Microwave-assisted synthesis of 1,3,4-thiadiazole aroylurea derivatives

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A rapid and efficient microwave-assisted synthesis method for the preparation of 1-aroyl-3-(5-aryl-1,3,4-thiadiazol-2-yl)urea is described. These 1,3,4-thiadiazole aroylureas (5a–f) were identified by IR, ^{1}H NMR, elemental analyses and N-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]-2,6-difluorobenzamide was confirmed by single-crystal X-ray diffraction. The target compounds were prepared under microwave in a shorter reaction time compared with conventional heating methods.

Keywords: 1,3,4-thiadiazole, aroylurea, microwave-assisted synthesis, crystal structure

During recent years there has been intense investigation of different thiadiazole compounds. Many of them are well known to possess interesting biological properties such as antimicrobial, antituberculosis, anti-inflammatory, anticonvulsant, antihypertensive, anticancer, and hypoglycemic activities.[1-8]

Benzoylureas are promising and effective insecticides used for the control of insects attacking a wide range of crops. These compounds are generally recognised as insect growth regulators which interfere with chitin synthesis in target pests, causing death or abortive development.[9,10] Due to their attractive properties such as high selectivity, low acute toxicity for mammals, and high biological activity,[11] they are considered to be a fourth generation of insecticides.

Conventional synthesis reactions suffered from drawbacks such as the use of high boiling solvents, long reaction time and lower yields. Compared with the traditional heating reactions, the microwave (MW) reaction technique is often rapid, more convenient and has environmental, and economic advantages.[12] MW irradiation is currently used to carry out a wide range of reactions.[13,14]

In connection with our research interest directed toward the synthesis of novel aroylurea derivatives, we have designed and synthesised a series of new compounds containing the 1,3,4-thiadiazole and aroylurea under microwave irradiation.

Results and discussion

Previously the aroylureas were synthesised by substituted aryl amines and aroyl isocyanate with yields of 47–60%. Aroyl isocyanate was added dropwise to the solution of substituted aryl amines in toluene, and then refluxed for several hours.

In this study, the 1-aroyl-3-(5-aryl-1,3,4-thiadiazol-2-yl) urea **(5a–f)** were prepared by the reaction of 2-amino-5-aryl-1,3,4-thiadiazole **(3a–d)** and aroyl isocyanate **(4a–c)** under microwave irradiation as shown in Scheme 1. The results are reported in Table 1.

In conclusion, we have developed a fast, convenient, and efficient draft for the preparation of 1-aroyl-3-(5-aryl-1,3,4-thiadiazol-2-yl)urea under MW irradiation. The ease of the reaction procedure and workup, high yields, and a very short reaction time make this procedure useful and attractive compared with the currently available methods.

