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Research Article

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A green method for the preparation of phoxim based on high-boiling nitrite

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Abstract: Phoxim is a significant insecticide, and its current synthesis method has some shortcomings such as the high risk of explosion and the *trans* structure (main impurity) is hard to control. Our work solved the above disadvantages by introducing macromolecular alcohol (benzyl alcohol, etc.) as the starting material and optimizing the intermediate reaction conditions. Compared with the current synthesis route, the synthetic method has the following advantages: (1) intermediate benzyl nitrite has a high boiling point and strong safety; (2) intermediate α-cyanobenzaldehyde oxime sodium are almost (≥99%) *cis* structure, and no further refinement was required, which greatly reduced the amount of waste water produced; and (3) The high yield of phoxim was maintained at 72.9%.

Keywords: benzyl alcohol, phoxim, α-cyanobenzaldehyde oxime sodium, drug synthesis

1 Introduction

Phoxim, *O,O*-diethyl-α-cyano benzoxime phosphorothioate, is a broad-spectrum, highly efficient, and low-toxic organophosphorus insecticide, which had widely been used because of its strong application characteristics of unstable to light and short residual period in the field. Generally, the procedure of synthesizing phoxim was achieved using methanol or ethanol as the starting material to generate α-cyanobenzaldehyde oxime sodium (hereinafter also referred to as sodium oxime) [1–4], followed by further reaction with diethyl chlorothiophosphate to generate phoxim (see Scheme 1). Nevertheless, the method still has many shortages, for example, irrespective of the starting material used – methanol or ethanol – the boiling point [bp. from –11°C to –13°C (760 mm Hg) or bp. 16–18°C (760 mm Hg)] of the intermediate produced by their esterification is not high enough to keep safety; ethyl nitrite or methyl nitrite is easy to blow up, which is comparatively dangerous during the manufacturing operation. In addition, quiet a lot of *trans* structure (40%) is found in these sodium oximes, so that further refinement was required to adjust *trans* to *cis* structure, thus a large amount of waste water and waste acid produced increased the complexity of the experiment. Some researchers changed the treatment of waste water and waste acid, but they did not solve the safety problem of intermediates [5,6]. Other researchers [7–11] used isoamyl nitrite to react with phenylacetonitrile to generate sodium oxime, but it also generated lots of *trans* oxime sodium. After isopentanol was used to synthesize sodium oxime, further purification was required, which increased the complexity of the experiment.

This article designed a new route (Scheme 2) for the synthesis of phoxim, and the route is characterized by the introduction of macromolecular alcohol (benzyl alcohol, etc.) to prepare the key intermediates benzyl nitrite and sodium oxime. Možina et al. [12], Aellig et al. [13], Sheng et al. [14], and other researchers used benzyl alcohol as the raw material to generate benzyl nitrite, which was considered a better selectivity for benzaldehyde but less for benzyl nitrite. The new method has several advantages, such as the intermediate benzyl nitrite has a great selectivity and high bp. of 70–72°C (760 mm Hg), so that the safety factor greatly improved compared with methyl nitrite and ethyl nitrite. It was found that the intermediate sodium oxime was almost *cis* structure (≥99%) without further refinement. At the same time, the reaction can maintain a good yield, 72.9% totally (consisting of three steps).

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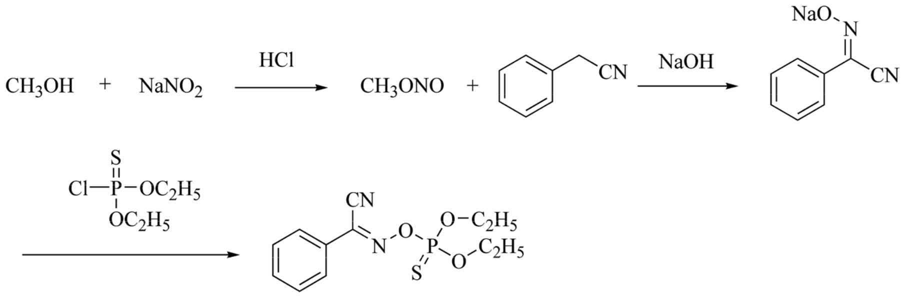
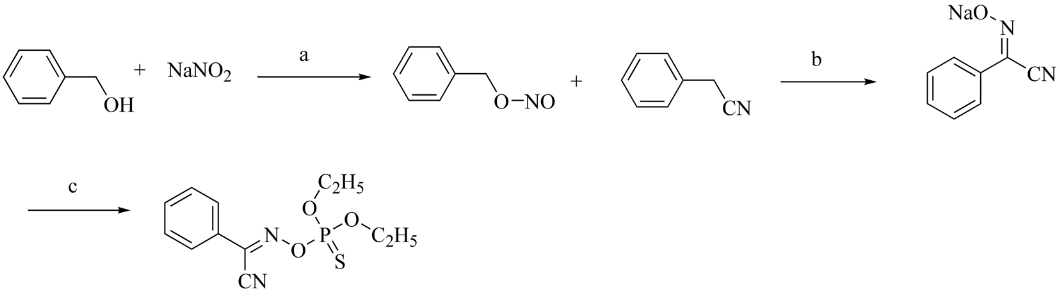


