Hz, 1H), 6.15 (s, 3H), 7.21–7.34 (m, 6H), 7.39–7.44 (m, 2H), 7.65–7.67 (m, 1H), 7.77 (s, 1H), 8.22 (dd, J = 8 Hz, $J = 1.6$ Hz, 1H)	228–229
5	C, 53.72 (53.74); H, 2.97 (3.01); N, 3.43 (3.48)	401 (M^+)	3.77 (d, $J = 15.2$ Hz, 1H), 4.11 (dd, $J = 15.2$ Hz, $J = 1.4$ Hz, 1H), 6.09 (s, 1H), 7.21–7.24 (m, 2H), 7.41–7.46 (m, 4H), 7.66–7.68 (m, 1H), 7.76 (s, 1H), 8.21 (dd, $J = 7.8$ Hz, $J = 1.8$ Hz, 1H)	183–184
6	C, 67.63 (67.64); H, 4.46 (4.48); N, 4.10 (4.15)	337 (M^+)	2.30 (s, 3H), 3.76 (d, $J = 15.6$ Hz, 1H), 4.09 (d, $J = 15.2$ Hz, 1H), 6.14 (s, 3H), 7.01–7.24 (m, 4H), 7.40–7.44 (m, 2H), 7.65–7.69 (m, 1H), 7.78 (s, 1H), 8.21 (dd, $J = 8$ Hz, $J = 1.6$ Hz, 1H)	184–185
7	C, 68.26 (68.36); H, 4.86 (4.88); N, 3.92 (3.99)	351 (M^+)	2.27 (s, 3H), 2.44 (s, 3H), 3.76 (d, $J = 15.6$ Hz, 1H), 4.09 (d, $J = 15.2$ Hz, 1H), 6.09 (s, 1H), 7.11 (d, $J = 8.8$ Hz, 2H), 7.20 (d, $J = 8$ Hz, 2H), 7.8 (d, $J = 8.4$ Hz, 1H), 7.45 (dd, $J = 8.4$ Hz, $J = 2$ Hz, 1H), 7.74 (s, 1H), 8.00 (s, 1H)	183–184
8	C, 61.46 (61.37); H, 3.78 (3.79); N, 3.71 (3.77)	371 (M^+)	2.45 (s, 3H), 3.77 (d, $J = 15.6$ Hz, 1H), 4.11 (dd, $J = 15.6$ Hz, J = 1.4 Hz, 1H), 6.08 (s, 1H), 7.25–7.32 (m, 5H), 7.47 (dd, $J = 8.6$ Hz, $J = 1.8$ Hz, 1H), 7.74 (s, 1H), 7.99 (s, 1H)	202–203
9	C, 65.37 (65.38); H, 4.66 (4.66); N, 3.75 (3.81)	367 (M^+)	2.45 (s, 3H), 3.73 (s, 3H), 3.76 (d, $J = 15.2$ Hz, 1H), 4.12 (dd, $J = 15.2$ Hz, $J = 1.4$ Hz, 1H), 6.00 (s, 1H), 6.82–6.85 (m, 2H), 7.18–7.20 (m, 2H), 7.29 (d, $J = 8.4$ Hz, 1H), 7.46 (dd, $J = 8.6$ Hz, $J = 2.2$ Hz, 1H), 7.74 (s, 1H), 8.00 (s, 1H)	180–181
10	C, 67.64 (67.64); H, 4.31 (4.48); N, 4.01 (4.15)	337 (M^+)	2.45 (s, 3 H), 3.77 (d, $J = 15.6$ Hz, 1H), 4.10 (dd, $J = 15.6$ Hz, 1.4 Hz, 1H), 6.14 (s, 1H), 7.19–7.34 (m, 4H), 7.46 (dd, $J = 8.6$ Hz, $J = 2.2$ Hz, 1H), 7.75 (s, 1H), 8.00 (s, 1H)	231–233
11	C, 54.96 (54.82); H, 3.34 (3.39); N, 3.35 (3.36)	415 (M^+)	2.45 (s, 3H), 3.77 (d, $J = 15.6$ Hz, 1H), 4.10 (d, $J = 15.6$ Hz, 1H), 6.08 (s, 1H), 7.20–7.32 (m, 4H), 7.43–7.49 (m, 3H), 7.74 (s, 1H), 7.99 (s, 1H)	195–197
12	C, 68.16 (68.36); H, 4.97 (4.88); N, 3.91 (3.99)	351 (M^+)	2.29 (s, 3H), 2.45 (s, 3H), 3.76 (d, $J = 15.6$ Hz, 1H), 4.09 (dd, $J = 15.2$ Hz, 1.2 Hz, 1H), 6.13 (s, 1H), 7.00 (d, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 8$ Hz, 1H), 7.16–7.31 (m, 3H), 7.46 (dd, J = 8.4 Hz, $J = 2$ Hz., 1H), 7.75 (s, 1H), 8.00 (s, 1H)	192–194
13	C, 61.27 (61.37); H, 3.71 (3.79); N, 3.72 (3.77)	371 (M^+)	2.28 (s, 3H), 3.77 (d, $J = 15.6$ Hz, 1H), 4.09 (d, $J = 15.6$ Hz, 1H), 6.08 (s, 1H), 7.12–7.19 (m, 4H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.59 (dd, $J = 8.8$ Hz, $J = 2.8$ Hz., 1H), 7.76 (s, 1H), 8.18 (s, 1H)	219–220
14	C, 55.27 (55.12); H, 2.82 (2.83); N, 3.52 (3.57)	393 (M^+)	3.77 (d, $J = 15.6$ Hz, 1H), 4.10 (dd, $J = 15.2$ Hz, 1.2 Hz, 1H), 6.06 (s, 1H), 7.24–7.39 (m, 5H), 7.61 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 1H), 7.76 (s, 1H), 8.16 (d, $J = 2.4$ Hz, 1H)	210–211
15	C, 58.95 (58.84); H, 3.61 (3.64); N, 3.57 (3.61)	387 (M^+)	3.75 (s, 3H), 3.77 (d, $J = 15.6$ Hz, 1H), 4.10 (dd, $J = 15.2$ Hz, $J = 1.6$ Hz, 1H), 5.99 (s, 1H), 6.84 (dd, $J = 7.0$ Hz, $J = 2.2$ Hz, 2H), 7.17 (dd, $J = 7.0$ Hz, $J = 2.2$ Hz, 2H), 7.35 (d, $J = 9.2$ Hz, 1H), 7.59 (dd, $J = 8.8$ Hz, $J = 2.8$ Hz, 1H), 7.76 (s, 1H), 8.17 (d, $J = 2.8$ Hz, 1H)	188–189

