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A novel salicylaldehyde based mineral supported expedient synthesis of benzoxazinone nucleosides

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Abstract—An expedient mineral (montmorillonite K-10 clay) catalysed cycloisomerisation of salicylaldehyde 4-(β-D-ribo- or β-D-2′-deoxyribofuranosyl)semicarbazones yields benzoxazinone nucleosides, 4-hydrazino-3,4-dihydro-3-(β-D-ribo- or β-D-2′-deoxyribofuranosyl)-2*H*-benz[*e*]-1,3-oxazin-2-ones, which readily undergo reductive dehydrazination on alumina-supported copper(II) sulfate to furnish 3,4-dihydro-3-(β-D-ribo- or β-D-2′-deoxyribofuranosyl)-2*H*-benz[*e*]-1,3-oxazin-2-ones under solvent-free microwave irradiation.

Recently, benzoxazinones have gained recognition as non-nucleoside reverse transcriptase inhibitors. The most outstanding of these, Efavirenz (Sustiva), has been approved by the FDA (September 17, 1998) and is currently in clinical use for the treatment of AIDS. Consequently, various benzoxazinones have been synthesised and evaluated with a view to developing more efficacious drugs than Efavirenz (Sustiva).[1–6] Notably, most available drugs approved by the FDA to treat AIDS patients are nucleoside analogues. However, no attempt has been made so far to synthesise a nucleoside analogue incorporating a benzoxazinone unit as a nucleobase although it is an attractive scaffold for exploiting chemical diversity and generating a drug-like library to screen for lead candidates.

Recent years have witnessed a phenomenal growth in the application of microwave (MW) irradiation[7–11] and recyclable less expensive mineral supports for organic transformations.[12–14] The application of MW irradiation in conjunction with the use of mineral supported reagents under solvent-free conditions provides unique chemical processes.[7–14]

Considering the above and in pursuing our work on new solvent-free cyclisation procedures,[15–18] we devised a montmorillonite K-10 catalysed MW activated cycloisomerisation of salicylaldehyde 4-(β-D-ribo- or β-D-deoxyribofuranosyl)semicarbazones **1** to hitherto unknown benzoxazinone nucleosides **5** (Scheme 1). Interestingly, this is the first example of the synthesis of 4-hydrazinobenzoxazinone nucleosides **5** and their reductive dehydrazination to **6**. The key element in our approach is the novel utilization of salicylaldehyde as a bifunctional building block whose application to the construction of various benzo-fused oxygen heterocycles of chemical and biological interest is well documented.[19–24]

After some preliminary experimentation, it was found that the cycloisomerisation (**1** → **5**) can be effected using montmorillonite K-10 clay under intermittent MW irradiation† at 560 W for the time specified in Table 1.[25] Other mineral supports, viz. silica gel, neutral or basic alumina, were far less effective resulting in either no reaction (in the case of basic alumina) or relatively very low yields (10–30%) of **5** (in the cases of silica gel and neutral alumina). Hydrazines **5** readily formed hydrazones with benzaldehyde thereby providing further confirmation of their identity. Hydrazino nucleosides **5** underwent MW-assisted reductive dehydrazination on alumina-supported copper(II) sulfate under solvent-free conditions to furnish the corresponding benzoxazinone nucleosides **6** (Table 1).[26]

Keywords: Salicylaldehyde semicarbazones; Mineral supported; Microwaves; Solvent-free; Benzoxazinone nucleosides.
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† An unmodified domestic microwave oven (Kenstar, Model MWO 9808, operating at 2450 MHz) was used at an output of 560 W for all the experiments.

