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Solvent-free microwave activated three-component synthesis of thiazolo-*s*-triazine *C*-nucleosides

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Abstract—Novel three-component one-pot reactions of thiazole Schiff's bases, ammonium acetate and an aldose, under solvent-free microwave irradiation, expeditiously and diastereoselectively yield acyclic *C*-nucleosides incorporating the thiazolo-*s*-triazine structure as a nucleobase.
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In general, multi-component reactions (MCRs) are economically and environmentally very advantageous because multi-step syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. MCRs are perfectly suited for combinatorial library syntheses, thus are finding increasing use in the discovery process for new drugs and agrochemicals.[1–7]

Prompted by the above reports and the recently reported results of the MW accelerated version of the Ugi three-component coupling (3cc) reactions[8–10] as well as by our interest in devising new solvent-free cyclisation methods,[11–13] we decided to investigate the potential of microwaves to accelerate the present 3cc reaction between thiazole Schiff's bases, ammonium acetate and an aldose yielding new acyclic *C*-nucleosides **5** (Scheme 1). Interestingly, this reaction is one of the few examples showing increased stereoselectivity under MW irradiation compared to conventional heating,[14,15] and is the first report on the application of MW methodology to the synthesis of *C*-nucleosides. These nucleosides were required in connection with an ongoing research project on the search for antiviral agents. Owing to their biological versatility, a combination of thiazole and *s*-triazine units was incorporated as the nucleobase.

After some preliminary experimentation, it was found that the envisaged three-component synthesis (Scheme 1) was successful with an intimate mixture of the thiazole Schiff's bases **1**, ammonium acetate and an aldose under intermittent MW irradiation[†] at 480 W for the time specified in Table 1. Isolation and purification by recrystallisation from ethanol afforded the *C*-nucleosides **5** in excellent yields (76–88%) with >96% diastereoselectivity (Table 1).[16]

For comparison purposes, the final temperature was measured by immersing a glass thermometer immediately after the MW irradiation and found to be <95°C. The reactions were carried out using a thermostated oil bath under the same conditions of time (9–15 min, Table 1) and temperature (95°C) as for the MW activated method. It was found that significantly lower yields (19–31%) were obtained using oil-bath heating rather than the MW activated method. This observation may be rationalised on the basis of the formation of a dipolar activated complex from an uncharged educt in these reactions (as an example, Scheme 1 shows an activated complex **2**), and the greater stabilisation of the more dipolar activated complex by dipole–dipole interactions with the electric field of microwaves as compared to the less dipolar educt, which may reduce the activation energy ($G^{\neq}$) resulting in the rate enhancement.[14]

Keywords: solvent-free; multi-component reactions; microwaves; stereoselective synthesis; thiazolo-*s*-triazines; *C*-nucleosides.
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[†] An unmodified domestic microwave oven (Kenstar, Model MWO 9808, operating at 2450 MHz) was used at an output of 480 W for all the experiments.

