DOI: 10.1002/adsc.201200276

Study on the Reactions of Acetylenic Aldehydes with Dimethyl Phosphite in Basic Media: Phosphonate-Phosphate Rearrangement *versus* 5-*exo*-dig Cyclization Reactions

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Received: April 3, 2012; Revised: June 25, 2012; Published online: September 28, 2012

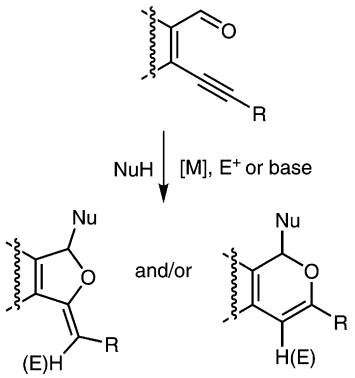
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200276.

Abstract: Tandem reactions of various acetylenic aldehydes with dimethyl phosphite in basic media were investigated. It was shown that in the case of a non-activated triple bond of the starting materials, the well-known Pudovik reaction followed by a subsequent phosphonate-phosphate rearrangement took place. On the other hand when the triple bond of the starting materials is activated by electron-withdrawing heterocycles, a smooth and regioselective tandem 5-*exo*-dig cyclization reactions becomes possible.

Keywords: acetylenic aldehydes; phosphonate-phosphate rearrangement; regioselective 5-*exo*-dig cyclization; tandem nucleophilic addition

Introduction

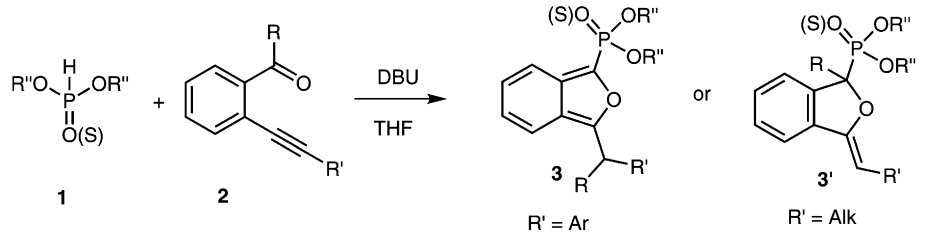
Over the past few years, a huge variety of intramolecular cyclizations of acetylenic aldehydes with nucleophilic components has been studied. These reactions are a powerful and atom-economic strategy for the construction of dihydrofuran and dihydropyran derivatives *via* 5-*exo*-dig or 6-*endo*-dig cyclization modes (Scheme 1). During these transformations transition metal catalysts,[1] electrophiles[2] and bases[3] can be employed as activating agents; and the choice of activation has a crucial influence on the regioselectivity of the reactions. The roles of nucleophiles are usually played by various alcohols, amides and activated aromatic compounds (anilines, phenols, thiophenes and pyrroles).



Scheme 1. Literature results.

In the 2008 a paper entitled "Efficient Syntheses of (Thio)phosphonylated Isobenzofurans by Tandem Nucleophilic Addition and Regioselective 5-*exo*-dig Addition to Carbon-Carbon Triple Bond: Cooperative Effect to 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)" by Z. Miao, R. Chen and co-workers was published.[4] According to the procedure in this paper, various isobenzofuran (thio)phosphonate derivatives (**3**) or (**3′**) were prepared by means of *via* cooperative DBU intramolecular cyclization of *o*-alkynylbenzaldehydes or *o*-alkynylacetophenones (**2**) and dialkyl phosphite or dialkyl phosphonothioate (**1**) (Scheme 2).

During the continuation of our ongoing program aimed at alkynyl-substituted heterocycles[5] in the synthesis of various condensed compounds, we became particularly interested in the results of Miao and Chen, especially in the phenomenon of 1,5-sigmatropic hydrogen or methyl shifts[4] and in the novel use of phosphorus nucleophiles for tandem intramolecular cyclizations of acetylenic aldehydes. Having in mind the fact that carbocyclic and heterocyclic substrates can react by different pathways, we decided to study the reactions of various starting alkynylaldehydes containing quinoline and pyrimidine rings with dimethyl phosphite in basic media. However, to our surprise, our obtained results were not consistent with the previously published results of Miao and Chen. Moreover, we noted interesting evidence that the re-



Scheme 2. Results published by Miao, Chen and co-workers.[4]

action outcome mainly depends on the electron density on the C≡C triple bond. In order to shed some light on the reactions of acetylenic aldehydes with dialkyl phosphites in basic media herein we present the results of our investigations.

Results and Discussion

First of all we prepared the corresponding 2-alkynylquinoline-3-carbaldehydes **4a–e** and 6-alkynylpyrimidine-5-carbaldehydes **5a–k** (Figure 1). For the preparation of the starting materials we utilized the classical Sonogashira coupling[6] between commercially available 2-chloroquinoline-3-carbaldehyde or 4-chloropyrimidine-5-carbaldehydes and terminal acetylenes.

