Synthesis of asymmetric semicarbazides using a coumarin ring

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A series of asymmetric semicarbazides were synthesised using 3-coumarin isocyanate, which was prepared from 3-coumarinyl azide by Curtius rearrangement, with acid hydrazides under microwave irradiation using a one-pot procedure. This method has the advantages of mild conditions, easy handling and high yields. The products, which have been characterised by analytical and spectral data, have many medicinal and agrochemical applications.

Keywords: Curtius rearrangement, isocyanate, semicarbazides, microwave irradiation

The rapid heating effect of microwave irradiation has been gained attention because of its remarkable reduction of reaction time and enhancement of reaction yield.[1–3] Semicarbazide derivatives are widely used as medicines and agrochemicals because of their anti-convulsive,[4] herbicidal,[5] anti-neoplastic,[6] and hypotensive activities.[7] Coumarin derivatives have diverse biological applications, such as anti-bacterial, anti-coagulants, anti-allergic, hypotensive, anti-HIV and anti-cancer activities.[8–10]

The synthetic protocols for the synthesis of semicarbazides generally utilise phosgene or phosgene-based isocyanates as starting materials,[11,12] both of which are toxic or unstable. These methods also require long reaction times. Therefore, phosgene-free and shorter routes to semicarbazides are needed.

We have tried to develop an environmentally benign method to synthesise a new series of compounds having both semicarbazide and coumarin moieties, with the objective of investigating the property and structure–activity relationship of these new compounds and obtaining new biologically active compounds.

Results and discussion

We report here an expeditious, one-pot and efficient method for the preparation of a series of asymmetric semicarbazides. As shown in Scheme 1, 1-benzoyl-4-(3-coumarin) semicarbazides **(1a–h)** and 1-aryloxyacetyl-4-(coumarin-3-yl) semicarbazides **(2a–h)** were synthesised by the reactions of coumarin isocyanate with various aryl carboxylic acid hydrazides and aryloxyacetic acid hydrazides, respectively, under microwave irradiation. Coumarin-3-yl isocyanate was prepared by treating coumarin-3-carboxylic acid with sodium azide and ethyl chloroformate in the presence of triethylamine followed by a Curtius rearrangement.[13–14]

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 rates of the microwave irradiated reaction were at least 32 times quicker and also gave high yields. The results are reported in Table **1**.

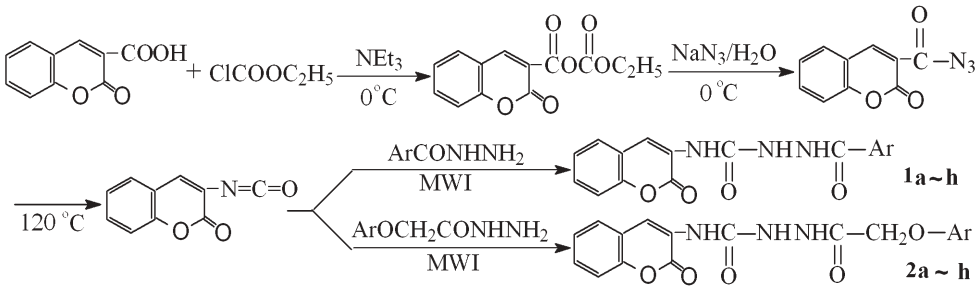
We selected the synthesis of compound **1b** as a model reaction to study the effects of irradiation power and time on the yields. The best yields obtained were 88% after 14 minutes of irradiation with 490 W and using toluene as the solvent. Greater power or longer irradiation time induces a decrease in yield (only 74% with 700 W or 76% after 16 minutes) due to the decomposition of coumarin-3-yl isocyanate.

In summary, the synthesis of asymmetric semicarbazides has been accomplished employing the Curtius rearrangement of 3-coumarinyl azide followed by nucleophile addition of hydrazines to the NCO moiety under microwave irradiation. Compared to conventional thermal heating, microwave irradiation decreased the reaction time from 8–14 h to 14–25 min. The main advantages of this method are short reaction times, high yields, less byproducts and simple handling of starting materials and products.