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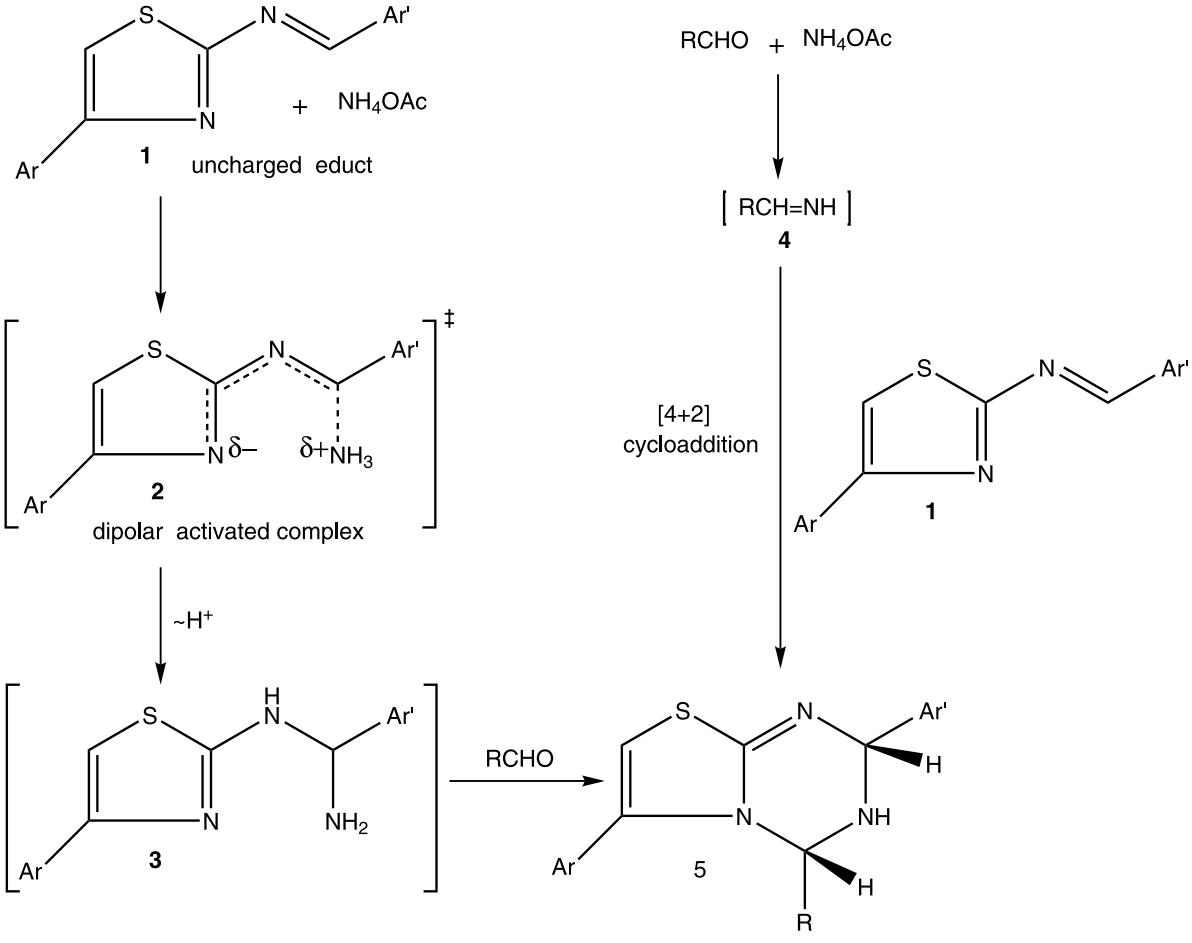
The formation of **5** may tentatively be rationalised by the conjugate addition of ammonia to the Schiff's base **1** followed by condensation of the adducts **3** with aldoses to yield the final products **5** (Scheme 1). However, the possibility of in situ generation of aldimines **4** followed by a [4+2] cycloaddition to the Schiff's bases **1** leading to the formation of **5** (Scheme 1) could not be ruled out.

The formation of **5** was highly diastereoselective in favour of the *cis* isomers. The diastereomeric ratios of the crude products were checked by ^{1}H NMR prior to purification, to ensure that accurate and true diastereomeric ratios are reported. The diastereomeric ratios in the cases of MW activation were found to be >96:<4 and those from oil-bath heating were >56:<44 as determined by ^{1}H NMR spectroscopy. In order to probe whether the kinetic product (ratio) is being formed in the thermal reaction and MW goes to the thermodynamic product, the product mixtures obtained from oil-bath heating were subjected to intermittent MW irradiation under the same conditions of time (9–15 min, Table 1) and temperature (~95°C) as for the synthesis of the respective compound **5** by the MW activated method. It was found that the diastereomeric ratios (>56:<44) remained unaffected indicating that there is a specific MW effect. The high diastereoselectivity (>96%) in favour of the *cis* isomers under MW



5	Ar	Ar'	R	5	Ar	Ar'	R
a	Ph	Ph	D-arabinobutyl	**g**	4-MeC$_6$H$_4$	Ph	D-arabinobutyl
b	Ph	4-MeOC$_6$H$_4$	D-arabinobutyl	**h**	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	D-arabinobutyl
c	Ph	Ph	D-ribobutyl	**i**	4-MeC$_6$H$_4$	Ph	D-ribobutyl
d	Ph	4-MeOC$_6$H$_4$	D-ribobutyl	**j**	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	D-ribobutyl
e	Ph	Ph	D-glucopentyl	**k**	4-MeC$_6$H$_4$	Ph	D-glucopentyl
f	Ph	4-MeOC$_6$H$_4$	D-glucopentyl	**l**	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	D-glucopentyl

Scheme 1.

Table 1. Solvent-free three-component synthesis of thiazolo-*s*-triazine *C*-nucleosides **5**

Product	Time (min)[a]		Yield (%)[b]		*cis*:*trans* ratio[c]		Mp (°C)[d]
	MW	Thermal	MW	Thermal	MW	Thermal	
5a	9	9	88	29	99:1	59:41	135–136
5b	12	12	83	24	97:3	57:43	148–150
5c	9	9	86	31	98:2	60:40	130–131
5d	12	12	80	26	97:3	58:42	138–139
5e	12	12	84	27	98:2	59:41	145–146
5f	15	15	79	23	97:3	58:42	159–161
5g	12	12	83	21	98:2	57:43	155–157
5h	15	15	80	19	97:3	57:43	163–165
5i	12	12	81	22	98:2	58:42	149–150
5j	15	15	78	20	97:3	57:43	154–155
5k	15	15	79	24	98:2	58:42	161–163
5l	15	15	76	21	97:3	57:43	169–171

[a] Microwave irradiation time (power = 480 W).
[b] Yield of isolated and purified product.
[c] As determined by ^{1}H NMR spectroscopy.
[d] All compounds gave C, H and N analyses within ±0.30%.

irradiation may be explained if the activated complex leading to the formation of the *cis* isomers is more polar than that leading to the *trans* isomers because MW irradiation favours reactions occurring via more polar activated complexes.[14]

In conclusion, we have developed a general, straightforward and highly diastereoselective three-component synthesis of thiazolo-*s*-triazine *C*-nucleosides from readily and widely available substrates (thiazole Schiff's bases and aldoses) employing solvent-free microwave irradiation, which should prove useful for the library synthesis of such nucleosides.

