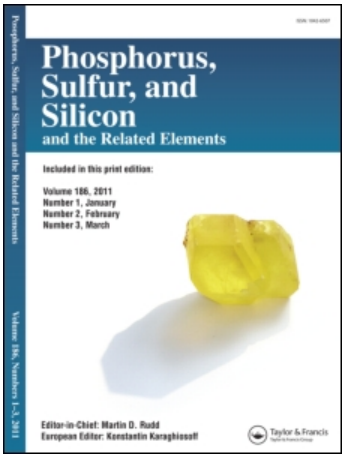

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Synthesis of Benzofuryl Substituted Unsymmetrical Ureas Under Microwave Irradiation

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Synthesis of Benzofuryl Substituted Unsymmetrical Ureas Under Microwave Irradiation

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A series of 2-benzofuryl substituted unsymmetrical ureas were synthesized by reactions of benzofuroyl isocyanate, which was prepared from benzofuroyl azide by Curtius rearrangement, with various aromatic amines, 2-amino-5-(benzo-2-furyl)-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 1,3,4-thiadiazoles; curtius rearrangement; isocyanate; microwave irradiation (MWI); 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] anti-bacterial,[10] and anti-convulsant activities.[11] The synthetic protocols of ureas generally utilize phosgene or phosgene-based isocyanates

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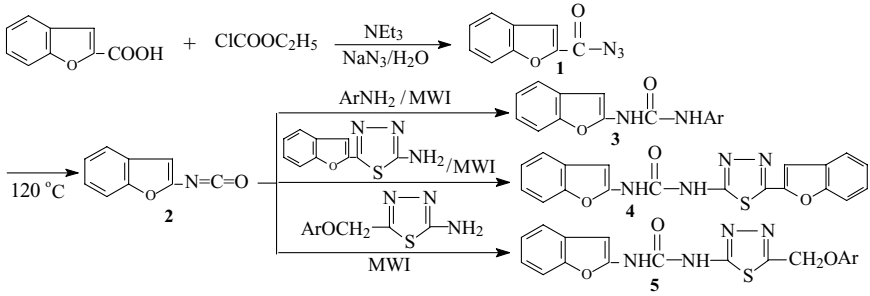
as starting materials,[12,13] both of which are toxic or unstable. These methods also involve longer reaction times. Therefore, it is necessary to develop phosgene-free and straight-torward routes for unsymmetrical ureas.

These reasons prompted us to develop an environmentally benign methodology to synthesize some new series of compounds bearing both urea 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

We herein report a fast and efficient method for the preparation of a series of unsymmetrical ureas. As described in Scheme 1, N-aryl-N′-(benzofuran-2-yl) ureas **(3a–k)**, N-benzofuran-2-yl-N′-[5-(benzofuran-2-yl)-1,3,4-thiadiazol-2-yl] urea **(4a)**, and N-benzofuran-2-yl-N′-(1,3,4-thiadiazol-2-yl) ureas **(5a–i)** were synthesized by reactions of benzofuran isocyanate with various aromatic amines, 2-amino-5-(benzo-2-furyl)-1,3,4-thiadiazole, and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles, respectively, under microwave irradiation. Benzofuran-2-yl isocyanate was prepared by treating benzofuran-2-carboxylic acid with sodium azide and ethyl chlorocarbamate in the presence of triethylamine followed by Curtius rearrangement.[14]



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.

