DOI: 10.1002/adsc.201000852

Preparation of 5-Membered Rings *via* Radical Addition-Translocation-Cyclization (RATC) Processes Mediated by Diethyl Thiophosphites

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Received: November 14, 2010; Revised: February 21, 2011; Published online: May 17, 2011

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000852.

Abstract: A practical method for the formation of thiophosphonates bearing functionalized monocyclic, fused bicyclic and spirocyclic residues is presented. The procedure requires the easily available terminal alkynes as starting materials as well as commercially and readily available reagents such as diethyl thiophosphite. The experimental procedure consists of a one-pot process without any slow addition of one of the reagents.

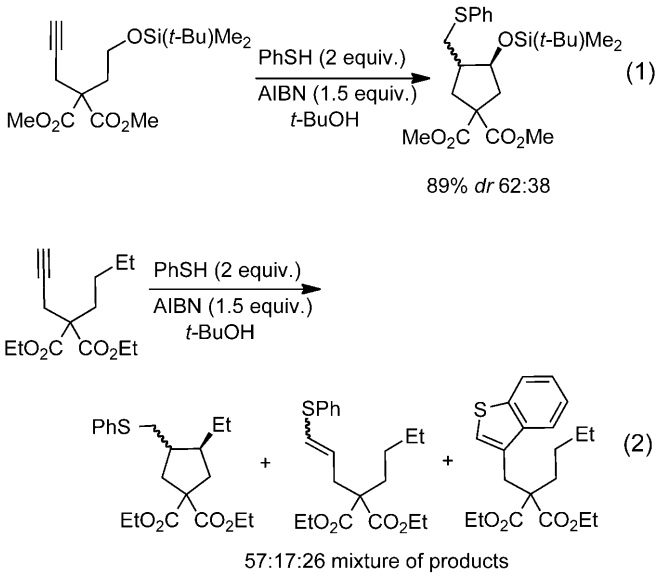
Keywords: alkynes; dialkyl phosphites; dialkyl thiophosphites; 1,5-hydrogen transfer; radical initiators; radical reactions

Introduction

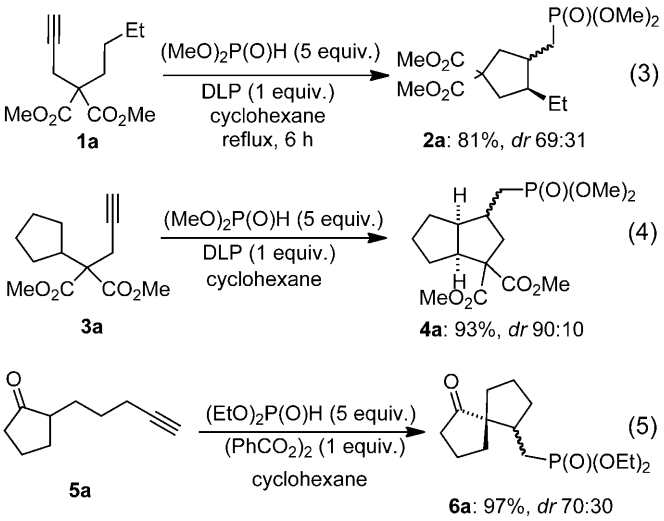
Organophosphorus compounds represent a very important class of natural and non-natural compounds, which possess important biological properties.[1] For instance, phosphonates present a structural analogy with phosphates, and their higher stability toward hydrolysis makes them very attractive to act as enzyme inhibitors. Phosphonates show neurotoxic activity, and they have found applications as antibiotics, herbicides, blood pressure regulators, antiviral and anticancer agents.[2] Therefore, the formation of carbon-phosphorus bonds has attracted the attention of synthetic chemists for a long time.[3] The main ionic procedures known to date are the well-known Michaelis–Arbuzov rearrangement,[4] as well as the Kabachnik–Fields[5] and Pudovik[6] reactions. This last reaction is particularly interesting since it involves the addition of an organophosphorus compound containing a labile P–H bond to alkenes and alkynes. This reaction is known to work either *via* a polar or *via* a radical mechanism depending on the substrates and the reaction conditions.[7] The radical addition has been thoroughly investigated by Parsons who developed efficient addition-cyclization processes leading to cycloalkane derivatives by using either dialkyl phosphites or dialkyl thiophosphites.[8–11] Interestingly, the radical processes concern mostly addition to alkenes, the radical addition of P radicals to terminal alkynes is less documented in the literature.[12,13]

