Phosphorus, Sulfur, and Silicon, 182:2491–2496, 2007

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701407441

Taylor & Francis
Taylor & Francis Group

One-Pot Synthesis of Phenylallyl Substituted Unsymmetrical Ureas Under Microwave Irradiation

Lan-Qin Chai
Wei-Peng Chen
Xiao-Qiang Wang
Jian-Lin Ge
School of Chemical and Biological Engineering, Lanzhou Jiaotong University, Lanzhou, Gansu, P. R. China

A series of phenylallyl-substituted unsymmetrical ureas were synthesized in a one-pot procedure by reactions of cinnamoyl isocyanate, which was prepared from cinnamoyl azide by Curtius rearrangement, with various aromatic amines, 2-amino-5-aryl-1,3,4-thiadiazoles 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; isocyanate; microwave irradiation (MWI); one-pot synthesis; 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.

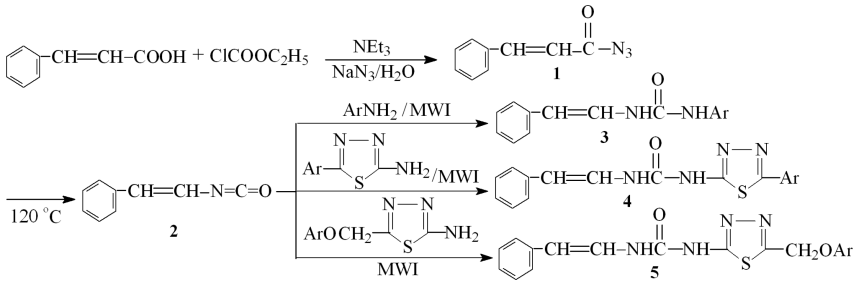
Unsymmetrically substituted ureas are widely used as herbicides, pesticides, plant growth regulators, and medicinal intermediates.[4–6] Ureas bearing heterocyclic substitutents, for example 1,3,4-thiadiazole,

Received January 6, 2007; accepted March 18, 2007.
Financial support of this work by the Foundation (No. 06-40611) of Lanzhou Jiaotong University is acknowledged.
Address correspondence to Lan-Qin Chai, School of Chemistry and Biological Engineering, Lanzhou Jiaotong University, Lanzhou, 730070, Gansu, P. R. China. E-mail: chailq@mail.lzjtu.cn

have been shown to exert anti-inflammatory,[7–9] antibacterial,[10] and anticonvulsant activities.[11] The synthetic protocols of ureas generally utilize phosgene or phosgene-based isocyanates 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-forward routes for unsymmetrically substituted ureas.

These reasons prompted us to develop an environmentally benign methodology for the synthesis of some new series of compounds bearing both urea and 1,3,4-thiadiazole moieties, with the objective to investigate property and structure-activity relationship of these new compounds and to obtain new biologically active compounds.

We herein report a fast and efficient one-pot method for the preparation of a series of unsymmetrically substituted ureas. As described in Scheme 1, N-aryl-N′-phenylallyl ureas (**3a–h**), *N*-phenylallyl-*N*′-(5-aryl-1,3,4-thiadiazol-2-yl) ureas (**4a–b**) and *N*-phenylallyl-*N*′-(5-aryloxy- methylene-1,3,4-thiadiazol-2-yl) ureas (**5a–h**) were synthesized by reactions of cinnamoyl isocyanate with various aromatic amines, 2-amino-5-aryl-1,3,4-thiadiazoles and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles, respectively, under microwave irradiation. Cinnamoyl isocyanate was prepared by treating cinnamic acid with sodium azide and ethyl chlorocarbamate in the presence of triethylamine, followed by Curtius rearrangement.[14]



SCHEME 1

RESULTS AND DISCUSSION

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 32 times faster and proceed with high yields. The results obtained are reported in Table I.