TABLE I Yields, Reaction Time, Melting Points, and Elemental Analyses of Compounds 3a–k, 4a, and 5a–i

		Yield (%)		Reaction Time			Elemental analysis (%) found (calcd.)		
	Ar	MWI[a]	Reflux[b]	MWI (min)[a]	Reflux (hour)[b]	M.p.°C lit.	C	H	N
3a	C_6H_5	84	74	10	5	232–233 (180–181)[15c]	71.54 (71.42)	4.91 (4.79)	11.23 (11.10)
3b	2-$CH_3C_6H_4$	82	77	8	4	244–246	71.89 (72.17)	5.66 (5.30)	10.48 (10.52)
3c	4-$CH_3C_6H_4$	85	78	8	4	250–252 (214–215)[15c]	71.83 (72.17)	5.59 (5.30)	10.67 (10.52)
3d	2-$NO_2C_6H_4$	75	64	14	8	224–226	60.40 (60.61)	4.06 (3.73)	14.09 (14.14)
3e	3-$NO_2C_6H_4$	71	61	14	8	226–228	60.84 (60.61)	4.01 (3.73)	14.28 (14.14)
3f	4-$NO_2C_6H_4$	72	62	14	8	>300	60.78 (60.61)	3.94 (3.73)	14.39 (14.14)
3g	2-ClC_6H_4	79	69	10	6	240–241	62.67 (62.84)	4.01 (3.87)	9.91 (9.77)
3h	4-ClC_6H_4	80	70	10	6	256–258 (216–218)[15c]	62.61 (62.84)	4.06 (3.87)	9.95 (9.77)
3i	4-BrC_6H_4	81	71	12	7	222–224 (230–232)[15c]	54.24 (54.40)	3.57 (3.35)	8.63 (8.46)
3j	1-Naphthyl	80	70	12	7	252–254	75.72 (75.48)	4.80 (4.67)	9.46 (9.27)
3k	2-Naphthyl	78	74	12	7	276–278	75.69 (75.48)	4.86 (4.67)	9.39 (9.27)
4a	benzofuran-2	78	70	25	14	280–282	60.85 (60.63)	3.38 (3.21)	15.11 (14.89)
5a	C_6H_5	80	73	25	14	288–290	59.25 (59.01)	3.93 (3.85)	15.45 (15.29)
5b	4-$CH_3OC_6H_4$	82	78	20	12	>300	57.64 (57.57)	4.23 (4.07)	14.28 (14.13)
5c	2-$CH_3C_6H_4$	80	75	20	13	268–270	60.14 (59.99)	4.46 (4.24)	14.91 (14.73)
5d	3-$CH_3C_6H_4$	73	68	22	13	246–248	60.21 (59.99)	4.40 (4.24)	14.95 (14.73)
5e	4-$CH_3C_6H_4$	76	70	22	13	272–274	60.18 (59.99)	4.38 (4.24)	14.89 (14.73)
5f	4-ClC_6H_4	72	66	25	15	290–292	53.78 (53.94)	3.38 (3.27)	13.79 (13.98)
5g	2,4-$Cl_2C_6H_3$	68	64	25	15	294–296	49.88 (49.67)	2.93 (2.78)	12.76 (12.87)
5h	4-$NO_2C_6H_4$	65	61	28	16	276–278	52.73 (52.55)	3.34 (3.19)	17.25 (17.02)
5i	1-Naphthyl	70	65	25	14	>300	63.59 (63.45)	3.98 (3.87)	13.57 (13.45)

[a]Irradiated by microwave at less than 490 W; [b]Heated at 120°; [c]Recrystallized from either acetone or alcohol, recorded in an open capillary tube and are uncorrected.

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 84% after 10 min of irradiation with 490 W using toluene as solvent. A greater power or longer irradiation time induces a decrease in yield (only 78% with 700 W or 68% after 12 min) due to the decomposition of benzofuran-2-yl isocyanate.

In summary, the synthesis of unsymmetrical ureas has been accomplished employing the Curtius rearrangement of 2-benzofuroyl 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 4–16 h to 8–28 min. The main advantages of this method are short reaction times, high yields, less byproducts, and simple handling of slashing materials and products.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on a Nicolet AVATAR 360 FT-IR spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker Avanci-D2X-200 instrument using DMSO-d_6 as solvent and TMS as internal standard. Elemental analyses were performed on a Vario E-l 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.