Recently, we reported an efficient procedure to prepare functionalized 5-membered rings involving a thiophenol-mediated radical addition-translocation-cyclization process (RATC) [Scheme 1, Eq. (1)].[14–16] This process complements nicely the alkenyl radical translocation-cyclization process pioneered by Curran.[17–19] Although thiophenol turned out to be extremely efficient in mediating the radical translocation with most substrates, this reagent showed limitations when a slow hydrogen-transfer was involved. In this case, the desired cyclized product was contaminated by a mixture of uncyclized compounds (*E*:*Z* mixture of diastereoisomers) and benzothiophene derivatives resulting from the cyclization of the intermediate alkenyl radical onto the benzene ring of thiophenol [Scheme 1, Eq. (2)].[15,16]

Phosphorus P–H reducing agents such as dialkyl phosphites are known to be slower reducing agents



Scheme 1. Scope and limitations of the thiophenol-mediated RATC reaction.



Scheme 2. RATC reactions with dimethyl phosphite.

than tributyltin hydride and thiophenol. The lower reducing properties of dialkyl *H*-phosphonates are mainly due to the difference in BDE of the heteroatom–H bond: the S–H bond in thiophenol has a value[20] of about 331 kJ mol^{-1} while that of the P–H bond in diakyl *H*-phosphonate[11] is about 365 kJ. mol^{-1}. The moderate reducing power of the P–H reducing agents and the high reactivity of P-centered radicals towards alkenes and alkynes motivated us to test them in radical addition-translocation-cyclization (RATC) processes with the aim of avoiding the high dilution conditions and/or slow addition techniques required in both the tin hydride and the thiophenol processes.

In a preliminary communication, we have reported that dialkyl phosphites are powerful reagents for radical translocation-cyclization reactions starting from terminal alkynes.[21] This represents an efficient method for the synthesis of cycloalkyl phosphonate derivatives. Three typical examples illustrating the synthetic utility of this process for the preparation of monocyclic, fused bicyclic and spirocyclic compounds are depicted in Scheme 2 [Eqs. (3)-(5)].

For instance, it was established that highly reproducible results and high yields are obtained by treating a 0.1 M solution of the alkyne **1a** with 5 equivalents of dimethyl phosphite and 1 equivalent of dilauroyl peroxide (DLP) in refluxing cyclohexane. The desired cyclized product **2a** was obtained in 81% yield and no trace of the product of direct reduction was observed [Eq. (3)]. Interestingly, the reaction was performed by mixing all reagents together at the beginning. Removal of the excess of reagent by evaporation and filtration through a short pad of silica gel afforded a pure crude product with a purity $\geq$95%. In this particular example, neither the tin hydride procedure developed by Curran[18] nor our thiophenol procedure[14,15,16] [see Scheme 1, Eq. (2)] gave satisfactory results due to the slowness of the H-atom abstraction step. The malonate **3a**, prepared by alkylation of dimethyl propargylmalonate with bromocyclopentane,[15] gave under similar reaction conditions the expected bicycloalkane **4a** in 93% yield [Eq. (4), *dr* 90:10]. Similarly, substrate **5a**, easily prepared by alkylation of the corresponding β-keto ester followed by decarboxylation, was efficiently converted into spiroketone **6a** (97%, *dr* 70:30) [Eq. (5)].[22]

Since alkyl phosphonates could not easily engage in subsequent olefination reactions, we decided to investigate the use of other phosphorus reagents that are known to facilitate further olefination processes. We report herein a detailed study of the use of thiophosphites for RATC reactions. These substrates present several advantages over the phosphites in term of reaction efficacy and for further transformations of the products.

