

A practical synthetic method for vinyl chlorides and vinyl bromides from ketones via the corresponding vinyl phosphate intermediates

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Abstract—A new synthetic method for the preparation of vinyl chlorides and vinyl bromides from acyclic and cyclic ketones is described. Vinyl halides are practically obtained from the corresponding vinyl phosphate intermediates with triphenylphosphine dihalide.

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Vinyl halides have become important intermediates in organic synthesis for C–C and C–N bond formation such as Pd-catalyzed coupling reaction¹ and vinyl radical cyclization.² Recently, we have reported SUN N4057, which has a vinyl chloride moiety, as a pharmaceutical candidate for the treatment of acute phase of cerebral infarction (Figure 1).³ In this research project, we need to develop a practical synthetic method for vinyl halides. Although vinyl halides in general are prepared from alkynes⁴ and/or aldehydes,⁵ these methods are restricted to the application of simple substrates such as terminal vinyl halides. Vinyl halides can also be synthesized from ketones by using acetyl halide in a strong acid solvent,⁶ thionyl chloride,⁷ phosphorus trihalide,⁸ phosphorus pentahalide,⁹ phosphorus oxyhalide,^{3,10} and so on.^{11,12} However these methods suffer from disadvantages such as usage of a large amount of acid

halide, low yields in some cases, contamination of inseparable *gem*-halide compounds¹¹ and/or various other by-products.^{8,12,13} To make matters worse, at the work-up procedure there are risks of generating acid gas, a sudden rise in temperature and a bumping in the neutralization reaction for treatment and decomposition of the excessive acid halide and, therefore, these method are unsuitable for the industrial scale of application.

In this letter, we present a facile preparation of vinyl halides **3** from ketones **1** via the corresponding vinyl phosphate intermediates **2** with triphenylphosphine dichloride and triphenylphosphine dibromide (Scheme 1).

Triphenylphosphine dichloride (Ph₃P·Cl₂) and triphenylphosphine dibromide (Ph₃P·Br₂) were used as obtained from commercial sources. Vinyl phosphates **2** were obtained from ketones **1** in reasonable yields (67–100%) according to the procedure similar to that described in the literatures.¹⁴ Vinyl phosphate **2** was treated with 1.2 equiv of fresh Ph₃P·Cl₂ or Ph₃P·Br₂ in acetonitrile at room temperature, giving the corresponding vinyl halide **3** in 2 h.¹⁵ As shown in Table 1, chlorination and bromination of vinyl phosphates **2** with Ph₃P·Cl₂ and Ph₃P·Br₂ proceeded smoothly in suitable yields (54–91%). Not only acyclic ketone **1a** but also cyclic ketones **1b**, **1c** were converted to vinyl halide derivatives (entries 1–6). We have found that this method was

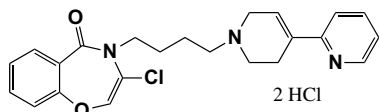
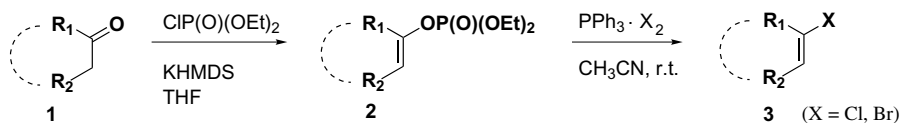


Figure 1. Structure of SUN N4057.

Keywords: Vinyl chlorides; Vinyl bromides; Ketones; Vinyl phosphates; Triphenylphosphine dihalides; SUN N4057.

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Scheme 1. Preparation of vinyl halides **3** from ketones **1** via the corresponding vinyl phosphates **2**.

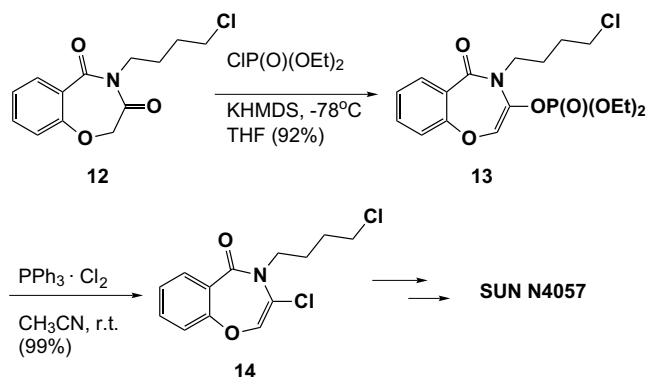
Table 1. Chlorination and bromination of vinyl phosphate **2**

| Entry | Ketone 1 | Vinyl phosphate 2 | Reagent | Vinyl halide 3 | % Yield from 2 |
|-------|-----------------|--------------------------|-----------------------------------|-----------------------|-----------------------|
| 1 | | | PPh ₃ ·Cl ₂ | | 70 |
| 2 | 1a | 2a | PPh ₃ ·Br ₂ | | 69 |
| 3 | | | PPh ₃ ·Cl ₂ | | 83 |
| 4 | 1b | 2b | PPh ₃ ·Br ₂ | | 54 |
| 5 | | | PPh ₃ ·Cl ₂ | | 61 |
| 6 | 1c | 2c | PPh ₃ ·Br ₂ | | 64 |
| 7 | | | PPh ₃ ·Cl ₂ | | 91 |
| 8 | 1d | 2d | PPh ₃ ·Br ₂ | | 87 |

applicable to the imide **1d** as well, giving vinyl halides in high yields (entry 7, 8). By the same procedure the vinyl chloride **14**, the intermediate compound for SUN N4057, was synthesized from imide **12**³ via the corresponding vinyl phosphate **13** in good yield (Scheme 2). In all cases, no by-product was observed and the work-up process was easy and safe (see a typical procedure¹⁵).

