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Novel Salicylaldehyde-Based Mineral-Supported Expeditious Synthesis of Benzoxazin-2-ones

Lal Dhar S. Yadav* and Ritu Kapoor

Department of Chemistry, University of Allahabad, Allahabad-211002, India

lds-yadav@hclinfinet.com

Received May 6, 2004

Abstract: One-pot montmorillonite K-10 clay supported reactions of either salicylaldehyde/2-hydroxyacetophenone hydrazones and aryl-/alkylureas or salicylaldehydes/2-hydroxyacetophenone and 4-aryl-/alkylsemicarbazides expeditiously yield 3,4-dihydro-4-hydrazino-2*H*-benz[*e*]-1,3-oxazin-2-ones (**9**) via cycloisomerization of the intermediate salicylaldehyde/2-hydroxyacetophenone 4-aryl-/alkylsemicarbazones (**5**) under solvent-free microwave irradiation. Under the same conditions, hydrazines (**9**) readily underwent reductive dehydrazination on alumina-supported copper(II) sulfate to furnish 2*H*-benz[*e*]-1,3-oxazin-2-ones (**10**).

Efavirenz (Sustiva), a benzoxazinone derivative, is a nonnucleoside reverse transcriptase inhibitor that was approved by the FDA in 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 derivatization which has attained considerable attention.[1–6]

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 with special attributes such as enhanced reaction rates, higher yields of pure products, easier workup, rapid optimization of reactions in parallel, and several ecofriendly advantages in the context of green chemistry.[7–14] Thus, this protocol should be welcome in these environmentally conscious days.

Considering the above reports and in pursuing our work on new solvent-free cyclization procedures,[15–18] we devised an original montmorillonite K-10 clay catalyzed MW-activated synthesis of hitherto unknown 4-hydrazinobenzoxazinone derivatives **9** which involves cycloisomerization of the intermediate salicylaldehyde/2-hydroxyacetophenone semicarbazones **5** (Scheme 1).

Interestingly, this is the first example of the synthesis of 4-hydrazinobenzoxazinones **9** and their reductive dehydrazination to **10**. 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 synthesis of hydrazines **9** envisaged can be effected either starting from salicylaldehyde/2-hydroxyacetophenone hydrazones **1** and aryl-/alkylureas **2** (route 1) or salicylaldehydes/2-hydroxyacetophenone **3** and 4-aryl-/alkylsemicarbazides **4** (route 2) (Scheme 1). Moreover, the synthesis of the target compounds **9** is more convenient through route 1 because route 2 utilizes 4-aryl-/alkylsemicarbazides **4** whose preparation usually involves highly toxic, corrosive, and hygroscopic aryl isocyanates demanding special care in handling. Therefore, although almost the same yield is obtained through both routes, we have preferred route 1.

The present synthesis in its entirety involves intermittent irradiation of an mixture of the reactants (**1** and **2** or **3** and **4**) and montmorillonite K-10 clay for 2 min in an MW oven[25] at 560 W followed by thorough mixing for 2 min outside the oven. This intermittent irradiation−mixing cycle was repeated for the total irradiation time specified in Table 1 to afford 4-hydrazinobenzoxazin-2-ones **9** in 78−89% 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 reaction (in the case of basic alumina) or relatively very low yields (20−35%) of **9** (in the case of silica gel and neutral alumina). Moreover, the reactions did not take

