Synthesis of 3-(1,3-Diaryl-4,6-dioxo-2-thioxoperhydropyrimidin-5-yl)-2*H*-[1,4]benzothiazines†

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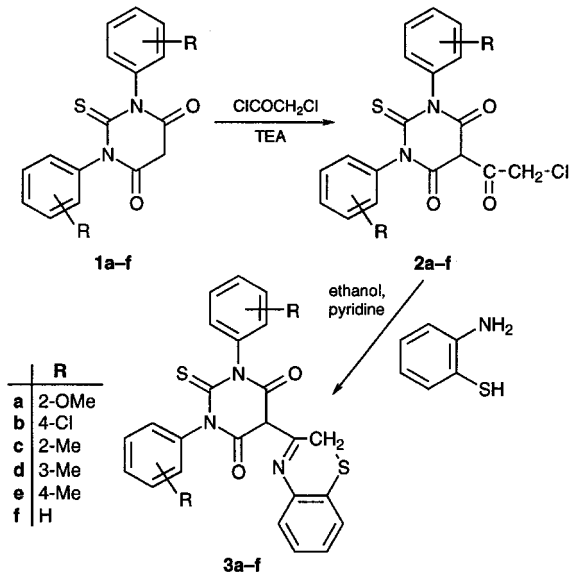
Condensation of 1,3-diaryl-5-chloroacetyl-4,6-dioxo-2-thioxoperhydropyrimidines (**2a–f**) with 2-aminobenzenethiol in ethanol in the presence of pyridine gives the title compounds (**3a–f**), under both microwave irradiation and classical conditions; reactions are *ca*. 180 times faster using the microwave rather than the classical method.

Highly accelerated rates of chemical reactions observed under microwave irradiation are receiving considerable attention from synthetic chemists. Recently chemists have adopted domestic microwave ovens as useful laboratory instruments for carrying out reactions in a non-classical way. Microwave-irradiated reactions have been carried out in the solid phase and in sealed or open vessels.[1]

Benzothiazines and their pyrimidine analogues have found a number of uses such as model compounds for mechanistic studies of the action of neuroleptic drugs related to chloropromazine[2] and as muscle relaxants.[3] They are cytotoxic to human epidermoid carcinoma KB cells and human non-small cell lung carcinoma A 549[4] and show antimicrobial and antimycotic activity.[5] They are used as antibacterial[5,6] anti-inflammatory agents.[7]

The increasing importance of MORE (Microwave-induced Organic Reaction Enhancement) chemistry in laboratory and industrial syntheses and the biological importance of benzothiazines form the backdrop for our interest in newer methods of organic synthesis under mild conditions. The synthesis of 3-(1,3-diaryl-4,6-dioxo-2-thioxoperhydropyrimidin-5-yl)-2*H*-[1,4]benzothiazines (**3a–f**), starting from 1,3-diaryl-5-chloroacetyl-4,6-dioxo-2-thioxoperhydropyrimidines (**2a–f**), is now reported.



Scheme 1

The chloroacetyl compounds **2a–f** were prepared by condensation of chloroacetyl chloride and 1,3-diaryl-4,6-dioxo-2-thioxoperhydropyrimidines (**1a–f**) in the presence of triethylamine.[8] The reaction pathway is shown in Scheme 1.

Reaction of **2a–f** with 2-aminobenzenethiol in absolute ethanol in the presence of pyridine, under both microwave irradiation and classical conditions, gave the benzothiazines **3a–f** whose IR spectra showed absorption bands at *ca*. 1600 (C=N), 1630 and 1670 cm^{-1} (amide C=O). Their ^1H NMR spectra each showed, besides other usual signals, a singlet at δ 4.6–4.7 integrating for two protons (CH_2), while the mass spectra each showed an $M^+ - 1$ peak. Elemental analysis supported the assigned structures.

Experimental

Mps are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer and ^1H NMR spectra on a Perkin Elmer R-32 (90 MHz) spectrometer using TMS as an internal standard. Mass spectra were recorded on a Jeol JMS-D 300 instrument. A Brownie microwave oven (2450 MHz), high power level, was used in all the reactions.

Compounds **1a–f**[9,10] and **2a–f**[8] were prepared by reported procedure. The physical and spectral data for all the new compounds synthesized are given in Tables 1 and 2. Light petroleum used was the fraction of bp range 60–80 °C.

