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Microwave activated solvent-free cascade reactions yielding highly functionalised 1,3-thiazines

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Abstract—One-pot cascade reactions of *N*-acylglycines, acetic anhydride, anhydrous sodium acetate, aromatic aldehydes, and ammonium *N*-aryldithiocarbamates expeditiously and diastereoselectively yield 5-acylamino-3,6-diarylperhydro-2-thioxo-1,3-thiazin-4-ones (**5a–j**) in solvent-free conditions under microwave irradiation.

Multi-step syntheses produce considerable amounts of waste mainly due to a series of complex isolation procedures often involving environmentally unfavourable solvents after each step. Thus, the combination of steps into a multi-step, one-pot reaction sequence under solvent-free conditions can be economically and environmentally very advantageous as long as the overall yield and efficiency are not adversely affected.

The 1,3-thiazine nucleus is the active core of cephalosporins which are among the widely used β-lactam antibiotics. Owing to their chemical and biological interest, syntheses of various 1,3-thiazine derivatives have been reported in the literature but all of these processes use plenty of organic solvents,[1–8] and in certain cases the yield does not exceed 30%.[1,2]

The application of microwave (MW) irradiation as a non-conventional energy source for activation of reactions, in general and under solvent-free conditions in particular, has now gained popularity over the usual homogeneous and heterogeneous reactions, as it leads to enhanced reaction rates, higher yields of pure products, easier work-up and, sometimes, to selective conversions.[9–13]

Considering the above reports and our interest in devising solvent-free procedures,[14–16] we report herein a one-pot highly diastereoselective synthesis of 1,3-thiazines **5** using microwaves in solvent-free conditions (Scheme 1). The results are especially promising in view of the one-pot approach to 1,3-thiazines involving the generation of azalactones **2** in situ and induction of the subsequent reactions in the same pot (Scheme 1). Furthermore, this reaction is one of the few examples showing increased stereoselectivity under microwave irradiation compared to conventional heating,[13,17] and is the first report on the application of MW methodology to the synthesis of 1,3-thiazines.

The present method in its entirety involves intermittent irradiation of an intimate mixture of *N*-acylglycine **1**, acetic anhydride, anhydrous sodium acetate, an aromatic aldehyde and ammonium *N*-aryldithiocarbamate **3** for 2 min in an unmodified domestic microwave oven at 480 W followed by thorough mixing for 2 min outside the oven to ensure minimum loss of acetic anhydride by evaporation. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (Table 1) to afford the highly functionalised 1,3-thiazines **5** (Table 1).

For comparison purposes, the final temperature was measured by immersing a glass thermometer into the reaction mixture immediately after MW irradiation and was found to be <80°C. The reactions were carried out using a thermostated oil bath under the same conditions of time (8–12 min,Table 1) and temperature (80°C) as for the MW activated method. It was found that significantly lower yields (26–39%) were obtained using oil-bath heating rather than the MW activated method (Table 1). Specific MW effects might be originating from the formation of more polar transition states in these cascade reactions (Scheme 1), which are

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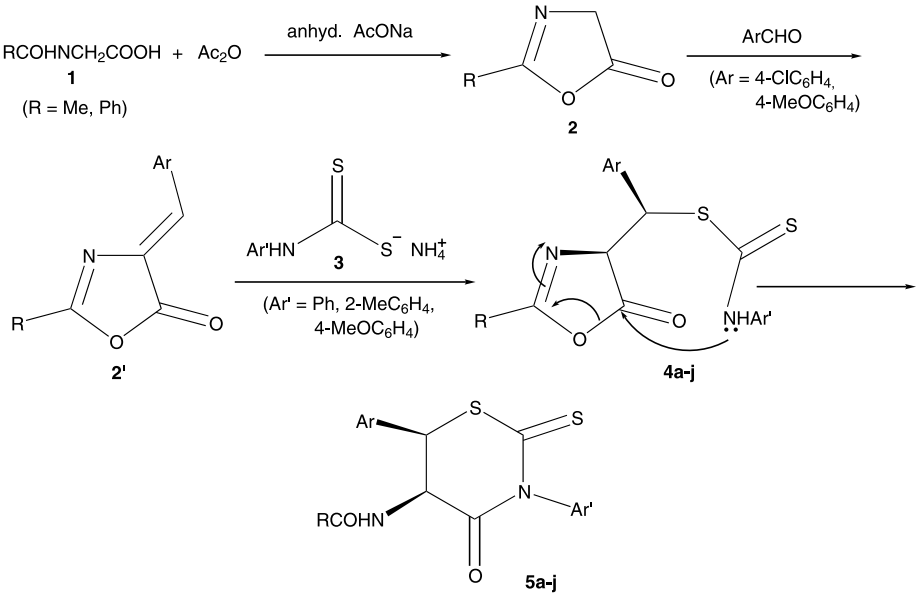

