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Three-component coupling strategy for the expeditious synthesis of novel 4-aminobenzoxazinone N-nucleosides

Lal Dhar S. Yadav* and Vijai K. Rai

Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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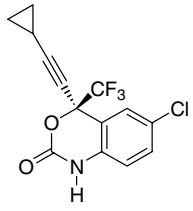
Abstract—One-pot montmorillonite K-10 clay-supported three-component reactions of substituted salicylaldehydes, ribosyl/deoxyribosylureas and ammonium acetate expeditiously yield the novel N-nucleosides, 4-amino-3,4-dihydro-3-(β-D-ribo- or β-D-2′-deoxyribofuranosyl)-2*H*-benz[*e*]-1,3-oxazin-2-ones, via cycloisomerisation of an aldimine intermediate under solvent-free microwave irradiation conditions.

Efavirenz (Sustiva), a benzoxazinone derivative, is a non-nucleoside reverse transcriptase inhibitor that has been approved by the FDA (September 17, 1998) and is presently in clinical use for the treatment of AIDS. The fight against HIV, by developing more efficacious drugs than Efavirenz, has been the prime driving force for benzoxazinone derivatisation which has received considerable attention.[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 nucleoside analogues incorporating an aminobenzoxazinone unit as a nucleobase although they appear to be attractive scaffolds for exploiting chemical diversity and generating a drug-like library to screen for lead candidates.



Sustiva

One-pot multi-component reactions (MCRs) have gained significant and steadily increasing academic, economical and ecological interest because they address fundamental principles of synthetic efficiency and reaction design. Thus, MCRs have emerged as an improved synthetic strategy for tailor-made structural scaffolds and combinatorial libraries in drug discovery processes.[7–13] Recent years have witnessed a phenomenal growth in the application of microwave (MW) irradiation[14–18] and recyclable less expensive mineral supports for organic transformations.[19–21] The application of MW irradiation in conjunction with the use of mineral supported reagents under solvent-free conditions provides chemical processes with special attributes such as enhanced reaction rates, higher yields of pure products, better selectivity, improved ease of manipulation, rapid optimisation of reactions in parallel, and several eco-friendly advantages in the context of green chemistry.[14–21]

Prompted by the above reports and pursuing our work on new solvent-free cyclisation procedures,[22–25] we devised a novel montmorillonite K-10 clay-catalysed MW activated synthesis of hitherto unknown 4-aminobenzoxazinone derivatives **3**.

In order to achieve our goal expeditiously, we relied upon the significant advantages of multi-component reactions (MCRs) under solvent-free MW irradiation conditions. The key element in our approach is the utilisation of salicylaldehyde as a bifunctional building block whose application to the construction of various

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* Corresponding author. Tel.: +91 5322500652; fax: +91 5322545021; e-mail: lds-yadav@hclinfinet.com

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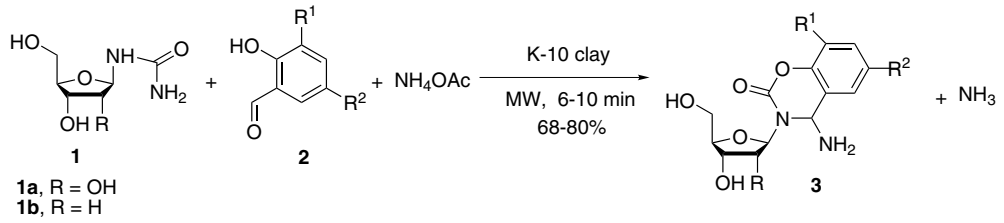


1a, R = OH
1b, R = H

2/3	R	R^1	R^2	2/3	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.

benzo-fused oxygen heterocycles of chemical and biological interest is well documented.[26–31]

