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Novel clay-catalysed cyclisation of salicylaldehyde semicarbazones to 2*H*-benz[*e*]-1,3-oxazin-2-ones under microwave irradiation

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Abstract—A microwave-expediated, high yielding, synthesis of 2*H*-benz[*e*]-1,3-oxazin-2-ones (**2a–j**) involving cyclodehydrazination of salicylaldehyde semicarbazones (**1a–j**) on montmorillonite K 10 clay in solvent-free conditions is reported. © 2002 Published by Elsevier Science Ltd.

Efavirenz (sustiva), a benzoxazinone derivative, is presently in clinical use for the treatment of AIDS. Recently, various benzoxazinones have been synthesised and evaluated with a view to achieving antiviral agents of choice.[1–3] Most of the methods available for the construction of the benzoxazinone nucleus often suffer from one or more drawbacks such as the long reaction time required to obtain a good yield of the desired product or the use of expensive and hazardous reagents and solvents.[1–6] Salicylaldehyde has been used as a bifunctional building block for the synthesis of various oxygen heterocycles of chemical and biological interest.[7–11]

Clay-catalysed organic transformations have generated considerable interest because of their inexpensive nature and special catalytic attributes under heterogeneous reaction conditions.[12–14] The use of microwave (MW) methodology in organic synthesis has attracted much attention in recent years because it offers several advantages, such as rapid reaction rates and higher yields of pure products,[15–18] as a consequence of the selective absorption of microwave energy by polar molecules or polar intermediates formed during the course of the reaction.[18] Furthermore, with increasing environmental consciousness the development of environmentally friendly synthetic methods has become desirable. In this respect organic syntheses under solvent-free conditions are basic protocols because solvents are often toxic and are agents that pollute the environment.

Prompted by the above reports and in pursuing our work on new synthetic routes to potentially bioactive compounds,[11,19–21] we have devised a salicylaldehyde-based, clay-catalysed, expeditious synthesis of benzoxazinones **2** using microwaves (Scheme 1). It is noteworthy that all the benzoxazinones **2** reported herein are new and not accessible through any of the known synthetic routes for benzoxazinones.[1–6] After some preliminary experimentation, it was found that the envisaged dehydrazinative cyclisation (**1**→**2**) was effective with montmorillonite K 10 clay under microwave irradiation for the time specified in Table 1 to afford benzoxazinones **2** in 83–94% yield (Table 1). However, the use of other mineral supports, viz., silica gel, neutral or basic alumina, was far less effective resulting in either no cyclisation (in the case of basic alumina) or relatively very low yields (13–49%) (in the cases of silica gel and neutral alumina). That the effect of microwaves may not be purely thermal[22] is supported by the fact that the reaction could not be completed, e.g., only 60% conversion over 20 h at the same bulk temperature (90°C) employing conventional heating in an oil bath. The mechanism shown in Scheme 1 is supported by the formation of hydrazine during the reaction.

In conclusion, we have developed an expeditious method for the synthesis of 2*H*-benz[*e*]-1,3-oxazin-2-ones by cyclodehydrazination of salicylaldehyde semicarbazones on a clay surface under microwave irradiation under solvent-free conditions. The applica-

Keywords: benzoxazinones; cyclodehydrazination; K 10 clay; microwave-expediated synthesis; salicylaldehyde semicarbazones.

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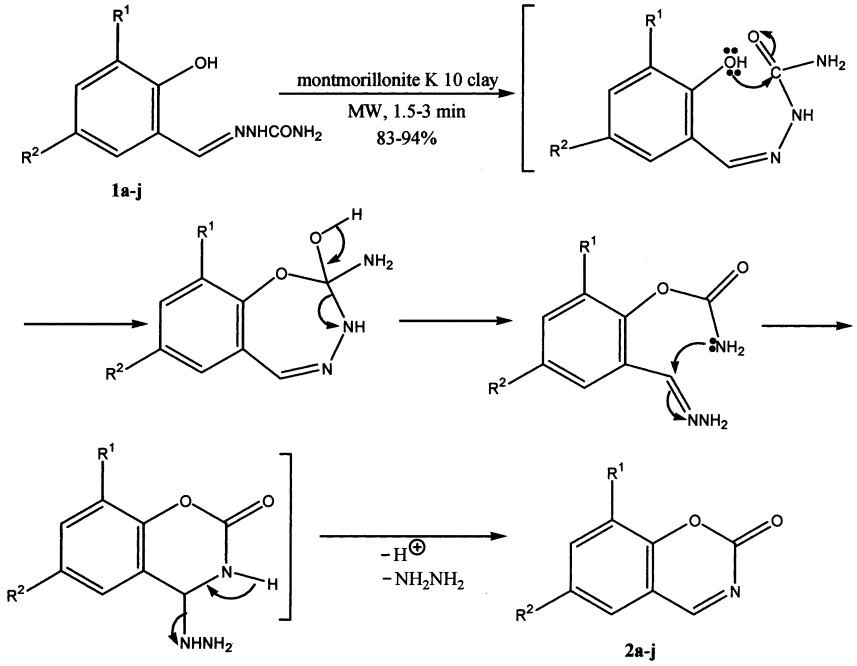

1, 2	R^1	R^2	1, 2	R^1	R^2
a	H	H	**f**	F	H
b	H	Br	**g**	MeO	H
c	Br	Br	**h**	H	NO_2
d	H	Cl	**i**	NO_2	NO_2
e	Cl	Cl	**j**	I	I

Scheme 1.