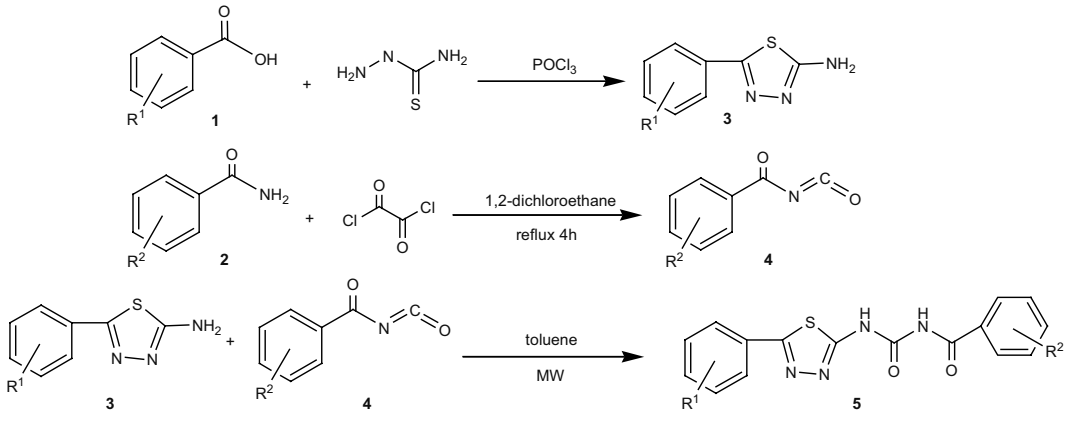
Experimental

Instrumentation and chemicals

Melting points were recorded on an X-4 binocular microscope melting point apparatus. ^{1}H NMR spectra were recorded on an Avance Bruker-500 instrument and chemical shifts in ppm are reported with TMS as the internal standard. IR spectra in KBr were recorded by a Perkin-Elmer PE-683 IR spectrometer. Elemental analyses were performed on an Elementer Vario EL III elementary analysis instrument. MW experiments were carried out on a WF-4000M microwave fast reaction system (Shanghai Qiyao Analysis Instrument Co., Shanghai, China). Crystal structure determination was carried out on an Enraf-Nonius CAD-4 diffractometer.

General synthetic procedure for the preparation of **3a–d**

A mixture of substituted benzoic acid **1a–d** (0.1 mol) and thiosemicarbazide (0.1 mol) was added $POCl_3$ (0.3 mol) dropwise at 0–5 °C and maintained for 30 min. The reaction mixture was allowed



3a R^1=4-methoxy **3b** R^1=3,5-dimethyl **3c** R^1=2,4-dichloro **3d** R^1=3-fluoro
4a R^2=2,6-difluoro **4b** R^2=4-methoxy **4c** R^2=H
5a R^1=4-methoxy R^2=2,6-difluoro **5b** R^1=3,5-dimethyl R^2=2,6-difluoro
5c R^1=2,4-dichloro R^2=4-methoxy **5d** R^1=3,5-dimethyl R^2=4-methoxy
5e R^1=3-fluoro R^2= H **5f** R^1=4-methoxy R^2= H

Scheme 1 The synthetic route of compounds **5a–f**.

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Table 1 Synthesis of compounds **5a–f**

Entry	R^1	R^2	Mode of activation	Time	Power/ temp.	Yield/%
5a	4-Methoxy	2,6-Difluoro	MW	6 min	300 W	87
5b	3,5-Dimethyl	2,6-Difluoro	MW	7 min	300 W	83
5c	2,4-Dichloro	4-Methoxy	MW	6 min	300 W	82
5d	3,5-Dimethyl	4-Methoxy	MW	6 min	300 W	78
5e	3-Fluoro	H	MW	6 min	300 W	90
5f	4-Methoxy	H	MW	6 min	300 W	85
5a	4-Methoxy	2,6-Difluoro	CH	5 h	110°C	52

MW = microware irradiation; CH = conventional heating.

to raise temperature until reflux and stirred for 4 h. After cooling, 50 mL water was added into the reaction mixture. The pH of the reaction solution was adjusted to the range of 8–9 with 50% NaOH solution. The crude product precipitated, filtered, washed with water, dried, and recrystallised from ethanol to afford compounds **3a–d**.

General synthetic procedure for the preparation of **4a–c**
A mixture of substituted benzamide **2a–c** (0.1 mol) and ethylene dichloride was chilled in an ice bath and stirred while oxalyl dichloride (0.24 mol) was added dropwise to the mixture. The mixture was warmed and stirred for 1 h at room temperature, and then heated to reflux for 5 h. After completion of the reaction, the remaining oxalyl chloride was evaporated under reduced pressure. The compounds **4a–c** was collected under vacuum.

General synthetic procedure for the preparation of **5a–f**
A mixture of compounds **3a–d** (0.01 mol) and **4a–c** (0.014 mol) in toluene was stirred and irradiated in WF-4000M microwave fast reaction system under 300W for minutes. After cooling and filtering, crude compound **5a–f** was obtained. Pure compound was obtained by recrystallisation from DMF.

Crystals of **(5a)** suitable for X-ray diffraction were obtained by slow evaporation of a DMF solution.
N-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]-2,6-difluorobenzamide **5a**: (87%): M.p. 203–205 °C, ^{1}H NMR(DMSO-d6, 300 MHz) δ: 3.84(s, 3H, OCH_3), 7.07–7.90(m, 7H, ArH), 11.73(s, 2H, NH), IR(KBr)υ: 679(C-S), 1632(C=N), 3203(N-H), 1696(C=O) cm^{-1}; Anal Calcd for $C_{17}H_{12}F_2N_4O_3S$: C, 52.31; H, 3.10; N, 14.35. Found: C, 52.26; H, 3.11; N, 14.30%.

