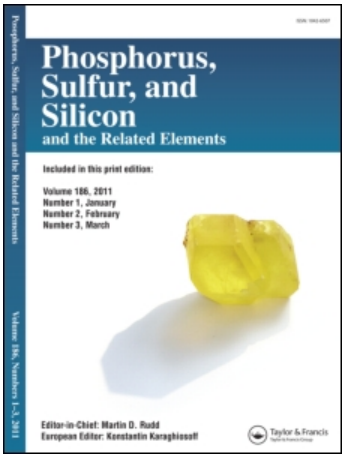

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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Online publication date: 03 July 2010

To cite this Article Chai, Lan-Qin , Zhang, Hong-Song , Dong, Wen-Kui and Zhao, Yan-Ling(2010) 'Synthesis of Unsymmetrical Ureas with Coumarin and Thiadiazole Ring Under Microwave Irradiation', Phosphorus, Sulfur, and Silicon and the Related Elements, 185: 7, 1332 — 1337
To link to this Article: DOI: 10.1080/10426500903036022
URL: http://dx.doi.org/10.1080/10426500903036022

Phosphorus, Sulfur, and Silicon, 185:1332–1337, 2010

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500903036022

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SYNTHESIS OF UNSYMMETRICAL UREAS WITH COUMARIN AND THIADIAZOLE RING UNDER MICROWAVE IRRADIATION

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A series of coumarin-3-yl substituted unsymmetrical ureas were synthesized by the reaction of 3-coumarin isocyanate, which was prepared from 3-coumarinyl azide by Curtius rearrangement, with various aromatic amines, 2-amino-5-phenyl-1,3,4-thiadiazole, and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles under microwave irradiation. Compared to conventional methods, this synthesis has the advantages of mild reaction conditions, easy handling, and high yields. The products have been characterized by analytical and spectral (IR and ^{1}H NMR) data.

Keywords Coumarin; Curtius rearrangement; isocyanate; microwave irradiation (MWI); 1,3,4-thiadiazoles; unsymmetrical urea

INTRODUCTION

In recent years, the use of microwave irradiation to promote reactions has received considerable attention, and dramatic rate enhancements have been reported.[1] Organic cyclization reactions yielding heterocycles under microwave irradiation have attracted the attention of chemists.[2,3] Examples of such applications are the syntheses of unsymmetrically substituted ureas. Unsymmetrical ureas are widely used as herbicides, pesticides, plant growth regulators, and medicinal intermediates.[4–6] Ureas bearing heterocyclic substitutents, for example 1,3,4-thiadiazole, have been shown to exert anti-inflammatory,[7–9] antibacterial,[10] and anticonvulsant activities.[11] Meanwhile, coumarin derivatives have also attracted much attention due to their diverse biological activities, such as antibacterial, anticoagulant, antiallergic, hypotensive, anti-HIV, and anticancer activities.[12–14] The synthetic protocols of ureas generally utilize phosgene or phosgene-based isocyanates as starting materials,[15,16] both of which are toxic or unstable. These methods also involve longer reaction times. Therefore, it is necessary to develop phosgene-free and straightforward routes for unsymmetrical ureas.

Received 8 February 2009; accepted 8 May 2009.

We are thankful for the financial support from the Foundation of Lanzhou Jiaotong University (No. 06-40611) and the Foundation of Lanzhou Chengguan Science and Technology Bureau (No. 09-5-9).

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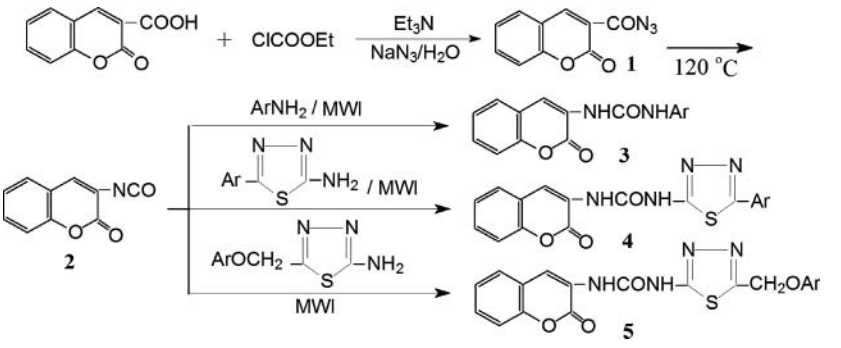
These reasons prompted us to develop an environmentally benign methodology to synthesize some new series of urea compounds bearing both coumarin ring and 1,3,4-thiadiazole moieties, with the objective to investigate the properties and structure–activity relationships of these new compounds and to obtain new biologically active compounds.

