A simple process for the preparation of pralidoxime chloride

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Pralidoxime chloride (2-PAM chloride) is an important drug included in National List of Essential Medicines-2003 for treating pesticide poisoning. However, the current methods for its preparation use hazardous methyl halides such as methyl chloride or methyl iodide. In the present work, reaction of pyridine-2-aldoxime with methyl methanesulfonate in acetonitrile gave 2-PAM mesylate in high yields (90%). Use of methyl tosylate in toluene resulted in 2-PAM tosylate (90% yield). Both 2-PAM mesylate and 2-PAM tosylate on treatment with dry hydrogen chloride in isopropanol, resulted in 2-PAM chloride in high yields (90%) and purity (>99%).

Keywords: Pralidoxime chloride, 2-PAM chloride, Pesticide antidote, methyl mesylate, methyl tosylate

The organophosphorous compounds (OPC) are widely used as pesticides and are involved in a large number of accidental poisoning worldwide\textsuperscript{12}. Unfortunately, the OPC pesticides are also a common cause of intentional self-poisoning. In recent years agriculture farmers committing suicide by OPC pesticide for economic reasons is reported from several states of India, especially Andhra Pradesh and Maharashtra and the number is growing each year\textsuperscript{3}.

Pralidoxime chloride (2-formyl-1-methylpyridinium chloride oxime), also referred to as 2-PAM chloride (2-Pyridine aldoxime methyl chloride) (3b, Scheme I) is an important drug used in treating poisoning due to OPC\textsuperscript{4,5}. It acts by reactivating the cholinesterase enzyme inactivated by OPC\textsuperscript{6}.

One of the earliest drugs used in treating OPC poisoning is 2-PAM Iodide (3a, Scheme I)\textsuperscript{7,8}. Even today, 3a is widely used in many Primary Health Care Centers in India\textsuperscript{9}. The 3a is not an ideal drug because of its high iodine content (48.07%). The dose of 3a is about 2g as intravenous injection\textsuperscript{7}. Higher doses are also recommended. Thus treatment with 3a results in very high intake of iodide which may result in Iodism\textsuperscript{10}. Further, the solubility of 3a is only about 20 mg/mL in water at room temperature\textsuperscript{10}. This also results in the large volume of the injection. The actual activity in 3a is due to N-methyl pyridinium oxime cation and the iodide is only a balancing anion which is not essential. In order to find an alternative, 2-PAM Chloride (3b) was developed and is currently preferred for treating OPC poisoning\textsuperscript{11}. Its importance can be understood by the fact that 3b is one of the drugs in the National List of Essential Medicines-2003 (NLEM 2003)\textsuperscript{12}. It was also included in the earlier 1996 edition of NLEM.

Although 3b is an important essential medicine, its availability is very limited, mainly because of lack of a good economically viable process. The reported procedures are expensive and complicated. Ellin et al. prepared 2-PAM chloride by passing methyl chloride 2b gas to a solution of pyridine-2-aldoxime (1, Scheme I) in dimethylformamide under pressure\textsuperscript{13}. Mc Dowel et al. prepared 3b by first methylating α-picoline using methyl chloride followed by the reaction with nitrosyl chloride (Scheme II)\textsuperscript{14}. Methyl chloride is a highly toxic and flammable gas and difficult to handle at industrial scale. Several methods describe the preparation of 3b through the salt exchange principle starting from 3a (Scheme III).

Ginsburg and Wilson reacted 3a with an aqueous solution of silver chloride to obtain 3b (Ref 15). Kondritzer et al used strong anion-exchange resins, Amberlite IRA-400 and Dowex-1, to prepare first the chloride resin from sodium chloride solution and later passed aqueous solution of 3a solution to obtain 3b (Ref 10). A similar process is described using Dowex-IX2 ion-exchange resin and 3a (Ref 16). One of the best methods reported till now is by dissolving 3a in a methanolic solution containing anhydrous HCl, concentrating the solution to a small volume and adding acetone to precipitate 3b in about 80% yield\textsuperscript{17}. Recently, an Indian patent from DRDO describes a similar process where an alcoholic solution of 3a was bubbled with dry HCl gas to obtain crude 3b which was crystallized from diethyl ether. The reaction was carried out at 50-55°C as per the claim and at 40-50°C as per the examples\textsuperscript{18}.