Then we tried to apply Miao, Chen and co-workers procedure for the synthesis of dimethyl furo[3,4-*b*]quinolin-1-ylphosphonates or dimethyl 1,3-dihydrofuro[3,4-*b*]quinolin-1-ylphosphonates. When the mixtures of compounds **4a–d**, dimethyl phosphite and DBU were stirred at 50 °C temperature, we observed the quick and selective conversions of the starting materials by TLC. The same outcome of the reactions was observed when we change DBU to potassium *tert*-butoxide in dichloroethane. The spectral elucidation of purified products **6a–d** led us to conclude that under the reaction conditions the Pudovik reaction[7] and phosphonate-phosphate rearrangement[8] sequences took place. In the ^{1}H NMR spectra of isolated products **6a–d** there were doublets for equivalent methoxy groups at 3.75–3.79 ppm and doublets of doublets for methylene groups at 5.32–5.48 ppm with the coupling constants of 7.2–7.8 Hz and 0.9 Hz, respectively. The smaller couplings were due to splitting of methylene groups to the proton at the quinoline ring position 4, what was well-seen from the H,H-correlation spectra and multiplicity of C-4–H (d, $J = 0.9$ Hz). In the ^{13}C NMR spectra of **6a–d** there were two signals at 73.1–86.0 and 94.9–104.9 ppm regions, peculiar to the carbons of C≡C bonds. And finally, the presence of an alkynyl moiety in the products was proved by IR spectra, where we found the sharp absorption peaks at 2212–2233 cm^{-1}. The intermediates **7a**, **b** were isolated and fully characterized when we used 1 equivalent of base (Scheme 3).

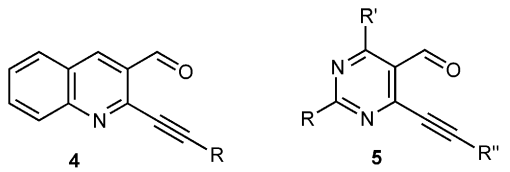
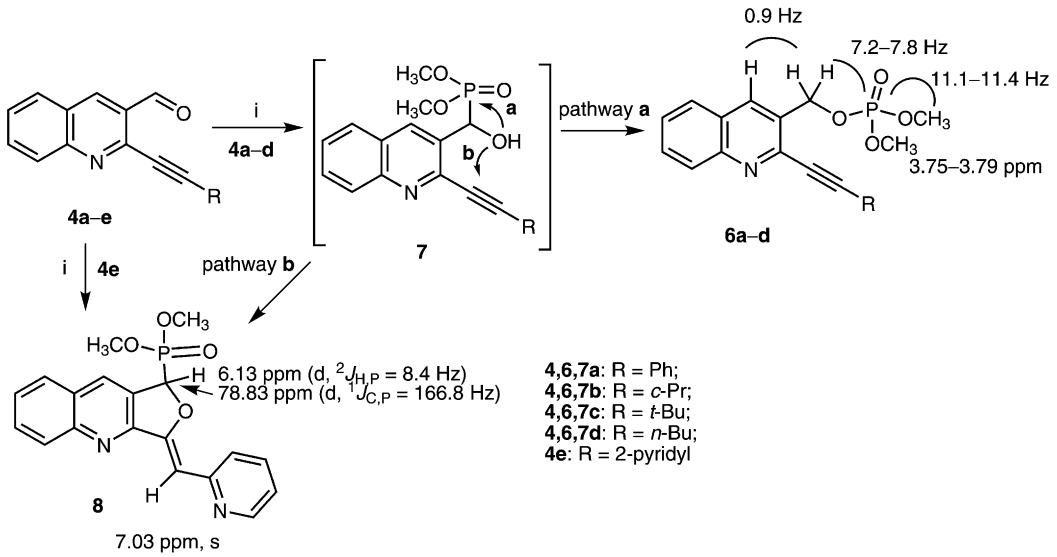


Figure 1. *Starting materials.* [**4**: R = Ph (**a**); *c*-Pr (**b**); *t*-Bu (**c**); *n*-Bu (**d**); 2-pyridyl (**e**). **5**: R = H; R′ = $N(CH_2)_4$; R″ = Ph (**a**); R = H; R′ = $N(CH_2)_4O$; R″ = Ph (**b**); R = SCH_3; R′ = $N(C_2H_5)_2$; R″ = Ph (**c**); R = SCH_3; R′ = $N(C_2H_5)_2$; R″ = 4-$CH_3C_6H_4$ (**d**); R = SCH_3; R′ = $N(C_2H_5)_2$; R″ = 4-$C_2H_5C_6H_4$ (**e**); R = SCH_3; R′ = $N(CH_2)_4O$; R″ = Ph (**f**); R = SCH_3; R′ = NHPh; R″ = Ph (**g**); R = SCH_3; R′ = NHC_2H_5; R″ = Ph (**h**); R = SCH_3; R′ = $N(CH_2)_4O$; R″ = Bu (**k**)].