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 the 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 were uncorrected. Microwave irradiations were carried out in a Galanz domestic microwave oven in which a hole was made in the roof of the oven to permit a condenser to be fitted to the flask undergoing irradiation. Irradiation was carried out at 490 W typically for about 14–25 minutes. During periods of irradiation, precautions were taken by the experimentalists to avoid exposure.

Coumarin-3-carboxylic acid, aryl carboxylic acid hydrazides,[15] and aryloxyacetic acid hydrazides[16] were prepared according to literature procedures. Aryloxyacetic acids were commercially available and used as received.



Scheme 1

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Table 1 Yields, reaction times, melting points and elemental analyses of compounds **1a–h** and **2a–h**

Compd	Ar	Yield/%		Reaction time		M.p./°C
		MWI[a]	Reflux[b]	MWI/min[a]	Reflux/h[b]	
1a	C_6H_5	81	75	15	8	211–212
1b	4-$CH_3OC_6H_4$	88	81	14	8	>300
1c	3-$CH_3C_6H_4$	85	80	14	8	219–220
1d	4-$CH_3C_6H_4$	72	66	18	9	238–239
1e	3-$NO_2C_6H_4$	70	64	18	9	220–221
1f	4-$NO_2C_6H_4$	76	70	16	9	222–224
1g	2-ClC_6H_4	74	69	16	9	184–186
1h	4-ClC_6H_4	84	78	16	10	>300
2a	C_6H_5	83	80	20	10	215–216
2b	2-$CH_3C_6H_4$	82	79	20	11	230–231
2c	4-$CH_3C_6H_4$	81	78	20	12	221–223
2d	4-$CH_3OC_6H_4$	84	81	18	8	217–218
2e	4-$NO_2C_6H_4$	86	82	18	12	216–217
2f	2, 4-$Cl_2C_6H_4$	73	69	25	14	232–233
2g	1-Naphthyl	70	65	24	10	227–228
2h	2-Naphthyl	76	72	22	12	229–230

[a]Irradiated by microwave at 490 W; [b]heated at 120 °C.

Preparation of 3-coumarinyl azide

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 completed (monitored by TLC), the mixture was poured onto ice. Then the suspension was filtered and the product was obtained. Yield: 91.3 %, yellowish crystals; m.p. 85–86 °C. IR (KBr, ν/cm-1): 2167 (N≡N), 1753, 1680 (C=O), 1378 (N=N). ^{1}H NMR (400 MHz, DMSO-d6) δ = 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%.

Synthesis of compounds **1a–h** *and* **2a–h**; *general procedure*

The solution of 3-coumarinyl azide (0.5 mmol) in toluene (20 mL) was heated at 120 °C for 16 h to give coumarin-3-yl isocyanate, which was not isolated originally and treated *in situ* with various aryl carboxylic acid hydrazides and aryloxyacetic acid hydrazides, respectively, under microwave irradiation at 490 W for the time given in Table 1. After the completion of the reaction, monitored by TLC using ethyl acetate and petroleum ether (2:3) as the eluent, the solvent was removed under reduced pressure and from the residue the products **1a–h** and **2a–h** were isolated by recrystallisation from DMF-EtOH.

1-Benzoyl-4-(coumarin-3-yl) semicarbazide **(1a)**: IR (KBr, ν/cm^{-1}): 3323, 3084 (N–H), 1695, 1536 (C=O); ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.80 (s, 1H, NH), 9.04 (s, 1H, NH), 9.01 (s, 1H, NH), 8.81–7.26 (m, 10H, ArH and coumarin H). MS: *m/z* = 323. Anal. Calcd for $C_{17}H_{13}N_3O_4$: C, 63.16; H, 4.05; N, 13.00. Found: C, 63.22; H, 4.11; N, 13.15%.

1-(4-Methoxybenzoyl)-4-(coumarin-3-yl) semicarbazide **(1b)**: IR (KBr, ν/cm^{-1}): 3312, 3078 (N–H), 1690, 1530 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.78 (s, 1H, NH), 9.03 (s, 1H, NH), 8.98 (s, 1H, NH), 8.78–7.23 (m, 9H, ArH and coumarin H), 3.78 (s, 3H,CH_3O). MS: *m/z* = 353. Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.24; H, 4.23; N, 11.85%.