Note

\textsuperscript{a}Centers in India
The problem with the reported salt exchange methods is that, all of them use 3a as the starting material. This is mainly because, the Menshutkin reaction for N-methylation of pyridine aldoxime is carried out using methyl iodide (Scheme I). Other methyl halides such as chloride and bromide are more hazardous to handle at large scale. However, methyl iodide is also very hazardous and a volatile liquid (b.p: 42-43°C). It causes acute toxicity on inhalation and ingestion. Further, it is considered a potential occupational carcinogen.

In this work, we have carried out N-methylation using safer methylating agents. Earlier, Creasey and Green used methyl methanesulfonate for N-methylation of pyridine aldoxime to obtain 2-PAM mesylate (3c, Ref 19,20). Similarly we used methyl tosylate to prepare 2-PAM tosylate 3d (Scheme I). Earlier 3d has been prepared from 3a using p-toluene sulfonic acid17. Both 3c and 3d are weak organic salts and undergo salt exchange easily with HCl to give 3b in good yields and purity. These methods are superior to existing methods and are safer and are better suited on an industrial scale. Because of the importance of 3b in health care and being listed in National List of Essential Medicines, we are sharing this knowledge in public domain without claiming any intellectual property rights.

Results and Discussion

Earlier Creasey and Green had used benzene as the solvent for the preparation of 2-PAM mesylate. Since benzene is carcinogenic, we explored other solvents
(Table 1). When the reaction was conducted in toluene, complete reaction was not observed and the removal of solvent resulted in a gummy product which on crystallization from ethanol-ethylacetate (1:2) gave pure product in 70% yield. Use of polar solvents did not improve the yields. 1,4-Dioxane gave only 55% yield, whereas monoglyme and methyl-t-butyl ether gave 60 and 52% respectively after crystallization. However, surprisingly, when acetonitrile was used as solvent, after completion of the reaction, the product crystallized out directly in high yields (90%) and in high purity (99.5% HPLC). Exchange of mesylate with chloride was easily achieved by treating an isopropanolic solution of 2-PAM mesylate with dry HCl gas. The yields were very high (92%). This is the first report of preparing 3b from 3c.

While exploring other N-methylating agents, it was found that methyl tosylate (2d) is also an excellent reagent for N-methylation of pyridine-2-aldoxime. Refluxing pyridine-2-aldoxime with methyl tosylate in acetonitrile resulted in 2-PAM tosylate (3d) in 70% yield. However, when solvent was changed to toluene, yield improved to 91% with a purity of 99.9% (Table 1). Further 3d underwent salt exchange with HCl efficiently to give 3b in good yields (90%).

Conclusions
N-methylation of pyridine-2-aldoxime can be efficiently carried out using methyl mesylate and methyl tosylate which are safer and more suitable reagents than the hazardous methyl halides used in prior art. Further, the corresponding mesylate and tosylate salts, being weak salts, undergo salt exchange easily to give 2-PAM chloride. Thus, the process described in the present publication is a much better process than the existing methods for the preparation of pralidoxime chloride (2-PAM chloride), a drug which is included in the National List of Essential Medicines-2003.

Materials and Methods
All chemicals used were obtained from commercial suppliers and used without further purification. IR spectra were recorded on Perkin FT-IR spectrophotometer using KBr pellets. $^1$H and $^{13}$C NMR spectra were recorded in a Bruker 300 MHz spectrometer using TMS as internal standard (chemical shift in δ, ppm). Mass spectra were recorded on a Thermo scientific ion trap mass spectrometer. Purity was analyzed by HPLC using Shimadzu LC2010 Prominance System equipped with a photo diode array (PDA) detector and Cosmisil Aura ODS, 4.6 mm × 250 mm (5 µm particle size) column.

