

Novel and Cleaner Synthesis of Pyridinium Salts from Pyridoxal Oxime and Substituted Phenacyl Bromides

Valentina Bušić,* Dajana Gašo-Sokač, and Spomenka Kovač

Faculty of Food Technology, University J. J. Strossmayer, Kuhačeva 18, 31000 Osijek, Croatia

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Abstract. An efficient green synthesis of quaternary pyridinium salts by liquid-assisted grinding (LAG) is reported. A series of reactions of pyridoxal oxime with substituted phenacyl bromides was carried out in a mortar and pestle. This new and cleaner method provides several advantages such as being environmentally friendly, using a simple workup procedure, and affording moderate to excellent yields. All products were deduced from their IR, NMR spectroscopic and elemental analysis data. (doi: [10.5562/cca2364](http://dx.doi.org/10.5562/cca2364))

Keywords: liquid-assisted grinding (LAG), mechanochemistry, phenacyl bromides, pyridoxal oxime, quaternary pyridinium salts, quaternization

INTRODUCTION

The consciousness about environmental problems nowadays has encouraged chemists to develop chemical reactions that are less harmful for the environment and can be called green. One of them is mechanochemistry referring to reactions induced by the input of mechanical energy. Such reactions between solids are intensively studied because they are fast and quantitative and are mostly performed without solvents or by using only minimal amounts of them. The growing interest in mechanochemical processes was experienced in the past decade, when several review articles were published.^{1–6} Mechanochemistry has been used with great success for organic coupling reactions and condensations,⁷ Diels–Alder cycloadditions,⁸ Michael additions,^{9,10} Biginelli reaction,¹¹ Wittig reactions,¹² Suzuki palladium-catalyzed reaction¹³ and Knoevenagel condensation.¹⁴ Huskić and co-workers¹⁵ demonstrated a mechanochemical methodology for the oxidation of anilines into nitrobenzenes, accompanied by solvent-free product isolation. An entirely solvent-free route to chemical synthesis and product isolation are furthering the goals of green chemistry. Stojaković and co-workers¹⁶ developed an automated grinding method based on a vortex mixer which enables UV-irradiation applied to a cocrystallization, supramolecular catalysis, and preparation of a metal-organic framework. Whereas laboratory-scale mechanochemical synthesis is often

conducted by mortar and pestle techniques¹⁷ the application of a digitally controlled laboratory mill allows a higher level of reproducibility through clearly delineated reaction conditions such as reaction time, impact force and grinding intensity.¹⁸

For the first time here we present a mechanochemical methodology for quaternization of pyridinium ring. This paper is a continuation of our previous work where we prepared a series of novel pyridinium oximes by quaternization reactions of pyridoxal oxime with substituted phenacyl bromides.¹⁹ Under classical conditions, these reactions have some major disadvantages such as a long reaction time (1–3 weeks), high energy consumption and the usage of large amounts of solvents. For this reason we decided to use the mechanochemical procedure, a nonconventional green method. The aim of this work is to prove the basic concepts of mechanochemical synthesis in quaternization of "solid + solid" organic systems and to consider how they work being applied to pyridoxal oxime and a series of substituted phenacyl bromides.

Herein, we report an efficient method for the preparation of pyridinium quaternary salts by simply grinding the reactants utilizing a mortar and pestle by liquid-assisted grinding (LAG). Quaternary salts contain one oxime group on the pyridinium ring so they are potential antidotes and reactivate acetylcholinesterase inhibited by organophosphorous poisoning.

* Author to whom correspondence should be addressed. (E-mail: vbusic@ptfos.hr)

EXPERIMENTAL

Solvents and reagents were purchased from Fluka and Aldrich and used without further purification. Silica gel (Aldrich, 0,063–0,200 nm; 70–230 mesh) was used. TLC was performed on TLC-sheets ALUGRAM SIL G/uv 254 nm. IR spectra were measured on an FTIR-8400 S, SHIMADZU spectrophotometer with KBr pellets. $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were measured on a Varian XL-GEM 300 spectrophotometer in DMSO- d_6 solutions and chemical shifts are reported in δ values downfield from TMS as an internal standard. The compounds are also characterized by elemental analyses. Melting points were determined using a SMP3 capillary melting point apparatus.

General Procedure for Synthesis of Pyridinium Salts

Pyridoxal oxime (**1**) (0.18 g; 1 mmol) and phenacyl bromide (1 mmol) were added into the mortar and the mixture was ground with a pestle in the presence of silica gel (500 mg) and 300 μL of abs. ethanol. The progress of the reaction was monitored by TLC. After finishing the reaction, the mixture was extracted in hot acetone. The silica gel was removed from the mixture by filtration under reduced pressure. A small amount of remained product adsorbed at the silica gel was extracted in hot ethanol and the silicagel was removed by filtration. The ethanol extract evaporated and the product was dissolved in hot acetone and associated with previous acetone extract. After crystallization crude product was collected by filtration and purified by recrystallization from appropriate solvents. All products were analyzed by $^1\text{H-}$ and $^{13}\text{C-NMR}$, IR spectroscopy.