Results and Discussion

Dialkyl Thiophosphite-Mediated Reactions

In an effort to develop a RATC reaction combining the practicability of the dialkyl phosphite method and the flexibility of the thiophenol method relative to further transformation of the products, we decided to investigate alternative P–H reagents. Thiophosphites have a BDE of 337 kJ mol^{-1} positioned close to that of thiophenol (331 kJ mol^{-1})[21] and well below that of dialkyl *H*-phosphonates (365 kJ mol^{-1}).[11] They are known to add efficiently onto alkenes and alkynes *via*

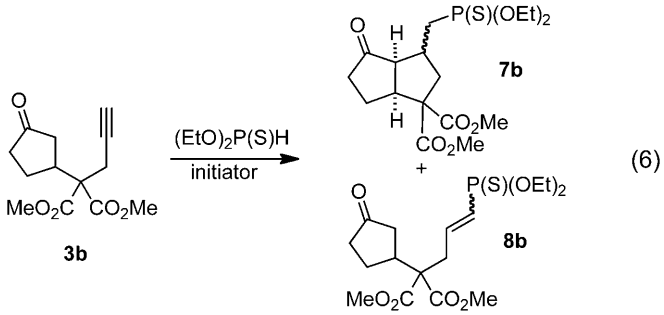
Table 1. Preliminary attempts to run a diethyl thiophosphite-mediated RATC reaction with **3b** according to Eq. (6).

Entry	P(S)–H (equiv.)	Initiator (mol%)	Solvent (T °C)	**7b** (*endo*/*exo*)
1	2	AIBN (50)	THF (refl.)	61%[a,b]
2	2	AIBN (50)	*t*-BuOH (refl.)	81% (82:18)
3	1.5	DTBHN (20)	*t*-BuOH (45)	89% (95:5)

[a] Stereoselectivity not determined.
[b] **8b** (27%) was also isolated.

a radical pathway.[11,13,23] Moreover, Parsons has demonstrated that thiophosphonates are very suitable for further olefination reactions.[9,11]

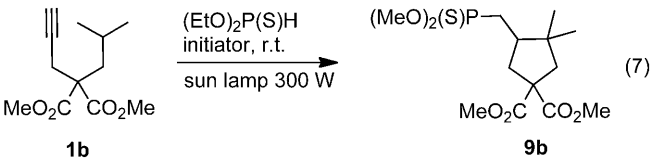
The cyclopentanone **3b** was used for preliminary experiments according to Eq. (6), and the results are collected in Table 1. The AIBN-initiated reaction was investigated first with 2 equivalents of thiophosphite in refluxing THF. Under these reaction conditions,



(6)

the desired bicyclic ketone **7b** was obtained in 61% yield, along with 27% of the reduced product **8b** (Table 1, entry 1). The formation of **8b** could be avoided by running the reaction in a less good H-donor solvent. For instance, under similar reaction conditions in refluxing *t*-BuOH, **7b** was isolated in 81% yield as a mixture of stereoisomers (Table 1, entry 2). By using di-*tert*-butyl hyponitrite (DTBHN) as an initiator, the reaction could be carried out at a lower temperature, affording **7b** as a single product in 89% yield and with a very good stereocontrol (Table 1, entry 3). Interestingly, the use of di-*tert*-butyl hyponitrite allows the amount of initiator to be reduced from 50 mol% down to 20 mol%. This indicates, that alkoxyl radicals are more suitable to initiate the reaction by abstracting an H-atom from diethyl thiophosphite than the 2-cyanoprop-2-yl radicals generated from AIBN.