4, 5	R	Ar	Ar'	4, 5	R	Ar	Ar'
a	Ph	4-ClC$_6$H$_4$	Ph	**f**	Me	4-ClC$_6$H$_4$	4-MeOC$_6$H$_4$
b	Ph	4-ClC$_6$H$_4$	2-MeC$_6$H$_4$	**g**	Ph	4-MeOC$_6$H$_4$	Ph
c	Ph	4-ClC$_6$H$_4$	4-MeOC$_6$H$_4$	**h**	Ph	4-MeOC$_6$H$_4$	2-MeC$_6$H$_4$
d	Me	4-ClC$_6$H$_4$	Ph	**i**	Me	4-MeOC$_6$H$_4$	Ph
e	Me	4-ClC$_6$H$_4$	2-MeC$_6$H$_4$	**j**	Me	4-MeOC$_6$H$_4$	2-MeC$_6$H$_4$

Scheme 1.

stabilised by dipole–dipole interaction with the electric field of the microwaves compared to the less polar ground states, consequently the activation energy is reduced and the reaction rate is enhanced.[9,13]

The formation of 1,3-thiazines **5** is best explained by Michael type addition of ammonium *N*-aryldithiocarbamates **3** to azalactones **2′** generated in situ, to afford the corresponding Michael adducts **4** which undergo ring transformation to yield the final products **5** (Scheme 1). This conclusion is based on the observation that the representative intermediate compounds **4a**, **4d** and **4g** could be isolated in 38–47% yields, and that these could be converted into the corresponding 1,3-thiazines **5a**, **5d** and **5g** in quantitative yield.

The formation of Michael adducts **4** and their ring transformation to **5** were highly diastereoselective in favour of the *cis* (*syn*) isomers. The diastereomeric ratios of the crude products were checked by ^{1}H NMR, prior to purification, to ensure accurate and true diastereomeric ratios are reported. The diastereomeric ratios in the case of MW activation was found to be >97:<3 and those from the oil-bath heating were >59:<41 as determined by ^{1}H NMR spectroscopy. The high diastereoselectivity (>97%) in favour of *cis* (*syn*) isomers under MW irradiation may be explained if the transition state leading to the formation of the *cis* (*syn*) isomers is more polar than that leading to the *trans* (*anti*) isomers because MW radiation favours reactions occurring via more polar transition states.[9,13]

In conclusion, we have developed an approach for diastereoselective synthesis of highly functionalised 1,3-thiazines via a multi-step one-pot reaction sequence starting from readily available substrates (*N*-acylglycines and ammonium *N*-aryldithiocarbamates) employing microwave irradiation.

5-Acylamino-3,6-diarylperhydro-2-thioxo-1,3-thiazin-4-ones 5. General procedure

Thoroughly mixed *N*-acylglycine **1** (10.0 mmol), an aromatic aldehyde (10.0 mmol), anhydrous sodium acetate 0.82 g (10.0 mmol), acetic anhydride 3 mL (32 mmol) and ammonium *N*-aryldithiocarbamate **3** (10.0 mmol) were taken in a 100 mL conical flask and subjected to MW irradiation at 480 W for 2 min. The reaction mixture was then thoroughly mixed outside the microwave oven for 2 min and again irradiated for another 2 min. This intermittent-mixing cycle was repeated for the total irradiation time (Table 1). After completion of the reaction as indicated by TLC (hexane:AcOEt, 8:2, v/v), water (40 mL) was added to the reaction mixture and stirred well. The yellowish precipitate thus obtained was washed with water to give the crude product which was recrystallised from ethanol to afford a diastereomeric mixture (>97:<3; in the crude products the ratio was >95:<5 as determined by ^{1}H NMR spectroscopy). The product on second recrystallisation from ethanol furnished an analytical sample of a single diastereomer **5** (Table 1). On the basis of ^{1}H NMR spectra and literature precedent,[18–23] the *cis*