At this stage of the investigation, it appeared that tandem 5-*exo*-dig reactions of 2-alkynylquinoline-3-carbaldehydes (**4**) with phosphorus nucleophiles are impossible, because of more favourable phosphonate-phosphate rearrangement process of the products of the Pudovik reaction. However, to our pleasant surprise, when 2-(2-pyridinylethynyl)quinoline-3-carbaldehyde **4e** was treated with dimethyl phosphite in the presence of potassium *tert*-butoxide in dichloroethane at room temperature the formation of cyclized product **8** took place (Scheme 3).

In the ^{1}H NMR spectrum of **8** there were two doublets for diastereotopic methoxy groups at 3.65 and 3.93 ppm, respectively. The signal of proton at C-1 of the dihydrofuran ring appeared as doublet at 6.13 ppm with a coupling constant 8.4 Hz. The proton of ethene moiety appeared as a singlet at 7.03 ppm. Neither ^{13}C NMR, nor IR spectra showed the presence of a C≡C bond. These data together with HSQC, HMBC, TOCSY spectra and molecular formula obtained by HR-MS confirmed the structure of **8**.

Therefore, we assumed that activation of the triple bond by electron-withdrawing quinoline and pyridine moieties in the starting compound **4e** is sufficient for enabling a tandem cyclization reaction. The formation of rearrangement products **6** and cyclization product **8** takes place *via* the same intermediates **7**. The latter compounds can undergo phosphonate-phosphate rearrangement *via* a three-membered transition state



Scheme 3. *Reagents and conditions:* i) dimethyl phosphite (2 equiv.), DBU (2 equiv.), THF, 50 °C, 2–3 h. or dimethyl phosphite (2 equiv), KO-*t*-Bu (2 equiv.), DCE, 50 °C, 2 h.

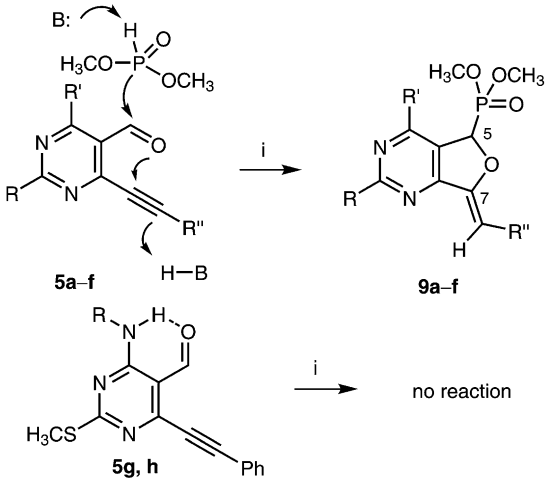
(Scheme 3, pathway a). On the other hand, when the C≡C bond is activated by electron-withdrawing moieties, the tandem 5-*exo*-dig cyclization reaction takes place (Scheme 3, pathway b).

It is obvious, that the triple bond of the starting pyrimidine substrates **5** is more activated due to the electron-deficient pyrimidine moiety and its formyl group, so we envisioned that the pyrimidines **5** could be able to undergo the smooth tandem cyclization process with dimethyl phosphite in basic media. Indeed, after the treatment of starting compounds **5a–f** with dimethyl phosphite and potassium *tert*-butoxide in dichloroethane at room temperature, the smooth and regioselective reactions were observed by TLC (Scheme 4). Transformations of the starting compounds were completed in 30 min. when 1 equivalent of base was used. Potassium *tert*-butoxide gave the best results in terms of yields and duration. While potassium carbonate and DBU provided a slightly lower yield of the cyclized products than *tert*-butoxide, Et_3N proved to be far less effective. Moreover, we did not succeed to isolate the Pudovik addition intermediates from the reaction mixtures. This fact indicated that during the treatment of 6-alkynylpyrimidine-5-carbaldehydes **5** with dimethyl phosphite in basic media, the tandem nucleophilic addition–cyclization reactions took place (Scheme 4).

In the ^{1}H NMR spectra of compounds **9a–f** besides of other signals there were two doublets of diastereotopic methoxy groups at 3.53–3.60 ppm and 3.81–3.89 ppm, respectively. In the ^{13}C NMR spectra of **9a–f** doublets at 80.13–80.88 ppm with the coupling constants of 163–166 Hz due to resonances of O–C-5–P of dihydrofuran rings were observed. The presence of an ethene moiety was proved by the broad singlets or doublets with small coupling constants at 6.51–6.62 ppm in the ^{1}H NMR spectra and signals in the ^{13}C NMR spectra at 100.86–103.52 ppm. Neither ^{13}C NMR nor IR spectra indicated the presence of C≡C bonds. The molecular formulae obtained from HR-mass spectra corresponded to the composition of **9a–f**.