In a second series of experiments, we tried to develop reaction conditions that would involve a cheap and commercially available radical initiator such as di-*tert*-butyl peroxide (DTBP) while carrying out the reaction at room temperature in order to ensure good levels of stereocontrol. Since di-*tert*-butyl peroxide is usually used for thermal initiation (typically in refluxing chlorobenzene), we envisioned using irradiation to promote the fragmentation of the peroxide. Substrate **1b** was used as a model substrate for this second optimization of the diethyl thiophosphite-mediated RATC process [Eq. (7)]. Results are summarized in Table 2. The reaction was tested in the presence of 1.5 equivalents of the thiophosphite and

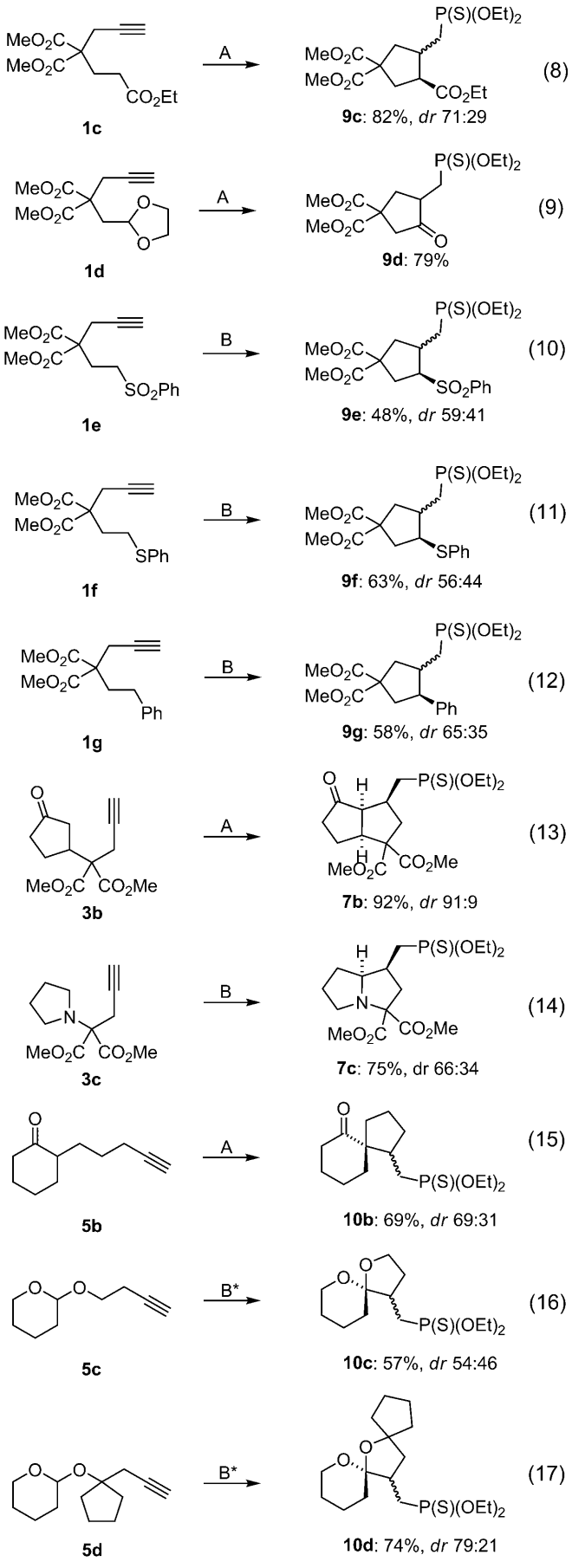


(7)