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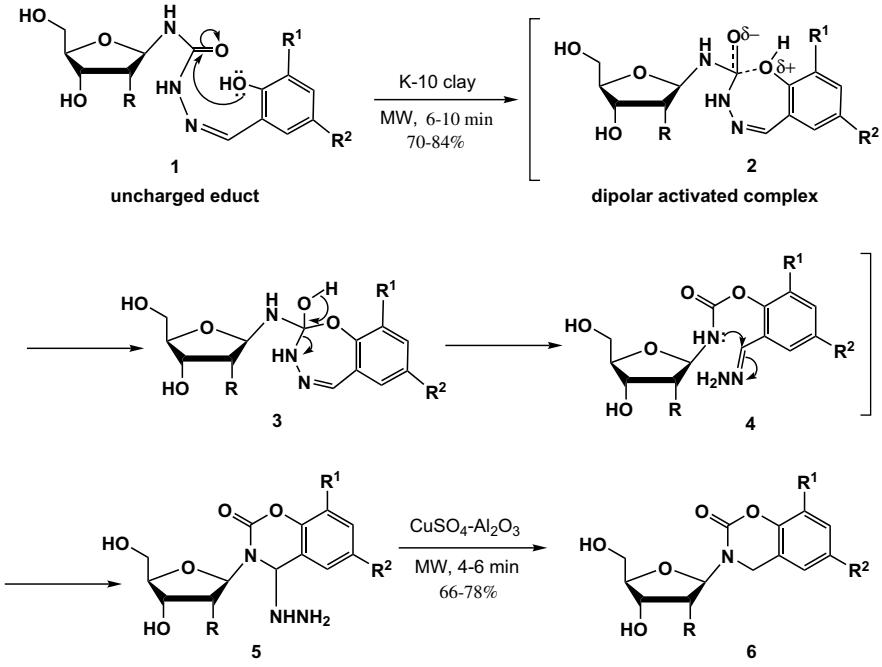

1-6	R	R^1	R^2	1-6	R	R^1	R^2
a	OH	H	H	**f**	H	H	H
b	OH	H	Br	**g**	H	H	Br
c	OH	H	Cl	**h**	H	H	Cl
d	OH	MeO	H	**i**	H	MeO	H
e	OH	H	NO_2	**j**	H	H	NO_2

Scheme 1.

Table 1. Benzoxazinone nucleosides **5** and **6** prepared on mineral support under solvent-free microwave irradiation

Product	Time[a] (min)	Yield[b,c] (%)	Product	Time[a] (min)	Yield[b,c] (%)
5a	10 (10)	76 (23)	**6a**	6 (6)	70 (14)
5b	8 (8)	80 (20)	**6b**	4 (4)	78 (12)
5c	6 (6)	84 (32)	**6c**	4 (4)	76 (15)
5d	10 (10)	78 (22)	**6d**	6 (6)	72 (17)
5e	8 (8)	82 (26)	**6e**	6 (6)	74 (19)
5f	10 (10)	70 (18)	**6f**	6 (6)	66 (11)
5g	10 (10)	73 (21)	**6g**	4 (4)	71 (13)
5h	8 (8)	76 (23)	**6h**	4 (4)	73 (15)
5i	10 (10)	73 (24)	**6i**	6 (6)	68 (16)
5j	8 (8)	78 (20)	**6j**	6 (6)	75 (15)

[a] Values in parentheses denote the time. Microwave irradiation time (power = 560 W). Parentheses show the time for oil-bath heating at 85 °C.
[b] Values in parentheses denote the yields obtained. 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 satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

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 <85 °C. The cycloisomerisations (**1** → **5**) and reductive dehydrazinations (**5** → **6**) were also carried out using a thermostated oil bath under the same conditions of time (Table 1) and temperature (85 °C) as for the MW-activated method. It was found that significantly lower yields (11–32%) were obtained using oil-bath heating rather than the MW-activated method (Table 1). Similar results were obtained in the case of the reductive dehydrazinations of **5** → **6** (Table 1). These observations may be rationalised on the basis of the formation of a dipolar activated complex from an uncharged educt in these cycloisomerisations (Scheme 1 shows an activated complex **2** as an example) and the greater stabilisation of the more polar activated complex by dipole–dipole interactions with the electric field of

microwaves, in comparison to a less dipolar educt, which may reduce the activation energy ($G^{\neq}$) resulting in the rate enhancement.[11]

In conclusion, we have developed a general, straightforward synthesis of various potentially pharmaceutically useful benzoxazinone nucleosides from readily and widely available salicylaldehyde semicarbazones under solvent-free MW irradiation conditions. The present expeditious cycloisomerisations result in synthetically readily manipulable products, which should prove useful for the library synthesis of such aglycon modified nucleosides.