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16. Thiazolo[3,2-*a*]-s-triazine *C*-nucleosides **5**. *General procedure*: An intimate mixture of thiazole Schiff's base **1** (10.0 mmol), ammonium acetate (15.0 mmol) and an aldose (10.0 mmol) was taken in a 100 mL conical flask and subjected to MW irradiation at 480 W for 3 min. The reaction mixture was then thoroughly mixed outside the MW oven for 3 min and again irradiated for another 3 min. This intermittent irradiation-mixing cycle was repeated for the total irradiation time (9 min). After completion of the reaction as indicated by TLC (hexane:AcOEt, 8:2, v/v), water 50 mL was added to the reaction mixture and stirred well. The yellow precipitate thus obtained was washed with water to give the crude product which was recrystallised from ethanol to afford a diastereomeric mixture (>96:<4; in the crude products the ratio was >95:<5 as determined by ^{1}H NMR spectroscopy). The product on second recrystallisation from ethanol furnished analytically pure pale yellow needles of a single diastereomer **5** (Table 1), which was assigned the *cis* stereochemistry on the basis of ^{1}H NMR spectra. The spectral data of representative compounds: **5a**. IR ν_{max} N-H, O-H: 3342, 3328 cm^{-1}. ^{1}H NMR: δ 3.12 (br s, 1H, NH, exchanges with D_2O), 3.48–3.57 (m, 2H, 1′-, 3′-H), 3.69–3.78 (m, 2H, 4′-H), 3.87 (m, 1H, 2′-H), 5.61 (br s, 4H, 4×OH), 6.62 (dd, 1H, J = 5, 8 Hz, 4-H), 6.78 (d, 1H, J = 8 Hz, 2-H), 7.62–7.86 (m, 11H arom). ^{13}C NMR: δ 61.7, 66.1, 66.4, 66.6 (D-arabinobutyl), 68.2 (4-C), 76.4 (2-C), 118.4 (7-C), 127.1, 127.8, 128.8, 129.7, 131.2, 132.1, 132.8, 133.6 (2×Ph), 150.0 (6-C), 159.6 (SC=N). EIMS (m/z): 413 (M^+). **5f**. IR ν_{max} N-H, O-H: 3344, 3328 cm^{-1}. ^{1}H NMR: δ 2.44–3.02 (m, 2H, 5′-H), 3.12 (br s, 1H, NH, exchanges with D_2O), 3.72 (s, 3H, OMe), 3.77–3.88 (m, 1H, 1′-H), 4.05–4.16 (m, 3H, 2′-, 3′-, 4′-H), 5.67 (br s, 5H, 5×OH), 6.67 (dd, 1H, J = 5, 8 Hz, 4-H), 6.82 (d, 1H, J = 8

Hz, 2-H), 7.18–7.93 (m, 10H arom). ^{13}C NMR: δ 21.3 (OMe), 61.4, 65.3, 65.9, 66.6, 66.9 (D-glucopentyl), 68.2 (4-C), 76.5 (2-C), 118.5 (7-C), 127.1, 127.5, 128.8, 129.6, 131.2, 132.6, 133.6, 134.8 (Ph, 4-MeOC_6H_4), 150.1 (6-C), 159.3 (SC=N). EIMS (m/z): 437 (M^+). **5j**. IR ν_{max} N-H, O-H: 3348, 3335 cm^{-1}. ^{1}H NMR: δ 2.26 (s, 3H, Me), 3.14 (br s, 1H, NH, exchanges with D_2O), 3.73 (s, 3H, OMe), 3.45–3.56 (m, 2H, 1′-, 3′-H), 3.63–3.77 (m, 2H, 4′-H), 3.84 (m, 1H, 2′-H), 5.60 (br s, 4H, 4×OH), 6.61 (dd, 1H, $J=5$, 8 Hz, 4-H), 6.73 (d, 1H, $J=8$ Hz, 2-H), 7.15–7.94 (m, 9H_{arom}). ^{13}C NMR: δ 20.1 (Me), 21.5 (OMe), 61.5, 66.0, 66.6, 66.9 (D-ribobutyl), 68.2 (4-C), 76.3 (2-C), 118.3 (7-C), 127.0, 128.2, 129.6, 131.1, 132.2, 133.5, 134.4 (4-MeC_6H_4, 4-MeOC_6H_4), 150.1 (6-C), 159.3 (SC=N). EIMS (m/z): 457 (M^+).