Moreover the structure of **9d** was firmly confirmed by X-ray crystallographic analysis (Figure 2).[9]

It is noteworthy, that compounds **5g** and **5h** bearing a secondary ethylamino or anilino group in position 4



Scheme 4. *Reagents and conditions:* i) Dimethyl phosphite (1.2 equiv), KO-*t*-Bu (1 equiv.), DCE, room temperature, 30 min. Compounds **9**: R = H; R′ = $N(CH_2)_4$; R″ = Ph (**a**); R = H; R′ = $N(CH_2)_4O$; R″ = Ph (**b**); R = SCH_3; R′ = $N(C_2H_5)_2$; R″ = Ph (**c**); R = SCH_3; R′ = $N(C_2H_5)_2$; R″ = 4-$CH_3C_6H_4$ (**d**); R = SCH_3; R′ = $N(C_2H_5)_2$; R″ = 4-$C_2H_5C_6H_4$ (**e**); R = SCH_3; R′ = $N(CH_2)_4O$; R″ = Ph (**f**).

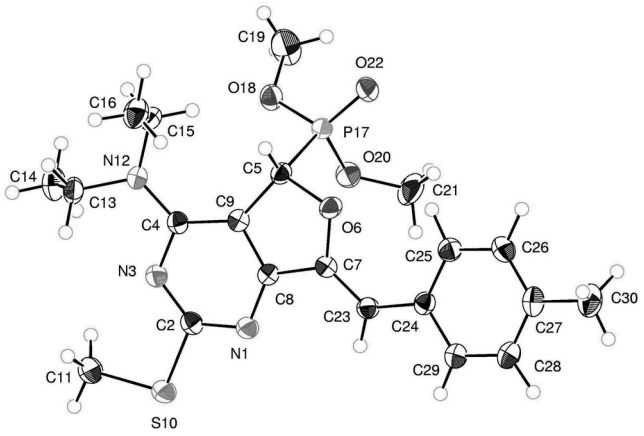


Figure 2. ORTEP view of compound **9d**.

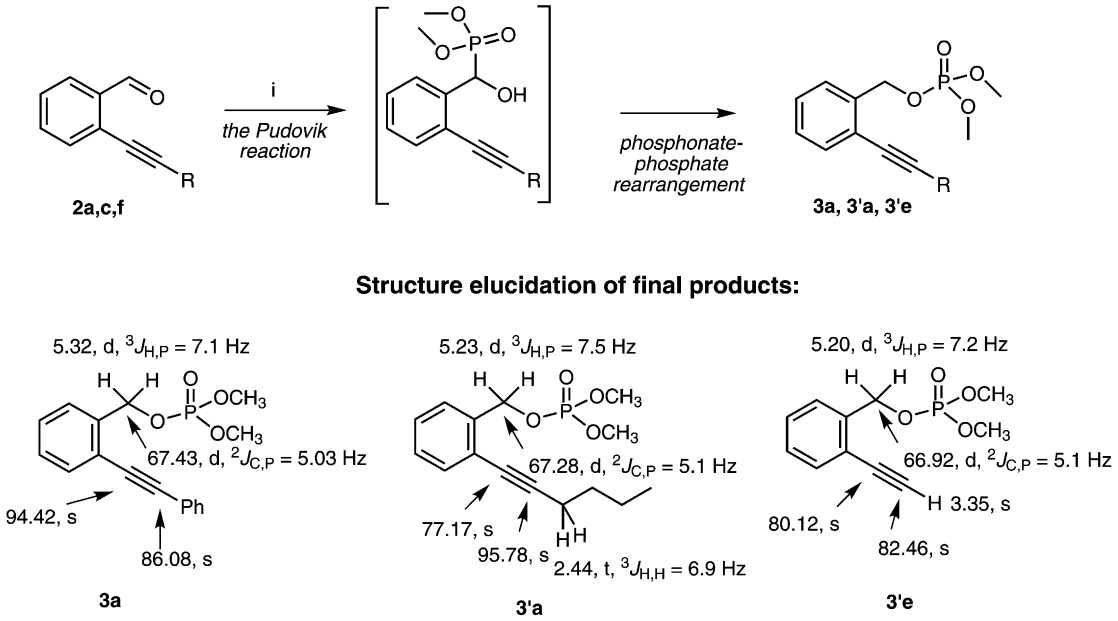
of the pyrimidine ring did not undergo cyclization reactions with dimethyl phosphite. In both these cases the starting materials were recovered after the work-up of reaction mixtures. We suppose, that compounds **5g** and **5h** exist in the unfavourable conformation where carbonyl group is turned towards the NHR moiety to form an intramolecular hydrogen bond and directed away from the C≡C bond, therefore tandem reactions become impossible. The same consistent pattern was observed during investigation of tandem reactions of 4-alkynylpyrimidine-5-carbaldehydes with alcohols in basic media.[5i] Moreover, the reaction of the starting material **5k**, bearing an alkyl moiety on the alkynyl substituent, with dimethyl phosphite in basic media was complicated, leading to the mixture of various products (observed by TLC).