Continued

TABLE 4 Continued

Compound	*Anal., %, (Calc.)*	*MS (m/z, %)*	*^{1}H NMR ($CDCl_3$, δ)*	*mp (°C)*
16	C, 60.39 (60.42); H, 3.34 (3.38); N, 3.88 (3.91)	357 (M^+)	3.78 (d, $J = 15.6$ Hz, 1H), 4.09 (d, $J = 15.2$ Hz, 1H), 6.12–7.38 (m, 6H), 7.59 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 1H), 7.77 (s, 1H), 8.17 (d, $J = 2.4$ Hz, 1H)	205–206
17	C, 49.49 (49.51); H, 2.51 (2.54); N, 3.19 (3.21)	435 (M^+)	3.77 (d, $J = 15.6$ Hz, 1H), 4.09 (dd, $J = 15.6$ Hz, $J = 1.6$ Hz, 1H), 7.19–7.47 (m, 5H), 7.60 (dd, $J = 9$ Hz, $J = 2.6$ Hz, 1H), 7.75 (s, 1H), 8.17 (d, $J = 2.4$ Hz, 1H)	207–208
18	C, 61.02 (61.37); H, 3.78 (3.79); N, 3.68 (3.77)	371 (M^+)	2.30 (s, 3H), 3.76 (d, $J = 15.6$ Hz, 1H), 4.07 (dd, $J = 15.4$ Hz, $J = 1.4$ Hz, 1H), 6.11 (s, 1H), 7.02–7.24 (m, 4H), 7.36 (d, $J = 9.2$ Hz, 1H), 7.59 (dd, $J = 9$ Hz, $J = 2.6$ Hz, 1H), 7.77 (s, 1H), 8.17 (d, $J = 2.8$ Hz, 1H)	205–206
19	C, 63.11 (63.34); H, 5.61 (5.65); N, 4.55 (4.62)	303 (M^+)	0.92 (t, $J = 7.2$ Hz, 3H), 1.27–1.35 (m, 2H), 1.50–1.57 (m, 2H), 2.73–2.80 (m, 1H), 3.59 (d, $J = 15.6$ Hz, 1H), 3.77–3.86 (m, 2H), 5.76 (d, $J = 2.0$ Hz, 1H), 7.43–7.50 (m, 2H), 7.69–7.74 (m, 1H), 7.74 (s, 1H), 8.23 (dd, $J = 8.0$ Hz, $J = 1.6$ Hz, 1H)	110–111
20	C, 62.07 (62.37); H, 3.98 (4.00); N, 4.20 (4.28)	327 (M^+)	3.63 (d, $J = 15.2$ Hz, 1H), 3.99 (dd, $J = 15.2$ Hz, $J = 2.0$ Hz, 1H), 4.05 (d, $J = 15.6$ Hz, 1H), 4.87 (d, $J = 15.2$ Hz, 1H), 5.57 (d, $J = 1.6$ Hz, 1H), 6.24 (d, $J = 1.6$ Hz, 2H), 7.29 (s, 1H), 7.44–7.48 (m, 2H), 7.70–7.71 (m, 1H), 7.70 (s, 1H), 8.21 (dd, $J = 8.2$ Hz, $J = 1.8$ Hz, 1H)	111–112
21	C, 62.16 (62.26); H, 5.20 (5.23); N, 4.74 (4.84)	289 (M^+)	0.88–0.92 (m, 3H), 1.52–1.66 (m, 2H), 2.73–2.81 (m, 1H), 3.60–3.79 (m, 2H), 3.83 (dd, $J = 15.6$ Hz, $J = 1.6$ Hz, 1H), 5.76 (d, $J = 1.6$ Hz, 1H), 7.43–7.50 (m, 2H), 7.70–7.74 (m, 1H), 7.84 (s, 1H), 8.22 (dd, $J = 8.0$ Hz, $J = 1.6$ Hz, 1H)	117–118