Scheme 1: Synthesis of phoxim from methanol.



Scheme 2: Synthesize of phoxim. Reagent and conditions: (a) H_2O, 12 M HCl, from −5°C to 5°C, 30 min, 90% yield; (b) NaOH, 60°C, 6 h, 90% yield; (c) 30% NaOH, diethylthiophosphoryl chloride, 45–55°C, 2–3 h, 90% yield.

2 Materials and methods

All the reagents and solvents used for the experiment were purchased from Macklin and used without further purification. The synthesized compound structure was confirmed by ^{1}H NMR and IR. ^{1}H NMR were recorded on Varian 400 MHz NMR spectrometer (DMSO or D_2O is solvent); IR were recorded on Nexus 470 infrared spectrometer. Analytical thin-layer chromatography (TLC) was performed on precoated plates, and spots were visualized under ultraviolet light (254 nm).

2.1 Synthesis of benzyl nitrite

Sodium nitrite (0.5 mol) and benzyl alcohol (0.5 mol) were dissolved in 100 mL water, 0.925 mol hydrochloric acid (37%) was added dropwise, and the temperature of reaction system was maintained at less than 5°C. The reaction mixture is stirred for 0.5 h. TLC (petroleum ether: ethyl acetate = 3:1) detects whether the reaction was completed. Separate the organic layer and dry with anhydrous magnesium sulfate, 61.6 g yellow liquid benzyl nitrite was obtained, with a yield of 90%.

Benzyl nitrite: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 (s, 2H), 7.36 (s, 5H). IR (KBr) ν: 1,654, 1,400, 1,496, 1,560, 1,654, 669, 744, 787 cm^{-1}.

2.2 Synthesis of *α*-cyanobenzaldehyde oxime sodium

Into the reaction system of 0.4 mol phenylacetonitrile and 0.4 mol sodium hydroxide, slowly add 0.52 mol benzyl nitrite dropwise and the temperature was maintained at below 60°C. After the completion of the dropwise addition, the temperature was maintained but with stirring for 2–3 h. TLC (petroleum ether:ethyl acetate = 2:1) detects whether the reaction is complete; 100 mL water was added and saved it for later use.

α-Cyanobenzaldehyde oxime sodium, yellow-brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (s, 3H), 7.69 (s, 2H). IR (KBr) ν: 2,236, 1,498, 3,130, 1,685, 1,654, 1,617, 1,560, 1,498, 1,413, 1,282, 968, 765, 689 cm^{-1}.

2.3 Synthesis of phoxim

The aqueous solution of sodium oxime obtained in the previous step (Section 2.2) was taken and the pH of the reaction system was adjusted to 10 or 11. Subsequently, 1 equivalent of *O*,*O*-diethylthiophosphoryl chloride was added dropwise to the reaction system to maintain the temperature below 55°C. Keeping the temperature constant for 2 h, then check whether the reaction is complete by TLC (petroleum ether:ethyl acetate = 1:1). Then the pH of the reaction solution was adjusted to 8–9 by 30% liquid alkali. Separating it by the separating funnel, the aqueous layer was extracted with dichloromethane and incorporated into the organic layer. Next 70% hot water (50°C) was added to the organic layer, the pH adjusted to 8–9 by NaOH (30%), and the organic layer was separated. Repeat the step mentioned above, but adjust the pH to 6 after the addition of hot water (50°C) to the organic layer. The organic layer was dehydrated and rotary evaporated to obtain the yellow transparent liquid, phoxim, with a yield of 90%.