So, it could be concluded that the tandem nucleophilic addition–cyclization reactions of acetylenic aldehydes with dialkyl phosphites are possible only in the case of electron-poor C≡C bonds, activated by electron-withdrawing pyridine and pyrimidine rings. When the activation of an alkyne moiety is unsufficient, the classical Pudovik reaction followed by a phosphonate–phosphate rearrangement takes place.

In the light of these facts we turned our attention to the contrary results published earlier.[4] The triple bonds of *o*-alkynylbenzaldehydes and *o*-alkynylacetophenones are electron-rich, so the fact that these materials undergo smooth tandem 5-*exo*-dig cyclization reaction with dialkyl phosphites in basic media disagrees with our observations.

So, we synthesized some of *o*-alkynylbenzaldehydes (**2a**, **c**, **f**) used by the original authors and repeated the optimized reaction of the substrates with dimethyl phosphite (Scheme 5). After quick and selective conversions of the starting materials and purification of products **3a**, **3′a** and **3′e**, we performed careful structure elucidations and moreover, we turned our attention to the spectral data of isobenzofuran-1-ylphosphonates (**3**) and 1,3-dihydroisobenzofuran-1-ylphosphonates (**3′**), published in the original publication. It should be noted that, besides minor discrepancies between chemical shifts, we obtained the same NMR spectra as Miao et al.[4]

In the ^{1}H NMR spectra of **3a**, **3′a** and **3′e**, there were doublets for methylene groups at 5.20–5.32 ppm. The coupling constants of 7.1–7.5 Hz pointed to vicinal coupling to neighbouring phosphorus nuclei (Scheme 5). In the ^{13}C NMR spectra of **3a**, **3′a** and **3′e**



Scheme 5. Reaction between 2-alkynylbenzaldehydes (**2**) and dimethyl phosphite (**1**) in basic media. *Reagents and conditions:* i) dimethyl phosphite (2 equiv.), DBU (2 equiv.), THF, 50 °C, 2–10 h.