22	C, 64.13 (64.33); H, 5.93 (6.03); N, 4.31 (4.41)	318 (M^+)	0.88 (t, $J = 7.2$ Hz, 3H), 1.27–1.35 (m, 2H), 1.51–1.57 (m, 2H), 2.47 (s, 3H), 2.74–2.80 (m, 1H), 3.59 (d, $J = 15.2$ Hz, 1H), 3.78–3.86 (m, 2H), 5.77 (d, $J = 2.0$ Hz, 1H), 7.37 (d, $J = 8.8$ Hz, 1H), 7.50–7.53 (m, 1H), 7.82 (s, 1H), 8.01 (s, 1H)	109–110
23	C, 63.13 (63.33); H, 4.31 (4.43); N, 4.08 (4.10)	342 (M^+)	2.46 (s, 3H), 3.62 (d, $J = 14.8$, 1H), 3.98–4.07 (m, 1H), 4.87 (d, $J = 15.6$ Hz, 1H), 5.57 (d, $J = 1.6$Hz, 1H), 6.23–6.26 (m, 2H), 7.29–7.38 (m, 2H), 7.49 (dd, $J = 8.6$ Hz, $J = 2.2$ Hz, 1H), 7.77 (s, 1H), 8.00 (d, $J = 1.2$ Hz, 1H)	132–133
24	C, 63.14 (63.34); H, 5.61 (5.65); N, 4.51 (4.62)	303 (M^+)	0.87 (t, $J = 14.8$ Hz, 3H), 1.55–1.64 (m, 2H), 2.80–2.90 (m, 1H), 3.69–3.73 (m, 2H), 3.97 (dd, $J = 15.4$ Hz, $J = 1.4$ Hz, 1H), 5.79 (d, $J = 1.6$ Hz), 7.41 (d, $J = 8.4$ Hz, 1H), 7.54 (dd, $J = 8.6$ Hz, $J = 2.2$ Hz, 1H), 7.99 (s, 1H), 7.99 (d, $J = 1.2$ Hz, 1H), 8.02 (s, 1H)	121–122
25	C, 56.78 (56.89); H, 4.66 (4.77); N, 4.07 (4.15)	336 (M^+)	0.75–0.99 (m, 3H), 1.01–1.39 (m, 2H), 1.46–1.64 (m, 2H), 2.77–2.81 (m, 1H), 3.67–3.85 (m, 2H), 3.94 (d, $J = 15.2$ Hz, 1H), 5.77 (s, 1H), 7.50–7.56 (m, 1H), 7.64–7.72 (m, 1H), 8.05 (s, 1H), 8.14 (s, 1H)	112–113
26	C, 56.23 (56.44), H, 3.32 (3.34), N, 3.79 (3.87)	361 (M^+)	3.62 (d, $J = 15.2$ Hz, 1H), 3.97 (dd, $J = 15$ Hz, $J = 1.8$ Hz, 1H), 4.08 (d, $J = 15.6$ Hz, 1H), 4.83 (d, $J = 15.6$ Hz, 1H), 5.56 (s, 1H), 6.24 (s, 1H), 7.26 (d, $J = 6.4$ Hz, 1H), 7.42 (d, $J = 9.2$ Hz, 1H), 7.63–7.66 (m, 1H), 7.78 (s, 1H), 8.17 (d, $J = 2.0$ Hz, 1H)	152–154
27	C, 55.55 (55.64), H, 4.31 (4.36), N, 4.27 (4.33)	323 (M^+)	0.85–0.93 (m, 3H), 1.54–1.64 (m, 2H), 2.73–2.79(m, 1H), 3.60 (d, $J = 15.2$ Hz, 1H), 3.69–3.78 (m, 1H), 3.82 (dd, $J = 15.6$ Hz, $J = 1.4$ Hz, 1H), 5.74 (s, 1H), 7.47 (d, $J = 9.2$ Hz, 1H), 7.64–7.67 (m, 1H), 7.85 (s, 1H), 8.18 (d, $J = 1.2$ Hz, 1H)	155–156

