

Unexpected synthesis of N-methylbenzo[d]isoxazolium hydroxides under microwave irradiation conditions

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Abstract Microwave-assisted condensation of salicylaldehydes and N-methyl hydroxylammonium hydrochloride in the presence of K_2CO_3 under solvent-free conditions afforded, unexpected N-methylbenzo[d]isoxazolium hydroxides (**2a–d**).

Keywords Benzo[d]isoxazolium · Microwave irradiation · Nitrone · Solvent-free · Methylhydroxylamine

Introduction

The early reports of the application of commercial microwave (MW) ovens for the synthesis of small organic molecules appeared in 1986 [1,2]. MW irradiation proved then to be extremely useful for promoting and simplifying many condensation reactions which can be carried both in solvent and solvent-free conditions [3,4]. MW technology has gained value as a synthetic platform, especially when combined with solvent-free (neat) procedures. Avoiding organic solvents in organic synthesis leads to a clean, efficient, and economical technology; safety is largely increased, and the process is considerably simplified [5,6]. MW heating, along with solventless system, has been widely used for many organic reactions in our laboratory [7–12].

Nitrone is highly valuable synthetic intermediates in organic synthesis. Much attention has been paid to the chem-

istry of nitrone because of their widely applicable reactivities [13–15]. 1,3-Dipolar cycloadditions of nitrone and their functionalization at the α -position have great synthetic utilities [15]. Nitrone has a positive charge on the nitrogen atom which can be delocalized between the nitrogen atom and the α -carbon atom [13]. The extent of the delocalization is naturally influenced by substituents on the α -carbon and the nitrogen. They behave as electrophiles toward organometallics and as 1,3-dipoles in cycloadditions [16].

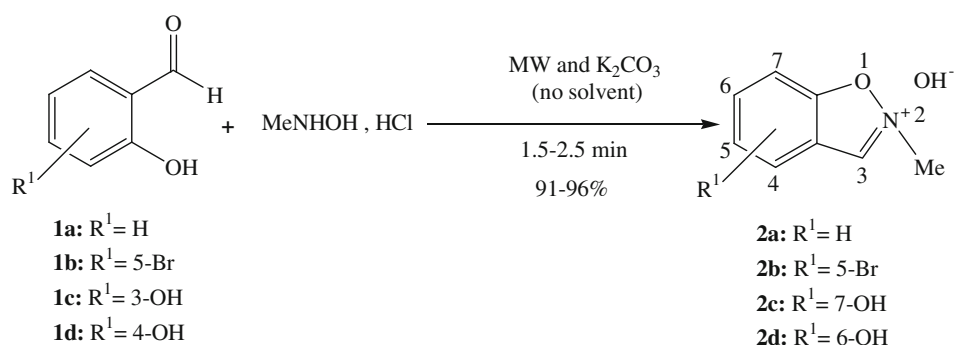
One of the most common procedures for the synthesis of nitrone is the condensation of aldehydes with N-mono-substituted hydroxylamines [17,18]. In our continuing interest in the development of solvent-free systems for the sake of environmentally benign chemical transformations [19–21], we explored the use of microwave-assisted synthesis of nitrone through K_2CO_3 catalyzed condensation reaction of monosubstituted hydroxylamines with salicylaldehydes under solventless conditions. Using methylhydroxylamine in this procedure, unexpectedly we did not obtain nitrone but N-methylbenzo[d]isoxazolium hydroxide salts (**2a–d**). In this article, we wish to disclose our results for a new, efficient, and expeditious cyclization of (Z)-N-methyl-C-(2-hydroxyphenyl)-nitrone, as an intermediate to N-substituted benzo[d]isoxazolium hydroxides (**2a–d**), in excellent yields. The formation of these fused isoxazolium salts is very interesting from a biological and chemical point of view [22–24]. Kemp et al. have reported the synthesis of N-ethyl-benzoisoxazolium cations via the nucleophilic reaction of benzoisoxazoles with Meerwein's triethyloxonium fluroborate in dichloromethane solution [25].

Results and discussions

Our approach is based on the condensation reaction of N-methylhydroxylamine and N-phenylhydroxylamine with

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Scheme 1 Solventless synthesis of N-methylbenzo[d]isoxazolium hydroxides

Table 1 Condensation of salicylaldehydes with N-monosubstituted hydroxylamines under MW irradiation