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References and notes

1. Patel, M.; Ko, S. S.; McHugh, R. J., Jr; Markwalder, J. A.; Srivastava, A. S.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2805–2810.
2. Patel, M.; McHugh, R. J., Jr.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S.; Trainor, G. L.; Koo, S. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3221–3226.
3. Waxman, L.; Darke, P. L. *Antivir. Chem. Chemother.* **2000**, *11*, 1–6.
4. Klasek, A.; Koristek, K.; Polis, J.; Kosmrlj, J. *Tetrahedron* **2000**, *56*, 1551–1560.
5. Girgis, A. S. *Pharmazie* **2000**, 426–430.
6. Mindl, J.; Hrabik, O.; Sterba, V.; Kavalek, J. *Coll. Czech. Chem. Commun.* **2000**, *65*, 1262–1272.
7. Caddick, S. *Tetrahedron* **1995**, *51*, 10403–10432.
8. Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boulller, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213–1234.
9. Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
10. Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283.
11. Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199–9223.
12. Balogh, M.; Laszlo, P. *Organic Chemistry Using Clays*; Springer: Berlin, 1993.
13. Chisem, J.; Chisem, I. C.; Rafelt, J. S.; Macquarrie, D. J.; Clark, J. H. *Chem. Commun.* **1997**, 2203–2204.
14. Meshram, H. M.; Shekhar, K. C.; Ganesh, Y. S. S.; Yadav, J. S. *Synlett* **2000**, 1273–1275.
15. Yadav, L. D. S.; Singh, A. *Tetrahedron Lett.* **2003**, *44*, 5637–5640.
16. Yadav, L. D. S.; Dubey, S.; Yadav, B. S. *Tetrahedron* **2003**, *59*, 5411–5415.
17. Yadav, L. D. S.; Kapoor, R. *Tetrahedron Lett.* **2003**, *44*, 8951–8954.
18. Yadav, L. D. S.; Singh, S. *Synthesis* **2003**, 63–66.
19. O'Callaghan, C. N.; McMurry, T. B. M. *J. Chem. Res. (S)* **1997**, 78–79 (M) 0643–0649.
20. Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1996**, *61*, 7355–7359.
21. Varma, R. S.; Kumar, D.; Liesen, P. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4093–4096.
22. Bandgar, B. P.; Uppalla, L. S.; Kurule, D. S. *Green Chem.* **1999**, *1*, 243–245.
23. Varma, R. S.; Dahiya, R. *J. Org. Chem.* **1998**, *63*, 8038–8041.
24. Yadav, L. D. S.; Saigal, S.; Pal, D. R. *J. Chem. Res. (S)* **1998**, 307.
25. 4-Hydrazinobenzoxazinone nucleosides **5**. General procedure: To a solution of **1** (5.0 mmol) in a small amount of dichloromethane (10 mL) was added montmorillonite K-10 clay (7.5 g). After thoroughly mixing and drying under reduced pressure, the contents were taken in a 100 mL conical flask and subjected to MW irradiation at 560 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 irradiation-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), the product was extracted with dichloromethane (3×50 mL), the extract was filtered and the filtrate was evaporated under reduced pressure to leave