Continued

TABLE 4 Continued

Compound	*Anal., %, (Calc.)*	*MS (m/z, %)*	*^{1}H NMR ($CDCl_3$, δ)*	*mp (°C)*
28	C, 63.42 (63.33), H, 3.68 (3.54), N, 3.99 (4.10)	341 (M^+)	3.79 (d, $J = 15.2$ Hz, 1H), 4.19 (d, $J = 15.2$ Hz, 1H), 6.02 (s, 1H), 7.02 (t, $J = 9$ Hz, 2H), 7.26–7.29 (m, 2H), 7.41–7.47 (m, 2H), 7.67–7.71 (m, 1H), 7.81 (s, 1H), 8.23 (d, $J = 8.0$ Hz, 1H)	210–211
29	C, 57.92 (57.53), H, 3.03 (2.95), N, 3.54 (3.73)	375 (M^+)	3.79 (d, $J = 15.2$ Hz, 1H), 4.17 (d, $J = 15.2$ Hz, 1H), 5.99 (s, 1H), 7.01 (t, $J = 8.6$ Hz, 2H), 7.24–7.28 (m, 2H), 7.38 (d, $J = 8.8$ Hz, 1H), 7.62 (dd, $J = 9.0$ Hz, $J = 2.6$ Hz, 1H), 7.64 (s, 1H), 8.17 (d, $J = 2.8$ Hz, 1H)	224–225
30	C, 57.40 (57.53), H, 3.07 (2.95), N, 3.72 (3.73)	375 (M^+)	3.78 (d, $J = 15.2$ Hz, 1H), 4.16 (d, $J = 15.2$ Hz, 1H), 6.02 (s, 1H), 7.11–7.14 (m, 2H), 7.24–7.28 (m, 2H), 7.28 (d, $J = 8.8$ Hz, 1H), 7.62 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 1H), 7.88 (s, 1H), 8.16 (d, $J = 2.8$ Hz, 1H)	210–211
31	C, 52.44 (52.16), H, 3.29 (3.21), N, 12.34 (12.17)	345 (M^+)	2.58 (s, 3H), 3.99 (d, $J = 15.6$ Hz, 1H), 4.26 (d, $J = 16.0$ Hz, 1H), 6.58 (s, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.81 (t, $J = 7.6$ Hz, 1H), 8.02 (d, $J = 8.0$ Hz, 1H), 8.64 (s, 1H)	278–280
32	C, 53.49 (53.47), H, 3.70 (3.65), N, 12.01 (11.69)	359 (M^+)	2.40 (s, 3H), 2.58 (s, 3H), 3.99 (d, $J = 16.0$ Hz, 1H), 4.25 (d, $J = 16.0$ Hz, 1H), 6.58 (s, 1H), 7.56 (d, $J = 8.8$ Hz, 1H), 7.63 (d, $J = 8.4$, 1H), 7.81 (s, 1H), 8.59 (s, 1H)	258–260