Experimental Section
2-PAM mesylate, 3c. To a stirred solution of pyridine-2-aldoxime 1 (5.0 g, 0.04 mol) in 7 mL of acetonitrile was added a solution of methyl mesylate 2c (8.8 g, 0.08 mol). The reaction mixture was stirred for 7 hr at 80-85°C. After completion of the reaction

<table>
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<tr>
<th>Compd</th>
<th>Solvent</th>
<th>Yield (%)*</th>
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<tbody>
<tr>
<td>3c</td>
<td>Toluene</td>
<td>70</td>
</tr>
<tr>
<td>3c</td>
<td>1, 4-Dioxane</td>
<td>55</td>
</tr>
<tr>
<td>3c</td>
<td>Monoglyme</td>
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<tr>
<td>3c</td>
<td>Methyl-t-butyl ether</td>
<td>52</td>
</tr>
<tr>
<td>3c</td>
<td>Acetonitrile</td>
<td>90</td>
</tr>
<tr>
<td>3d</td>
<td>Acetonitrile</td>
<td>70</td>
</tr>
<tr>
<td>3d</td>
<td>Toluene</td>
<td>91</td>
</tr>
</tbody>
</table>

*Yield is the actual yield isolated after crystallization from ethanol-ethylacetate (1:2). For 3c, in acetonitrile, no crystallization was required and is the direct yield.
(monitored by TLC), reaction mixture was allowed to cool to RT and then to 10-15°C. The resulting precipitate was filtered, washed with acetonitrile, and dried in vacuo to give 3c (8.55 g, 90%) as a white solid, 99.5% pure by HPLC; m.p. 137°C; IR (KBr): 3443, 3080, 2942, 2831, 2732, 1582, 1503, 1319, 1180, 1017, 925 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 13.27 (s, 1H), 9.07-9.05 (d, 2H), 8.68 (s, 1H), 8.55-8.50 (m, 1H), 8.39-8.35 (d, 1H), 8.09-8.04 (m, 1H), 4.38 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 147.52, 146.53, 144.84, 141.47, 127.01, 124.72, and 46.05; ESI-MS: m/z 137 [M⁺].

2-PAM tosylate, 3d. A mixture containing pyridine-2-aldoxime (5.0 g, 0.04 mol), methyl tosylate 2d (14.9 g, 0.08 mol) and toluene (30 mL) was added to precipitate 2d as a solid (11.5 g, 91%) with 99.9% purity (HPLC), m.p. 133-34°C (Litt.¹⁷ 149-52°C; IR (KBr): 3452, 3080, 2937, 2840, 2733, 1626, 1593, 1581, 1505, 1326, 1239, 1193, 1059, 1011, 943 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 13.13 (s, 1H), 8.99-8.97 (d, 1H), 8.68 (s, 1H), 8.55-8.50 (m, 1H), 8.39-8.36 (s, 1H), 8.08-8.03 (m, 1H), 4.37 (s, 3H), 2.30 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 147.41, 146.62, 144.91, 141.68, 127.10, 124.83, 46.10, and 40.04; ESI-MS: m/z 137 [M⁺].

Preparation of 2-PAM chloride 3b from 3d. 2-PAM tosylate 3d (10.0 g, 0.032 mol) was dissolved in 20 mL of isopropyl alcohol. To this clear solution was passed dry HCl gas for 30 min at 0-5°C. The reaction mixture was stirred for 2 hr. The precipitate obtained was collected, washed with cold isopropyl alcohol and dried in vacuo to afford 5.0 g of 3b, 90% yield and 99.9% purity by HPLC. IR (KBr): 3443, 3080, 2942, 2831, 2732, 1582, 1503, 1319, 1180, 1017, 925 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 13.27 (s, 1H), 9.07-9.05 (d, 2H), 8.68 (s, 1H), 8.55-8.50 (m, 1H), 8.39-8.35 (d, 1H), 8.09-8.04 (m, 1H); 4.38 (s, 3H); ¹³C NMR (75 MHz, DMSO-d₆): δ 147.52, 146.53, 144.84, 141.47, 127.01, 124.72, and 46.05; ESI-MS: m/z 137 [M⁺].

References