N-[5-(3,5-dimethylphenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]-2,6-difluorobenzamide **5b**: (83%): M.p. 256–257 °C, ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.34 (s, 6H, CH_3), 7.16–7.66 (m, 6H, ArH),11.72 (s, 2H, NH), IR(KBr)υ: 670 (C-S), 1625 (C=N), 3123 (N-H), 1695 (C=O) cm^{-1}; Anal. Calcd for $C_{18}H_{14}F_2N_4O_2S$: C, 55.66; H, 3.63; N, 14.43. Found: C, 55.62; H, 3.71; N, 14.41%.

N-[5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]-4-methoxybenzamide **5c**: (82%): M.p. 272–274 °C, ^{1}H NMR(DMSO-d6, 300 MHz) δ: 3.86 (s, 3H, OCH_3),7.09–8.28 (m, 7 H, ArH),11.52 (s, 1H, NH),12.37 (s, 1H, NH), IR(KBr)υ: 686 (C-S), 1604 (C=N), 3151 (N-H), 1699 (C=O) cm^{-1}; Anal. Calcd for $C_{17}H_{12}Cl_2N_4O_3S$: C, 48.24; H, 2.86; N, 13.24. Found: C, 48.30; H, 2.82; N 13.20%.

N-[5-(3,5-dimethylphenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]-4-methoxybenzamide **5d**: (78%): M.p. 264–265 °C, ^{1}H NMR(DMSO-d6, 300 MHz) δ: 2.54 (s, 6H, CH_3), 3.87 (s, 3H, OCH_3), 7.09–8.09 (m, 7 H, ArH), 11.51 (s, 1 H, NH),12.29 (s, 1H, NH), IR(KBr)υ: 688 (C-S), 1604 (C=N), 3286 (N-H), 1699 (C=O) cm^{-1}; Anal. Calcd for $C_{19}H_{18}N_4O_3S$: C, 59.67; H, 4.74; N 14.65. Found: C, 59.67; H, 4.72; N, 14.69%.

N-[5-(3-fluorophenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]benzamide **5e**: (90%): M.p. 249–250° C, ^{1}H NMR(DMSO-d6, 300 MHz) δ: 7.37–8.06 (m, 9H, ArH), 11.66 (s, 1H, NH),12.22 (s, 1H, NH), IR(KBr) υ: 680 (C-S), 1594 (C=N), 3296 (N-H), 1691 (C=O) cm^{-1}; Anal. Calcd for $C_{16}H_{11}FN_4O_2S$: C, 56.13; H, 3.24; N, 16.37. Found: C, 56.17; H, 3.28; N, 16.30%.

N-[5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-ylcarbamoyl]benzamide **5f**: (85%): M.p. 296–297° C, ^{1}H NMR(DMSO-d6, 300 MHz) δ: 3.84 (s, 3H, OCH_3), 6.99–8.04 (m, 9 H, ArH), 11.61 (s, 1H, NH),12.12 (s, 1H, NH), IR(KBr)υ: 669 (C-S), 1604 (C=N), 3236 (N-H), 1703 (C=O) cm^{-1}; Anal. Calcd for $C_{17}H_{14}N_4O_3S$: C, 57.62; H, 3.98; N, 15.81. Found: C, 57.57; H, 3.90; N, 15.93%.

The compound **5a** was subjected to single crystal X-ray crystallography and intensity data were collected 298(2) K on the Enraf-Nonius CAD-4 diffractometer and use graphite Monochromatic MoK_α radiation (λ = 0.71073Å). The structure was solved and refined with the SHELXL-97 program.[15] All H atoms bonded to the C atoms were placed geometrically and constrained to ride on their parent atoms. The thermal ellipsoids were plotted with the SHELXL-97 program at 50% probability. The molecular structure is shown in Fig. 1. Selected crystal data and structure refinement details are listed in Table 2. Selected bond distances and angles are listed in Table 3.