microwave power range of 90–150 W for 10 min, and the reaction temperature was increased from 80 to 150°C in increments of 10°C; the yields were determined by HPLC (Table 1).

As shown in Table 1, the yield increased monotonically as the temperature increased from 80°C to 140°C. Further increase of the temperature to 150°C caused a reduction in the yield and the formation of side products, presumably due to the breakup of the thiazolidinone. Therefore, a temperature of 140°C was used in the determination of the optimal reaction time. For optimization of the reaction time, reactions were carried out for times varying from 0.5 min to 13 min in increments of about 2 min, and the product yields were determined by HPLC. The results are shown in Table 2. The yields varied from 50% at 0.5 min to a maximum of 81% at 5 min. Prolonging the reaction time beyond 5 min did not give a noticeable change in the yield up to 11 min, after which the yield decreased.

Because the yields obtained for reaction times of 5, 7, 9, and 11 min were very similar, we carried out another three reactions for further validation of the reaction time; the results are summarized in Table 3. The HPLC results indicated that all of the reactions were completed at 5 min, and that the yields dropped if the reactions were continued up to 11 min. Thus, the results of these syntheses showed that microwave irradiation for 5 min is much better than irradiation for 11 min. Hence, the optimized conditions for microwave irradiation with an adjustable microwave power range from 90 to 150 W are a temperature of 140°C and a reaction time of 5 min. We used these conditions in the microwave-assisted synthesis of all of the 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinone derivatives in the library, and compared the yields with those obtained by conventional synthesis (Table 4).

Comparison of the results for the 32 compounds shows that microwave-assisted irradiation improved the yields by 10% to 56% compared to those obtained using conventional heating technique. All compounds were obtained in moderate to good yields via microwave irradiation. Although the yield of compound **30** was rather low, it was still greater than that achieved under conventional heating, and was obtained in a reaction time of 5 min rather than 39 h. Among the various primary amines tested, alkylamine and heterocyclic amine gave more satisfactory results than substituted aniline (compounds **19–27, 31**, and **32** in Table 4), possibly due to the greater reactivity of alkylamine and heterocyclic amine compared to the substituted aniline [15]. The electronic effect of substituents on the phenyl ring of aniline and 3-formyl chromone influenced the yields of the products. When aniline and/or the 3-formyl chromones bore an electron-withdrawing group such as a halogen substituent, the yields of the thizaolidinones were usually relatively low regardless of whether conventional heating or microwave irradiation was used (compounds **13–18, 29**, and **30** in Table 4). The structures of the synthesized compounds were confirmed by ^{1}H NMR, MS, and elemental analysis.

CONCLUSION

In summary, we have established a rapid and economical procedure for constructing a library of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones by combining microwave irradiation with a liquid-phase combinatorial chemistry strategy. Microwave irradiation dramatically accelerated the reaction rate and shortened the reaction time of the liquid-phase one-pot three-component synthesis of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones. Comparison of the proposed method with conventional parallel syntheses of the same library showed that the microwave-assisted syntheses were characterized by much shorter reaction times and higher product yields. It is noteworthy that the synthetic procedure was performed without any polymer support and without azeotropic removal of water. To our knowledge, this is the first report of the rapid synthesis of 2-(4-oxo-4*H*-1-benzopyran-3-yl)-4-thiazolidinones using liquid-phase one-pot three-component strategy under microwave irradiation. Given the time saved during synthesis and the improved product yields, the coupling of microwave technology with combinatorial chemistry constitutes a novel and attractive avenue for the rapid generation of structurally diverse libraries, and will likely become a routine tool for medicinal chemists in the near future. The biological activities of synthetic libraries will be reported in due course.