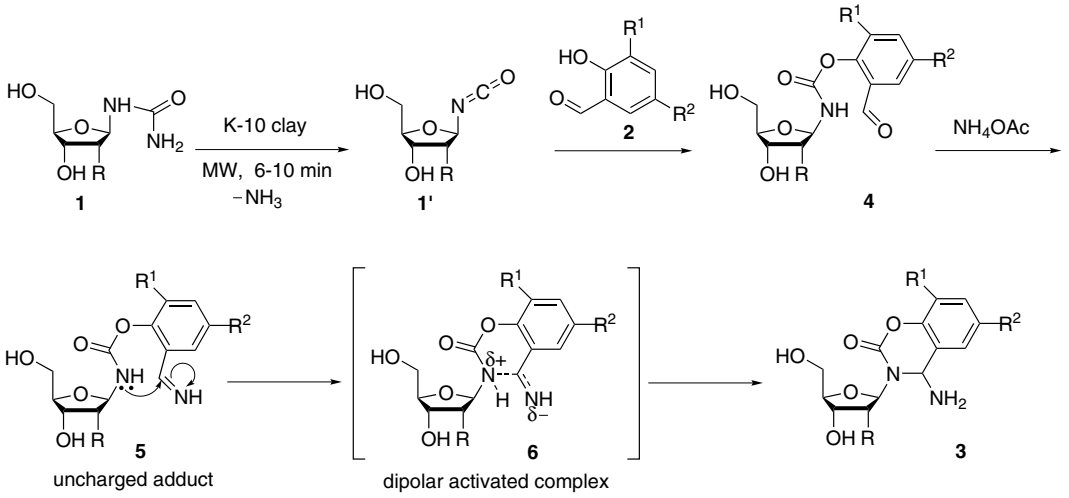
After preliminary experimentation, it was found that the envisaged three-component synthesis (Scheme 1) was successful with a montmorillonite K-10 clay supported intimate mixture of ribosyl/deoxyribosylureas **1**, substituted salicylaldehydes **2** and ammonium acetate under intermittent MW irradiation at 560 W for the times specified in Table 1. Isolation and purification by recrystallisation from ethanol afforded 4-aminobenzoxazinone N-nucleosides **3** in excellent yields (Table 1).[32] 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 (12–26%) of **3** (in the case of silica gel and neutral alumina). That the first step in the synthesis involves the conversion of ribosyl/deoxyribosylureas **1** into the corresponding isocyanate intermediates **1′** (Scheme 2) was supported by trapping their *p*-tolylurea derivatives.

Table 1. Mineral supported solvent-free synthesis of 4-aminobenzoxazinone N-nucleosides **3**

Product	Time		Yield (%)[c,d]		Mp (°C)
	MW[a] (min)	Thermal[b] (h)	MW	Thermal	
3a	8	4	71	35	134–135
3b	10	5	80	41	158–159
3c	6	3	77	36	143–144
3d	8	4	73	34	138–139
3e	6	3	75	37	147–148
3f	8	5	68	35	123–124
3g	8	5	72	38	140–141
3h	10	4	74	39	129–130
3i	8	5	69	37	125–126
3j	10	4	76	40	136–137

[a] Microwave irradiation time (power = 560 W). A CEM Discover Microwave Synthesis System operating at 2450 MHz was used for all the experiments.
[b] Time with oil-bath heating at 90 °C.
[c] Yield of isolated and purified products.
[d] All compounds gave C, H and N analyses within ±0.35% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

For comparison purposes, the final temperature was recorded and found to be <90 °C. The reactions were also carried out using a thermostated oil-bath at the same temperature (90 °C) as for the MW-activated



Scheme 2.

method but for a longer (optimised) period of time (Table 1) to ascertain whether the MW method improved the yield or simply increased conversion rates. It was found that significantly lower yields (34–41%) were obtained using oil-bath heating rather than the MW-activated method (Table 1). This observation can be rationalised on the basis of the formation of a dipolar activated complex from an uncharged adduct in these reactions (as an example, Scheme 2 shows a dipolar activated complex **6**), and the greater stabilisation of the more dipolar activated complex by dipole–dipole interactions with the electric field of the microwaves as compared to the less dipolar adduct, which may reduce the activation energy ($G^{\neq}$) resulting in the rate enhancement.[18]

In summary, we have developed a novel, mineral-supported simple synthetic protocol for the preparation of various potentially pharmaceutically useful benzoxazinone N-nucleosides starting from readily and widely available simple substrates under solvent-free MW irradiation conditions. The present high yielding and expeditious conversions led to synthetically readily manipulable products and may find application in library synthesis of such aglycon modified N-nucleosides.