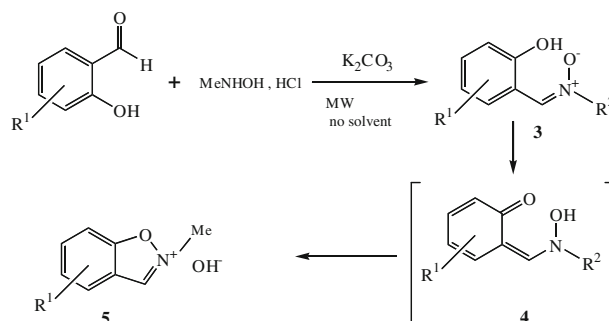
Entry	R^1	Product (Z/E)	Time (min)	M.P (°C)	Yield ^a (%)
1	H	2a	1.5	136.5–137.5	96
2	5-Br	2b	2	161–162.5	90
3	3-OH	2c	2.5	128.5–130	95
4	4-OH	2d	2	195–196	91
5	H	6a (100/0)	2.5	129–131	94
6	3-OH	6b (36/64)	2	159–161	94
7	5-Br	6c (100/0)	2.5	172–176	91

^a Isolated yields after recrystallization

2-hydroxybenzaldehyde derivatives in the presence of potassium carbonate. We started with the reaction of salicylaldehyde and N-methylhydroxylamine hydrochloride in the presence of potassium carbonate as a model reaction. Different reaction conditions were adopted for this reaction under microwave irradiation. The use of a 1:1 ratio of starting materials under microwave irradiation in solventless system gave the product in a short period of time with excellent yield. The use of an excess amount of any of the reagents deters the one-spot TLC monitoring of this conversion.

The spectroscopic data of the crude product indicated that this reaction did not produce the expected and desired yields of N-methyl-C-(2-hydroxyphenyl)nitron. The ^1H -NMR spectrum of the re-crystallized product indicated the unexpected formation of N-methylbenzo[d]isoxazolium hydroxide **2a** (Scheme 1). The structure of compound **2a** was confirmed and elucidated by ^{13}C -NMR, IR, elemental analysis, and mass spectrometry.

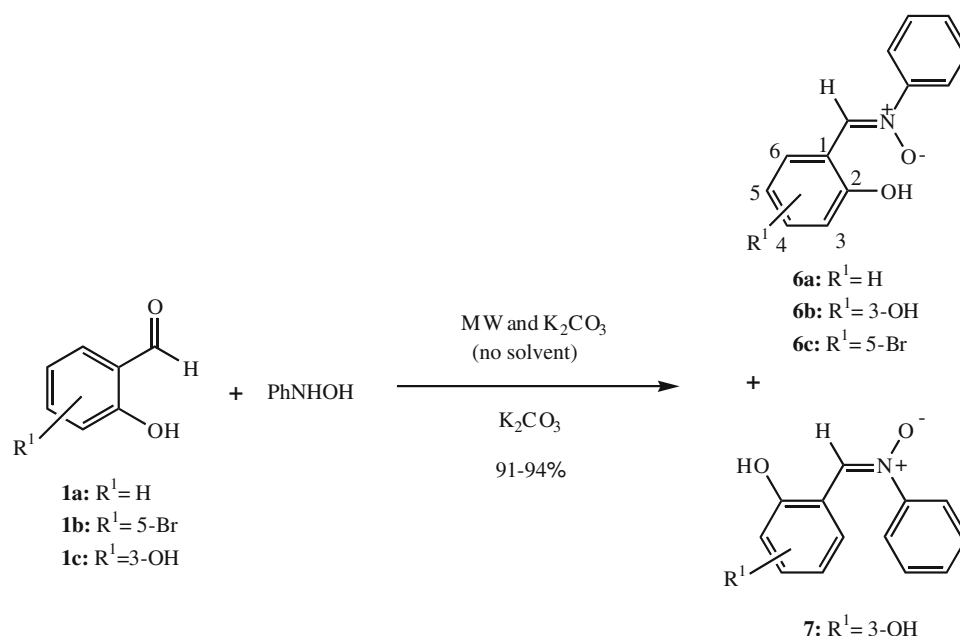
We extended the methodology to the other substituted salicylaldehydes in the presence of N-methylhydroxylamine hydrochloride to investigate the scope and generality of this process. The results are summarized in Table 1. It was observed that under similar conditions, there is no significant substituent effect on the salicylaldehyde in this procedure. The products were purified by re-crystallization from ethanol and characterized by ^1H -NMR, ^{13}C -NMR, IR, elemental analysis, and mass spectrometry.



Scheme 2 Plausible mechanism for the formation of the products **2a–d**

A plausible mechanism for the formation of the products is outlined in Scheme 2. We believe the pathway involves the intermediacy of Z-nitron **3** since its formation via condensation of reactants is facile at high temperature. Subsequent tautomerization of nitron **3** leads to hydroxylamine form **4**, which then intramolecularly cyclizes to produce the condensed N-methylbenzo[d]isoxazolium derivative **5**. According to isolated and well-identified products **2a–d**, the E-isomer of nitron is not produced in this procedure.