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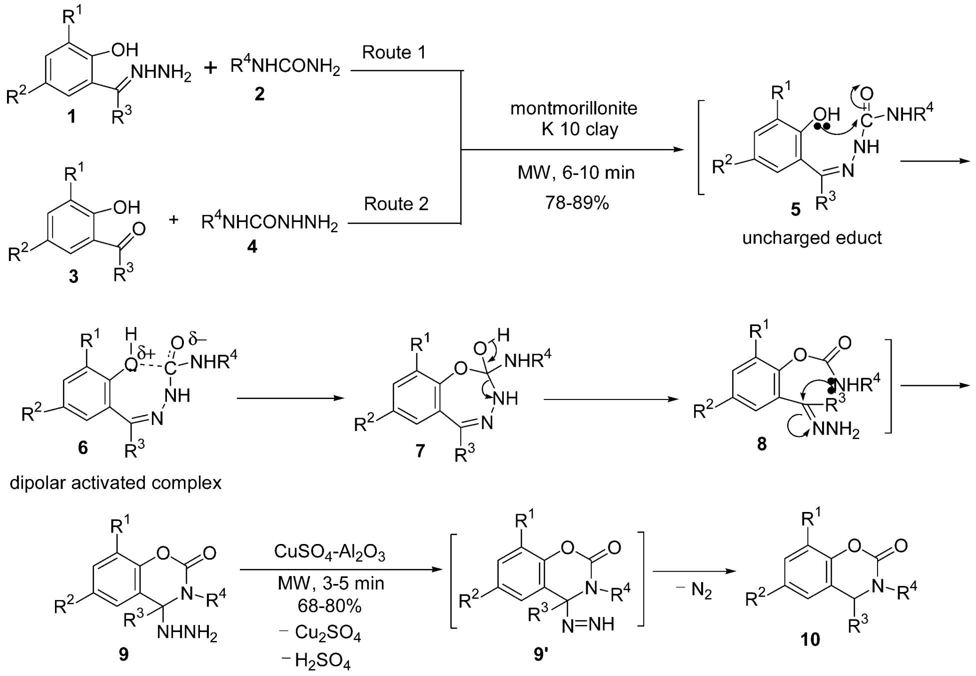
(25) An unmodified domestic microwave oven (operating at 2450 MHz) was used at an output of 560 W for all of the experiments.

10.1021/jo0492315 CCC: $27.50

SCHEME 1



5-10	R^1	R^2	R^3	R^4	5-10	R^1	R^2	R^3	R^4	5-10	R^1	R^2	R^3	R^4
a	H	H	H	Ph	g	H	Br	H	2-MeC_6H_4	m	Br	Br	H	Et
b	H	Br	H	Ph	h	Br	Br	H	2-MeC_6H_4	n	H	Cl	H	Et
c	Br	Br	H	Ph	i	H	Cl	H	2-MeC_6H_4	o	Cl	Cl	H	Et
d	H	Cl	H	Ph	j	Cl	Cl	H	2-MeC_6H_4	p	H	H	Me	Et
e	Cl	Cl	H	Ph	k	H	H	H	Et	q	H	H	Me	Ph
f	H	H	H	2-MeC_6H_4	l	H	Br	H	Et	r	H	H	Me	2-MeC_6H_4

TABLE 1. Products 9 and 10 Prepared on Mineral Support under Solvent-Free Microwave Irradiation

product	time[a] (min) (h)	yield[b] (%)	product	time[a] (min) (h)	yield[b] (%)
9a	8 (3)	83 (50)	**10a**	4 (2)	75 (35)
9b	8 (3)	85 (47)	**10b**	4 (2)	78 (39)
9c	6 (4)	86 (50)	**10c**	3 (3)	80 (38)
9d	8 (6)	88 (51)	**10d**	4 (3)	74 (36)
9e	6 (4)	89 (53)	**10e**	3 (2)	79 (36)
9f	10 (6)	78 (43)	**10f**	5 (3)	68 (34)
9g	10 (6)	84 (40)	**10g**	4 (3)	77 (37)
9h	10 (6)	81 (42)	**10h**	5 (4)	72 (35)
9i	8 (3)	87 (41)	**10i**	5 (4)	73 (34)
9j	6 (4)	89 (51)	**10j**	3 (2)	76 (34)
9k	8 (4)	80 (48)	**10k**	3 (2)	70 (36)
9l	8 (4)	81 (48)	**10l**	4 (2)	72 (38)
9m	6 (5)	83 (51)	**10m**	5 (3)	71 (35)
9n	8 (5)	82 (50)	**10n**	5 (3)	73 (37)
9o	6 (4)	85 (52)	**10o**	4 (2)	75 (39)
9p	8 (5)	80 (46)	**10p**	5 (3)	70 (35)
9q	10 (6)	78 (42)	**10q**	5 (3)	69 (34)
9r	10 (6)	78 (40)	**10r**	5 (3)	68 (34)

[a] Microwave irradiation time (power = 560 W). Parentheses show the time in hours for oil-bath heating at 90°C. [b] Yield of isolated and purified product. Parentheses show yield obtained using oil-bath heating.

place if they were peformed using the microwave without the montmorillonite K-10, either neat or in an organic solvent. Hydrazines **9** readily formed hydrazones with benzaldehyde, which is a further confirmation of their identity. 4-Hydrazinobenzoxazin-2-ones **9** underwent MW-assisted reductive dehydrazination on alumina supported copper(II) sulfate under solvent-free conditions to furnish the corresponding benzoxazin-2-ones **10** (Table 1).

