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SHORT COMMUNICATION

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Fluorinated Alkynylphosphonates in *C,C*-Cyclizations: Regioselective Formation of Polysubstituted Fluorinated Arylphosphonates

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The regioselective *C,C*-cyclization of selected 1,4-bipolar substrates with fluorinated alkynylphosphonates provided polysubstituted benzenes and naphthalenes in up to 98% yield. For the case in which tetraethyl ethynylbisphosphonate was used, an unexpected phosphonate–phosphoramidate rearrangement was, for the first time, observed, which occurred in excellent yield.

Introduction

The regioselective synthesis of arenes is of significant interest from synthetic organic chemistry and medicinal chemistry point of views.[1] Compounds containing arene functionalities are, therefore valuable in medicine, agricultural, and materials science. Special attention has been paid to the synthesis of arenes that contain different functional groups. The selective introduction of various functional groups into aromatic rings at specified positions to produce polysubstituted arenes is undoubtedly very desirable and also if atom-economic synthesis is considered.[1,2]

For example, the so-called acceptor–donor–acceptor[3] (A–D–A) system on the aryl ring (e.g., 2,4-dicyanoanilines) has shown important potential in artificial photosynthetic systems and also in nonlinear optical properties.[4] It is well documented that incorporating fluoroalkyl or phosphonate groups into aromatic systems changes their physical, chemical. and biological properties remarkably.[5] Owing to the presence of a P–C bond, a phosphonate group is more stable in a biological environment, and thereby the compound retains its biological properties.[6] Fluorine-containing groups are more lipophilic than their non-fluorinated counterparts, and they are also metabolically more stable.[5] For other instances, aromatic compounds containing fluoroalkyl groups along with phosphonate motifs were found as additives in elastomer compositions[7] and in photostabilizers[8] and have been used in ethylene polymerization[9] and as antidiabetes agents.[10]

From a synthetic perspective, polysubstituted arenes have been mostly synthesized by sequential introduction of particular substituents by electrophilic and nucleophilic aromatic substitutions, transformation of functional groups, as well as coupling reactions.[1,11] Transition-metal-catalyzed cyclizations such as [2+2+2][2] and [4+2] Diels–Alder cycloadditions[12] of the corresponding unsaturated substrates to produce aromatic compounds have been well documented.[13] However, these cycloadditions suffer from poor regioselectivity. Synthetic methods to obtain fluoroalkylarenes and/or arylphosphonates are numerous, but they always suffer from low yields, low atom economy, and low regioselectivity; furthermore, they involve harsh conditions and long reaction times.[5a,14] In addition, if two groups are introduced, the common procedure is to fluoroalkylate or phosphonylate particular arylphosphonates or fluoroalkylarene precursors, respectively.[14e,15] Inspired by our recent findings regarding *O,C*-[16] and *N,C*-type[17] cyclizations of fluorinated alkynylphosphonates **3a**–**e**, we turned our attention to *C,C*-cyclization to produce polysubstituted fluorinated arylphosphonates with high regioselectivity and, more importantly, to introduce both functional groups simultaneously at *ortho* positions to each other.

Results and Discussion

The initial experiment involved the reaction of F_3C–C≡C–P(O)$(OEt)_2$ (**3a**) with 2-(cyanomethyl)benzonitrile (**1**) in the presence of a base, such as K_2CO_3, in toluene under reflux (Table 1, entry 2; Scheme 1). Surprisingly, by monitoring the progress of the reaction by ^{19}F and ^{31}P NMR spectroscopy we detected 100% conversion and isolated the