RESULTS AND DISCUSSION

In this article, we report a fast and efficient method for the preparation of a series of unsymmetrical ureas. As described in Scheme 1, N-aryl-N′-(coumarin-3-yl) ureas (**3a–h**), N-(coumarin-3-yl)-N′-(2-amino-5-phenyl-1,3,4-thiadiazol-2-yl) urea (**4a**), and N-(coumarin-3-yl)-N′-(2-amino-5-aryloxymethylene-1,3,4-thiadiazol-2-yl) ureas **5a–i** were synthesized by reactions of coumarin isocyanate with various aromatic amines, 2-amino-5-phenyl-1,3,4-thiadiazole, and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles, respectively, under microwave irradiation. Coumarin-3-yl isocyanate was prepared by treating coumarin-3-carboxylic acid with sodium azide and ethyl chlorocarbamate in the presence of triethylamine followed by Curtius rearrangement.[17,18]



Scheme 1

To investigate the effects of microwave irradiation, all the reactions were performed in an oil bath at 120°C. When compared to classical heating, the reactions performed under microwave irradiation are at least 30 times faster and proceed with high yields. The results obtained are reported in Table I.

We selected the synthesis of compound **3a** as a model reaction to study the effects of irradiation power and time on the yields. The best yields obtained are 78% after 20 min of irradiation with 490 W using toluene as a solvent. A greater power or longer irradiation time induces a decrease in yield (only 68% with 700 W or 63% after 22 min) due to the decomposition of coumarin-3-yl isocyanate.

In summary, the synthesis of unsymmetrical ureas has been accomplished employing the Curtius rearrangement of 3-coumarinyl azide followed by nucleophile addition of amines to the NCO moiety under microwave irradiation. Compared to conventional thermal heating, microwave irradiation decreased the reaction time from 15–21 h to 18–28 min. The main advantages of this method are short reaction times, high yields, fewer byproducts, and simple handling of starting materials and products.

Table I Yields, reaction times, melting points, and elemental analyses of compounds **3a–h**, **4a**, **and 5a–i**

		Yield (%)		Reaction time			Elemental analysis (%) found (calcd.)		
	Ar	MWI[a]	Reflux[b]	MWI (min)[a]	Reflux (hour)[b]	Mp (°C)	C	H	N
3a	C_6H_5	78	71	20	15	211–213	68.62 (68.57)	4.41 (4.32)	10.05 (9.99)
3b	2-$CH_3C_6H_4$	82	76	18	15	>300	69.62 (69.38)	4.92 (4.79)	9.67 (9.52)
3c	4-$CH_3C_6H_4$	80	74	18	15	219–220	69.58 (69.38)	4.95 (4.79)	9.73 (9.52)
3d	4-ClC_6H_4	78	72	19	16	238–239	61.21 (61.06)	3.74 (3.52)	8.83 (8.90)
3e	2-$NO_2C_6H_4$	68	62	22	17	220–221	59.23 (59.08)	3.62 (3.41)	12.78 (12.92)
3f	4-$NO_2C_6H_4$	74	68	22	17	222–224	59.34 (59.08)	3.67 (3.41)	12.73 (12.92)
3g	1-Naphthyl	73	69	20	16	184–186	72.94 (72.72)	4.43 (4.27)	8.71 (8.48)
3h	2-Naphthyl	78	63	20	16	284–285	72.91 (72.72)	4.46 (4.27)	8.76 (8.48)
4a	C_6H_5	81	60	22	16	>300	59.56 (59.33)	3.54 (3.32)	15.52 (15.38)
5a	C_6H_5	80	68	25	18	254–256	57.98 (57.86)	3.41 (3.58)	14.43 (14.21)
5b	2-$CH_3C_6H_4$	78	62	24	16	>300	58.99 (58.82)	4.07 (3.95)	13.93 (13.72)
5c	4-$CH_3C_6H_4$	81	70	24	16	239–241	59.03 (58.82)	4.12 (3.95)	13.97 (13.72)
5d	4-$CH_3OC_6H_4$	82	68	22	16	243–244	56.81 (56.60)	3.94 (3.80)	13.45 (13.20)
5e	4-ClC_6H_4	72	51	24	18	260–262	53.45 (53.21)	3.21 (3.06)	13.23 (13.06)
5f	2, 4-$Cl_2C_6H_4$	75	66	26	20	>300	49.41 (49.26)	2.83 (2.61)	12.21 (12.09)
5g	4-$NO_2C_6H_4$	68	42	28	21	272–274	52.02 (51.94)	3.13 (2.98)	16.11 (15.94)
5h	1-Naphthyl	73	56	25	18	240–242	62.31 (62.15)	3.81 (3.63)	12.78 (12.61)
5i	2-Naphthyl	71	44	25	18	252–254	62.36 (62.15)	3.78 (3.63)	12.83 (12.61)

