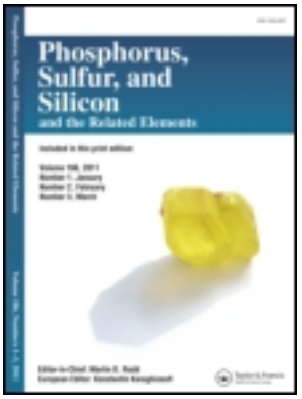


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

Investigation on the Acylation of Heterocyclic Alcoholate Anions with O,O-Dialkyl Phosphorochloridothioate in Water Solvent

Xin Ge [a] , Chao Qian [a] & Xinzhi Chen [a]

[a] Key Laboratory of Biomass Chemical Engineering of Ministry of Education , Zhejiang University , Hangzhou , China

Accepted author version posted online: 22 Jun 2012.Published online: 31 May 2013.

To cite this article: Xin Ge , Chao Qian & Xinzhi Chen (2013): Investigation on the Acylation of Heterocyclic Alcoholate Anions with O,O-Dialkyl Phosphorochloridothioate in Water Solvent, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:6, 739-744

To link to this article: http://dx.doi.org/10.1080/10426507.2012.702824

Phosphorus, Sulfur, and Silicon, 188:739–744, 2013

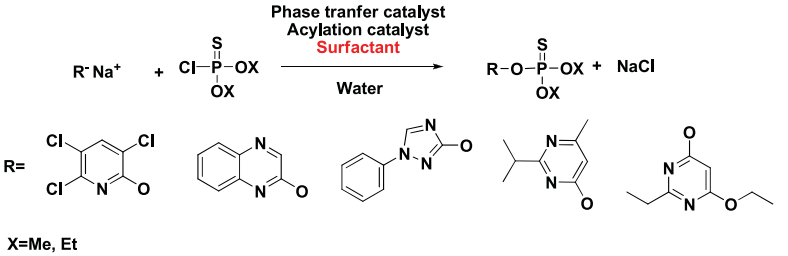
ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2012.702824

Taylor & Francis
Taylor & Francis Group

INVESTIGATION ON THE ACYLATION OF HETEROCYCLIC ALCOHOLATE ANIONS WITH O,O-DIALKYL PHOSPHOROCHLORIDOTHIOATE IN WATER SOLVENT

Xin Ge, Chao Qian, and Xinzhi Chen
Key Laboratory of Biomass Chemical Engineering of Ministry of Education, Zhejiang University, Hangzhou, China

GRAPHICAL ABSTRACT



Abstract *The acylation of some heterocyclic alcoholate anions with O,O-dialkyl phosphorochloridothioate has been investigated. Higher yields and fewer byproducts were achieved in water at 50 °C by employing an effective phase-transfer catalyst (PTC) (benzyl triethylammonium chloride [BTEAC]), acylation catalyst (AC) (4-dimethylaminopyridine), and surfactant (sodium dodecyl sulfate), under weakly basic (pH 9.5∼10) conditions. This reaction can also be applied to synthesize other insecticides with excellent yields.*

Keywords Acylation; heterocyclic alcoholate anion; O,O-dialkyl phosphorochloridothioate

INTRODUCTION

Phosphorothionate esters such as Chlorpyrifos (O,O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate), Quinalphos (O,O-diethyl O-quinoxalin-2-yl phosphorothioate), and Triazophos (O,O-diethyl O-1-phenyl-1H-imidazol-4-yl phosphorothioate) are known as powerful organophosphorus insecticides.[1–3] The major synthetic route to these products is the acylation of heterocyclic alcoholate anions with O,O-dialkyl phosphorochloridothioate.[2–12]

This reaction was performed in a single-phase[4–8] or two-phase solvent system[3,9–12] using several types of catalysts. To inhibit the hydrolysis of O,O-dialkyl phosphorochloridothioate, especially O,O-diethyl phosphorochloridothioate, whose hydrolyzate is the

