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Dimethyl Phosphite Mediated Hydrogen Atom Abstraction: A Tin-Free Procedure for the Preparation of Cyclopentane Derivatives**

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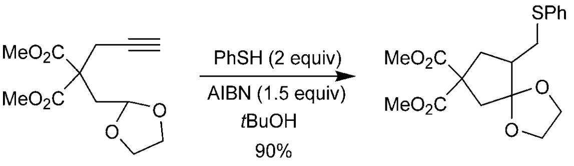
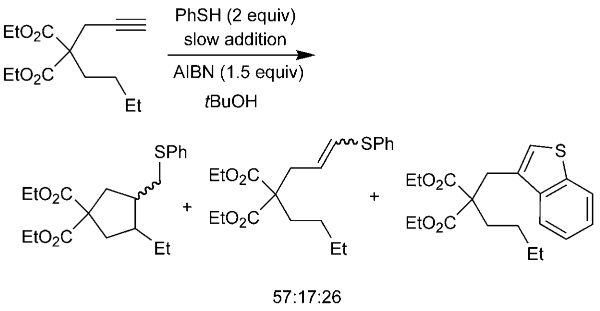
Radical reactions have been investigated intensively over the last two decades.[1] The new synthetic methods that have emerged from this work are complementary to ionic processes and are characterized by mild reaction conditions and broad functional-group tolerance. The potential of these reactions is immense, as demonstrated by their recent use in the synthesis of complex natural products. However, several aspects of this chemistry merit further investigation to increase the synthetic efficiency of the radical approach. Among these objectives, the development of nontoxic and environmentally friendly reagents to perform efficient radical reactions represents a challenging target.

The tin hydride mediated alkenyl radical translocation/cyclization process developed by Curran et al. represents a powerful procedure for the preparation of functionalized five-membered rings by selective activation of a C–H bond.[2,3] Recently, we reported an efficient tin-free version of this reaction involving thiophenol for the preparation of cyclopentane derivatives through a 1,5-hydrogen transfer/cyclization sequence [Eq. (1); AIBN = azobisisobutyronitrile].[4]



(1)

This method using thiophenol proved to be very efficient with a wide range of substrates but required high dilution (10^{-2} M of substrate) and the slow addition of thiophenol with a syringe pump [Eq. (1)]. Some limitations were also noticed, with some substrates undergoing slow hydrogen transfers. For example, the generation of a nonstabilized acyclic secondary alkyl radical proved to be difficult because of the reduction of the alkenyl radical and its cyclization onto the phenylthio group, thus leading to benzothiophene derivatives [Eq. (2)].[5]

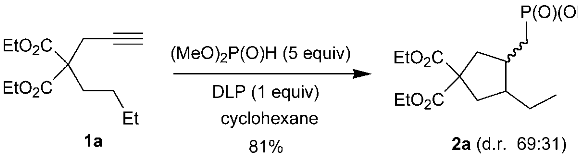


(2)

Recent developments in radical reactions involving phosphorus reagents have attracted our attention. Hypophosphorous acid and its corresponding 1-ethylpiperidine salt have been used to mediate radical cyclization reactions as an alternative to tributyltin hydride.[6,7] Diethyl phosphine oxide (DEPO)[8] and diethyl phosphite[9,10] were also recently used in radical processes.[11,12]

As diethyl phosphite is known to be a slower reducing agent than tributyltin hydride and thiophenol,[13] we were motivated to test the use of a phosphorus reagent in a radical cascade involving the addition of a P radical onto a triple bond followed by 1,5-hydrogen abstraction. To the best of our knowledge, only one radical addition of a dialkyl phosphite to a terminal triple bond has been reported, which was by Ishii and co-workers using Mn(OAc)$_2$ as a radical initiator in the presence of air.[14] Parsons and co-workers reported the failure of such a radical addition but presented one example of a clean addition of a thiophosphite to a terminal alkyne.[15] Herein, we report that dimethyl phosphite is a particularly efficient reagent for radical additions to terminal alkynes followed by 1,5-hydrogen transfer/cyclization processes.

Optimization of the reaction conditions were conducted on substrate **1a** [Eq. (3); DLP = dilauroyl peroxide]. Highly reproducible results and excellent yields were obtained by treating a 0.1 M solution of the alkyne **1a** with five equivalents of dimethyl phosphite and one equivalent of DLP[16] in cyclohexane at reflux for 6 h. The desired cyclized product **2a** was obtained in 81% yield, and no trace of the product from direct reduction was observed. In this particular example, neither the procedure using tin hydride developed by Curran and Shen[3] nor our procedure using thiophenol[4] [see Eq. (2)] gave satisfactory results because of the slow rate of the hydrogen-abstraction step.



(3)

Propargylmalonates **1b–e** were then tested according to Equation (4). The generation of a tertiary alkyl radical from **1b** is very efficient with dimethyl phosphite (Table 1, entry 1),

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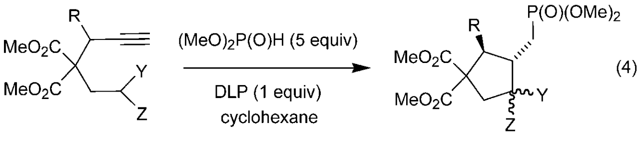


1b–e **2b–e**

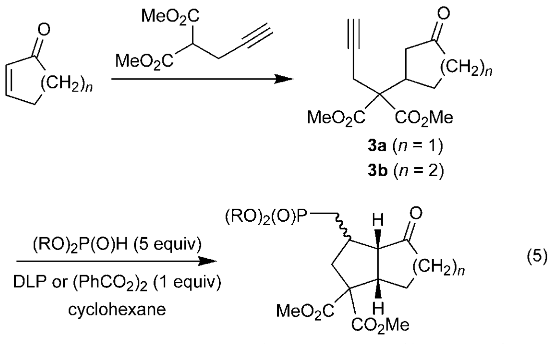
Table 1: Dimethyl phosphite mediated hydrogen abstraction [cyclization according to Eq. (4)].