We also tested the condensation of N-phenylhydroxylamine with substituted salicylaldehydes. It is interesting to notice that only the expected N-phenyl-C-(2-hydroxyphenyl)nitrones **6** and **7** were obtained by this procedure (Scheme 3).



Scheme 3 Solventless synthesis of N-phenyl-C-(2-hydroxyphenyl) nitrones

Condensation of salicylaldehyde and 5-bromosalicylaldehyde with N-phenylhydroxylamine afforded only Z-isomer of corresponding nitrones **6a** and **6c**, but the 3-hydroxysalicylaldehyde afforded two geometrical isomers (Z and E) of nitrone in this procedure (**6b** and **7**). The reaction mixtures were irradiated for longer times for possible conversion of the nitrones into the N-phenylbenzoxisoxazolium salts, but no conversion was observed for any case. The stereochemical structures of these nitrones were further validated from ^1H -NMR measurements.

In summary, we have successfully applied microwave irradiation combined with solventless system in the synthesis of N-methylbenzo[d]isoxazolium hydroxides. This methodology is highly practicable in terms of convenience, fast, and safe synthesis of methylbenzo[d]isoxazolium hydroxides in pure form without requiring further purification, with excellent yields.

Materials and methods

All the reagents were purchased from Merck Company and used without further purification. ^1H and ^{13}C -NMR spectra were recorded on a Bruker Avance AC-400 or 300 MHz using CDCl_3 as the deuterated solvent, and TMS as internal standard. Mass spectra were recorded on Shimadzu GCMS-QP-2000A mass spectrometer with E.I or C.I ionization techniques. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance. All the melting points are uncorrected and measured in open-glass capillaries using Stuart

melting point apparatus. Microwave experiments were conducted in a Milestone MicroSYNTH apparatus.

General procedure for N-methylbenzo[d]isoxazolium hydroxides **2a–d** and nitrones **6a–d**

In a 10-mL glass microwave vessel, salicylaldehyde derivatives (0.5 mmol), N-methylhydroxylamine hydrochloride (0.5 mmol) or phenylhydroxylamine (0.5 mmol) and K_2CO_3 (0.5 mmol) were placed. The mixture was subjected to MW irradiation at 60 W for a few minutes (depending on the reactants, see Table 1). The completion of reaction was monitored by TLC using (EtOAc / petroleum 1:8) as eluent. After completion of the reaction, the crude product was recrystallized from ethanol / water to yield products.

N-methylbenzo[d]isoxazolium hydroxide (**2a**)

IR (KBr): 1586, 1158, 1037 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.55 (s, 1H, N=CH), 7.38 (dt, J = 1.6 Hz and J = 8.4 Hz, 1H), 7.10 (dd, J = 1.5 Hz and J = 8.4 Hz, 1H), 6.96 (dd, J = 1.6 Hz, J = 8.4, 1H), 6.84 (dt, J = 1.5 Hz and J = 8.4 Hz, 1H), 3.88 (s, 3H, N-Me). ^{13}C -NMR (CDCl_3 , 100 MHz) δ = 158.59, 140.92, 133.09, 130.93, 119.18, 117.99, 115.54, 51.06. MS-QP m/z (%), $[\text{M}]^+$ 134(100). Anal Calcd (%) for $\text{C}_8\text{H}_9\text{NO}_2$: C, 63.56; H, 6.00; N, 9.27. Found (%): C, 63.10; H, 5.91; N, 9.01.

5-Bromo-N-Methylbenzo[d]isoxazolium hydroxide (**2b**)

IR (KBr): 1576, 1151, 1026 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.46 (s, 1H, N=CH), 7.44 (dd, J = 2.3 Hz, J

= 8.9 Hz 1H), 7.16 (d, $J = 2.3$ Hz, 1H), 6.84 (d, $J = 8.9$ Hz, 1H), 3.87 (s, 3H, N-Me). ^{13}C -NMR (CDCl_3 , 100 MHz) $\delta = 156.59, 141.90, 131.19, 130.80, 119.19, 118.80, 114.55, 52.66$. MS-QP m/z (%), $[\text{M}]^+$ 214(97.88), 212(100). Anal Calcd (%) for $\text{C}_8\text{H}_8\text{BrNO}_2$: C, 41.77; H, 3.51; N, 6.09. Found (%): C, 41.47; H, 3.39; N, 5.97.

7-Hydroxy-*N*-Methylbenzo[d]isoxazolium hydroxide (2c)

IR (KBr): 3250–3030, 1576, 1151, 1026 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.53$ (s, 1H, N=CH), 7.04 (dd, $J = 1.4$ Hz, $J = 7.8$ Hz, 1H), 6.76 (t, $J = 7.9$ Hz, 1H), 6.59 (dd, $J = 1.4$ Hz, $J = 7.9$ Hz, 1H), 6.51 (broad, OH), 3.88 (s, 3H, N-Me). ^{13}C -NMR (CDCl_3 , 100 MHz) $\delta = 151.23, 140.05, 128.11, 125.75, 119.13, 116.68, 115.10, 56.22$. MS-QP m/z (%), $[\text{M}]^+$ 150(100). Anal. Calcd (%) for $\text{C}_8\text{H}_9\text{NO}_3$: C, 57.48; H, 5.43; N, 8.38. Found (%): C, 57.01; H, 5.30; N, 8.11.