Spectral Data

In our previous papers^{19,20} we deal with spectral data of compounds **2**, **4**, **5**, **7**, **8** and **10**.

1-(4'-Bromophenacyl)-3-hydroxy-4-hydroxyiminomethyl-5-hydroxymethyl-2-methylpyridinium bromide (3)
M.p. after crystallization from ethanol 195–198 °C. IR (KBr): 3385, 3071–2731, 1686, 1640–1586, 1260, 1052–980 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ 12.9 (bs, 1H, NOH); 8.8 (bs, 1H, OH); 8.6 (s, 1H, H-6); 8.0 (d, $J = 8.4$ Hz, 2H, H-3", H-5"); 7.9 (d, $J = 8.3$ Hz, 2H, H-2", H-6"); 6.6 (s, 2H, CH_2CO); 4.8 (m, 2H, CH_2OH); 3.4 (bs, 1H, CH_2OH); 2.5 (s, 3H, CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6) δ 190.0, 152.6, 145.5, 145.5, 137.3, 135.1, 132.6, 132.1, 130.5, 128.9, 128.2, 64.5, 58.5, 13.3. *Anal. calc.* for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_4\text{Br}_2$ ($M = 460.1$ g mol^{-1}): C 41.77, H 3.50, N 6.09 %; found: C 41.96, H 3.61, N 5.97 %. MS m/z : 460 (17 %), 379 (100 %), 361 (39 %), 349 (39 %), 199 (34 %); 160 (39 %).

3-Hydroxy-4-hydroxyiminomethyl-5-hydroxymethyl-1-(4'-nitrophenacyl)-2-methylpyridinium bromide (6)
M.p. after crystallization from ethyl acetate 235–237 °C. IR (KBr): 3346, 3069–2871, 1713, 1644–1528, 1264, 1033–1000 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ 12.9 (bs, 1H, NOH), 8.7 (bs, 1H, OH), 8.5 (s, 1H, H-6), 8.5 (d, $J = 8.1$ Hz, 2H, H-3", H-5"), 8.4 (d, $J = 8.1$ Hz, 2H, H-2", H-6"), 6.7 (s, 2H, CH_2CO), 4.8 (m, 2H, CH_2OH), 3.4 (bs, 1H, CH_2OH), 1.0 (s, 3H, CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6) δ 190.1, 152.6, 150.7, 145.6, 138.2, 137.3, 135.1, 130.1, 128.3, 123.9, 64.9, 58.5, 13.4. *Anal. calc.* for $\text{C}_{16}\text{H}_{16}\text{BrN}_3\text{O}_6$ ($M = 425.0$ g mol^{-1}): C 45.09, H 3.78, N 9.86 %; found: C 44.70, H 4.00, N 9.67 %. MS m/z : 425 (5 %), 344 (100 %), 326 (31 %), 314 (21 %), 164 (52 %), 161 (36 %), 106 (26 %).

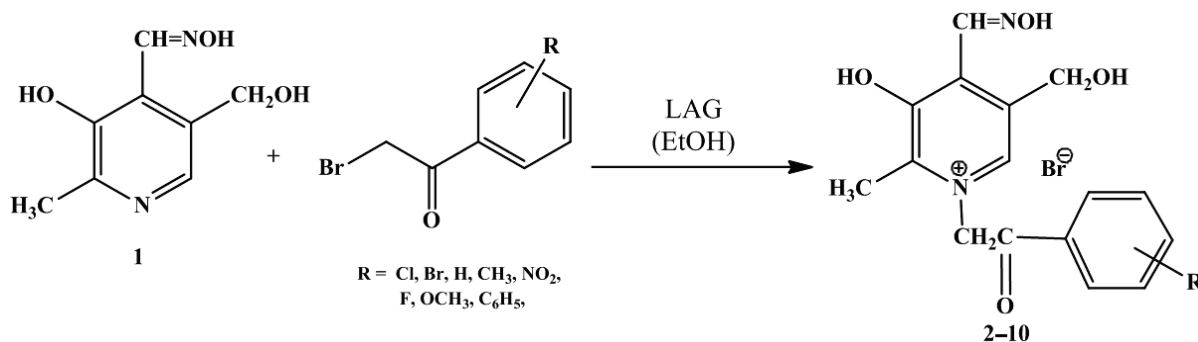
3-Hydroxy-4-hydroxyiminomethyl-5-hydroxymethyl-2-methyl-1-(4'-phenylphenacyl)-pyridinium bromide (9)
M.p. after crystallization from ethyl acetate 227–228 °C. IR (KBr): 3397, 3075–2789, 1691, 1604–1451, 1237, 1088–995 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ 13.0 (bs, 1H, NOH), 12.7 (bs, 1H, OH), 8.7 (s, 1H, H-6), 8.6 (s, 1H, H-4'), 8.2 (d, $J = 8.5$ Hz, 2H, H-3", H-5"), 7.9 (d, $J = 8.5$ Hz, 2H, H-2", H-6"), 7.8–7.6 (m, 5H, Ph), 6.7 (s, 2H, CH_2CO), 4.8 (m, 2H, CH_2OH), 3.4 (bs, 1H, CH_2OH), 2.5 (s, 3H, CH_3). $^{13}\text{C-NMR}$ (DMSO- d_6) δ 189.9, 152.5, 145.5, 145.5, 139.7, 137.4, 135.1, 132.3, 130.5, 128.2, 64.5, 58.5, 13.4. *Anal. calc.* for $\text{C}_{22}\text{H}_{21}\text{N}_2\text{O}_4\text{Br}$ ($M = 457.3$ g mol^{-1}): C 57.78, H 4.63, N 6.13, Br 17.47 %; found: C 57.63, H 4.46, N 6.03 %. MS m/z : 457 (100 %), 375 (87 %), 357 (15 %), 345 (31 %), 164 (62 %).