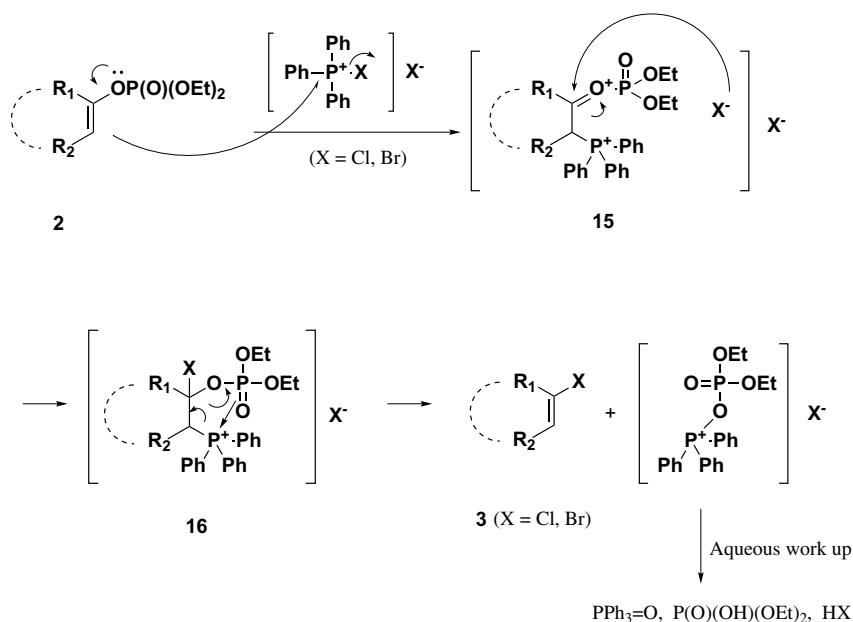
Although a reaction of β -diketones with triphenylphosphine dihalides has been reported,¹⁶ in which conjugate addition of halide ion to β -triphenylphosphoniumoxy α,β -unsaturated ketones afford β -halo α,β -unsaturated ketones, monocarbonyl compound did not directly react with triphenylphosphine dihalides. In our new method, once a monocarbonyl compound **1** is converted to the corresponding vinyl phosphate intermediate **2**, it may be easily transformed into vinyl halide **3**.¹⁷

A tentative reaction mechanism is as follows (Scheme 3). A vinyl phosphate intermediate **2** reacts with PPh₃ activ-



Scheme 2. Application to the intermediate **12** of SUN N4057.

ated by X₂ (X = Cl, Br), giving an oxonium-triphenylphosphonium derivative **15**. A halide ion consecutively attacks carbonyl moiety to form a carbon–halide bond. Intramolecular transfer and elimination reaction of **16**



Scheme 3. A tentative reaction mechanism.

smoothly occurs to generate the vinyl halide **3** and PPh₃=O.

In summary, we described a new practical synthetic method for the preparation of vinyl chlorides and vinyl bromides from acyclic ketones as well as cyclic ketones via the corresponding vinyl phosphate intermediates. This new process is satisfactory in an industrial scale of production since the work-up procedure is easy to operate. Moreover, this method is applicable to imide carbonyl moiety, and now we have applied to the industrial production of SUN N4057. The reaction mechanism in detail and applications to more versatile substrates are currently under investigation.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2004.11.075](https://doi.org/10.1016/j.tetlet.2004.11.075).

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- A typical procedure is as follows:* to a stirred solution of 4-methyl-1,4-benzoxazepin-5(4H)-one-3-yl diethyl phosphate **2d** (176 mg, 0.54 mmol) in 4 mL of anhydrous acetonitrile was added triphenylphosphine dichloride (214 mg, 0.65 mmol) at room temperature under argon atmosphere, and then stirring was continued for 2 h. The reaction mixture was diluted with EtOAc (20 mL) and washed with a saturated solution of NaHCO₃ and brine. After drying over MgSO₄, removal of the solvent in vacuo gave a residue, which was chromatographed over SiO₂ using *n*-hexane/EtOAc (6:1) as an eluent to give the vinyl chloride **10** (103 mg, 91%). Colorless oil; ¹H NMR (CDCl₃)δ 3.30 (s, 3H), 6.65 (s, 1H), 7.02 (d, 1H, *J* = 8 Hz), 7.24 (t, 1H, *J* = 8 Hz), 7.45 (t, 1H, *J* = 8 Hz), 7.91 (d, 1H, *J* = 8 Hz); IR (CHCl₃) cm⁻¹: 1657, 1605,

- 1454, 1358, 1339; FABMS m/z : 210 $[MH]^+$; HRMS: calcd for $C_{10}H_9ClNO_2$ 210.0322 $[MH]^+$. Found 210.0316.
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17. In Ref. 11, a reaction of cyclohexanone with $Ph_3P \cdot Cl_2$ has been described. Although we took a makeup, 1-chloro-cyclohexene was not generated at all. It was also found that all substrates **1a–d**, **12** were unreactive with $Ph_3P \cdot Cl_2$ directly.