We selected the synthesis of compound **5a** as a model reaction to study the effects of irradiation power and time on the yields. The best yields obtained are 80% after 16 min of irradiation with 490 W using toluene as solvent. A higher power or a longer irradiation time induces a decrease in yield (only 74% with 700 W or 68% after 18 min) due to the decomposition of cinnamoyl isocyanate.

In summary, the synthesis of unsymmetrically substituted ureas has been accomplished employing the Curtius rearrangement of cinnamoyl azide followed by the nucleophilic addition of amines to the *NCO* moiety under microwave irradiation. Compared to conventional thermal heating, microwave irradiation decreased the reaction time from 4–13 h to 8–20 min. The main advantages of this method are short reaction times, high yields, less by-products, and simple handling of starting 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 Avance-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.

2-amino-5-aryl-1,3,4-thiadiazoles[15] and 2-amino-5-aryloxymethylene-1,3,4-thiadiazoles[16] were prepared according to literature procedures. Aryloxy acetic acids were commercially available and used as received.

Preparation of Cinnamoyl Azide 1

A mixture of cinnamic acid (10 mmol, 1.48 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 of 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: 97.3%. White crystals. M.p. 86–87°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, ArH). MS: m/z = 173. Anal. Calcd. for $C_9H_7ON_3$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.58; H, 4.19; N, 24.45.

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

		Yield (%)		Reaction Time			Elemental analysis (%) found (calcd.)		
	Ar	MWI[a]	Reflux[b]	MWI (min)[a]	Reflux (h)[b]	m.p. (°C)	C	H	N
3a	C_6H_5	80	74	10	5	188–190	75.42 (75.61)	5.79 (5.92)	11.51 (11.76)
3b	2-$CH_3C_6H_4$	82	77	8	4	182–183	76.33 (76.16)	6.48 (6.39)	11.25 (11.10)
3c	4-$CH_3C_6H_4$	85	78	8	4	184–185	76.37 (76.16)	6.45 (6.39)	11.28 (11.10)
3d	4-ClC_6H_4	75	64	12	7	180–181	66.21 (66.06)	4.92 (4.80)	10.41 (10.27)
3e	2-$NO_2C_6H_4$	71	61	14	8	174–175	63.53 (63.60)	4.48 (4.63)	14.72 (14.83)
3f	3-$NO_2C_6H_4$	72	62	14	8	135–137	63.71 (63.60)	4.52 (4.63)	14.69 (14.83)
3g	1-Naphthyl	79	69	10	6	128–130	79.28 (79.14)	5.67 (5.59)	9.87 (9.72)
3h	2-Naphthyl	80	70	10	6	220–222	79.26 (79.14)	5.71 (5.59)	9.93 (9.72)
4a	C_6H_5	81	71	12	7	268–270	63.48 (63.34)	4.55 (4.38)	17.56 (17.38)
4b	2-$CH_3C_6H_4$	82	74	10	5	254–256	64.45 (64.27)	4.93 (4.79)	16.82 (16.65)
5a	C_6H_5	80	71	16	11	>300	61.52 (61.35)	4.67 (4.58)	15.73 (15.90)
5b	4-$CH_3OC_6H_4$	82	76	14	10	264–266	59.57 (59.67)	4.91 (4.74)	14.78 (14.65)
5c	2-$CH_3C_6H_4$	80	72	15	10	207–208	62.42 (62.28)	4.86 (4.95)	15.38 (15.29)
5d	3-$CH_3C_6H_4$	79	68	15	10	218–220	62.48 (62.28)	4.82 (4.95)	15.43 (15.29)
5e	4-$CH_3C_6H_4$	81	70	15	10	227–228	62.40 (62.28)	4.88 (4.95)	15.36 (15.29)
5f	2,4-$Cl_2C_6H_3$	72	66	18	13	>300	56.19 (56.03)	3.72 (3.66)	14.63 (14.52)
5g	4-$NO_2C_6H_4$	68	64	20	13	>300	54.23 (54.40)	3.91 (3.80)	17.84 (17.62)
5h	1-Naphthyl	76	67	18	12	270–272	65.81 (65.65)	4.69 (4.51)	13.80 (13.92)

