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LETTERS

The 'Hirao reduction' revisited: a procedure for the synthesis of terminal vinyl bromides by the reduction of 1,1-dibromoalkenes

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Abstract

A convenient procedure for the synthesis of vinyl bromides is described, which involves the selective reduction of the corresponding 1,1-dibromoalkenes with dimethylphosphite and triethylamine. The 1,1-dibromoalkenes are obtained in excellent yields from the corresponding aldehydes via olefination with carbon tetrabromide and triphenylphosphine. © 2000 Elsevier Science Ltd. All rights reserved.

(*E*)- and (*Z*)-Vinyl bromides are extremely useful intermediates in organic chemistry and the development of methods for their stereoselective synthesis is of considerable importance. Their use as precursors to vinyl anions (vinyllithiums, Grignards, etc.) and as coupling partners in a wide range of transition metal-mediated coupling reactions has stimulated a great deal of interest in their synthesis. A number of excellent one- or two-step procedures exist for the stereoselective synthesis of (*Z*)-vinyl bromides from aldehydes, with this usually being accomplished via a Wittig olefination using bromomethylene triphenylphosphorane.[1] More recently, a two-step procedure, involving the stereoselective palladium-catalysed reduction of intermediate 1,1-dibromoalkenes, has been reported.[2] Unfortunately, however, similar methodology for the efficient synthesis of (*E*)-vinyl bromides seems to be somewhat underdeveloped, although the bromoform/$CrCl_2$ conditions of Takai perform this transformation well in a number of favourable cases.[3] In 1981 Hirao et al. reported a procedure for the reduction of 1,1-dibromoalkenes to the corresponding vinyl bromides using diethylphosphite and triethylamine.[4a] Almost two decades have passed since this initial report, and during this time very little attention has been paid to this potentially valuable procedure.[5] In this letter we wish to report our own studies in this area which have led to the synthesis of a range of vinyl bromides via the reduction of 1,1-dibromoalkenes using dimethylphosphite and triethylamine (Fig. 1).

Our interest in this particular transformation was stimulated by a purely serendipitous discovery. As part of a research program examining the synthesis of oligonucleic acid analogues bearing modified backbones,[6] we had reason to study the palladium(0)-catalysed coupling reaction of the thymidine-derived 1,1-dibromoalkene **1** with commercially available dimethylphosphite. Surprisingly, we found that when the coupling was performed at 70°C the major product formed was the (*E*)-vinyl phosphonate

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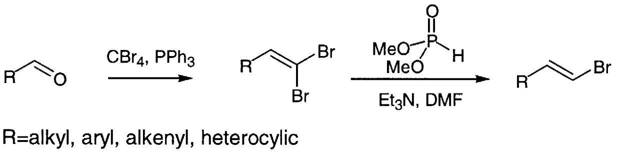
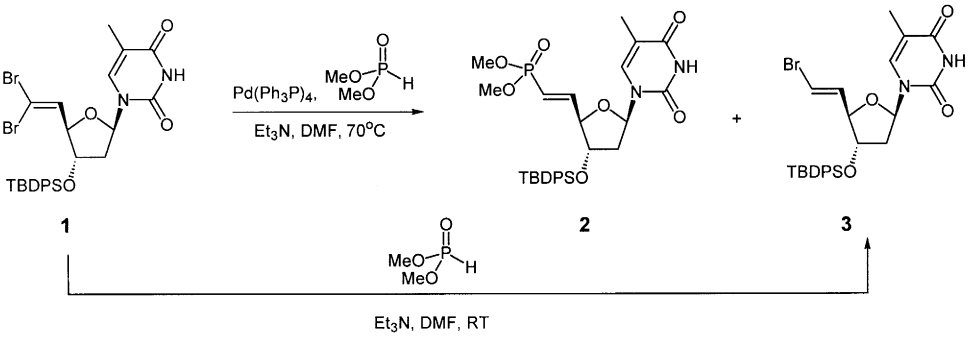


Fig. 1.

2 (Scheme 1). To our knowledge, only one previous attempt to achieve this particular transformation has been reported in the literature and this was unsuccessful.[4b] We were intrigued by this result and began to speculate about the nature of the reaction mechanism involved. The overall transformation requires two processes to occur: (i) reduction of a carbon–bromine bond and (ii) cross-coupling with dimethylphosphite. Initially, the order of these transformations was not known, but the isolation of small amounts of the (*E*)-vinyl bromide **3** gave us circumstantial evidence that the reduction process occurred first, followed by the palladium-catalysed cross-coupling reaction of the newly formed (*E*)-vinyl bromide **3**. Confirmation of this hypothesis was secured when the coupling reaction was performed at room temperature. Under these conditions the major product was the (*E*)-vinyl bromide **3**, accompanied by a small amount of the corresponding (*Z*)-isomer and no cross coupling was seen after 24 h.