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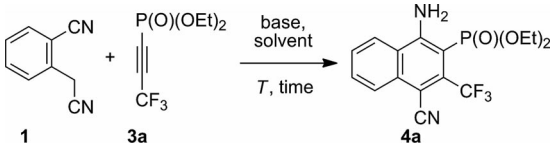
product in 95% yield within only 10 h (Table 1, entry 2). The absence of a base in the reaction mixture did not give any results, even after 24 h of refluxing in toluene. In addition, different bases and solvents were screened further (Table 1). Tertiary amines, namely, NEt_3, iPr_2NEt, and DABCO (1,4-diazabicyclo[2.2.2]octane), also provided desired naphthalene **4a** with comparable results (Table 1, entries 8–10). K_2CO_3 turned out to be the best choice, and it gave **4a** in 95% yield. Notably, the presence of a transition-metal catalyst [e.g. $Pd(OAc)_2$, $CeCl_3$, CuI] did not promote any reaction between alkyne **3a** and **1**, and the substrate was almost quantitatively recovered. Furthermore, different reaction media including toluene, benzene, acetone, CH_2Cl_2, and DMSO were screened. A very good conversion as well as a short reaction time was found with the use of DMSO (T = 100 °C) according to NMR spectroscopy. Desired **4a** was, however, isolated in only 12% yield (Table 1, entry 7). Additional signals in the ^{19}F NMR and ^{31}P NMR spectra (δ_P = 0.1 ppm, δ_F = –80 ppm) suggested the possible decomposition of the intermediates, as well as acetylene derivatives. CH_2Cl_2 turned out to be inefficient, as it gave only trace amounts of **4a** (Table 1, entry 6). Moreover, benzene could also be used as a solvent, and it produced **4a** in 85% yield (Table 1, entry 5).

Table 1. Reaction of **1** with alkyne **3a**: Screening of the reaction conditions.[a]



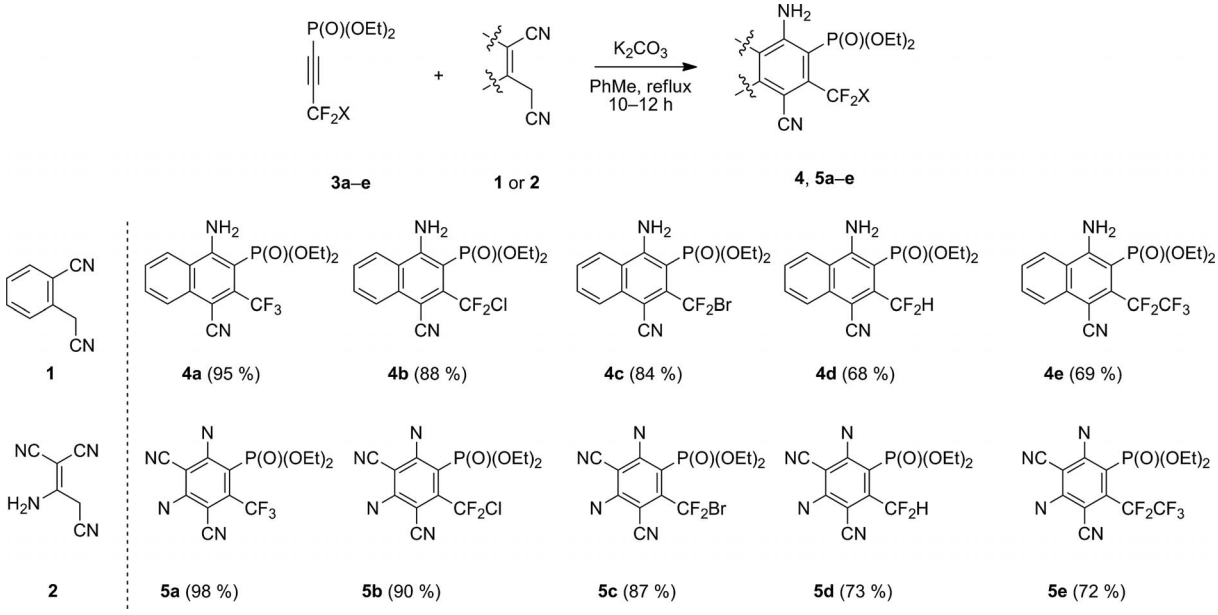
1 **3a** **4a**

Entry	Base	Solvent	T [°C]	Conv.[b] [%]	Time [h]	Yield[c] [%]
1	K_2CO_3	toluene	25	24	24	15
2	K_2CO_3	toluene	112	100	10	95
3	–	toluene	112	–	24	–
4	K_2CO_3	benzene	25	–	24	–
5	K_2CO_3	benzene	80	94	15	85
6	K_2CO_3	CH_2Cl_2	40	16	24	5
7	K_2CO_3	DMSO	100	90	5	12
8	DABCO	toluene	112	80	16	71
9	NEt_3	toluene	112	92	17	85
10	iPr_2NEt	toluene	112	95	14	86

[a] General conditions: **1** (5 mmol), **3a** (5 mmol), base (6 mmol), solvent (15 mL). [b] Conversion was established by ^{19}F NMR and ^{31}P NMR spectroscopy. [c] Yield of isolated product.