[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–b, and 5a–h

	IR (KBr) cm^{-1}	^{1}H NMR δ (ppm)
3a	3314, 3276 (N-H); 1649 (C=O); 1614 (C=C)	9.72 (s, 1H, NH); 9.03 (s, 1H, NH); 7.86–6.55 (m, 10H, ArH)
3b	3282, 3272 (N-H); 1651 (C=O); 1614 (C=C)	9.66 (s, 1H, NH); 9.01 (s, 1H, NH); 7.82–6.50 (m, 9H, ArH); 2.42 (s, 3H, CH_3)
3c	3284, 3274 (N-H); 1653 (C=O); 1616 (C=C)	9.68 (s, 1H, NH); 9.00 (s, 1H, NH); 7.84–6.52 (m, 9H, ArH); 2.44 (s, 3H, CH_3)
3d	3278, 3270 (N-H); 1650 (C=O); 1612 (C=C)	9.74 (s, 1H, NH); 9.04 (s, 1H, NH); 7.90–6.58 (m, 9H, ArH)
3e	3282, 3271 (N-H); 1655 (C=O); 1610 (C=C)	9.78 (s, 1H, NH); 9.06 (s, 1H, NH); 7.93–6.62 (m, 9H, ArH)
3f	3281, 3272 (N-H); 1659 (C=O); 1612 (C=C)	9.80 (s, 1H, NH); 9.08 (s, 1H, NH); 7.96–6.63 (m, 9H, ArH)
3g	3279, 3270 (N-H); 1658 (C=O); 1613 (C=C)	9.75 (s, 1H, NH); 9.04 (s, 1H, NH); 7.88–6.58 (m, 12H, ArH)
3h	3280, 3273 (N-H); 1656 (C=O); 1615 (C=C)	9.73 (s, 1H, NH); 9.02 (s, 1H, NH); 7.85–6.56 (m, 12H, ArH)
4a	3278, 3176 (N-H); 1659 (C=O); 1613 (C=C)	10.83 (s, 1H, NH); 10.16 (s, 1H, NH); 7.95–6.86 (m, 10H, ArH)
4b	3280, 3178 (N-H); 1660 (C=O); 1616 (C=C)	10.81 (s, 1H, NH); 10.14 (s, 1H, NH); 7.93–6.85 (m, 9H, ArH); 2.26 (s, 3H, CH_3)
5a	3278, 3178 (N-H); 1666 (C=O); 1614 (C=C); 1577, 1496, 1321, 1045 (C=N-N=C-S)	11.82 (s, 1H, NH); 10.20 (s, 1H, NH); 7.96–6.89 (m, 10H, ArH); 5.42 (s, 2H, CH_2O)
5b	3283, 3170 (N-H); 1661 (C=O); 1610 (C=C); 1585, 1496, 1320, 1049 (C=N-N=C-S)	11.80 (s, 1H, NH); 10.18 (s, 1H, NH); 7.95–6.87 (m, 9H, ArH); 5.39 (s, 2H, CH_2O); 2.28 (s, 3H, CH_3O)
5c	3279, 3175 (N-H); 1655 (C=O); 1611 (C=C); 1575, 1494, 1323, 1047 (C=N-N=C-S)	11.79 (s, 1H, NH); 10.17 (s, 1H, NH); 7.92–6.84 (m, 9H, ArH); 5.37 (s, 2H, CH_2O); 2.26 (s, 3H, CH_3)
5d	3280, 3172 (N-H); 1658 (C=O); 1613 (C=C); 1583, 1494, 1325, 1048 (C=N-N=C-S)	11.81 (s, 1H, NH); 10.15 (s, 1H, NH); 7.96–6.85 (m, 9H, ArH); 5.40 (s, 2H, CH_2O); 2.27 (s, 3H, CH_3)
5e	3278, 3170 (N-H); 1653 (C=O); 1612 (C=C); 1576, 1493, 1326, 1046 (C=N-N=C-S)	11.78 (s, 1H, NH); 10.16 (s, 1H, NH); 7.93–6.86 (m, 9H, ArH); 5.38 (s, 2H, CH_2O); 2.24 (s, 3H, CH_3)
5f	3286, 3172 (N-H); 1650 (C=O); 1614 (C=C); 1571, 1490, 1317, 1042 (C=N-N=C-S)	11.84 (s, 1H, NH); 10.18 (s, 1H, NH); 7.98–6.92 (m, 8H, ArH); 5.47 (s, 2H, CH_2O)
5g	3289, 3165 (N-H); 1652 (C=O); 1616 (C=C); 1568, 1489, 1315, 1040 (C=N-N=C-S)	11.88 (s, 1H, NH); 10.23 (s, 1H, NH); 8.01–6.95 (m, 9H, ArH); 5.48 (s, 2H, CH_2O)
5h	3285, 3171 (N-H); 1656 (C=O); 1615 (C=C); 1572, 1487, 1325, 1043 (C=N-N=C-S)	11.82 (s, 1H, NH); 10.21 (s, 1H, NH); 7.98–6.89 (m, 12H, ArH); 5.44 (s, 2H, CH_2O)

