IN SITU GENERATION OF FORMALDEHYDE AND TRIPHENYLPHOSPHINE FROM (HYDROXYMETHYL)TRIPHENYLPHOSPHONIUM AND ITS APPLICATION IN WITTIG OLEFINATION

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GRAPHICAL ABSTRACT

Abstract The reaction of (hydroxymethyl)triphenylphosphonium with benzylic or allylic halide under basic conditions at room temperature affords terminal alkenes in 61–89% yields. In this reaction, both formaldehyde and triphenylphosphine are in situ generated from (hydroxymethyl)triphenylphosphonium and further undergo Wittig olefination with benzylic or allylic halide.

Keywords Formaldehyde; (hydroxymethyl)triphenylphosphonium; triphenylphosphine; terminal alkene; Wittig olefination

INTRODUCTION

Formaldehyde is a hazardous, self-reactive chemical and is usually in situ generated from either its oligomer (paraformaldehyde) or aqueous solution (formalin).\textsuperscript{[1]} A large excess of paraformaldehyde or formalin is often required to complete a reaction, in particular under basic conditions. For example, in the Wittig olefination of formaldehyde with semistabilized ylides, the molar ratio of formaldehyde to the phosphonium salt is often 5–10\textsuperscript{[2–5]} and even greater than 50.\textsuperscript{[6]} Therefore, development of new methods to in situ generate formaldehyde under...
basic conditions is highly desired. In 2007, Deguest and coworkers reported\textsuperscript{[7]} a novel method to generate formaldehyde in situ using benzotriazolylmethanol or $N$-hydroxymethyl phthalylimide under basic and anhydrous conditions, as shown in the upper part of Scheme 1. They have applied this method in the hydroxymethylation of organolithium reagents and enolates. They have also employed this method in the Wittig olefination of one semistabilized ylide but the corresponding phosphonium salt needs to be prepared in advance and a strong base (lithium tetramethylpiperidide) is required. Recently, Priede and coworkers also reported\textsuperscript{[8]} that methoxymethanol is a source of formaldehyde in the hydroxymethylation of lithium enamides. Herein, we report an alternative method to generate formaldehyde in situ by treating (hydroxymethyl)phosphonium with $K_2CO_3$, as shown in the bottom part of Scheme 1. Both formaldehyde and the concomitantly released $Ph_3P$ are utilized to participate in Wittig olefination of benzylic or allylic halides to afford terminal alkenes.

**RESULTS AND DISCUSSION**

Initially we chose (hydroxymethyl)triphenylphosphonium tetrafluoroborate 1\textsubscript{a} as a model compound to explore the possibility of the in situ generation of formaldehyde. This salt is a bench-stable solid and readily prepared from triphenylphosphine and paraformaldehyde according to the reported method.\textsuperscript{[9]} It is noteworthy that a 1:1 molar ratio of formaldehyde to triphenylphosphine is used to prepare this salt. To utilize the concomitant release of $Ph_3P$ during the in situ generation of formaldehyde, we hypothesized that a benzylic or allylic halide would trap it to form the corresponding phosphonium salt, which under basic condition would further react with formaldehyde to form terminal alkene 3, as shown in Scheme 2. Therefore, we chose 2-bromomethylnaphthalene 2\textsubscript{a} as another model compound to test our hypothesis.

When a mixture of 1\textsubscript{a} and 2\textsubscript{a} were treated with $K_2CO_3$ in tetrahydrofuran (THF), 2-vinylnaphthalene 3\textsubscript{a} was obtained in 16\% yield (Table 1, entry 1). After screening solvents including $CH_2Cl_2$, dimethylsulfoxide (DMSO), and $CH_3CN$ (entries 2–4), $CH_3CN$ was found to be the best solvent to afford 3\textsubscript{a} in 87\% yield. Replacing 1\textsubscript{a} with the corresponding iodide 1\textsubscript{b} and chloride 1\textsubscript{c} reduced the yield...
of 3a to 38% and 59%, respectively, indicating that the anion might play a key role in the reaction. We have also prepared tricyclohexyl(hydroxymethyl)phosphonium tetrafluoroborate 1d according to the similar method for the preparation of 1a. This salt could also lead to the formation of 3a albeit in a lower yield (53%).

We next examined a variety of benzylic and allylic halides, and the results were summarized in Table 2. For benzylic bromides 2b–d with an electron-donating group at the para-position of aromatic ring, 3b–d were obtained in 73–79% yields (entries 2–4). 1,4-Bis(bromomethyl)benzene 2e underwent diolefination smoothly to give 3e in 69% yield when 2 equiv of 1a was used (entry 5). Allylic halides such as cinnamyl bromide 2f and α-bromomethylstyrene 2h afforded the corresponding 1,4-dienes in 82% and 61% yields (entries 6 and 8), respectively. Benzylic bromides with an electron-withdrawing group at either ortho- or para- or meta-position of aromatic ring furnished olefination in good yields (81–89%) (entries 9, 10, and 12–18). For cinnamyl chloride 2g and 4-chlorobenzyl chloride 2k, however, 3f and 3i was obtained in very poor yields (entries 7 and 11), probably because the reaction of Ph3P is slower with benzylic or allylic chloride than with the corresponding bromide. By replacing 1a with 1b, the yields of 3f and 3i dramatically increased to 61% and 69%, respectively, possibly due to the chloride–iodide exchange to form benzylic or allylic iodide, which is much more reactive toward Ph3P than the corresponding chloride. Attempts to expend this reaction to alkyl halides other than benzylic or allylic halides were unsuccessful.