Benzofuran-2-carboxylic acid,[16] 2-amino-5-(benzo-2-furyl)-1,3,4-thiadiazole,[17] and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles[18] were prepared according to literature procedures. Aryloxy acetic acids were commercially available and used as received.

Preparation of Benzofuroyl Azide 1

A mixture of benzofuran-2-carboxylic acid (10 mmol, 1.87 g), triethylamine (11 mmol, 1.111 g), and ethyl chlorocarbamate (11 mmol, 1.194 g) in dry acetone (30 mL) was stirred at 0°C for 1 h. Then sodium azide (11 mmol, 0.715 g) dissolved in 15 mL water was added and the mixture was kept at 0°C for 7 h. After the reaction was completed (monitored by TLC), the mixture was poured onto ice. The precipitated product was separated by filtration. Yield: 96.3 %. White crystal. M.p. 110–111°C. IR (KBr, ν/cm^{-1}): 2162 (N≡N), 1703 (C=O), 1333 (N=N); ^{1}H NMR (DMSO-d_6)δ: 6.90–7.36 (m, 5H, benzofuran H). MS: m/z = 187. Anal. Calcd. for $C_9H_5O_2N_3$: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.83; H, 2.71; N, 22.52.

TABLE II IR and ^{1}H NMR Spectroscopic Data for Compounds 3a–k, 4a, and 5a–i

Product	IR (KBr) cm^{-1}	^{1}H NMR /δ/(ppm)
3a	3314, 3276 (N—H); 1649 (C=O)	9.82 (s, 1H, NH); 9.01 (s, 1H, NH); 7.95–6.49 (m, 10H, ArH & benzofuran H).
3b	3284, 3264 (N—H); 1653 (C=O)	9.79 (s, 1H, NH); 8.99 (s, 1H, NH); 7.93–6.47 (m, 9H, ArH & benzofuran H); 2.44 (s, 3H, CH_3).
3c	3282, 3274 (N—H); 1659 (C=O)	9.78 (s, 1H, NH); 9.00 (s, 1H, NH); 7.94–6.48 (m, 9H, ArH & benzofuran H); 2.43 (s, 3H, CH_3).
3d	3288, 3269 (N—H); 1646 (C=O)	9.90 (s, 1H, NH); 9.04 (s, 1H, NH); 8.11–6.54 (m, 9H, ArH & benzofuran H).
3e	3280, 3261 (N—H); 1655 (C=O)	9.87 (s, 1H, NH); 9.03 (s, 1H, NH); 8.13–6.51 (m, 9H, ArH & benzofuran H).
3f	3302, 3273 (N—H); 1654 (C=O)	9.88 (s, 1H, NH); 9.04 (s, 1H, NH); 8.21–6.60 (m, 9H, ArH & benzofuran H).
3g	3290, 3271 (N—H); 1660 (C=O)	9.80 (s, 1H, NH); 9.01 (s, 1H, NH); 7.96–6.52 (m, 9H, ArH & benzofuran H).
3h	3281, 3264 (N—H); 1648 (C=O)	9.79 (s, 1H, NH); 9.03 (s, 1H, NH); 8.09–6.51 (m, 9H, ArH & benzofuran H).
3i	3288, 3269 (N—H); 1657 (C=O)	9.82 (s, 1H, NH); 9.02 (s, 1H, NH); 7.95–6.49 (m, 9H, ArH & benzofuran H).
3j	3278, 3261 (N—H); 1665 (C=O)	9.81 (s, 1H, NH); 9.01 (s, 1H, NH); 8.01–6.51 (m, 12H, ArH & benzofuran H).
3k	3275, 3265 (N—H); 1661 (C=O)	9.80 (s, 1H, NH); 9.00 (s, 1H, NH); 8.03–6.47 (m, 12H, ArH & benzofuran H).
4a	3283, 3175 (N—H); 1658 (C=O); and 1574, 1495, 1324, 1044 (C=N—N=C—S)	9.80 (s, 1H, NH); 9.22 (s, 1H, NH); 7.95–6.86 (m, 10H, benzofuran H); 5.41 (s, 2H, CH_2O).
5a	3277, 3179 (N—H); 1667 (C=O); and 1577, 1496, 1321, 1045 (C=N—N=C—S)	9.82 (s, 1H, NH); 9.20 (s, 1H, NH); 7.96–6.89 (m, 10H, ArH & benzofuran H); 5.42 (s, 2H, CH_2O).
5b	3283, 3176 (N—H); 1661 (C=O); and 1584, 1494, 1322, 1048 (C=N—N=C—S)	9.80 (s, 1H, NH); 9.18 (s, 1H, NH); 7.95–6.87 (m, 9H, ArH & benzofuran H); 5.38 (s, 2H, CH_2O); 2.28 (s, 3H, CH_3O).