EXPERIMENTAL

3-Formyl chromones were synthesized according to the method described in the literature [16]. All other materials were obtained from commercial sources and were used as received unless stated otherwise. The silica gel (200–300 mesh) for flash column chromatography was from Qingdao Marine Chemical (China), and the distillation range of petroleum was 60–90°C. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ solution on a Varian VNMR 400 MHz spectrometer. MS spectra were determined using a TraceMS 2000 organic mass spectrometer, and signals were recorded in *m*/*z*. Melting points were measured using a Buchi B-545 melting point apparatus. Element analysis was performed using a Vario ELIII CHNSO elemental analyzer. HPLC was performed on an Agilent 1100 system, and the components were detected using a photodiode array detector. A Zorbax XDB-C_8 column (4.6 × 150 mm) was used for HPLC analysis. All analyses were resolved under isocratic conditions with methanol/water (70:30) as the mobile phase. Conventional syntheses were carried out on Corning stirrer/hotplates with oil baths. Microwave syntheses were carried out on a Smith Synthesizer.

General Procedure for Conventional Synthesis of the Library

A mixture of 3-formyl chromone (5 mmol), primary amine (5 mmol), and *p*-toluene sulfonic acid (10 mg, 0.058 mmol) was refluxed and stirred in benzene (40 mL) for 1 h, and then mercaptoacetic acid (25 mmol) was added. The mixture was then refluxed for a further 8 h. The progress of the reaction was detected by TLC analysis. The solvent was removed in vacuo and the resulting oil was chromatographed on silica gel using a petroleum/acetone (1:6) mixture as the mobile phase or the resulting residue was washed with ethanol to afford the crude product, which was then recrystallized from ethanol to give a white or light-yellow solid.

General Procedure for Microwave-Assisted Synthesis of the Library

To a solution of 3-formyl chromone (0.5 mmol), aromatic amine (0.5 mmol) and mercaptoacetic acid (0.5 mmol) in dry benzene (4 mL), anhydrous sodium sulfate (2.5 g, 17.6 mmol) and *p*-toluene sulfonic acid (1 mg) were added. The resulting mixture was sealed in a 10-mL glass tube with a magnetic stirring bar and irradiated in a Smith Synthesizer at 140°C for 5 min under an adjustable microwave power range of 90–150 W. Completion of the reaction was checked by TLC and yields were determined by HPLC.

REFERENCES

[1] (a) Czarnik, A. W.; DeWitt, S. H. A Practical Guide to Combinatorial Chemistry; American Chemical Society: Washington, DC 1997; (b) Fenniri, H. Combinatorial Chemistry; Oxford University Press: New York, 2000; (c) Seneci, P. Solid-Phase Synthesis and Combinatorial Technologies; John Wiley & Sons: New York, 2000.
[2] (a) Eichler, J.; Houghten, R. A. Mol Med Today 1995, 174; (b) Choong, I. C.; Ellman, J. A. Annu Rep Med Chem 1996, 309; (c) Tietze, L. F.; Hippe, T.; Steinmetz, A. Synlett 1996, 11, 1043.
[3] Sugawara, T. J. Synth Org Chem 2002, 465.
[4] (a) Nielsen, J.; Hoel, A. M. L. Tetrahedron Lett 1999, 40, 3941; (b) Stadler, A.; Kappe, C. O. J Comb Chem 2001, 3, 624; (c) Brain, C. T.; Brunton, S. A. Synlett 2001, 3, 382; (d) Bendale, P. M.; Sun, C. M. J Comb Chem 2002, 4, 359; (e) Wu, C. Y.; Sun, C. M. Synlett 2002, 17, 1709; (f) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. Org Lett 2003, 5, 1205; (g) Chang, W. J.; Yeh, W. B.; Sun, C. M. Synlett 2003, 18, 1688; (h) Lin,

M. J.; Sun, C. M. Synlett 2004, 18, 663; (i) Lee, M. J.; Sun, C. M.; Tetrahedron Lett 2004, 45, 437; (j) Tung, C. L.; Sun, C. M. Tetrahedron Lett 2004, 45, 1159; (k) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. Green Chem 2004, 6, 128.

[5] (a) Gedye, R.; Smith, F.; Westway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. Tetrahedron Lett 1986, 27, 279; (b) Giguerre, R. J.; Bray, T. L.; Duncan, S. M. Tetrahedron Lett 1986, 27, 4945.