Phoxim: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.20 (t, $J = 6$ Hz, 3H), 1.29 (t, $J = 6$ Hz, 3H), 3.55–3.60 (m, 2H), 3.88–3.95 (m, 2H), 7.56 (t, $J = 8$ Hz, 3H), 7.80 (d, $J = 4$ Hz, 2H). IR (KBr) ν: 3,135, 2,980, 2,238, 1,496, 1,447, 1,400, 1,321, 1,162, 1,000, 855, 820, 768, 697, 669 cm^{-1}.

3 Results and discussion

Figure 1 shows that the types of alcohol affect the yield and *cis–trans* ratio of sodium oxime. The *cis–trans* isomer ratio of sodium oxime after the reaction of cyclohexyl methyl nitrite produced by cyclohexyl methanol with phenylacetonitrile, resulting in sodium oxime, is 3:2, the reason may be that the cyclohexyl ring is a twisted hexagonal structure with less steric hindrance and increased formation of sodium transoxime. Similarly, the ratio of *cis–trans* isomers of *n*-hexyl alcohol is 7:3; the reason may be that linear alkanes are not planar structures, and hence each bond-forming atom can freely rotate around the bond axis. Using benzyl alcohol as the starting material to produce benzyl nitrite, followed by further reaction with phenylacetonitrile, the sodium oxime produced under the optimal conditions generated almost (≥99%) *cis* structure under the premise that the yield was maintained at a high level. The mechanism may be that the benzene ring has a stable rigid structure and a large steric hindrance, making the reaction easier to generate a *cis* structure. In other words, the *α*-C of benzyl cyanide attacking the benzyl nitrite is more inclined to *cis* at a relatively high temperature, which greatly saved the cost of adjusting *cis–trans* isomerization and the safety is also improved.

When the reaction temperature is 45°C, the maximum yield of 90% of sodium oxime is obtained in 8–10 h, so 60°C is the optimal condition (Figure 2). Temperature will affect not only the yield of sodium oxime but also its *cis–trans*. Experiments show that at 60°C, not

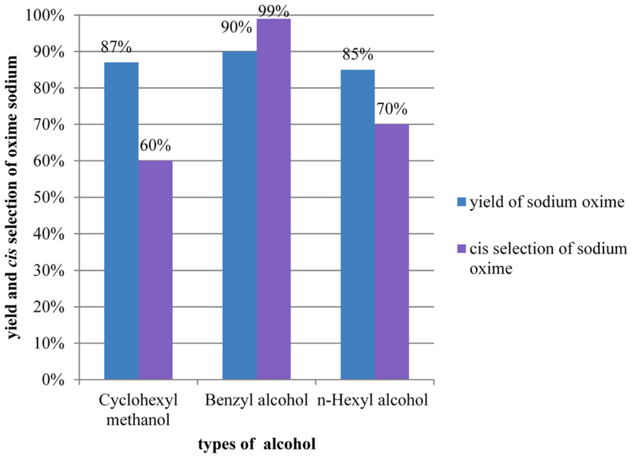


Figure 1: Effect of different alcohol on the yield of sodium oxime and proportion of *cis*-sodium oxime.

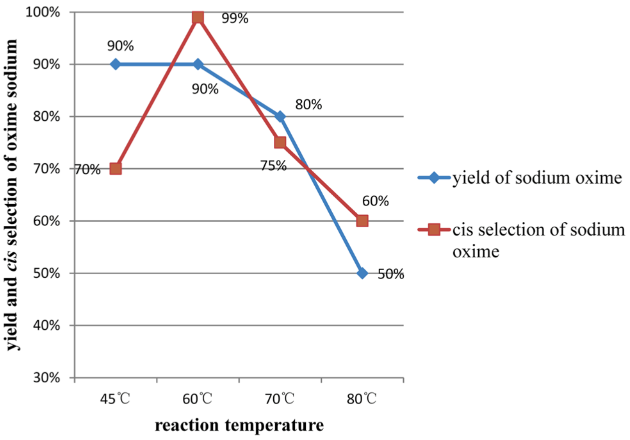


Figure 2: Effect of temperature on the yield of sodium oxime and proportion of *cis*-sodium oxime.