1-(3-Methylbenzoyl)-4-(coumarin-3-yl) semicarbazide **(1c)**: IR (KBr, ν/cm^{-1}): 3318, 3086 (N–H), 1694, 1532 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.76 (s, 1H, NH), 9.01 (s, 1H, NH), 8.96 (s, 1H, NH), 8.76–7.25 (m, 9H, ArH and coumarin H), 2.23 (s, 3H, CH_3). MS: *m/z* = 337. Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.12; H, 4.51; N, 12.52%.

1-(4-Methylbenzoyl)-4-(coumarin-3-yl) semicarbazide **(1d)**: IR (KBr, ν/cm^{-1}): 3324, 3081 (N–H), 1690, 1538 (C=O); ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.77 (s, 1H, NH), 9.02 (s, 1H, NH), 8.98 (s, 1H, NH), 8.78–7.27 (m, 9H, ArH and coumarin H), 2.22 (s, 3H, CH_3). MS: *m/z* = 337. Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46. Found: C, 64.13; H, 4.52; N, 12.51%.

1-(3-Nitrobenzoyl)-4-(coumarin-3-yl) semicarbazide **(1e)**: IR (KBr, ν/cm^{-1}): 3326, 3089 (N–H), 1698, 1535 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (s, 1H, NH), 9.06 (s, 1H, NH), 9.02 (s, 1H, NH), 8.81–7.31 (m, 9H, ArH and coumarin H). MS: *m/z* = 368. Anal. Calcd for $C_{17}H_{12}N_4O_6$: C, 55.44; H, 3.28; N, 15.21. Found: C, 55.41; H, 3.32; N, 15.26%.

1-(4-Nitrobenzoyl)-4-(coumarin-3-yl) semicarbazide **(1f)**: IR (KBr, ν/cm^{-1}): 3321, 3083 (N–H), 1690, 1540 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.85 (s, 1H, NH), 9.08 (s, 1H, NH), 9.03 (s, 1H, NH), 8.83–7.35 (m, 9H, ArH and coumarin H). MS: *m/z* = 368. Anal. Calcd for $C_{17}H_{12}N_4O_6$: C, 55.44; H, 3.28; N, 15.21. Found: C, 55.40; H, 3.31; N, 15.25%.

1-(2-Chlorobenzoyl)-4-(coumarin-3-yl) semicarbazide **(1g)**: IR (KBr, ν/cm^{-1}): 3318, 3088 (N–H), 1697, 1538 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.81 (s, 1H, NH), 9.06 (s, 1H, NH), 9.02 (s, 1H, NH), 8.79–7.25 (m, 9H, ArH and coumarin H). MS: *m/z* = 358. Anal. Calcd for $C_{17}H_{12}ClN_3O_4$: C, 57.07; H, 3.38; N, 11.75. Found: C, 57.12; H, 3.41; N, 11.79%.

1-(4-Chlorobenzoyl)-4-(coumarin-3-yl) semicarbazide **(1h)**: IR (KBr, ν/cm^{-1}): 3314, 3084 (N–H), 1694, 1533 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.82 (s, 1H, NH), 9.05 (s, 1H, NH), 9.01 (s, 1H, NH), 8.78–7.24 (m, 9H, ArH and coumarin H). MS: *m/z* = 358. Anal. Calcd for $C_{17}H_{12}ClN_3O_4$: C, 57.07; H, 3.38; N, 11.75. Found: C, 57.16; H, 3.45; N, 11.78%.

1-Phenyloxyacetyl-4-(coumarin-3-yl) semicarbazide **(2a)**: IR (KBr, ν/cm^{-1}): 3331, 3264 (N–H), 1698, 1553 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.13 (s, 1H, NH), 8.84 (s, 1H, NH), 8.78 (s, 1H, NH), 8.47–6.82 (m, 10H, ArH and coumarin H), 4.58 (s, 2H, CH_2O). MS: *m/z* = 353. Anal. Calcd for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.25; H, 4.24; N, 11.82%.