Received 18 April 2012; accepted 19 May 2012.
This work was supported by the National Natural Science Foundation of China (21076183, 21006087) and the Key Innovation Group of Zhejiang Province (2009R50002).
Address correspondence to Xinzhi Chen, Key Laboratory of Biomass Chemical Engineering of Ministry of Education, Zhejiang University, Hangzhou 310027, China. E-mail: chemtec@163.com

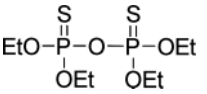


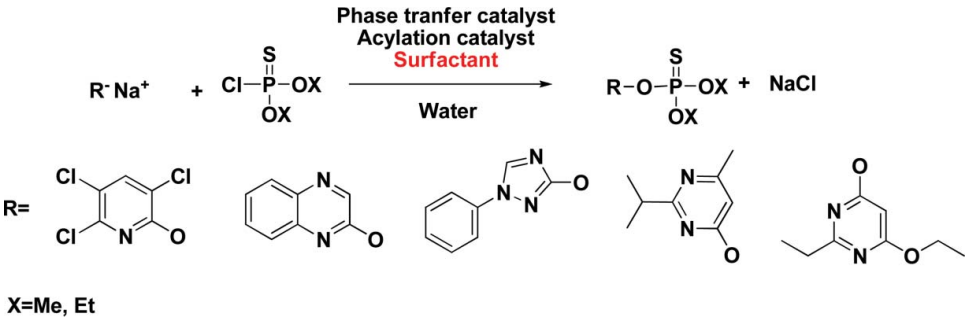
Figure 1 The structure of sulfotep.

highly toxic sulfotep (O,O,O',O'-tetraethyl dithiopyrophosphate, Figure 1), a two-phase solvent (water and a water-immiscible organic solvent) was extensively used.[3] O,O-dialkyl phosphorochloridothioate dissolves in the water-immiscible organic solvent to prevent hydrolysis in alkaline solution. However, it makes the process complex in that the water-immiscible organic solvent, e.g., toluene, must be distilled away and the product needs to be furnished by recrystallization. The single-phase solvent method (water) did not have these problems.[4–8] The focus on the single-phase solvent method was the inhibition of the O,O-dialkyl phosphorochloridothioate hydrolysis.

Efforts have been made to gain higher yields for this reaction through variations of solvent, catalyst, and concentration.[3–12] An acylation catalyst (AC) and a phase transfer catalyst (PTC) were used in combination to give a high yield in this acylation. AC increased the reaction rate to inhibit the hydrolysis of O,O-dialkyl phosphorochloridothioate. 4-Dimethylaminopyridine (DMAP) has been in a large range of applications as an AC for the acylation reaction of sterically hindered heterocyclic alcoholate anions.[13] Benzyl triethylammonium chloride (BTEAC) and benzyl trimethylammonium chloride (BTMAC) were the main compounds used as the PTC in this synthesis.[3–6,9,10,12] PEG26-2, both as PTC and surfactant, was used to increase the yield.[5]

Although the water solvent method has been reported in chlorpyrifos synthesis,[4–6,8] many factors of the process have not been discussed in detail. Sulfotep, which has been forbidden as an insecticide and affected the quality of the target product, was not studied further. On the other hand, the catalyst systems have not been systematically explored, even though several types of catalysts are used in the reaction. Except for chlorpyrifos synthesis, the water solvent method was not performed in the acylation between heterocyclic alcoholate anions and O,O-dialkyl phosphorochloridothioate.

In this article, we report a water solvent method to complete the acylation of heterocyclic alcoholate anions with O,O-dialkyl phosphorochloridothioate (Scheme 1), which can simplify the procedures. The experimental parameters are optimized for the yield and purity of the product.



Scheme 1 The acylation of some heterocyclic alcoholate anions with O,O-dialkyl phosphorochloridothioate in water.