[a]Irradiated by microwave at less than 490 W.
[b]Heated at 120°C.

Table II IR and ^{1}H NMR spectroscopic data for compounds **3a–h**, **4a**, and **5a–i**

Product	IR (KBr) cm^{-1}	^{1}H NMR / δ /(ppm)
3a	3321, 3192 (N−H); 1682, 1554 (C=O)	10.81 (s, 1H, NH); 10.05 (s, 1H, NH); 9.18–7.26 (m, 10H, ArH & coumarin H).
3b	3312, 3188 (N−H); 1676, 1546 (C=O)	10.78 (s, 1H, NH); 10.03 (s, 1H, NH); 9.15–7.23 (m, 9H, ArH & coumarin H); 3.52 (s, 3H, CH_3).
3c	3315, 3198 (N−H); 1669, 1542 (C=O)	10.76 (s, 1H, NH); 10.01 (s, 1H, NH); 9.13–7.25 (m, 9H, ArH & coumarin H); 3.48 (s, 3H, CH_3).
3d	3324, 3193 (N−H); 1690, 1548 (C=O)	10.80 (s, 1H, NH); 10.04 (s, 1H, NH); 9.15–7.27 (m, 9H, ArH & coumarin H).
3e	3326, 3189 (N−H); 1698, 1547 (C=O)	10.84 (s, 1H, NH); 10.06 (s, 1H, NH); 9.18–7.31 (m, 9H, ArH & coumarin H).
3f	3320, 3183 (N−H); 1708, 1541 (C=O)	10.86 (s, 1H, NH); 10.08 (s, 1H, NH); 9.21–7.35 (m, 9H, ArH & coumarin H).
3g	3312, 3188 (N−H); 1712, 1537 (C=O)	10.81 (s, 1H, NH);10.06 (s, 1H, NH); 9.16–7.31 (m, 12H, ArH & coumarin H).
3h	3324, 3185 (N−H); 1681, 1545 (C=O)	10.83 (s, 1H, NH); 10.08 (s, 1H, NH); 9.23–7.38 (m, 12H, ArH & coumarin H).
4a	3435, 3318 (N−H); 1705, 1603 (C=O); 1544, 1421, 1365, 1203 (C=N−N=C−S)	11.65 (s, 1H, NH); 11.02 (s, 1H, NH); 9.27–7.35 (m, 10H, ArH & coumarin H).
5a	3327, 3261 (N−H); 1728, 1607 (C=O); 1538, 1421, 1366, 1226 (C=N−N=C−S)	12.15 (s, 1H, NH); 11.14 (s, 1H, NH); 9.54–7.88 (m, 10H, ArH & coumarin H); 5.58 (s, 2H, CH_2O).
5b	3333, 3264 (N−H); 1713, 1611 (C=O); 1541, 1457, 1363, 1197 (C=N−N=C−S)	12.11 (s, 1H, NH); 11.12 (s, 1H, NH); 9.51–7.84 (m, 9H, ArH & coumarin H); 5.56 (s, 2H, CH_2O); 3.22 (s, 3H, CH_3).
5c	3324, 3279 (N−H); 1715, 1614 (C=O); 1538, 1464, 1369, 1206 (C=N−N=C−S)	12.13 (s, 1H, NH); 11.11 (s, 1H, NH); 9.53–7.87 (m, 9H, ArH & coumarin H); 5.58 (s, 2H, CH_2O); 3.24 (s, 3H, CH_3).
5d	3331, 3274 (N−H); 1701, 1610 (C=O); 1541, 1457, 1362, 1243 (C=N−N=C−S)	12.15 (s, 1H, NH); 11.13 (s, 1H, NH); 9.50–7.83 (m, 9H, ArH & coumarin H); 5.54 (s, 2H, CH_2O); 3.36 (s, 3H, CH_3O).
5e	3326, 3270 (N−H); 1676, 1601 (C=O); 1537, 1461, 1371, 1252 (C=N−N=C−S)	12.18 (s, 1H, NH); 11.17 (s, 1H, NH); 9.56–7.89 (m, 9H, ArH & coumarin H); 5.61 (s, 2H, CH_2O).
5f	3338, 3326 (N−H); 1718, 1671(C=O); 1535, 1462, 1368, 1229 (C=N−N=C−S)	12.16 (s, 1H, NH); 11.14 (s, 1H, NH); 9.55–7.86 (m, 8H, ArH & coumarin H); 5.58 (s, 2H, CH_2O).
5g	3327, 3276 (N−H); 1683, 1607 (C=O); 1538, 1459, 1372, 1228 (C=N−N=C−S)	12.21 (s, 1H, NH); 11.20 (s, 1H, NH); 9.58–7.92 (m, 9H, ArH & coumarin H); 5.64 (s, 2H, CH_2O).
5h	3323, 3270 (N−H); 1693, 1677 (C=O); 1536, 1458, 1364, 1228 (C=N−N=C−S)	12.15 (s, 1H, NH); 11.13 (s, 1H, NH); 9.52–7.84 (m, 12H, ArH & coumarin H); 5.53 (s, 2H, CH_2O).
5i	3325, 3273 (N−H); 1705, 1654 (C=O); 1541, 1462, 1364, 1228 (C=N−N=C−S)	12.18 (s, 1H, NH); 11.15 (s, 1H, NH); 9.54–7.87 (m, 12H, ArH & coumarin H); 5.56 (s, 2H, CH_2O).