1-(2-Methylphenyloxyacetyl)-4-(coumarin-3-yl) semicarbazide (**2b**): IR (KBr, ν/cm^{-1}): 3329, 3268 (N–H), 1710, 1548 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.11 (s, 1H, NH), 8.82 (s, 1H, NH), 8.76 (s, 1H, NH), 8.49–6.84 (m, 9H, ArH and coumarin H), 4.56 (s, 2H, CH_2O), 2.22 (s, 3H, CH_3). MS: *m/z* = 367. Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.18; H, 4.71; N, 11.49%.

1-(4-Methylphenyloxyacetyl)-4-(coumarin-3-yl) semicarbazide (**2c**): IR (KBr, ν/cm^{-1}): 3324, 3279 (N–H), 1715, 1545 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.13 (s, 1H, NH), 8.84 (s, 1H, NH), 8.79 (s, 1H, NH), 8.51–6.88 (m, 9H, ArH and coumarin H), 4.58 (s, 2H, CH_2O), 2.24 (s, 3H, CH_3). MS: *m/z* = 367. Anal. Calcd for $C_{19}H_{17}N_3O_5$: C, 62.12; H, 4.66; N, 11.44. Found: C, 62.17; H, 4.70; N, 11.50%.

1-(4-Methoxyphenyloxyacetyl)-4-(coumarin-3-yl) semicarbazide (**2d**): IR (KBr, ν/cm^{-1}): 3321, 3274 (N–H), 1710, 1550 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.15 (s, 1H, NH), 8.86 (s, 1H, NH), 8.77 (s, 1H, NH), 8.53–6.86 (m, 9H, ArH and coumarin H), 4.54 (s, 2H, CH_2O), 3.75 (s, 3H, CH_3O). MS: *m/z* = 383. Anal. Calcd for $C_{19}H_{17}N_3O_6$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.57; H, 4.50; N, 10.99%.

1-(4-Nitrophenyloxyacetyl)-4-(coumarin-3-yl) semicarbazide **(2e)**: IR (KBr, ν/cm^{-1}): 3329, 3270 (N–H), 1705, 1552 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.21 (s, 1H, NH), 8.92 (s, 1H, NH), 8.82 (s, 1H, NH), 8.61–6.98 (m, 9H, ArH and coumarin H), 4.65 (s, 2H, CH_2O). MS: *m/z* = 398. Anal. Calcd for $C_{18}H_{14}N_4O_7$: C, 54.28; H, 3.54; N, 14.07. Found: C, 54.33; H, 3.58; N, 14.13%.

1-(2, 4-Dichlorophenyloxyacetyl)-4-(coumarin-3-yl) semicarbazide **(2f)**: IR (KBr, ν/cm^{-1}): 3323, 3278 (N–H), 1718, 1545 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.16 (s, 1H, NH), 8.89 (s, 1H, NH), 8.78 (s, 1H, NH), 8.56–6.91 (m, 8H, ArH and coumarin H), 4.58 (s, 2H, CH_2O). MS: *m/z* = 422. Anal. Calcd for $C_{18}H_{13}O_5N_3Cl_2$: C, 51.20; H, 3.10; N, 9.95. Found: C, 51.47; H, 3.34; N, 9.82%.

1-(1-Naphthyloxyacetyl)-4-(coumarin-3-yl) semicarbazide **(2g)**: IR (KBr, ν/cm^{-1}): 3320, 3270 (N–H), 1716, 1550 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.15 (s, 1H, NH), 8.85 (s, 1H, NH), 8.75 (s, 1H, NH), 8.54–6.84 (m, 12H, ArH and coumarin H), 4.59 (s, 2H, CH_2O). MS: *m/z* = 403. Anal. Calcd for $C_{22}H_{17}O_5N_3$: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.63; H, 4.38; N, 10.53%.

1-(2-Naphthyloxyacetyl)-4-(coumarin-3-yl) semicarbazide **(2h)**: IR (KBr, ν/cm^{-1}): 3328, 3273 (N–H), 1709, 1554 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.16 (s, 1H, NH), 8.88 (s, 1H, NH), 8.78 (s, 1H, NH), 8.56–6.83 (m, 12H, ArH and coumarin H), 4.57 (s, 2H, CH_2O). MS: *m/z* = 403. Anal. Calcd for $C_{22}H_{17}O_5N_3$: C, 65.50; H, 4.25; N, 10.42. Found: C, 65.76; H, 4.51; N, 10.63%.

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