Table 1 Effects of pH on the yield and purity[a]

Entry	pH	Sulfotep[b]/%	Yield[c]/%	Purity[d]/%
1	8.5–9	2.5	92.1	91.5
2	9–9.5	0.89	93.3	94.7
3	9.5–10	0.06	97.5	97.8
4	10–10.5	0.47	96.1	96.5
5	10.5–11	1.21	95.2	95.2

[a]Conditions: NaTCP (0.2 mol), O,O-diethyl phosphorochloridothioate (0.21 mol), DMAP (4 mmol), BTEAC (4 mmol), and SDS (1 mmol). All reactions were carried out in water at 50 °C for 2 h.

[b]Determined by GC using capillary column.

[c]Isolated yield.

[d]Determined by HPLC using a reverse-phase C18 column with a mobile phase: acetonitrile/water/aceticacid = 750/245/5 (V) at 1.0 mL/min.

RESULTS AND DISCUSSION

Initially, we studied the synthesis of chlorpyrifos in water solvent as the model reaction. This reaction between the sodium salt of 3,5,6-trichloropyridin-2-ol (NaTCP) and O,O-diethyl phosphorochloridothioate depended on some main factors such as PTC, AC, surfactant, and their respective concentrations, pH, temperature, and the reaction time.

Control of the pH was the first task for the present study. The heterocyclic alcoholate anion was synthesized from a mineral base (such as NaOH) and the necessary heterocyclic alcohol.[14] Weak base reduced the reactivity of heterocyclic alcoholate anion (entries 1–2, Table 1), which decreased the main reaction rate resulting in lower yield and purity. Strong base could lead to the hydrolyzation of O,O-diethyl phosphorochloridothioate (entries 4–5, Table 1). Finally, the pH was controlled at 9.5–10, which was identified to be the best for the reactivity of heterocyclic alcoholate anion and the purity of the product.

Generally, steric hindrance of the heterocyclic alcohol determined the difficulty of the reactions. High steric hindrance led to weak nucleophilic ability of the heterocyclic alcohol.

Table 2 The acylation of NaTCP with O,O-diethyl phosphorochloridothioate in water under different conditions[a]

Entry	AC (mol %)	PTC (mol %)	Surfactant (mol %)	Time/h	Temp/°C	Sulfotep[b]/%	Yield[c]/%	Purity[d]/%
1	TMA(4)	–	–	4	60	–	Trace	–
2	TEA(4)	–	–	4	60	–	Trace	–
3	DMAP(4)	–	–	4	60	6.5	81.2	76.3
4	DMAP(2)	BTMAC(2)	–	2	50	3.5	91.7	92.7
5	DMAP(2)	TBAB(2)	–	2	50	2.4	93.0	93.5
6	DMAP(2)	BTEAC(2)	–	2	50	2.6	92.1	93.2
7	DMAP(2)	BTEAC(2)	PEG-400(0.5)	2	60	0.57	94.9	95.7
8	DMAP(2)	BTEAC(2)	SDS(0.5)	1	60	0.21	95.5	96.1
9	DMAP(2)	BTEAC(2)	SDS(0.5)	1	50	0.11	93.4	94.6
10	DMAP(2)	BTEAC(2)	SDS(0.5)	2	50	0.06	97.5	97.8

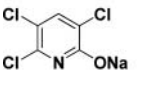
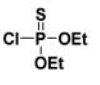
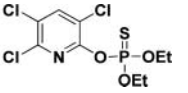
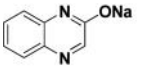
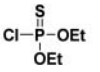
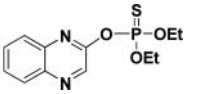
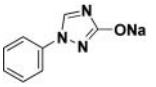
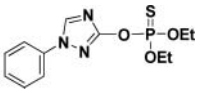
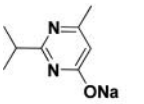
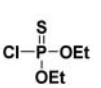
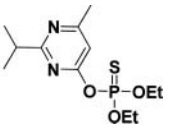
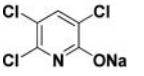
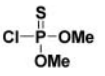
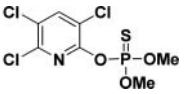
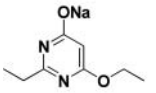
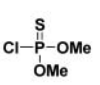
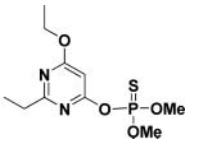
[a]Conditions: NaTCP (0.2 mol), O,O-diethyl phosphorochloridothioate (0.21 mol).