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

A solution of cinnamoyl azide (**1**) (0.5 mmol) in toluene (20 mL) was heated at 120°C for 4 h to give cinnamoyl isocyanate **2**, which is not isolated and treated in situ with the respective aromatic amine, 2-amino-5-aryl-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**–**h**, **4a**–**b**, and**5a**–**h** were isolated by recrystallization from DMF-EtOH.

REFERENCES

[1] A. Bose, M. S. Manhas, S. N. Ganguly, A. H. Sharma, and B. K. Banik, *Synthesis*, **32,** 1579 (2002).
[2] X. C. Wang, M. G. Wang, Z. J. Quan, and Z. Li, *Synth. Commun.*, **35,** 2881 (2005).
[3] L. Perrux and A. Loupy, *Tetrahedron*, **57,** 9199 (2001).
[4] M. Takumi, K. Takanobu, I. Takatoshi, and M. Toshiyuki, *Synth. Commun.*, **30,** 1675 (2000).
[5] M. J. Gil, M. A. Manu, C. Arteaga, M. Migliaccio, and I. Encio, *Bioorg. Med. Chem. Lett.*, **9,** 2321 (1999).
[6] E. G. Chalina, L. Chakarova, and D. T. Staneva, *Eur. J. Med. Chem. Chim. Ther.*, **33,** 985 (1998).
[7] M. Amir, A. Oberoi, and S. Alam, *Indian J. Chem.*, **38 B,** 237 (1999).
[8] H. S. Chen, Z. M. Li, and Y. F. Han, *J. Agric. Food Chem.*, **50,** 3757 (2002).
[9] X. C. Wang, Z. Li, and Y. X. Da, *Indian J. Chem.*, **40B,** 422 (2001).
[10] X. P. Hui, L. M. Zhang, Z. Y. Zhang, Q. Wang, and F. Wang, *Indian J. Chem.*, **38B,** 1066 (1999).
[11] E. E. Chufan, J. C. Pedregosa, O. N. Badini, and L. Bruno-Blanch, *Farmaco*, **54,** 838 (1999).
[12] A. Arrieta and C. Palomo,*Tetrahedron Lett.*, **22,** 1729 (1981).
[13] R. A. Batey, V. Santhakumar, C. Yoshina-Ishii, and S. D. Taylor, *Tetrahedron Lett.*, **39,** 6267 (1998).
[14] X. C. Wang, L. Q. Chai, M. G. Wang, Z. J. Quan, and Z. Li, *Synth. Commun.*, **36,** 645 (2006).
[15] A. A. F. Wasfy, S. A. Nassar, and A. M. F. Eissa, *Indian J. Chem.*, **35B,** 1218 (1996).
[16] X. C. Wang, Z. Li, Z. J. Quan, X. S. Lu, and R. H. Gou, *Synth. Commun.*, **33,** 2891 (2003).