3-(1,3-*Diaryl*-4,6-*dioxo*-2-*thioxoperhydropyrimidin*-5-*yl*)-2H-[1,4]*benzothiazines* (**3**): *General Procedure*.— *Method A.* A solution of **2a** (0.43 g, 0.001 mol) and 2-aminobenzenethiol (0.12 g, 0.001 mol) in absolute ethanol and in the presence of pyridine was refluxed on a steam bath for 3 h. The reaction mixture was concentrated to half its volume and cooled. The separated solid was filtered off, washed with ethanol and purified by column chromatography on a silica gel column [ethyl acetate–light petroleum (1:15 v/v) as eluent] to give 3-[1,3-*bis*-(2-*methoxyphenyl*)-4,6-*dioxo*-2-*thioxoperhydropyrimidin*-5-*yl*)-2H-[1,4]*benzothiazine* (**3a**) (0.33 g, 65%), mp 140–141 °C. Compounds **3b–f** were prepared similarly.

Table 1 Physical data from compounds **3a–f**

Compound no.	Microwave method		Classical method		
	Yield (%)	Reaction time (*t*/min)	Yield (%)	Reaction time (*t*/min)	Mp (*T*/°C)
3a	74	1	65	180	140–141
3b	77	2	67	210	230–231
3c	75	1	67	210	160–161
3d	73	1	64	180	155–156
3e	75	1	63	180	158–159
3f	76	1	68	180	210–211

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Method B. An equimolar mixture of **2a** and 2-aminobenzenethiol in absolute ethanol and in the presence of pyridine was irradiated with microwaves for 1–2 min. The reaction mixture was cooled and the separated product was filtered off, washed and purified by

Table 2 Analytical and spectral data for compounds **3a–f**

Compound no.	Molecular formula (mol. wt.)	Found (required) (%) C	H	N	Molecular ion peak observed (M^+-1)	ν_{max}/cm^{-1} (Nujol)	δ_H ($CDCl_3$/TFA)
3a	$C_{26}H_{21}N_3O_4S_2$ (503)	62.22 (62.03	4.34 4.17	8.20 8.35)	502	1600 (C=N), 1630, 1670 (C=O)	3.8 (s, 6 H, 2 × OCH_3), 4.7 (s, 2 H, CH_2), 6.9–7.6 (m, 13 H, 12 × Ar-H and 1 × C-H)
3b	$C_{24}H_{15}Cl_2N_3O_2S_2$ (511.5)	56.11 (56.25	2.82 2.93	8.09 8.20)	511	1610 (C=N), 1625, 1665 (C=O)	4.7 (s, 2 H, CH_2), 7.2–7.7 (m, 13 H, 12 × Ar-H and 1 × C-H)
3c	$C_{26}H_{21}N_3O_2S_2$ (471)	66.15 (66.24	4.84 4.46	8.81 8.92)	470	1600 (C=N), 1630, 1675 (C=O)	2.2 (s, 6 H, 2 × CH_3), 4.6 (s, 2 H, CH_2), 7.1–7.6 (m, 13 H, 12 × Ar-H and 1 × C-H)
3d	$C_{26}H_{21}N_3O_2S_2$ (471)	66.04 (66.24	4.78 4.46	8.71 8.92)	470	1610 (C=N), 1640, 1670 (C=O)	2.3 (s, 6 H, 2 × CH_3), 4.6 (s, 2 H, CH_2), 6.9–7.5 (m, 13 H, 12 × Ar-H and 1 × C-H)
3e	$C_{26}H_{21}N_3O_2S_2$ (471)	66.01 (66.24	4.73 4.46	8.87 8.92)	470	1605 (C=N), 1635, 1660 (C=O)	2.3 (s, 6 H, 2 × CH_3), 4.6 (s, 2 H, CH_2), 6.9–7.6 (m, 13 H, 12 × Ar-H and 1 × C-H)
3f	$C_{24}H_{17}N_3O_2S_2$ (443)	65.32 (65.01	4.09 3.84	9.82 9.48)	442	1600 (C=N), 1630, 1670 (C=O)	4.6 (s, 2 H, CH_2), 7.0–7.7 (m, 15 H, 14 × Ar-H and 1 × C-H)

column chromatography on a silica gel column [ethyl acetate–light petroleum (1:15 v/v) as eluent] to yield **3a**. Compounds **3b–f** were prepared similarly.

For physical and spectral data see Tables 1 and 2.

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