(Continued on next page)

TABLE II IR and ^{1}H NMR Spectroscopic Data for Compounds 3a–k, 4a, and 5a–i *(Continued)*

Product	IR (KBr) cm^{-1}	^{1}H NMR /δ/(ppm)
5c	3280, 3174 (N—H); 1653 (C=O); and 1575, 1493, 1323, 1047 (C=N—N=C—S)	9.79 (s, 1H, NH); 9.17 (s, 1H, NH); 7.92–6.84 (m, 9H, ArH & benzofuran H); 5.37 (s, 2H, CH_2O); 2.26 (s, 3H, CH_3).
5d	3285, 3172 (N—H); 1658 (C=O); and 1583, 1495, 1325, 1049 (C=N—N=C—S)	9.81 (s, 1H, NH); 9.16 (s, 1H, NH); 7.96–6.85 (m, 9H, ArH & benzofuran H); 5.40 (s, 2H, CH_2O); 2.27 (s, 3H, CH_3).
5e	3278, 3170 (N—H); 1653 (C=O); and 1576, 1490, 1326, 1046 (C=N—N=C—S)	9.78 (s, 1H, NH); 9.14 (s, 1H, NH); 7.93–6.86 (m, 9H, ArH & benzofuran H); 5.38 (s, 2H, CH_2O); 2.24 (s, 3H, CH_3).
5f	3281, 3168 (N—H); 1662 (C=O); and 1574, 1492, 1319, 1045 (C=N—N=C—S)	9.81 (s, 1H, NH); 9.21 (s, 1H, NH); 7.95–6.88 (m, 9H, ArH & benzofuran H); 5.45 (s, 2H, CH_2O).
5g	3288, 3174 (N—H); 1652 (C=O); and 1573, 1493, 1320, 1044 (C=N—N=C—S)	9.84 (s, 1H, NH); 9.18 (s, 1H, NH); 7.98–6.92 (m, 8H, ArH & benzofuran H); 5.47 (s, 2H, CH_2O).
5h	3293, 3167 (N—H); 1654 (C=O); and 1570, 1491, 1317, 1042 (C=N—N=C—S)	9.83 (s, 1H, NH); 9.23 (s, 1H, NH); 7.96–6.90 (m, 9H, ArH & benzofuran H); 5.48 (s, 2H, CH_2O).
5i	3287, 3173 (N—H); 1657 (C=O); and 1573, 1488, 1327, 1044 (C=N—N=C—S)	9.82 (s, 1H, NH); 9.21 (s, 1H, NH); 7.98–6.89 (m, 12H, ArH & benzofuran H); 5.44 (s, 2H, CH_2O)

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

A solution of 2-benzofuroyl azide **(1)** (0.5 mmol) in toluene (20 mL) was heated at 120°C for 4 h to give benzofuran-2-yl isocyanate **2**, which is not isolated and treated in situ with the respective aromatic amine, 2-amino-5-(benzo-2-furyl)-1,3,4-thiadiazole, or 2-amino-5-aryloxymethylene-1,3,4-thiadiazole 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–k, 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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