Additionally, a 1,4-bipolar substrate, namely, 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**2**), that can undergo two possible reaction pathways, *N*,*C*-[17] and *C*,*C*-cyclizations, was treated with alkyne **3a**. Adopting the optimized reaction conditions (K_2CO_3/$PhCH_3$/reflux), *C*,*C*-cyclization product **5a** was isolated as the only product (Scheme 1). Notably, **5a** was obtained in a higher yield than **4a** (Table 1, entries 1 and 6). The absence of the *N*,*C*-cyclization product in the ^{19}F NMR and ^{31}P NMR spectra suggests that the *C*,*C*-pathway is kinetically and thermodynamically more favorable. The structure of a benzene derivative was eventually confirmed by single-crystal X-ray diffraction analysis.[18] The ^{15}N NMR spectrum of **5a** showed four characteristic signals at δ_N = 275.2 (–C*N*), 266.6 (–C*N*), 83.1 (–*N*H_2), 72.7 ppm (–*N*H_2).

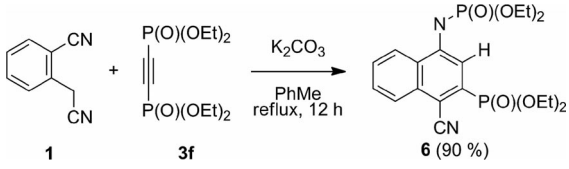
Studying different alkynes with varied fluorinated groups, such as $–CF_3$ (**3a**), $–CF_2Cl$ (**3b**), $–CF_2Br$ (**3c**), $–CF_2H$ (**3d**), and $–C_2F_5$ (**3e**) upon the *C*,*C*-cyclization revealed better results were obtained with more electron-withdrawing fluorinated groups (Scheme 1). The highest reaction yield with the shortest reaction time was observed for $F_3C–C{\equiv}C–P(O)(OEt)_2$ (**3a**). The $–CF_2Cl$ (**3b**) and $–CF_2Br$ (**3c**) analogs provided the target products in comparable yields, but lower than that for **3a** (Scheme 1); the $–CF_2H$



Scheme 1. The formation of CF_2X-substituted arylphosphonates **4** and **5a**–**e**.

(**3d**) and $-C_2F_5$ (**3e**) analogs experienced a significant electronic and steric effect, respectively (Scheme 1). Such a pattern in the reduction of the reaction yields has been found in other cyclizations.[19]

To compare the electronic effects of the triple bond towards the *C,C*-cyclization, symmetrically substituted tetraethyl ethynylbisphosphonate (**3f**) was employed. Under the optimized reaction conditions, **3f** was treated with **1** and **2** (Scheme 2). The reaction with **2** did not give any results, even after heating at reflux for 48 h. Interestingly, by monitoring the progress of the reaction of **3f** with **1** by ^{31}P NMR spectroscopy, we detected 100% conversion of **3f** within 12 h. After purification by column chromatography ($CHCl_3$/acetone, 5:1 v/v) we isolated unexpected phosphonate–phosphoramidate rearrangement product **6** in 90% yield. To the best of our knowledge, a similar rearrangement has, hitherto, not been reported. The structure was additionally confirmed by single-crystal X-ray diffraction analysis (Figure 1).[20] The ^{15}N NMR spectrum of this product showed a characteristic doublet at δ_N = 71.7 ppm with $^1J_{N,P}$ = 42 Hz and a singlet at δ_N = 265.9 ppm, which was assigned to the –CN group.



Scheme 2. Reaction of tetraethyl ethynylbisphosphonate (**3f**) with **1**.

We propose, as shown in Scheme 3, that **1** is first deprotonated by the base (K_2CO_3) to form carbanion **A**, which then attacks the triple bond through a Michael-type addition, and this results in derivative **B**. Conceivable further rapid deprotonation of **B** promotes the ring-closure process, and thus, thermodynamically unstable intermediate **C** through four-membered ring **D** provides rearranged product **6**.