6-Hydroxy-*N*-Methylbenzo[d]isoxazolium hydroxide (2d)

IR (KBr): 3210–3010, 1566, 1151, 1047 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): $\delta = 7.59$ (s, 1H, N=CH), 7.39 (dd, $J = 2.3$ Hz, $J = 8.8$ Hz 1H), 7.36 (d, $J = 2.3$ Hz, 1H), 7.01 (d, $J = 8.8$ Hz, 1H), 6.65 (broad, OH), 3.86 (s, 3H, N-Me). ^{13}C -NMR (CDCl_3 , 100 MHz) $\delta = 152.28, 140.71, 133.14, 131.23, 120.69, 118.80, 115.50, 54.56$. MS-QP m/z (%), $[\text{M}]^+$ 150(100). Anal. Calcd (%) for $\text{C}_8\text{H}_9\text{NO}_3$: C, 57.48; H, 5.43; N, 8.38. Found (%): C, 57.00; H, 5.31; N, 8.08.

N-phenyl-*C*-(2-hydroxyphenyl)nitron (6a)

IR (KBr): 3500–3150, 1586, 1159, 1033 cm^{-1} . ^1H -NMR (300 MHz, CDCl_3): $\delta = 11.99$ (s, 1H, OH), 7.92 (s, 1H, nitronyl H), 7.49 (m, 6H, ArH), 7.23 (t, $J = 7.3$ Hz, 1H), 7.04 (d, $J = 8.4$ Hz, 1H), 6.95 (t, $J = 7.8$ Hz, 1H). ^{13}C -NMR (CDCl_3 , 100 MHz) $\delta = 149.10, 149.01, 146.24, 143.34, 137.20, 131.45, 124.31, 121.11, 117.76, 117.15, 116.34$. MS-QP m/z (%), $[\text{MH}]^+$ 214(46). Anal. Calcd (%) for $\text{C}_{13}\text{H}_{11}\text{NO}_2$: C, 73.22; H, 5.20; N, 6.57. Found (%): C, 72.98; H, 5.13; N, 6.48.

N-phenyl-*C*-(2,3-dihydroxyphenyl)nitron (6b)

IR (KBr): 3500–3100, 1581, 1160, 1030 cm^{-1} . ^1H -NMR (300 MHz, CDCl_3): $\delta = 13.354$ (broad, 0.36H, OH), 8.09 (s, 1H, nitronyl H), 7.79 (m, 2H, ArH), 7.53 (m, 3H), 7.10 (dd, $J = 1.6$ Hz and $J = 7.6$ Hz, 1H), 6.83 (t, $J = 7.9$ Hz, 1H), 6.75 (dd, $J = 1.6$ Hz and $J = 7.6$ Hz, 1H), $\delta = 6.20$ (broad, 0.69H, OH). ^{13}C -NMR (CDCl_3 , 75 MHz) $\delta = 147.54, 147.42, 145.81, 141.30, 130.63, 129.41, 123.23, 121.84, 119.85, 117.73, 115.99$. MS-QP m/z (%), $[\text{MH}]^+$ 230(32). Anal.

Calcd (%) for $\text{C}_{13}\text{H}_{11}\text{NO}_3$: C, 68.11; H, 4.84; N, 6.11. Found (%): C, 68.05; H, 4.83; N, 6.09.

N-phenyl-*C*-(5-bromo-2-hydroxyphenyl)nitron (6c)

IR (KBr): 3450–3000, 1569, 1151, 1035 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): $\delta = 12.40$ (s, 1H, OH), 8.00 (s, 1H, nitronyl H), 7.76 (m, 2H, ArH), 7.49 (m, 4H, ArH), 7.30 (d, $J = 2.3$ Hz, 1H), 6.90 (d, $J = 8.9$ Hz, 1H). ^{13}C -NMR (CDCl_3 , 100 MHz) $\delta = 159.04, 145.92, 139.56, 137.07, 134.38, 130.82, 129.46, 122.29, 121.79, 118.70, 110.70$. MS-QP m/z (%), $[\text{MH}]^+$ 292(17.10), $[\text{MH}+2]^+$ 294(16.65). Anal. Calcd (%) for $\text{C}_{13}\text{H}_{10}\text{BrNO}_2$: C, 53.45; H, 3.45; N, 4.79. Found (%): C, 53.35; H, 3.42; N, 4.68.

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