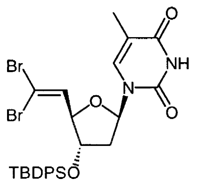
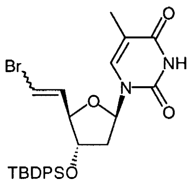
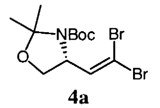
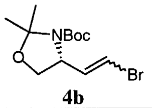
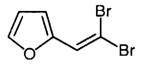
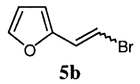
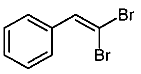
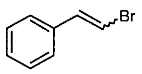
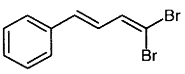
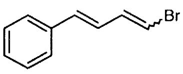
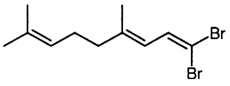
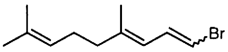
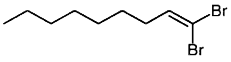
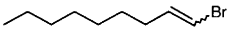
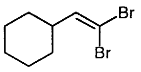
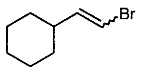
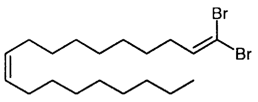
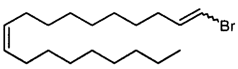
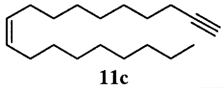


Scheme 1.

Further studies revealed that the reduction reaction (viz **1**–**3**) could be performed in the absence of the palladium catalyst by treating **1** with dimethylphosphite and triethylamine in DMF at room temperature for 24 h. This resulted in the production of the (*E*)-vinyl bromide **3**, along with its (*Z*)-isomer, in 84% yield as a 3:1 mixture of separable stereoisomers. This procedure is very similar to that described previously by Hirao and co-workers, with the only major difference being that ours uses DMF as a co-solvent.[4a] Due to the potential utility of this procedure for the synthesis of vinyl bromides, we began a study to test the scope and limitations of this transformation using a more extensive series of 1,1-dibromoalkenes. The 1,1-dibromoalkenes were synthesised in high yield from the corresponding aldehydes by reaction with carbon tetrabromide and triphenylphosphine in methylene chloride.[7] Each of these compounds was then treated with dimethylphosphite (4 equivalents) and triethylamine (4.5 equivalents) in DMF at 70°C. The reduction reactions were all complete after 16 h, and following aqueous workup, the desired vinyl bromides were purified by column chromatography (Table 1). In general, the reduction products could be isolated in moderate to high yield with a fair degree of *E*:*Z* selectivity.

In a few cases, however (entries 9, 10 and 11), we found that the isolated yields of the vinyl bromides were quite low even though TLC and ^{1}H NMR analysis of the crude mixtures indicated good conversions and generally clean reactions. Further analysis of the reaction mixture obtained from the reduction of **11** revealed that in this case a major by-product (48%) was produced in the reaction, which was identified as being the corresponding terminal acetylene **11c**. Closer inspection of the ^{1}H NMR spectra of the crude reaction mixtures of **9** and **10** also revealed trace amounts of the corresponding terminal acetylenic

Table 1

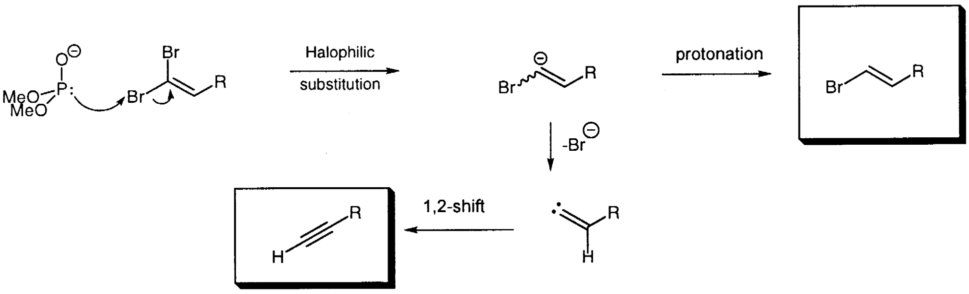
Substrate	Product[a]	%Yield of vinyl-bromide[b] (ratio *E* : *Z*)[c]
 **1**	 **3**	84 (75 : 25)
 **4a**	 **4b**	71 (75 : 25)
 **5a**	 **5b**	60 (70 : 30)
 **6a**	 **6b**	67 (100 : 0)
 **7a**	 **7b**	87 (68 : 32)
 **8a**	 **8b**	95 (60 :40)
 **9a**	 **9b**	22 (80 : 20)
 **10a**	 **10b**	8 (82 :18)
 **11a**	 **11b**  **11c**	15 (67 :33) 48

(a) Conditions: $(MeO)_2POH$ (4 equiv.), Et_3N (4.5 equiv.), DMF, 70°C, 16 h; (b) Isolated yield; (c) Ratio determined by ^1H NMR integration

products. In these latter cases, however, the acetylene-containing by-products were not isolated, as they were extremely volatile.

