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In situ generation of formaldehyde and triphenylphosphine from (hydroxymethyl)triphenylphosphonium and its application in Wittig olefination

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Abstract

The reaction of (hydroxymethyl)triphenylphosphonium with benzylic or allylic halide under basic condition 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.



R = Ar, vinyl; X = Br, Cl; Y = I, Cl, BF₄ 16 examples, 61-89%

KEYWORDS: formaldehyde; triphenylphosphine; Wittig olefination;

(hydroxymethyl)triphenylphosphonium; terminal alkene

INTRODUCTION

Formaldehyde is a hazardous, self-reactive chemical and usually in situ generated from either its oligomer (paraformaldehyde) or aqueous solution (formalin).^[1] A large excess of paraformaldehyde or formalin is often required to complete a reaction, in particular, under basic condition. For example, in the Wittig olefination of formaldehyde with semi-stabilized ylides, the molar ratio of formaldehyde to the phosphonium salt is often and even greater than 50.^[6] Therefore, to develop new methods to in situ 5-10.^[2-5] generate formaldehyde under basic condition is highly desired. In 2007, Bischoff and coworkers reported^[7] a novel method to in situ generate formaldehyde using benzotriazolylmethanol or N-hydroxymethyl phtahlimide 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 semi-stabilized ylide but the corresponding phosphonium salt needs to be prepared in advance and a strong base (lithium tetramethylpiperidide) is required. Recently, Suna and coworkers also reported^[8] that methoxymethanol is a source of formaldehyde in the hydroxymethylation of lithium enamides. Herein, we report an alternative method to in situ generate formaldehyde 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 tetrafluorobrate **1a** 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.^[9] It is noteworthy that a 1:1 molar ratio of formaldehyde to triphenylphosphine is used to prepare this salt. In order 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 **2a** as another model compound to test our hypothesis.

When a mixture of **1a** and **2a** were treated with K_2CO_3 in THF, 2-vinylnaphthalene **3a** was obtained in 16% yield (Table 1, entry 1). After screening solvents including CH_2Cl_2 , DMSO, and CH_3CN (entries 2-4), CH_3CN was found to be the best solvent to afford **3a** in 87% yield. Replacing **1a** with the corresponding iodide **1b** and chloride **1c** 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 low 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.

CONCLUSIONS

In conclusion, we have demonstrated that (hydroxymethyl)triphenylphosphonium salts can be used as a source of both formaldehyde and tiphenylphophine, 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 and 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. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 or 600 NMR spectrometer. IR spectra were recorded on a Thermo Nicolet Avatar 360 IR spectrometer. HRMS spectra were recorded on a Varian 7.0 T FTMS. PE = Petroleum ether, bp 60-90 °C. Phosphonium salts **1a**,^[9] **1b**,^[10] and **1c**^[10] 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_2CO_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 detail, ¹H and ¹³C NMR spectra for this article can be accessed on the

publisher's website.

REFERENCES

- 1. Shreiber, E. H.; Roberts, G. W. Chem. Ind. (Dekker) 2001, 82, 391.
- 2. Medard, G. Tetrahedron 2014, 70, 186.
- 3. Markovac, A.; LaMontagne, M. P. J. Med. Chem. 1980, 23, 1198.
- 4. Jacober, S. P.; Hanzlik, R. P. J. Am. Chem. Soc. 1986, 108, 1594.

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5. Garcia-Rubin, S.; Gonzalez-Rodriguez, C.; Garcia-Yebra, C.; Varela, J. A.;

Esteruelas, M. A.; Saa, C. Angew. Chem., Int. Ed. 2014, 53, 1841.

- 6. Jiang, X.-K.; Ji, G.-Z.; Wang, D. Z.-R. J. Fluorine Chem. 1996, 79, 173.
- 7. Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. Org Lett 2007, 9, 1165.
- Priede, M.; Kazak, M.; Kalnins, T.; Shubin, K.; Suna, E. J. Org. Chem. 2014, 79, 3715.
- 9. Burton, D. J.; Wiemers, D. M. J Fluorine Chem 1985, 27, 85
- 10. Davis, M. C.; Parrish, D. A. Synthetic Commun 2008, 38, 3909.

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1	2a					
Entry	R	Х	1	Solvent	Yield ^b	N.
					(%)	S
1	Ph	BF ₄	1a	THF	16	
2	Ph	BF ₄	1a	CH ₂ Cl ₂	40	
3	Ph	BF ₄	1a	DMSO	61	
4	Ph	BF ₄	1 a	CH₃CN	87	
5	Ph	Ι	1b	CH ₃ CN	38	
6	Ph	Cl	1c	CH ₃ CN	59	
7	Cyclohexyl	BF ₄	1d	CH ₃ CN	53	

(hydroxymethyl)phosphonium^a

^a Reaction conditions: 1 (0.5 mmol), 2a (0.5 mmol), K₂CO₃ (1.0 mmol), solvent (5 mL),

rt, overnight.^b Isolated yield by preparative TLC.



Table 2. Synthesis of terminal alkenes using (hydroxymethyl)phosphonium salts^a

^a Reaction conditions: 1a (0.5 mmol), 2 (0.5 mmol), K₂CO₃ (1.0 mmol), CH₃CN (5 mL), rt, overnight (15-20 h, monitored by TLC). ^b Isolated yield by preparative TLC. ^c Using 1a (1.0 mmol) and K₂CO₃ (2.0 mmol). ^d Using 1b instead of 1a which gave 3f in only 17% yield. ^e Using 1b instead of 1a which gave 3i in only 19% yield.





Scheme 2. Wittig olefination using (hydroxymethyl)phosphonium salt