20 mol% of di-*tert*-butyl peroxide under irradiation with a 300 W sunlamp in different solvents (Table 2, entries 1–3). Very low yields of **9b** were obtained in dichloromethane and dimethylformamide (Table 2, entries 1 and 2). However, promising results were obtained in benzene (60% yield, entry 3). We attributed this unusual solvent effect to the fact that benzene could act as a sensitizer to promote the homolytic fragmentation of di-*tert*-butyl peroxide.[24] It was expected that the use of dicumyl peroxide (DCP), a radical initiator that should be more prone to homolytic cleavage under irradiation conditions, should favour the overall process. Indeed, this cheap initiator could perform the tandem radical transformation equally well at room temperature in CH_2Cl_2 (entry 4), benzene (entry 5), and *t*-BuOH (entry 6), affording the cyclized compound **9b** in high yields (84–88%). To the best of our knowledge, this is the first use of this peroxide under photochemical conditions for small molecule synthesis. The loading of initiator could be reduced to 10 mol% for the reaction carried out in *t*-BuOH without any decrease in yield (entry 7). Finally, the use of a slightly larger excess of the thiophosphite (1.8 equivalents) led to **9b** in excellent yield (Table 2, entry 8).

Table 2. Optimization of the diethyl thiophosphite-mediated RATC reaction with **1b** according to Eq. (7).

Entry	P(S)–H (equiv.)	Initiator (mol%)	Solvent	**9b**
1	1.5	DTBP (20)	CH_2Cl_2	15%
2	1.5	DTBP (20)	DMF	–
3	1.5	DTBP (20)	benzene	60%
4	1.5	DCP (20)	CH_2Cl_2	88%
5	1.5	DCP (20)	benzene	88%
6	1.5	DCP (20)	*t*-BuOH	84%
7	1.5	DCP (10)	*t*-BuOH	89%
8	1.8	DCP (10)	*t*-BuOH	>95%



In order to demonstrate the scope of the reaction, several terminal alkynes were tested and the results are collected in Scheme 3. The reactions were carried out in *t*-BuOH under two sets of conditions. In procedure A, dicumyl peroxide (10 mol%) and irradiation at room temperature in the presence of 1.8 equivalents of diethyl thiophosphite was used. In procedure B, di-*tert*-butylhyponitrite (20 mol%) at 45 °C with 1.5 equivalents of diethyl thiophosphite was employed.

Ester, sulfonyl, sulfinyl, and phenyl substituted radicals [Eqs. (8), (10)-(12)] can be successfully generated and afford the desired cyclopentane derivatives in good yields by using procedure A or B. The relative configurations of the major isomers of **9c**, **9e**–**9g** have not been assigned, however, related systems possessing *gem*-diester substituents are known to give the *cis*-cyclopentanes as major isomers.[18,25] The reaction of the dioxolane **1d** afforded the cyclopentanone **9d** in 79% yield [Eq. (9)]. In this particular reaction, the radical cascade process was followed by a rapid hydrolysis of the acetal. Fused bicyclic skeletons are also obtained efficiently from simple alkynes, as demonstrated by the cyclization of **3b** and **3c**, which led to the formation of **7b** and **7c** in 92% and 75% yields [Eqs. (13)-(15)]. The relative *endo* configuration of the major isomer of **7b** was established by an X-ray crystal structure analysis (Figure 1).[26] Spirocyclic

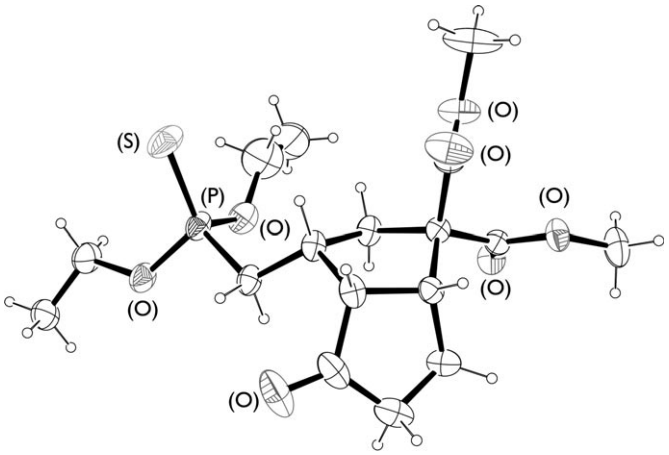


Figure 1. X-ray single crystal structure analysis of compound **7b** (major diastereomer).