In the case of fluorinated alkynylphosphonates **3a**–**e**, we suggest that the cyclization process occurs simultaneous to the nucleophilic attack of anion **A′**. Thus, imine derivative **E** aromatizes to give thermodynamically more stable aromatic products **4** and **5a**–**e** (Scheme 4). A Michael addition[21] product derived from the reaction of **A′** with **3a**–**e** was not detected by ^{19}F NMR and ^{31}P NMR spectroscopy, but additional signals at δ_F = –59 ppm (alkyne **3a** used, X = F) and δ_P = 11 ppm can be assigned to non-aromatic imine derivative **E**, which could not be isolated.

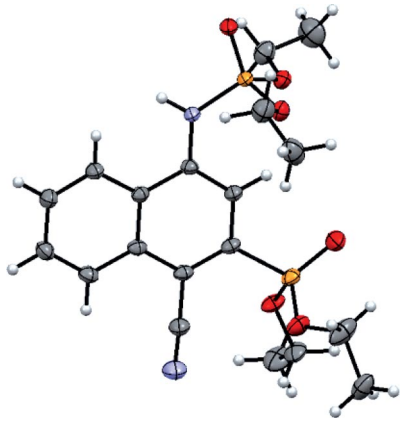
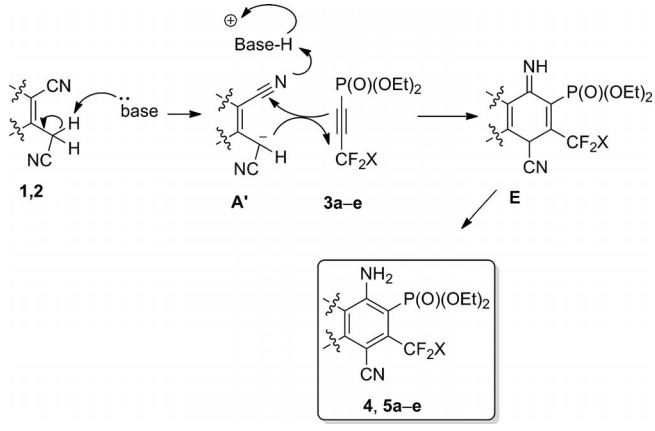
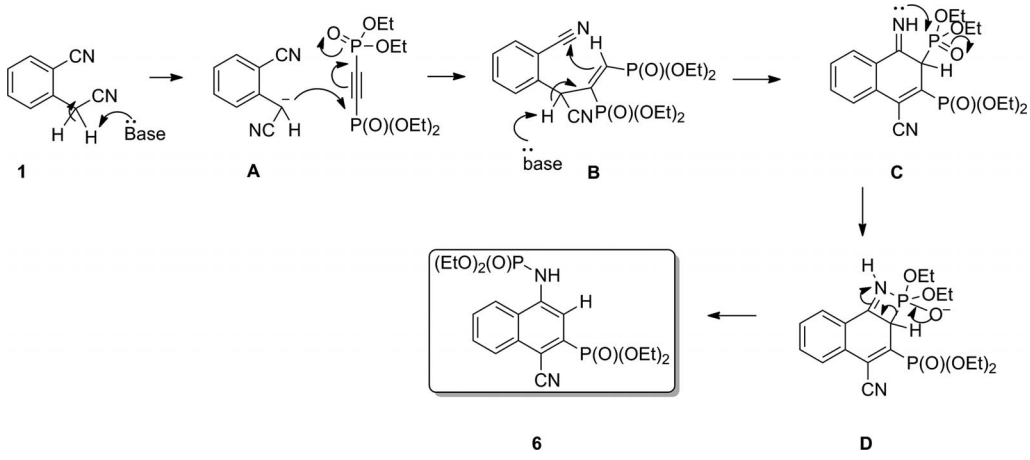


Figure 1. ORTEP image of **6** (blue: N, red: O, orange: P, gray: C).



Scheme 4. Proposed mechanism for the formation of **4** and **5a**–**e**.



Scheme 3. The proposed mechanism for the formation of **6**.