Acknowledgements

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32. General procedure for the synthesis of 4-aminobenzoxazinone N-nucleosides **3**: To a solution of ribosyl/deoxyribosylurea **1** (5.0 mmol) and salicylaldehyde **2** (5.0 mmol) in dichloromethane (10 mL) was added montmorillonite K-10 clay (0.50 g), with thorough mixing and the solvent then evaporated under reduced pressure. The contents were taken in a 20 mL vial and subjected to microwave 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 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 **3** as yellowish needles. Physical data of representative compounds: **3b**: Mp 158–159 °C. IR (KBr): ν_{max} 3388, 3368, 3035, 1693, 1605, 1585, 1456 cm^{-1}. ^1H NMR (400 MHz DMSO-d_6): δ 3.07 (br s, 2H, NH_2, exchangeable with D_2O), 4.09–4.15 (m, 1H, 4′-H), 4.21–4.25 (m, 3H, 2′-H, 5′-CH_2), 4.64–4.67 (m, 1H, 3′-H), 6.03 (d, 1H, $J = 4.2$ Hz, 1′-H), 6.40–6.46 (br s, 3H, $3 \times$ OH, exchangeable with D_2O), 6.78 (t, 1H, $J = 8$ Hz, 4-H), 7.31 (d, 1H, $J = 9.0$ Hz, 8-H), 7.91 (dd, 1H, $J = 9.0$, 2.4 Hz, 7-H), 8.23 (d, 1H, $J = 2.4$ Hz, 5-H). ^{13}C NMR (100 MHz DMSO-d_6): δ 60.7, 81.2, 71.5, 76.7, 78.8, 108.8, 123.0, 127.9, 129.0, 130.3, 150.3, 166.4, 192.0. EIMS (*m*/*z*): 376 (M^+) Analysis found: C, 41.27; H, 4.27; N, 7.42. Calcd for $C_{13}H_{15}BrN_2O_6$: C, 41.62; H, 4.03; N, 7.47. **3h**: Mp 129–130 °C. IR (KBr): ν_{max} 3390, 3371, 3038, 1695, 1603, 1574, 1448 cm^{-1}. ^1H NMR (400 MHz DMSO-d_6): δ 2.31–2.35 (m, 2H, 2′-H), 3.09 (br s, 2H, NH_2, exchangeable with D_2O), 3.98–4.33 (m, 4H, 5′-CH_2, 4′-, 3′-H), 6.17 (t, 1H, $J = 6.3$ Hz, 1′-H), 6.42–6.48 (br s, 2H, $2 \times$ OH, exchangeable with D_2O), 6.75 (t, 1H, $J = 8.2$ Hz, 4-H), 7.32 (d, 1H, $J = 9.1$ Hz, 8-H), 7.92 (d, 1H, $J = 9.1$, 2.5 Hz, 7-H), 8.25 (d, 1H, $J = 2.5$ Hz, 5-H). ^{13}C NMR (100 MHz DMSO-d_6): δ 37.6, 60.4, 64.5, 78.9, 82.5, 85.5, 122.8, 128.1, 129.5, 130.6, 150.2, 166.1, 191.9. EIMS (*m*/*z*): 314 (M^+). Analysis found: C, 49.29; H, 4.55; N, 8.66. Calcd for $C_{13}H_{15}ClN_2O_5$: C, 49.61; H, 4.80; N, 8.90.