compounds can be prepared from easily available starting materials such as **5b**, **5c** and **5d** according to

Scheme 3. Reaction of various terminal alkynes with diethyl thiophosphite. ***Procedure A:*** $(EtO)_2P(S)H$ (1.8 equiv.), dicumyl peroxide (10 mol%), *t*-BuOH, sun lamp irradiation, room temperature. ***Procedure B:*** $(EtO)_2P(S)H$ (1.5 equiv.), *t*-BuON=NO-*t*-Bu (20 mol%), *t*-BuOH, 45 °C. ***Procedure B*:*** benzene was used as solvent instead of *t*-BuOH.

Eqs. (15)-(17). For the spirocyclic ketals **10c** and **10d**, the best results were obtained by using benzene instead of *tert*-butyl alcohol as a solvent. It is noteworthy that the preparation of these highly acid-sensitive spiroketals is not possible by using our dialkyl phosphite procedure. Indeed, the thermal decomposition of the peroxides employed (dilauroyl and dibenzoyl peroxides) very likely results in the presence of carboxylic acid derivatives in the reaction medium, which led to decomposition of either the starting acetals or the spiroketals. The beneficial effect of benzene in the cyclization of **5c** and **5d** is attributed to a higher stability of the acetal functionality in non-protic solvent.

Conclusions

Dialkyl thiophosphites are powerful reagents for radical addition-translocation-cyclization (RATC) reactions starting from easily available terminal alkynes. As anticipated from the comparison of P–H bond dissociation energies, thiophosphites are more efficient than the corresponding phosphites and only a slight excess (1.5–1.8 equiv.) of the thiophosphite together with substoichiometric amounts of initiators (10–20 mol%) are necessary to ensure full conversion and high yields. The reaction can be carried out at room temperature or below 50 °C depending on the initiation method. The radical initiation system involving dicumyl peroxide and sunlamp irradiation is particularly attractive and should be applicable to a broad range of radical processes requiring initiation by alkoxyl radicals at moderate temperature. The different sets of reaction conditions developed showed a high functional group tolerance. The resulting cyclic thiophosphonates produced by this reaction cascade are particularly attractive for further transformations, as recently illustrated by Parsons and co-workers in their approach to quinuclidines.[9,10]

Experimental Section

General Procedures for the RATC Reaction with Diethyl Thiophosphite

Procedure A (photochemical initiation): A stirred solution of the alkyne (1.0 mmol), diethyl thiophosphite (277 mg, 1.8 mmol) and dicumyl peroxide (27 mg, 0.1 mmol) in *t*-BuOH (10 mL) was irradiated under nitrogen with a 300 W sunlamp (positioned at 20 cm from the pyrex flask) for 12 h. The solvent was evaporated under reduced pressure along with the excess of diethyl thiophosphite. The crude product was purified by flash chromatography.

Procedure B (thermal initiation, tert-butyl alcohol): A stirred solution of the alkyne (1.0 mmol), diethyl thiophosphite (231 mg, 1.5 mmol) and di-*tert*-butyl hyponitrite (35 mg, 0.2 mmol) in *t*-BuOH (10 mL) was heated at 45 °C for 16 h. The solvent was evaporated under reduced pressure along with the excess of diethyl thiophosphite. The crude product was purified by flash chromatography.

Procedure B* (thermal initiation, benzene): A stirred solution of the alkyne (1.0 mmol), diethyl thiophosphite (231 mg, 1.5 mmol) and di-*tert*-butyl hyponitrite (35 mg, 0.2 mmol) in benzene (10 mL) was heated at 45 °C for 16 h. The solvent was evaporated under reduced pressure along with the excess of diethyl thiophosphite. The crude product was purified by flash chromatography.

Acknowledgements

We thank the Swiss National Science Foundation (grants 21-67106.01 and 7SUPJ062348) for financial support.

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[26] CCDC 778530 contains supplementary crystallographic information for **7a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; E-mail: deposit@ccdc.cam.ac.uk.