[b]Determined by GC using capillary column.

[c]Isolated yield.

[d]Determined by HPLC using a reverse-phase C18 column with mobile phase: acetonitrile/water/aceticacid = 750/245/5 (V) at 1.0 mL/min.

Table 3 The acylation of heterocyclic alcoholate anions with O,O-dialkyl phosphorochloridothioate in water[a]

Entry	Substrate 1	Substrate 2	Product	Sulfotep[b] /%	Yield[c] /%	Purity[d] /%
1				0.06	97.5	97.8
2				0.12	94.1	95.7
3				0.09	93.1	95.3
4				0.03	98.4	97.6
5				—	93.4	94.6
6				—	94.1	95.2

[a]All reactions were run with substrate 1 (0.2 mol), substrate 2 (0.21 mol), DMAP(4 mmol), BTEAC(4 mmol), and SDS(1 mmol) in the solution of pH 9.5–10 at 50 °C for 2 h.

[b]Determined by GC using capillary column.

[c]Isolated yield.

[d]Determined by HPLC using a reverse-phase C18 column with mobile phase: acetonitrile/water/aceticacid = 750/245/5 (V) at 1.0 mL/min.

Further, the difficulty occurred in the reaction because O,O-diethyl phosphorochloridothioate is water insoluble. For sterically hindered heterocyclic alcohols, acylation is so difficult that AC is required. It was reported that tertiary amines such as trimethylamine (TMA), triethylamine (TEA), and DMAP gave the best performance for this reaction.[3] Therefore TMA, TEA, and DMAP as AC were employed early in this work. In the absence of PTC and surfactant, DMAP proved to be the most efficient AC for this reaction. Other ACs, such as TMA and TEA, could not promote the product formation (entries 1–2, Table 2). It was consistent with the previous report.[3] It made little difference when BTMAC, tetrabutyl ammonium bromide (TBAB), or BTEAC was used, respectively, in this reaction as the PTC (entries 4–6, Table 2). Taking the cost into account, BTEAC was chosen as the PTC. The amount of sulfotep, which was an unexpected byproduct, was significantly reduced to less than 1% in the presence of surfactant (entries 7–8, Table 2). Due to enhancement of the mass transfer of O,O-diethyl phosphorochloridothioate and NaTCP, the surfactant accelerated the reaction rate. Based on the diminution of sulfotep, sodium dodecyl sulfate

(SDS) was found to be better than PEG-400 in this reaction. Next, the temperature and the time were studied, and the optimal conditions were screened (entries 8–10, Table 2). 2 mol % DMAP, 2 mol % BTEAC, and 0.5 mol % SDS gave a satisfactory yield and a minimum of sulfotep at 50 °C for 2 h using water as the solvent in the chlorpyrifos synthesis.

After the optimal reaction conditions were identified, some insecticides were examined as shown in Table 3, including quinalphos, triazophos, diazinon (O,O-diethyl O-2-isopropyl-6-methylpyrimidin-4-yl phosphorothioate), chlorpyrifos-methyl (O,O-dimethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate), and etrimfos (O,O-dimethyl O-6-ethoxy-2-ethylpyrimidin-4-yl phosphorothioate), which were synthesized from heterocyclic alcoholate ions with O,O-dialkyl phosphorochloridothioate. It was confirmed that this protocol could be extended to some different heterocyclic alcoholate anions. The nitrogen atom with a large electronegativity character caused the electron density of the carbon atoms in the heterocycle to decrease. It decreased the nucleophilicity of alcoholate ions. An increased number of nitrogen atoms resulted in a lower yield (entries 2–3, Table 3). The heterocycle possessing electron-donating functional groups was found to give better yields than those with electron-withdrawing (entries 1–4, Table 3). It is notable that O,O-diethyl phosphorochloridothioate is more highly reactive than O,O-dimethyl phosphorochloridothioate (entries 5 vs. 1, 6, Table 3). To our delight, the reaction preceeded smoothly with these heterocyclic alcoholate anions and afforded the products in good yields. The byproduct was successfully inhibited.