Conclusions

In conclusion, 1,4-bipolar substrates, namely, 2-(cyanomethyl)benzonitrile (**1**) and 2-aminoprop-1-ene-1,1,3-tricarbonitrile (**2**), containing an acidic CH_2 group were successfully utilized in *C*,*C*-cyclizations with $XF_2C–C\equiv C–P(O)(OEt)_2$ (**3a**–**e**) to produce desired polyfunctionalized benzenes **4a**–**e** and naphthalenes **5a**–**e** in up to 98% yield. By testing different reaction conditions, such as basic mediators (iPr_2NEt, DABCO, NEt_3, and K_2CO_3) and solvents (DMSO, CH_2Cl_2, benzene, and toluene), we found that the best results were obtained if the K_2CO_3/$PhCH_3$/reflux system was used. Interesting phosphonate–phosphoramidate rearrangement product **6** was isolated upon treating 2-(cyanomethyl)benzonitrile (**1**) with tetraethyl ethynylbisphosphonate (**1f**). On the basis of the experimental data, we proposed a plausible mechanism for such a rearrangement. The reactivity of $XF_2C–C\equiv C–P(O)(OEt)_2$ towards the carbocyclization was found to be in the order $X = F > Cl \approx Br > H \approx CF_3$.

Experimental Section

General Procedure: XF_2C-acetylene **3a**–**e** (5 mmol) was added slowly to a mixture of 2-(cyanomethyl)benzonitrile **1** or 2-aminoprop-1-ene-1,1,3-tricarbonitrile **2** (5 mmol) and K_2CO_3 (5 mmol) in dry toluene (20 mL). The solution was then heated at reflux for an additional 10–16 h. The K_2CO_3 was filtered off, and the remaining solution was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel; CH_2Cl_2/EtOAc, 5:1 v/v).

4a: Yellowish crystals (95%); m.p. 149–151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, J = 7.1 Hz, 3 H), 1.33 (t, J = 7.0 Hz, 3 H), 4.17 (m, 2 H), 4.19 (m, 2 H), 7.63 (dd, J = 8.2, 1.0 Hz, 1 H), 7.74 (dd, J = 8.0, 1.0 Hz, 1 H), 7.94 (br. s, 2 H), 7.97 (d, J = 8.2 Hz, 1 H), 8.24 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz): δ = 16.1 (d, J = 7.3 Hz), 63.1 (d, J = 6.0 Hz), 96.9 (dq, $^1J_{C,P}$ = 186.6 Hz, $^3J_{C,F}$ = 1.2 Hz), 98.2 (dq, $^3J_{C,P}$ = 13.8 Hz, $^3J_{C,F}$ = 3.9 Hz), 115.9, 122.0, 122.8 (qd, $^1J_{C,F}$ = 278.3 Hz, $^3J_{C,P}$ = 5.3 Hz), 123.1 (d, $^3J_{C,P}$ = 14.3 Hz), 127.0, 128.9, 131.5, 133.4, 136.4 (qd, $^2J_{C,F}$ = 31.8 Hz, $^2J_{C,P}$ = 6.4 Hz), 155.7 (d, $^2J_{C,P}$ = 8.7 Hz) ppm. ^{19}F NMR (376 MHz): δ = –53.1 ppm. ^{31}P NMR (161 MHz): δ = 19.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{16}F_3N_2NaO_3P$ $[M + Na]^+$ 395.0754; found 395.0766.

Supporting Information (see footnote on the first page of this article): Experimental details for the synthesis and copies of the ^{1}H NMR, ^{13}C NMR, ^{15}N NMR, ^{19}F NMR, and ^{31}P NMR spectra of new compounds along with the crystallographic data for compounds **4a** and **6**.

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[18] CCDC-981319 (for **5a**) 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.

[19] B. Duda, S. N. Tverdomed, G.-V. Röschenthaler, *J. Fluorine Chem.* **2013**, *152*, 29.

[20] CCDC-981320 (for **6**) 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.

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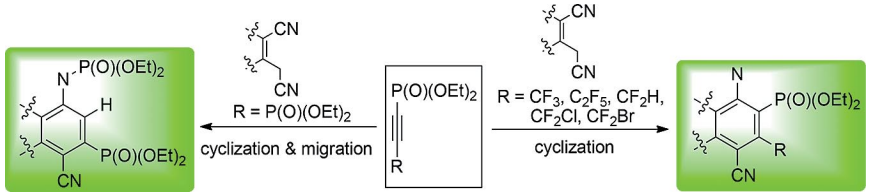
C,C-Cyclization



Keywords: Synthetic methods / Cyclization / Alkynes / Arenes / Fluorine

A regioselective synthetic approach towards polysubstituted benzenes and naphthalenes containing a phosphonate and fluorinated groups at the *ortho* position to each other is reported. By using mild reaction conditions such as K_2CO_3 as the base in refluxing toluene, the target arenes can be isolated in up to 95% yield within only 10–12 h.