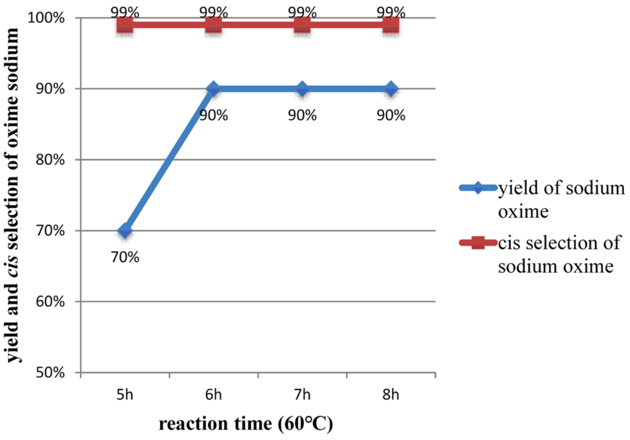
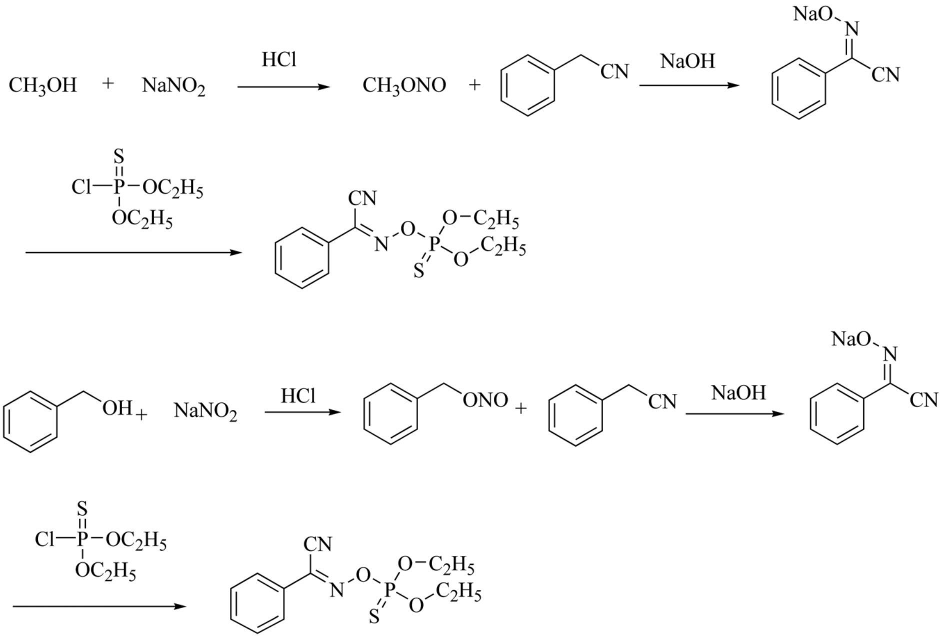


Figure 3: Effect of reaction time on the yield of sodium oxime and proportion of *cis*-sodium oxime at 60°C.



Scheme 3: Comparison of current and new methods.

only the yield of sodium oxime is the highest, but also the structure was required.

Figure 3 shows the best reaction condition is 6 h at 60°C, and extending the reaction time cannot have a more beneficial effect on the experiment.

After optimizing the experimental conditions, we know that the ratio of benzyl nitrite made in the first step to phenylacetonitrile is 1.3:1, the types of alkali has a great influence on the yield of sodium oxime, of which NaOH has the best effect, Na_2CO_3 has the poor effect and $NaHCO_3$ cannot even make the reaction proceed. Sodium hydroxide was used as the reaction reagent, and benzyl nitrite was added dropwise to control the temperature of system, after that the temperature was maintained for 2–3 h. Finally, the highest yield of sodium oxime was 90% and almost (≥99) in *cis* form, with no further refinement.

4 Conclusion

This article for the first time introduced macromolecular alcohol (benzyl alcohol, etc.) as the starting material in the synthesis of phoxim, compared with the current industrialized process using small molecular alcohols (methanol and ethanol) as the starting materials (Scheme 3). The new synthetic method has high safety that benzyl alcohol is not easy to blow up; good selectivity that sodium oxime is almost in a *cis* product (≥99%); cost reduction that reduce the procedure of waste water and waste acid dealing, which means that generated sodium oxime did not require further refinement. Through optimization of reaction conditions, the yield of phoxim was maintained at a high level (72.9%). Overall, our work provides a practical, safe, efficient and green method of phoxim synthesis.

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Author contributions: Changzan Dong, Guang Qian, and Jie Zhu contributed to the conception of the study; Changzan Dong and Jinwen Qiao performed the experiment; Hongwei Zhu and Guang Qian contributed significantly to analysis and manuscript preparation; Yupeng He and Jie Zhu helped in performing the analysis with constructive discussions; Changzan Dong and Guang Qian performed the data analysis and wrote the manuscript.

Conflict of interest: Authors state no conflict of interest.

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