CONCLUSION

In summary, good yields and purity make the water solvent method attractive for the acylation of heterocyclic alcoholate anions with O,O-dialkyl phosphorochloridothioate. The focus on this reaction was how to accelerate the reaction rate leading to inhibition of the O,O-dialkyl phosphorochloridothioate hydrolysis. As the most efficient AC against sterical hindrance, DMAP was introduced to this reaction. The PTC and surfactant were used in combination to enhance the mass transfer of O,O-dialkyl phosphorochloridothioate and the heterocyclic alcoholate anions. Thus, in the presence of DMAP, TEBAC, and SDS, the formation of sulfotep was almost prevented.

EXPERIMENTAL

General methods. Melting points were determined by using the capillary method on WRR mp apparatus. GC analyses were performed on GC Agilent 1790F series. HPLC analyses were executed on HPLC Agilent 1100 series charged with C18 column. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on a Bruker NMR spectrometer (400 MHz for ^{1}H NMR; 100 MHz for 13C NMR)

General procedure for the synthesis of chlorpyrifos. To a stirred solution of NaTCP 44.1 g (0.2 mol) and water 200 g at 50 °C was added DMAP 0.49 g (4 mmol), BTEAC 0.91 g (4 mmol), and SDS 0.29 g (1 mmol). Then 98 wt% O,O-diethyl phosphorochloridothioate 33.8 ml (0.21 mol) was added dropwise during 30 min. The pH of this solution was adjusted to 9.5–10 at 50 °C by adding 30 wt % K_2CO_3 dropwise. With continuous stirring, the reaction mixture changed to a light yellow emulsion from white suspension. Stirring was maintained for 2 h. The organic and aqueous layers were separated at 70 °C. The organic layer was washed with water (150 mL) at 70 °C. After vacuum recovery of water

(70 °C, 18 mmHg), the organic phase was crystallized by cooling to afford a colorless solid.

REFERENCES

1. Kolindandersen, H.; Lawesson, S. O. *Acta Chem. Scand.* **1975**, 29B, 430–440.
2. Kenaga, E. E.; Whitney, W. K.; Hardy, J. L.; Doty, A. E. *J Econ. Entom.* **1965**, 58, 1043–1050.
3. Fakhraian, H.; Moghimi, A.; Ghadiri, H.; Dehnavi, M. A.; Sadeghi, M. *Org. Process Res. Dev.* **2004**, 8, 680–684.
4. Xu, G. Q. *Xiandai Nongyao.* **2009**, 8, 22–24.
5. Steling, C. G.; Midland, M. US Patent, 4,814,451(A), *Chem. Abstr.* **1989**, 111, 214699.
6. Zonia, G. C.; Marc, E. H. US Patent, 5,120,846(A), *Chem. Abstr.* **1992**, 117, 90510.
7. SATO, Y. JP Patent, 07,082,284(A), *Chem. Abstr.* **1995**, 123, 228516.
8. Xu, G. Q. CN Patent, 1,858,055, *Chem. Abstr.* **2006**, 146, 7831.
9. Lorraine, M. K.; Masao, Y. US Patent, 4,016,225, *Chem. Abstr.* **1977**, 87, 23070.
10. Steling, C. G.; Karl, L. K. US Patent, 4,814,448(A), *Chem. Abstr.* **1989**, 111, 97504.
11. Kobayashi, H.; Maruyama, H.; Sanada, H.; Toukosono, K.; Noda, S. JP Patent, 3,153,694, *Chem. Abstr.* **1991**, 115, 256393.
12. Kobayashi, H.; Maruyama, H.; Kawata, H. Noda, S. US Patent, 5,169,955; *Chem. Abstr.* **1991**, 115, 232291.
13. Grondal, C. *Synlett.* **2003**, 10, 1568–1569.
14. Zhao, D. F.; Chen, X. R. *Chin. J. Org. Chem.* **2001**, 31, 768–771.