Table 2. Wittig olefination using (hydroxymethyl)phosphonium salt.

| Entry | R          | X      | Solvent | Yield (%) |
|-------|------------|--------|---------|-----------|
| 1     | Ph         | BF4    | THF     | 16        |
| 2     | Ph         | BF4    | CH2Cl2  | 40        |
| 3     | Ph         | BF4    | DMSO    | 61        |
| 4     | Ph         | BF4    | CH3CN   | 87        |
| 5     | Ph         | I      | CH3CN   | 38        |
| 6     | Ph         | Cl     | CH3CN   | 59        |
| 7     | Cyclohexyl | BF4    | CH3CN   | 53        |

*Reaction conditions: 1 (0.5 mmol), 2a (0.5 mmol), K2CO3 (1.0 mmol), solvent (5 mL), rt, overnight.  
Isolated yield by preparative TLC.*
Table 2. Synthesis of terminal alkenes using (hydroxymethyl)phosphonium salts

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\begin{align*}
\text{Ph}_3\text{P}^+\text{OH} + X = \text{R} & \xrightarrow{\text{K}_2\text{CO}_3} \text{R} \\
\text{1a} & \xrightarrow{\text{CH}_3\text{CN, rt}} \text{2} \rightarrow \text{3}
\end{align*}
\]

| Entry | 2 | 3, yield | Entry | 2 | 3, yield |
|-------|---|----------|-------|---|----------|
| 1     | \begin{align*} \text{2a} \\
& \text{3a, 87%} \end{align*} | 10  | Cl  | \begin{align*} \text{2j} \\
& \text{3i, 81%} \end{align*} |
| 2     | \begin{align*} \text{2b} \\
& \text{3b, 73%} \end{align*} | 11  | Cl  | \begin{align*} \text{2k} \\
& \text{3i, 69%} \end{align*} |
| 3     | \begin{align*} \text{2c} \\
& \text{3c, 79%} \end{align*} | 12  | MeOOC | \begin{align*} \text{2l} \\
& \text{3j, 85%} \end{align*} |
| 4     | \begin{align*} \text{2d} \\
& \text{3d, 79%} \end{align*} | 13  | NC  | \begin{align*} \text{2m} \\
& \text{3k, 85%} \end{align*} |
| 5     | \begin{align*} \text{2e} \\
& \text{3e, 69%} \end{align*} | 14  | CN  | \begin{align*} \text{2n} \\
& \text{3l, 87%} \end{align*} |
| 6     | \begin{align*} \text{2f} \\
& \text{3f, 82%} \end{align*} | 15  | O_2N | \begin{align*} \text{2o} \\
& \text{3m, 88%} \end{align*} |
| 7     | \begin{align*} \text{2g} \\
& \text{3f, 61%} \end{align*} | 16  | NO_2 | \begin{align*} \text{2p} \\
& \text{3n, 89%} \end{align*} |
| 8     | \begin{align*} \text{2h} \\
& \text{3g, 61%} \end{align*} | 17  | O_2N | \begin{align*} \text{3o, 88%} \end{align*} |
| 9     | \begin{align*} \text{2i} \\
& \text{3h, 88%} \end{align*} | 18  | 2r  | \begin{align*} \text{3p, 87%} \end{align*} |

\*Reaction conditions: 1a (0.5 mmol), 2 (0.5 mmol), K_2CO_3 (1.0 mmol), CH_3CN (5 mL), rt, overnight (15–20 h, monitored by TLC).
\*Isolated yield by preparative TLC.
\*Using 1a (1.0 mmol) and K_2CO_3 (2.0 mmol).
\*Using 1b instead of 1a, which gave 3f in only 17% yield.
\*Using 1b instead of 1a, which gave 3i in only 19% yield.
CONCLUSIONS

In conclusion, we have demonstrated that (hydroxymethyl)triphenylphosphonium salts can be used as a source of both formaldehyde and triphenylphosphine, which can be applied in Wittig olefination of benzylic and allylic halides. This olefination can be carried out under mild conditions and avoid using a large excess of formaldehyde and preparing benzylic or allylic triphenylphosphonium salts.

EXPERIMENTAL

Triphenylphosphine, benzylic, and allylic halides were purchased from a local company and used as received. All melting points were measured on a melting-point apparatus with a microscope and a hot stage and were uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance 400 or 600 NMR spectrometer. Infrared (IR) spectra were recorded on a Thermo Nicolet Avatar 360 IR spectrometer. High-resolution mass spectrogaphic (HRMS) spectra were recorded on a Varian 7.0 T FTMS. PE denotes petroleum ether, bp 60–90 °C. Phosphonium salts $1_a$, $1_b$, and $1_c$ were prepared according to the literature procedure.

**General Procedure for Wittig Olefination Using (Hydroxymethyl)triphenylphosphonium Salts**

To a round-bottom flask (25 mL), $1$ (0.5 mmol), $2$ (0.5 mmol), K$_2$CO$_3$ (1.0 mmol), and solvent (5 mL) were added. After stirring at room temperature overnight, the reaction mixture was evaporated under reduced pressure, and the residue was separated by preparative TLC (silica gel, eluted with PE or PE/EtOAc 50:1) to afford the alkene $3$.

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SUPPORTING INFORMATION

Full experimental details and $^1$H and $^{13}$C NMR spectra for this article can be accessed on the publisher’s website.

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