Table 1. Microwave activated one-pot synthesis of 1,3-thiazines **5a–j**

Product	Time[a] (min)	Yield[b] (%)	Mp (°C)	Molecular formula (wt)[c,d]	^{1}H NMR (DMSO-d_6/TMS) δ, J (Hz)	Ms m/z (M+)
5a	10 (10)	86 (36)	196–198	$C_{23}H_{17}ClN_2O_2S_2$ (452.98)	6.64 (d, 1H, $J=5$, 6-H), 6.76 (dd, 1H, $J=5$, 8, 5-H), 7.13–8.00 (m, 14H$_{arom.}$), 8.62 (br s, 1H, NH, exchanges with D_2O)	452
5b	8 (8)	92 (31)	201–203	$C_{24}H_{19}ClN_2O_2S_2$ (467.00)	2.25 (s, 3H, Me), 6.63 (d, 1H, $J=5$, 6-H), 6.75 (dd, 1H, $J=5$, 8, 5-H), 7.11–7.97 (m, 13H$_{arom.}$), 8.60 (br s, 1H, NH, exchanges with D_2O)	466
5c	8 (8)	89 (26)	208–210	$C_{24}H_{19}ClN_2O_3S_2$ (483.00)	3.73 (s, 3H, OMe), 6.25 (d, 1H, $J=5$, 6-H), 6.77 (dd, 1H, $J=5$, 8, 5-H), 7.13–7.99 (m, 13H$_{arom.}$), 8.62 (br s, 1H, NH, exchanges with D_2O)	482
5d	12 (12)	80 (39)	152–153	$C_{18}H_{15}ClN_2O_2S_2$ (390.91)	2.12 (s, 3H, Me), 6.63 (d, 1H, $J=5$, 6-H), 6.73 (dd, 1H, $J=5$, 8, 5-H), 7.11–7.98 (m, 9H$_{arom.}$), 8.60 (br s, 1H, NH, exchanges with D_2O)	390
5e	10 (10)	85 (34)	159–160	$C_{19}H_{17}ClN_2O_2S_2$ (404.94)	2.10 (s, 3H, MeCO), 2.26 (s, 3H, MeAr′), 6.62 (d, 1H, $J=5$, 6-H), 6.72 (dd, 1H, $J=5$, 8, 5-H), 7.12–7.96 (m, 8H$_{arom.}$) 8.61 (br s, 1H, NH exchanges with D_2O)	404
5f	10 (10)	82 (30)	169–171	$C_{19}H_{17}ClN_2O_3S_2$ (420.93)	2.11 (s, 3H, MeCO), 3.71 (s, 3H, MeO), 6.63 (d, 1H, $J=5$, 6-H), 7.73 (dd, 1H, $J=5$, 8, 5-H), 7.12–7.97 (m, 8H$_{arom.}$), 8.61 (br s, 1H, NH exchanges with D_2O)	420
5g	12 (12)	84 (39)	190–192	$C_{24}H_{20}N_2O_3S_2$ (448.56)	3.74 (s, 3H, OMe), 6.62 (d, 1H, $J=5$, 6-H), 6.74 (dd, 1H, $J=5$, 8, 5-H), 7.11–7.96 (m, 14H$_{arom.}$), 8.61 (br s, 1H, NH exchanges with D_2O)	448
5h	10 (10)	87 (33)	195–197	$C_{25}H_{22}N_2O_3S_2$ (462.59)	2.23 (s, 3H, MeAr′) 3.72 (s, 3H, MeO), 6.60 (d, 1H, $J=5$, 6-H), 6.73 (dd, 1H, $J=5$, 8, 5-H), 7.13–7.96 (m, 13H$_{arom.}$), 8.60 (br s, 1H, NH exchanges with D_2O)	462
5i	12 (12)	76 (32)	145–146	$C_{19}H_{18}N_2O_3S_2$ (386.49)	2.12 (s, 3H, MeCO) 3.72 (s, 3H, MeO), 6.62 (d, 1H, $J=5$, 6-H), 6.72 (dd, 1H, $J=5$, 8, 5-H), 7.13–7.97 (m, 9H$_{arom.}$), 8.62 (br s, 1H, NH exchanges with D_2O)	386
5j	10 (10)	81 (28)	152–153	$C_{20}H_{20}N_2O_3S_2$ (400.52)	2.21 (s, 3H, MeAr′), 2.12 (s, 3H, MeCO), 3.71 (s, 3H, MeO), 6.61 (d, 1H, $J=5$, 6-H), 6.72 (dd, 1H, $J=5$, 8, 5-H), 7.12–7.97 (m, 8H$_{arom.}$), 8.60 (br s, 1H, NH exchanges with D_2O)	400

[a] Microwave irradiation time (power = 480 W). Parentheses show the time for oil-bath heating at 80°C.
[b] Yield of isolated and purified product. Parentheses show yield obtained using oil-bath heating.
[c] All compounds gave C, H and N analyses within ±0.32%, and compared favourably with samples obtained by an alternative method.
[d] All compounds exhibited IR bands due to νC=O in the regions 1645–1655 and 1685–1690 cm^{-1}.

stereochemistry was assigned to **5**, as the coupling constant ($J_{5,6}=5$ Hz) for **5** was lower than that for the very minor (<3%) diastereomer (*trans*), $J_{5,6}=10$ Hz.

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