Table 2 Crystal data and structure refinement for $C_{17}H_{12}F_2N_4O_3S$

Empirical formula	$C_{17}H_{12}F_2N_4O_3S$
Formula weight	383.48 g mol^{-1}
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C 2/c
Unit cell dimensions	23.853(5) Å 7.1360(14)Å β = 109.55(3) 22.370(5) Å
Volume	3588.2(12) Å^{-3}
Z	8
Absorption correction	Psi-scan
F(000)	1660
Absorption coefficient	0.232 mm^{-1}
θrange for entire data collection	1.81°to 25.34°
Reflections collected	3354
Independent reflections	3271 (R_{int} = 0.0360)
Data/restraints/parameters	2331/0/254
Final R indices [I>2σ>(I)]	R^1 = 0.0817, wR^2 = 0.1677 R^1 = 0.0556, wR^2 = 0.1468
Goodness-of-fit on F^2	1.005
Final residual electron density	0.368 and –0.352 e. Å^{-3}

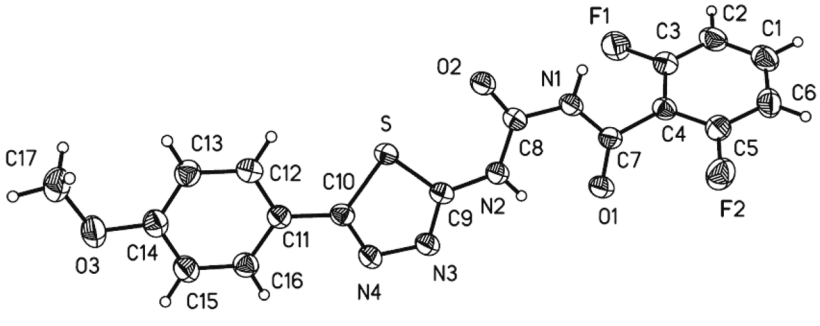

Fig.1 A view of the molecular structure of **5a**, showing atom displacement ellipsoids at the 50% level.

Table 3 Selected bond distances (Å) and angles (°) for compound (**5a**)

S– C9 1.710(3)	N2–C9 1.382(4)	C4–C7 1.489(4)
S–C10 1.736(3)	N2–C9 1.382(4)	C5–C6 1.372(5)
O1–C7 1.215(3)	O2–C8 1.214(3)	C10–C11 1.459(4)
F1–C3 1.358(4)	C2–C3 1.354(5)	C11–C12 1.390(4)
N1–C7 1.365(4)	O3–C14 1.366(4)	C11–C16 1.398(4)
N1–C8 1.387(4)	N3–C9 1.307(4)	C12–C13 1.378(4)
C1–C2 1.373(6)	N3–N4 1.374(3)	C13–C14 1.381(5)
C1–C6 1.383(5)	C3–C4 1.391(4)	C14–C15 1.388(5)
F2–C5 1.344(4)	N4–C10 1.300(4)	C15–C16 1.358(4)
N2–C8 1.351(4)	C4–C5 1.382(4)	
C9–S–C10 86.47(14)	C3–C4–C7 123.0(3)	N2–C9–S 124.7(2)
C7–N1–C8 128.7(2)	F2–C5–C6 118.9(3)	N4–C10–C11 123.7(3)
C2–C1–C6 121.2(3)	F2–C5–C4 117.8(3)	N4–C10–S 113.8(2)
C8–N2–C9 122.8(2)	C6–C5–C4 123.3(3)	C11–C10–S 122.5(2)
C3–C2–C1 118.4(4)	C5–C6–C1 118.0(4)	C12–C11–C16 117.4(3)
C14–O3–C17 118.3(3)	O1–C7–N1 123.1(3)	C12–C11–C10 122.1(3)
C9–N3–N4 111.5(2)	O1–C7–C4 121.8(3)	C15–C16–C11 121.6(3)
C2–C3 F1 119.9(3)	N1–C7–C4 115.1(2)	C13–C12–C11 121.5(3)
C2–C3–C4 123.8(3)	O2–C8–N2 122.5(3)	C12–C13–C14 119.7(3)
F1–C3–C4 116.3(3)	O2–C8–N1 121.0(3)	O3–C14–C13 124.9(3)
C10–N4–N3 113.0(2)	N2–C8–N1 116.5(3)	O3–C14–C15 115.6(3)
C5–C4–C3 115.3(3)	N3–C9–N2 120.0(3)	C13–C14–C15 119.6(3)
C5–C4–C7 121.6(3)	N3–C9–S 115.2(2)	C16–C15–C14 120.3(3)

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