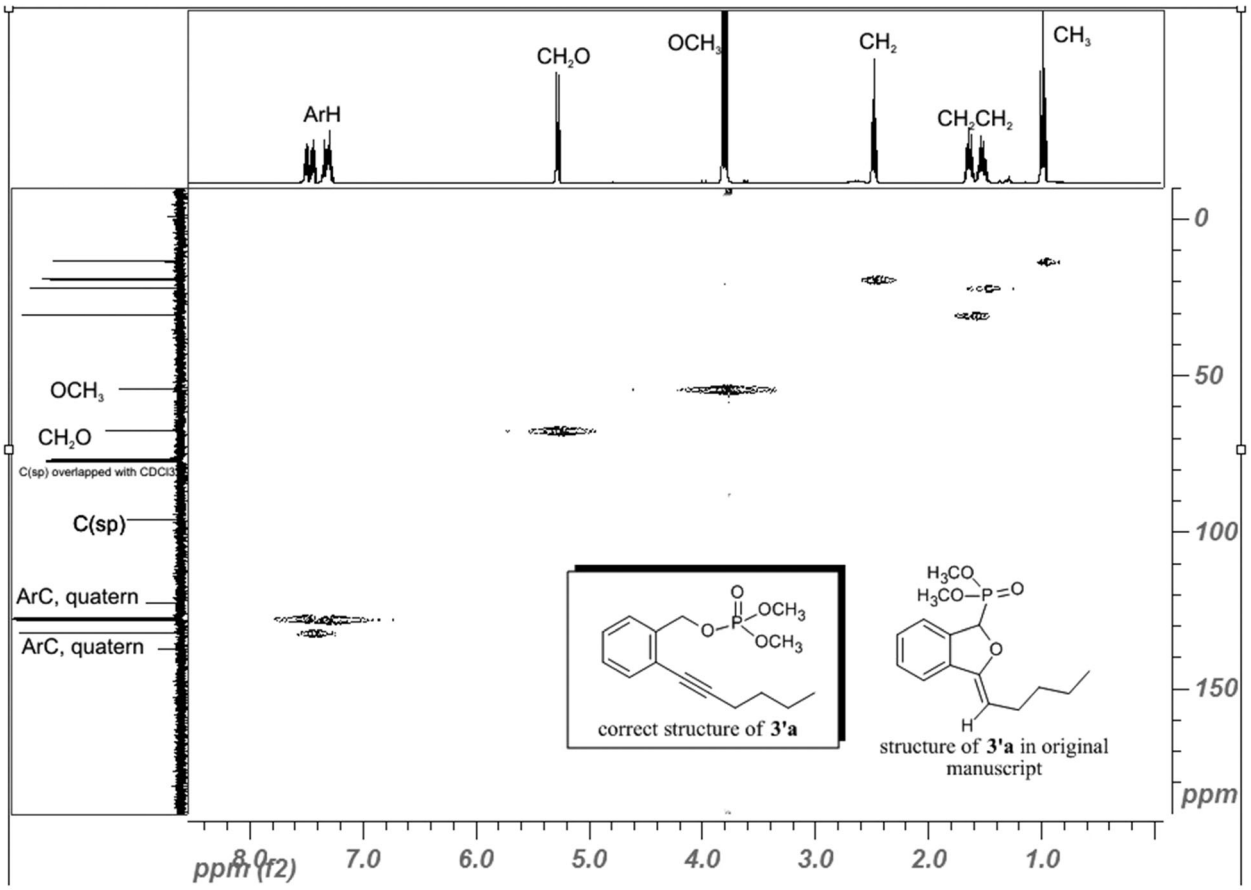


Figure 3. The HSQC spectrum of **3′a**.

besides, other signals, there were doublets at 66.92–67.43 with coupling constants of 5.03–5.1 Hz indicating the presence of CH_2OP moieties. Moreover, there were pairs of triple bond carbon signals at 86.08 and 94.42, at 77.17 and 95.78, and at 80.12 and 82.46 ppm respectively. And finally, in the IR spectra of **3a**, **3′a** and **3′e**, there were weak absorption bands at 2102–2226 cm^{-1} indicating the presence of C≡C bonds. All these data led us to conclusion that under the reaction conditions the classical Pudovik reaction[7] followed by phosphonate–phosphate rearrangement[8] had taken place. During these transformations the triple bonds of the starting materials remained unchanged. Therefore, the structures of **3a**, **3′a** and **3′e** could be the corresponding dimethyl (2-alkynylphenyl)methylphosphates (Scheme 5).[10]

However, in the original publication the NMR spectra of **3a**, **3′a** and **3′e** were differently interpreted and other structures for final compounds were proposed (see ref.[4] and the Supporting Information).

In order to definitely confirm the structures of compounds **3a**, **3′a** and **3′e** several additional NMR experiments were run. First of all, the phosphorus-decoupled ^{1}H NMR spectra of **3′a** and **3′e** showed that pairs of peaks at 5.26 and 5.28 ppm. (for compound **3′a**), and at 5.19 and 5.21 ppm (for compound **3′e**) are doublets due to phosphorus coupling, but not chemically shifted singlets. The same evidence was seen when the ^{1}H NMR spectra of **3′a** and **3′e** were run at a different fields (300 and 400 MHz operating frequency).

ATP (attached proton test) and DEPT (distortionless enhancement by polarization transfer) spectra showed that the ^{13}C signals at 66.92–67.43 ppm are of CH_2 groups, and the signals at 86.08 and 94.42 ppm (for compound **3a**), at 77.17 and 95.78 ppm (for compound **3′a)**, and at 80.12 ppm (for compound **3′e**) are unprotonated carbons. The cross-peak in the HetCor and HSQC spectra of **3′a** between two protons signals at 5.23 ppm and ^{13}C signal at 67.28 ppm indicated that signal at 5.23 ppm in the ^{1}H NMR spectrum belongs to the methylene group (Figure 3). The analogous correlation was seen from the HSQC spectra of compound **3′e** (see the Supporting Information).

The cross-peak in the HetCor and HSQC spectra of **3′e** between the proton signal at 3.35 ppm and the carbon signal at 82.97 ppm showed the presence of a terminal alkyne moiety. Moreover, HMBC spectra of all three compounds **3a**, **3′a** and **3′e** showed correlations between two ethynyl carbons and protons of the