For comparison purposes, the final temperature was measured by immersing a glass thermometer into the reaction mixture immediately after MW irradiations and was 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 method but for a longer (optimized) period of time (Table 1) to ascertain whether the MW and montmorillonite K-10 combination truly improves yields or simply increases conversion rates. It was found that significantly lower yields (34–53%) were obtained using oil bath heating rather than the MW activated method (Table 1) and that the MW-assisted reactions were quite cleaner than the corresponding conventional oil-bath reactions. Similar results were obtained in the case of reductive dehydrazination of **9** to **10** (Table 1). These observations may be rationalized on the basis of the formation of a dipolar activated complex from an uncharged adduct in these cycloisomerizations (Scheme 1 shows an activated complex **6** as an example) and the greater stabilization of the more polar activated complex by dipole–dipole interactions with the electromagnetic field of microwaves as compared to the less polar adduct which may reduce the activation energy ($\Delta G^{\ddagger}$) resulting in the rate enhancement.[11] The oxidation of arylhydrazines ($ArNHNH_2$) to aryldiazines ($ArN{=}NH$) and the formation of hydrocarbons (ArH) from these unstable aryldiazine intermediates has already been reported in the literature.[26,27] The dehydrazination of **9** to **10** may be assumed to follow a similar mechanism (Scheme 1).

In summary, we have developed an original, mineral-supported simple synthetic protocol for the preparation of various potentially pharmaceutically useful benzoxazin-2-ones starting from salicylaldehydes/2-hydroxyacetophenone under solvent-free MW irradiation. The present high-yielding, expeditious, and ecofriendly conversions lead to synthetically readily manipulable products and may find application in the library synthesis of compounds of this class.

Experimental Section

All chemicals used were reagent grade and were used as received without further purification. Silica gel-G was used for TLC.

General Procedure for the Synthesis of 3,4-Dihydro-3-aryl/alkyl-4-hydrazino-2*H*-benz[*e*]-1,3-oxazin-2-ones 9a−j. To a solution of hydrazone **1** (5 mmol) and aryl/alkylurea **2** (5 mmol) in a small amount of dichloromethane (10 mL) was added montmorillonite K 10 clay (7.5 g), the compounds were mixed thoroughly, and the mixture was dried 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 MW 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 recrystallized from ethanol to give an analytically pure sample of **9** as yellowish needles.

3,4-Dihydro-4-hydrazino-3-phenyl-2*H*-benz[*e*]-1,3-oxazin-2-one (9a): yellowish needles (yield 86%); mp 211−213 °C; IR 3365, 3004, 1713, 1595, 1573, 1448 cm^{-1}; ^{1}H NMR δ 3.06 (br s, 3H, exchanges with D_2O), 6.76 (d, 1H, $J = 8$ Hz), 7.19−7.89 (m, 9H); ^{13}C NMR δ 78.6, 113.2, 114.5, 118.5, 120.2, 122,6, 129.0, 129.8, 130.5, 150.2, 166.2, 177.4; MS m/z 255 (M$^+$). Anal. Calcd for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found: C, 65.58; H, 4.98; N, 16.68.

General Procedure for the Synthesis of 3, 4-Dihydro-3-aryl/alkyl-2*H*-benz[*e*]-1,3-oxazin-2-ones 10a−j. A mixture of **9** (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 1 min. The reaction mixture was then thoroughly mixed outside the MW oven for 2 min and again irradiated for another 1 min. This intermittent irradiation mixing cycle was repeated for a 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 recrystallized from ethanol to give an analytically pure sample of **10** as yellowish needles.

3,4-Dihydro-3-phenyl-2*H*-benz[*e*]-1,3-oxazin-2-ones 10a: yellowish needles (yield 78%); mp 198−200 °C; IR 3010, 1710, 1598, 1577, 1453 cm^{-1}; ^{1}H NMR δ 6.60 (d 1H, $J = 13$ Hz), 6.66 (d, 1H, $J = 13$ Hz), 7.15−7.82 (m, 9H); ^{13}C NMR δ 64.5, 11.28, 114.1, 118.4 120.1, 122.4, 129.0, 129.9, 130.6, 150.1, 166.1, 177.3; MS m/z 225 (M$^+$). Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.30; H, 4.73; N, 6.45.

Acknowledgment. We sincerely thank CSIR, New Delhi, for the award of a Senior Research Fellowship to R.K. and SAIF, CDRI, Lucknow, for providing microanalyses and spectra.

Supporting Information Available: Characterization data for compounds **9b−j** and **10b−j**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0492315

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