Entry	Substrate	R	Y	Z	Product	d.r.[a]	Yield [%][b]
1	**1b**	H	Me	Me	**2b**	–	91
2	**1c**	*i*Pr	CO_2Et	H	**2c**	82:18	91
3	**1d**	H	Ph	H	**2d**	92:8	55
4	**1e**	H	OTBS	H	**2e**	73:27	79

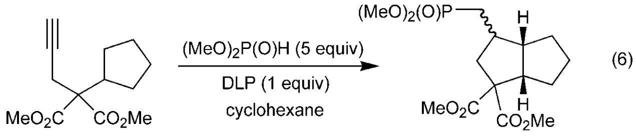
[a] Determined by GC or NMR analysis of the crude reaction mixture. [b] Yield of isolated product. TBS = *tert*-butyldimethylsilyl.

and the cyclic product **2b** is obtained in 91 % yield. Substrates **1c** and **1d**, which bear an ester and a phenyl substituent, respectively, undergo a radical translocation/cyclization process to the desired substituted cyclopentanes **2c** and **2d** in 91 and 55 % yield (entries 2 and 3), respectively. Finally, a radical reaction with substrate **1e** gave the cyclopentane derivative in 79 % yield[17] (entry 4).

On the basis of these initial results, a method for the rapid assembly of fused bicyclic compounds was investigated [Eq. (5)]. Conjugate addition of dimethyl propargylmalonate to cyclopentenone and cyclohexenone affords the radical precursors **3a** and **3b**, respectively. Reaction of **3a** and **3b** with dimethyl phosphite and diethyl phosphite proceeds [Eq. (5)] with complete regioselectivity and affords the fused bicycles **4a** and **4b** in 71 and 84 % yield as a mixture of two diastereomers (d.r. 85:15 and 61:39, respectively). Radical stabilization by the ketone explains the regioselectivity. Interestingly, the deoxygenated compound **3c** gives the expected bicycloalkanes **4c** in 93 % yield (d.r. 90:10) under similar reaction conditions, thus demonstrating that stabilization of the translocated radical is not a prerequisite for the formation of fused bicyclic systems [Eq. (6)].

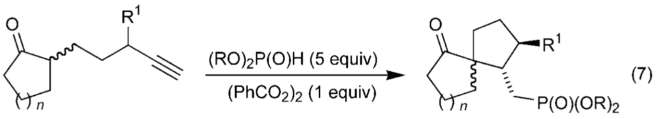


3a (*n* = 1)
3b (*n* = 2)
4a (*n* = 1, R = Me; 71%, d.r. 85:15)
4b (*n* = 2, R = Et; 84%, d.r. 61:39)

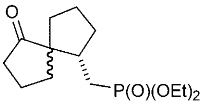


3c **4c** (93%, d.r. 90:10)

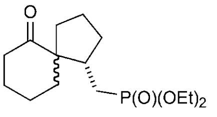
The synthesis of spiro compounds through 1,5-hydrogen transfer has been reported recently employing an iodoalkenyl derivative.[18] However, this method suffers from the use of tin hydride and the difficulty of preparing the starting alkenyl iodides. On the other hand, substrates **5a–c** are readily prepared by alkylation of the corresponding β-keto ester followed by decarboxylation and are efficiently converted [Eq. (7)] into the spiro ketone **6a** (97 %, d.r. 70:30), **6b** (77 %, d.r. 53:47), and **6c** (64 %, d.r. 79:21).



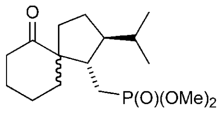
5a–c **6a–c**



6a (97%, d.r. 70:30)



6b (77%, d.r. 53:47)



6c (64%, d.r. 79:21)

In conclusion, we have reported herein that dialkyl phosphites are powerful reagents for radical translocation/cyclization reactions that start from readily available terminal alkynes. A simple one-pot procedure has been developed. The excess reagent is easily removed by evaporation, and filtration through a short pad of silica gel affords a clean reaction product. The cyclic phosphonates produced by this reaction cascade are particularly attractive for further transformations.[11,19,20] Application of this process to the synthesis of natural products is currently underway.

Experimental Section

A mixture of **1b** (1.0 mmol, 226 mg), DLP (1.0 mmol, 398 mg), and dimethyl phosphite (5 mmol, 550 mg) in cyclohexane (10 mL) was heated at 80 °C for 6 h. After completion (monitoring by GC), the solution was cooled and the cyclohexane evaporated under reduced pressure. CH_3CN (10 mL) was added to precipitate the by-products derived from DLP. After filtration and evaporation, the residue was purified by flash chromatography (EtOAc/cyclohexane, 80:20) to afford the phosphonate **2b** (306 mg, 91 %).

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Keywords: alkynes · cyclopentanes · fused-ring systems · hydrogen transfer · radical reactions

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