RESULTS AND DISCUSSION

Our first attempt was the solvent-free synthesis of quaternary pyridinium salts (**2–10**) by neat grinding in a mortar of pyridoxal oxime and substituted phenacyl bromides in the stoichiometric ratio 1 : 1 at room temperature. The progress of the reaction was monitored by TLC after every 5 min milling cycles. Even after 60 min of neat grinding, no traces of product were detectable, which meant that there was no reaction.

Guided by the observation that the small amount of liquid phase can significantly enhance the scope and rate of mechanochemical synthesis, we turned to LAG. In addition to the reaction mixture several drops of absolute ethanol and a small amount of silica gel and quaternary pyridinium salts (**2–10**) were obtained after grinding for 10 to 30 minutes. The products were easily removed from reaction the mixtures, and silica gel was both environmentally benign and readily recyclable.

Scheme 1 outlines the synthesis of **2–10**. Optimum conditions for carrying out the mechanochemical



Scheme 1. Synthesis of quaternary salts of pyridoxal oxime *via* mechanochemical reaction.

quaternization reaction were ascertained by performing a series of reactions of pyridoxal oxime with substituted phenacyl bromides. The results, which are summarized in Table 1, showed that a maximum yield of **8** (88 %) and a minimum yield of **10** (24 %) were obtained by the LAG mechanochemistry procedure. All the products thus obtained were powder-like solids. The lowest yield (24 %) obtained by quaternization of pyridoxal oxime with 2-bromo-1-(2-methoxyphenyl)ethanone can be explained by the existence of *ortho*-methoxy substituent in electrophile which prevents attack on pyridoxal oxime at the nitrogen atom due to the steric hindrance.

Although mechanochemical quaternization of pyridoxal oxime with phenacyl bromides did not proceed in quantitative yields it was achieved by adding a minimum amount of solvent. Interestingly, the same reactions carried out under conventional conditions using acetone as a solvent gave products **2–10** in lower yields and required longer reaction time.¹⁹

Despite numerous successes there is one principal disadvantage to establishing mechanochemistry as an absolutely eco-friendly solvent-free synthesis. Namely, organic reactions often require a post-synthetic solvent-based purification stage, thus diminishing the value of solvent-free synthesis.

Table 1. Synthesis of quaternary salts of pyridoxal oxime *via* mechanochemical and conventional condition reaction

Product	R	LAG (EtOH)		conventional ¹⁹	
		<i>t</i> / min	yield (%)	<i>t</i> / weeks	yield (%)
2	4'-Cl	30	82	3	66
3	4'-Br	15	75	3	44
4	4'-H	30	63	1	38
5	4'-CH ₃	20	61	1	62
6	4'-NO ₂	30	70	1	60
7	4'-F	20	38	3	36
8	4'-OCH ₃	15	88	3	67
9	4'-Ph	15	42	1	46
10	2'-OCH ₃	30	24	12	12

CONCLUSION

In summary, we have demonstrated a rapid and extremely simple method under mechanochemical conditions. The reported strategy of grindstone chemistry for conversion of pyridoxal oxime and substituted phenacyl bromides into quaternary pyridinium salts can be seen as a promising technique for achieving green chemistry goals. These developments indicate mechanochemistry will play a key role in future clean and sustainable technologies.

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