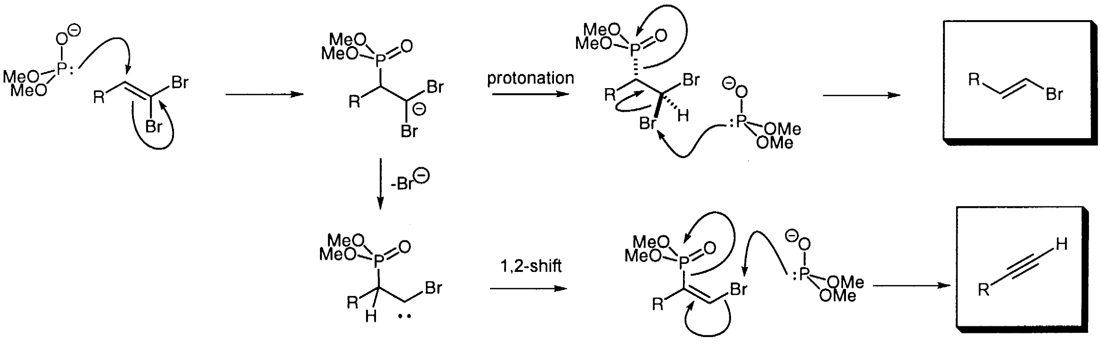
A mechanism for the reduction was proposed by Hirao et al. in their original publication,[4a] which involves halophilic attack[8,9] of the 1,1-dibromoalkene by a dialkylphosphite anion. Protonation of the resulting vinyl anion then gives the corresponding vinyl bromide. Initially, we were a little sceptical about certain aspects of this mechanism, especially the formation of an extremely basic vinyl anion, but it does adequately account for the formation of the acetylenic by-products observed in our work (cf. the Corey–Fuchs procedure).[10]

Hirao's proposal:



Proposed Mechanism 1

Obvious alternative mechanisms could involve single electron transfer and/or radical intermediates,[11,12] so we decided to investigate the effects of single electron and radical traps on the course of the reduction. We soon found that the presence of an excess of 1,3-dinitrobenzene, a known single electron trap,[8] had little effect on the course of the reduction, with no significant change in yield, reaction time or product distribution being observed. On the basis of this observation we believe that single electron transfer is not an important process in this transformation. To test for the presence of radical intermediates, we next performed the reduction under an oxygen atmosphere. Oxygen was bubbled through the reaction mixture, and the oxygen atmosphere (balloon) was maintained for the duration of the reduction. Once again, no noticeable difference in the course of the reaction was observed and no new products were detected. We also performed a series of experiments where the reaction mixture was shielded from light (a potential radical initiator), and like the previous experiments this also failed to inhibit the reduction process. We feel that these data combine to support a mechanism involving anionic intermediates. These findings are consistent with the mechanism proposed by Hirao, but another possibility exists, not involving vinyl anions, which involves an initial Michael-type addition of dimethylphosphite anion, followed by protonation and elimination. Both mechanisms adequately describe the formation of the vinyl bromide and acetylene products[13] but at present we are unable to distinguish between these two pathways and studies are continuing in this area.



Proposed Mechanism 2

In summary, this methodology should prove useful for the syntheses of a range of valuable vinyl bromide building blocks, especially when the use of organometallic intermediates is prohibited. At this point in time this procedure is only a partial solution to the problem of vinyl bromide synthesis, but it should be regarded as a simple, inexpensive and complementary alternative to existing methods.

Acknowledgements

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11. These possibilities were also proposed, and subsequently disproved in the analogous reduction of *gem*-dibromocyclopropanes (see Ref. 8).
12. For the use of compounds containing P–H bonds in radical processes, see: Graham, S. R.; Murphy, J. A.; Coates, D. *Tetrahedron Lett.* **1999**, *40*, 2415 and references cited therin.
13. When the vinyl bromide products were re-subjected to the reaction conditions, no formation of the corresponding acetylene was observed. We therefore conclude that the acetylene products are formed from an intermediate formed during the course of the reaction.