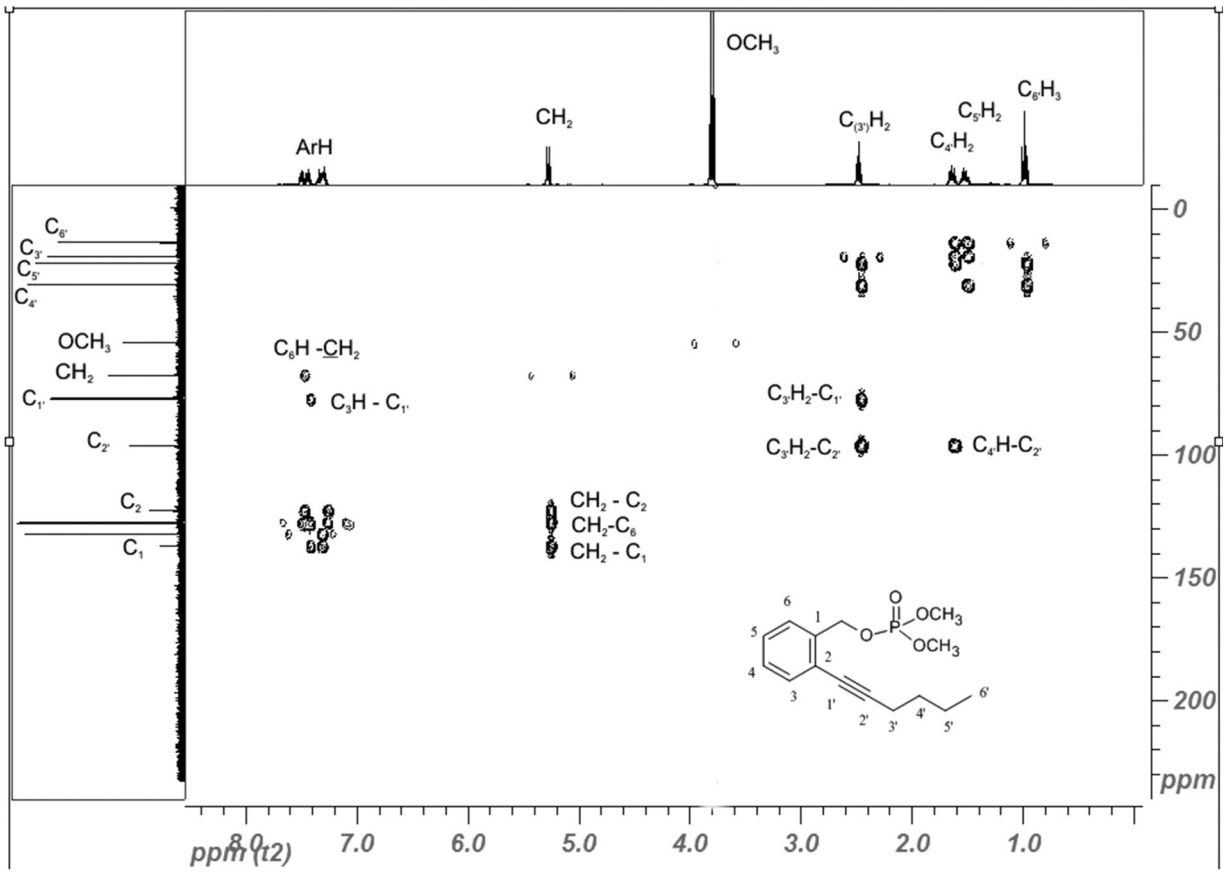
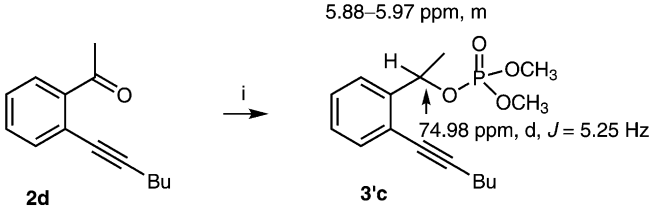


Figure 4. The HMBC spectrum of **3′a**.

attached groups and characteristic three cross-peaks between protons of CH_2 groups and three aromatic carbons. The HMBC spectrum of compound **3′a** is presented in Figure 4.

Following one reviewer's useful comment, we prepared 1-[2-(1-hexynyl)phenyl]ethanone **2d**, which was also be used in original publication and performed its reaction with dimethyl phosphite in the presence of DBU. After the isolation and spectral analysis of compound **3′c** we were thoroughly persuaded that an analogous phosphonate–phosphate rearrangement had taken place (Scheme 6). In the ^{1}H NMR spectrum of **3′c** there was a characteristic doublet for the methyl group at 1.64 ppm with coupling to the neighbouring CH proton ($J = 6.3$ Hz). The correlation peak



Scheme 6. *Reagents and conditions:* i) dimethyl phosphite (2 equiv.), DBU (2 equiv.), THF, 50 °C, 24 h.

between CH_3 and CH groups in the COSY spectrum of **3′c** confirmed this coupling. ^{13}C NMR and IR spectra showed the presence of the C≡C bond, the multiplicities of all carbons were verified by ATP experiments. All these results showed that the report about tandem nucleophilic addition–cyclization reaction of *o*-alkynylbenzaldehydes or *o*-alkynylacetophenones with dialkyl phosphites or dialkyl phosphonothioates in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene[4] was erroneous.