Table 1. Benzoxazinones **2** prepared on clay under microwave irradiation

Product	Time (min)	Yield[a] (%)	Mp (°C)	Mol. form.[b,c] (wt.)	^{1}H NMR δ, J (Hz)	MS m/z (M^+)
2a	3.0	84	138–139	$C_8H_5NO_2$ (147.13)	7.19–7.90 (m, 4H, Ar-H), 8.51 (s, 1H, 4-H)	147
2b	2.5	86	161–163	$C_8H_4BrNO_2$ (226.03)	7.30 (d, J 9.0, 1H, 8-H), 7.92 (dd, J 9.0, 2.4, 1H, 7-H), 8.24 (d, J 2.4, 1H, 5-H), 8.58 (s, 1H, 4-H)	225
2c	2.0	87	181–183	$C_8H_3Br_2NO_2$ (304.92)	7.87 (d, J 2.5, 1H, 7-H), 8.19 (d, J 2.5, 1H, 5-H), 8.62 (s, 1H, 4-H)	305
2d	2.5	90	151–152	$C_8H_4ClNO_2$ (181.58)	7.32 (d, J 9.2, 1H, 8-H), 7.97 (dd, J 9.2, 2.6, 1H, 7-H), 8.27 (d, J 2.6, 1H, 5-H), 8.61 (s, 1H, 4-H)	181
2e	2.0	94	157–159	$C_8H_3Cl_2NO_2$ (216.02)	7.89 (d, J 2.5, 1H, 7-H), 8.22 (d, J 2.5, 1H, 5-H), 8.65 (s, 1H, 4-H)	215
2f	2.0	91	145–146	$C_8H_4FNO_2$ (165.12)	7.66 (dd, J 9.4, 2.4, 1H, 5-H), 7.75 (dd, J 9.5, 9.4, 1H, 6-H), 7.95 (dd, J 9.5, 2.4, 1H, 7-H), 8.54 (s, 1H, 4-H)	165
2g	3.0	88	148–149	$C_9H_7NO_3$ (177.16)	4.01 (s, 3H, MeO), 7.63 (dd, J 9.3, 2.5, 1H, 5-H), 7.70 (dd, J 9.4, 9.3, 1H, 6-H), 7.82 (dd, J 9.4, 2.5, 1H, 7-H), 8.53 (s, 1H, 4-H)	177
2h	2.0	90	192–194	$C_8H_4N_2O_4$ (192.13)	7.35 (d, J 9.1, 1H, 8-H), 7.99 (dd, J 9.1, 2.5, 1H, 7-H), 8.29 (d, J 2.5, 1H, 5-H), 8.63 (s, 1H, 4-H)	192
2i	1.5	93	208–211	$C_8H_3N_3O_6$ (237.13)	7.92 (d, J 2.4, 1H, 7-H), 8.26 (d, J 2.4, 1H, 5-H), 8.67 (s, 1H, 4-H)	237
2j	3.0	83	177–180	$C_8H_3I_2NO_2$ (398.92)	7.85 (d, J 2.4, 1H, 7-H), 8.17 (d, J 2.4, 1H, 5-H), 8.61 (s, 1H, 4-H)	399

[a] Yield of purified and isolated product.
[b] All compounds gave C, H and N analyses within ±0.30%.
[c] All compounds exhibited IR bands due to $\nu_{C=O}$ in the region 1725–1735 cm^{-1}.

tion of this method to the synthesis of aglycon-modified potentially antiviral nucleosides is at present ongoing in our laboratory.

Experimental

All salicylaldehydes, semicarbazide hydrochloride, montmorollonite K 10 clay, silica gel and neutral alumina were obtained from Aldrich Chemicals and used as such without any further purification. An unmodified domestic household microwave oven (Padmini Essentia, Model Brownie) operating at 2450 MHz was used at an output of 600 W for all the experiments. The bulk temperature of the alumina bath immediately after MW-irradiations was found to be <90°C. Mps were determined in open glass capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 993 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 40 C (400 MHz) FT spectrometer using $CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded on a JEOL D-300 mass spectrometer at 70 eV. Elemental analyses were carried out using a Coleman automatic carbon, hydrogen and nitrogen analyser.

2H-Benz[e]-1,3-oxazin-2-ones ***2****. General procedure*: To a solution of salicylaldehyde semicarbazone **1** (2.0 mmol) in a small amount of dichloromethane (3 mL) was added montmorillonite K 10 clay (3.0 g), mixed thoroughly and dried. The contents were taken in a Pyrex test tube, placed in an alumina bath inside the microwave oven and irradiated for the time specified in Table 1. After completion of the reaction as indicated by TLC (hexane:AcOEt, 8:2, v/v), the product was extracted with dichloromethane (3×30 mL) and the extract was dried under reduced pressure to leave the crude product which was recrystallised from ethanol to obtain an analytical sample of benzoxazinone **2** (Table 1).

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