[6] (a) Kappe, C. O. Angew Chem Int Ed 2004, 43, 6250; (b) Lead Beater, N. E.; Torenius, H. M.; Tye, H. Comb Chem High Through Screen 2004, 7, 511.

[7] (a) Larhed, M.; Hallberg, A. Drug Discov Today 2001, 6, 406; (b) Kappe, C. O. Curr Opin Chem Bio 2002, 6, 314; (c) Santagada, V.; Frecentese, F.; Perissutti, E.; Favretto, L.; Caliendo, G. QSAR Comb Sci 2004, 23, 919; (d) Santagada, V.; Perissutti, E.; Caliendo, G. Curr Med Chem 2002, 9, 1251; (e) Katritzky, A. R.; Singh, S. K. Curr Top Med Chem 2004, 773.

[8] Rajak, H.; Mishra, P. J. Sci Ind Res 2004, 63, 641.

[9] (a) Nohara, A.; Kuriki, H.; Saijo, T.; Ukawa, K.; Murata, T.; Kanno, M.; Sanno, Y. J Med Chem 1975, 18, 34; (b) Joo, Y. H.; Kim, J. K.; Kang, S-H.; Noh, M-S.; Ha, J-Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. Bioorg Med Chem Lett 2003, 13, 413; (c) van Acker, F. A. A.; Hageman, J. A.; Haenen, G. R. M. M.; van der Vijgh, W. J. F.; Bast, A.; Menge, W. M. P. B. J Med Chem 2000, 43, 3752; (d) Pal, M.; Subramanian, V.; Parasuraman, K.; Yeleswarapu, K. R. Tetrahedron 2003, 59, 9563; (e) Maliar, T.; Jedinak, A.; Kadrabova, J.; Sturdik, E. Eur J Med Chem 2004, 39, 241–248; (f) Nussbaumer, P.; Lehr, P.; Billich, A. J. Med. Chem. 2002, 45, 4310.

[10] (a) Liu, H.; Li, Z.; Anthansen, T. Molecules 2000, 1055; (b) Lakhan, R. Agric Biol Chem 1981, 557; (b) Gursoy, A.; Terzioglu, N.; Otük, G. Eur J Med Chem 1997, 32, 753; (c) Goel, B.; Ram, T.; Tyagi, R.; Bansal, E.; Kumar, A.; Mukherjee, D.; Sinha, J. N. Eur J Med Chem 1999, 34, 265; (d) Kim, B. Y.; Ahn, J. B.; Lee, H. W.; Kang, S. K.; Lee, J. H.; Shin, J. S.; Ahn, S. K.; Hong, C.; Yoon, S. S. Eur J Med Chem 2004, 39, 433; (e) Fan, Y. H.; Chen, H.; Natarajan, A.; Guo, Y.; Harbinski, F.; Iyasere, J.; Christ, W.; Aktas, H.; Halperin, J. A. Bioorg Med Chem Lett 2004, 14, 2547.

[11] Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. Org Biomol Chem 2004, 2, 2809.

[12] Schlienger, N.; Bryce, M. R.; Hansen, T. K. Tetrahedron Lett 2000, 41, 5147, and references cited therein.

[13] Munson, M. C.; Cook, A. W.; Josey, J. A.; Rao, C. Tetrahedron Lett 1998, 39, 7223.

[14] (a) Cook, G. C.; Schullek, J. R.; Holmes, C. P.; Chinn, J. P.; Gordon, E. M.; Gallop, M. A. Biorg Chem Lett 1996, 6, 701; (b) Holmes, C. P.; Chinn, J. P.; Cook, G. C.; Gordon, E. M.; Gallop, M. A. J Org Chem 1995, 60, 7328.

[15] (a) Dandia, A.; Singh, R.; Arya, K. Phosphorus Sulfur Silicon 2004, 179, 551; (b) Gududuru, V.; Nguyen, V.; Dalton, J. T.; Miller, D. D. Synlett 2004, 13, 2357.

[16] Dubreuil, J. F.; Bazureau, J. P. Tetrahedron 2003, 59, 6121.

[17] Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. J Org Chem 1996, 61, 3849.

[18] Nohara, A.; Umetani, T.; Sanno, Y. Tetrahedron Lett 1973, 22, 1995.