the crude product, which was recrystallised from ethanol to obtain an analytically pure sample of **5** as yellowish needles. The physical data of representative compounds: Compound **5a**: Mp 143–145 °C. IR (KBr): ν_{max} 3386, 3370, 3025, 1692 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.08 (br s, 3H, $NHNH_2$, exchanges with D_2O), 4.08–4.12 (m, 1H, 4′-H), 4.20–4.26 (m, 3H, 2′-H, 5′-CH_2), 4.62–4.66 (m, 1H, 3′-H), 6.05 (d, 1H, $J = 4.2$ Hz, 1′-H), 6.41–6.47 (br s, 3H, 3×OH, exchanges with D_2O), 6.76 (d, 1H, $J = 8$ Hz, 4-H), 7.23–7.80 (m, 4H$_{arom}$). ^{13}C NMR (DMSO-d_6): δ 60.9, 71.6, 76.8, 78.6, 81.0, 108.9, 122.6, 128.4, 129.3, 130.4, 150.1, 166.3, 191.9. EIMS (*m*/*z*): 311 (M$^+$). Analysis found: C, 49.88; H, 5.32; N, 13.22. Calcd for $C_{13}H_{17}N_3O_6$: C, 50.16; H, 5.50; N, 13.50. Compound **5f**: Mp 122–123 °C. IR (KBr): ν_{max} 3380, 3368, 3022, 1688 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 2.34–2.36 (m, 2H, 2′-H), 3.06 (br s, 3H, $NHNH_2$, exchanges with D_2O), 3.96–4.34 (m, 4H, 5′-CH_2, 4′-, 3′-H), 6.15 (t, 1H, $J = 6.3$ Hz, 1′-H), 6.40–6.48 (br s, 2H, 2×OH, exchanges with D_2O), 6.74 (d, 1H, $J = 8$ Hz, 4-H), 7.20–7.78 (m, 4H$_{arom}$). ^{13}C NMR (DMSO-d_6): δ 37.5, 60.2, 64.4, 78.8, 82.3, 85.2, 122.4, 128.6, 129.7, 130.2, 150.0, 166.2, 191.8, EIMS (*m*/*z*): 295 (M$^+$). Analysis found: C, 52.54; H, 5.61; N, 14.01. Calcd for $C_{13}H_{17}N_3O_5$: C, 52.88; H, 5.80; N, 14.23%.
26. Reductive dehydrazination of nucleosides **5** to **6**. *General procedure*: An intimate mixture of **5** (2.5 mmol) and $CuSO_4$–Al_2O_3 (4.4 g, 2.5 mmol of $CuSO_4 \cdot 5H_2O$) was taken in a 100 mL conical flask and subjected to MW irradiation at 560 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 irradiation-mixing cycle was repeated for the total irradiation time (Table 1). After completion of the reaction as indicated by TLC (hexane–AcOEt, 9:1, v/v), the product was extracted with dichloromethane (3×25 mL) and the extract was evaporated under reduced pressure to leave the crude product, which was recrystallised from ethanol to obtain an analytically pure sample of **6** as yellowish needles. The physical data of a representative compound: Compound **6a**: Mp 102–103 °C. IR (KBr): ν_{max} 3382, 3018, 1690 cm^{-1}. ^{1}H NMR (DMSO-d_6): 4.06–4.11 (m, 1H, 4′-H), 4.18–4.27 (m, 3H, 2′-H, 5′-CH_2), 4.61–4.67 (1H, m, 3′-H), 6.03 (d, 1H, $J = 4.2$ Hz, 1′-H), 6.40–6.49 (br s, 3H, 3×OH), 6.60 (d, 1H, $J = 13$ Hz, axial 4-H), 6.67 (d, 1H, $J = 13$ Hz, equatorial 4-H), 7.18–7.75 (m, 4H$_{arom}$). ^{13}C NMR (DMSO-d_6): 60.8, 71.6, 76.7, 78.6, 81.1, 108.8, 122.7, 128.3, 129.4, 130.6, 150.0, 166.2, 191.8. EIMS (*m*/*z*): 281 (M$^+$). Analysis found: C, 55.20; H, 5.19; N, 4.82. Calcd for $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98.