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Nicolet VERTEX 70 FT-IR spectrophotometer. ^{1}H NMR spectra were obtained with a Mercury plus 400 instrument using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed on a GmbH Vario EL Elemental Analysis instrument. Melting points were determined with a XT-4 thermal apparatus and are uncorrected. Microwave irradiation was carried out in a Galanz domestic microwave oven.

Coumarin-3-carboxylic acid,[19] 2-amino-5-aryl-1,3,4-thiadiazole,[20] and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles[21] were prepared according to the procedures in the literature. Aryloxy acetic acids were commercially available and used as received.

Preparation of 3-Coumarinyl Azide 1

The mixture of coumarin-3-carboxylic acid (10 mmol, 1.90 g), triethylamine (11 mmol, 1.111 g), and ethyl chloroformate (11 mmol, 1.194 g) in dry acetone (40 mL) was stirred at 0°C for 1 h. Then sodium azide (11 mmol, 0.715 g) dissolved in water (15 mL) was added, and the mixture was kept at 0°C for 7 h. After the reaction was complete (monitored by TLC), the mixture was poured onto ice. Then the suspension was filtered, and the product was obtained. Yield: 91.3%, yellowish crystals. Mp 85–86°C. IR (KBr, ν/cm^{-1}): 2167 (N≡N), 1753, 1680 (C═O), 1378 (N═N). ^{1}H NMR (400 MHz, DMSO-d_6) $\delta = 7.80$–8.12 (m, 5H). MS: $m/z = 215$. Anal. calcd. for $C_{10}H_5N_3O_3$: C, 55.82; H, 2.34; N, 19.53. Found: C, 55.94; H, 2.48; N, 19.63.

General Procedure for the Synthesis of Compounds 3a–h, 4a, and 5a–i

The solution of 3-coumarinyl azide (**1**) (0.5 mmol) in toluene (20 mL) was heated at 120°C for 16 h to give coumarin isocyanate **2**, which was not isolated originally and treated in situ with various aromatic amines, 2-amino-5-phenyl-1,3,4-thiadiazole, and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles, respectively, under microwave irradiation at 490 W for the time given in Table I. After the completion of the reaction, monitored by TLC using ethyl acetate and petroleum ether (2:3) as eluent, the solvent was removed under reduced pressure, and from the residue, the products **3a–h**, **4a**, and **5a–i** were isolated by recrystallization from DMF-EtOH. The spectral data of compounds are listed in Table II.

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