Conclusions

It was found that various acetylenic aldehydes undergo smooth reactions with dimethyl phosphite in basic media. The outcome of the reactions is dictated by the electron density on the alkyne moiety. Electron-rich substrates undergo the classic Pudovik reaction followed by phoshonate–phosphate rearrangement. On the other hand, when the triple bond of the starting materials is activated by electron-withdrawing heterocycles, the novel tandem 5-*exo*-dig cyclization reactions take place. Our observed results disagree with those previously published in Miao and co-workers work[4] and moreover, bring some novelty to the un-

derstanding of cyclizations of functionally substituted alkynes.

Experimental Section

The spectroscopic data of all synthesized compounds are given in the Supporting Information.

General Procedure for the Synthesis of Dimethyl (2-Alkynylphenyl)methylphosphates (3a,3′a,3′e), Dimethyl 1-[2-(1-Hexynyl)phenyl]ethylphosphate (3′c), Dimethyl (2-Alkynyl-3-quinolinyl)methylphosphates (6a–d) and Dimethyl [(3*Z*)-1,3-Dihydro-3-(2-pyridinylmethylene)furo[3,4-*b*]quinolin-1-yl]phosphate (8)

o-Alkynylbenzaldehyde (**2a**, **c** **f**), *o*-alkynylacetophenone (**2d**) or 2-alkynylquinoline-3-carbaldehyde (**4**) (0.5 mmol) in THF (4 mL) was added dropwise to a stirred mixture of dimethyl phosphite (0.11 g, 1.0 mmol) and DBU (0.153 g, 1.0 mmol) in THF (4 mL) at room temperature with TLC (silica gel) monitoring. After 2–24 h stirring at 50 °C, the mixture was cooled to room temperature and worked-up with water (5 mL). The resulting mixture was then extracted by AcOEt and dried with anhydrous sodium sulfate. After concentration, the residue was purified by gradient column chromatography (silica gel, AcOEt/hexane) to afford the products **3**, **6** and **8**. The same results can be reached by using potassium *tert*-butoxide (1 mmol) in dichloroethane (5 mL).

Procedure for the Synthesis of Dimethyl [(7*Z*)-5,7-Dihydro-2,4-disubstituted-7-(arylmethylene)furo[3,4-*d*]pyrimidin-5-yl]phosphates (9a–f)

2,4-Disubstituted-6-arylalkynylpyrimidine-5-carbaldehyde (**5a–f**) (0.5 mmol) in DCE (5 mL) was added dropwise to a stirred mixture of dimethyl phosphite (0.11 g, 1.0 mmol) and potassium *tert*-butoxide (0.056 g, 0.5 mmol) in DCE (4 mL) at room temperature with TLC (silica gel) monitoring. After 30 min stirring at room temperature, the mixture was washed with water (2 × 15 mL). The organic layer was dried with anhydrous sodium sulfate. After concentration, the residue was purified by gradient column chromatography (silica gel, AcOEt/hexane) to afford the products **9a–f**.

Acknowledgements

*The research was funded by the European Social Fund under the Global Grant measure (Grant No. VP1-3.1-ŠMM-07 K-01–002). The authors thank Dr. Martin Murray (Bristol University, U.K.) for the expertise on NMR data and for the suggestion of some NMR experiments. Mrs. Maryte Kreneviciene (Vilnius University) is thanked for the recording of all regular NMR spectra and for helpful discussions. Mr. Marius Morkunas (Tuebingen University) is kindly acknowledged for the recording of ^{1}H-{^{31}P} NMR, DEPT, HSQC and HMBC spectra of compounds **3a**, **3a** and **3e**. Dr. Tadeusz Bieg (Silesian University of Technology) is kindly acknowledged for the running of HSQC, HMBC and TOCSY spectra of compound **8**.*

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[9] CCDC 874365 (**9d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or on request to Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, U.K. Crystal structure analysis for **9d**: $C_{21}H_{28}N_3O_4PS$, $M_r = 449.510\ g\,mol^{-1}$, monoclinic, space group P 21/c, $a = 10.5209(2)$, $b = 19.0797(4)$, $c = 12.1081(3)$ Å, $\alpha = \gamma = 90.00$, $\beta = 113.7875(10)$, $V = 2224.05(8)$ Å^3, $\rho = 1.342\ g\,cm^{-3}$, $F(000) = 952$.

[10] The splitting patterns of **3a**, **3′a** and **3′e** in their NMR spectra are similar to the splitting in NMR spectra of the known compound dimethyl benzylphosphate: C. Lherbet, R. Castonguay, J. W. Keillor, *Tetrahedron Lett.* **2005**, *46*, 3565.

