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Multicomponent Reactions of Phosphines, Diynedioates, and Aryl Aldehydes Generated Furans Appending Reactive Phosphorus Ylides through Cumulated Trienoates as Key Intermediates: A Phosphine α-Addition-δ-Evolvement of an Anion Pathway

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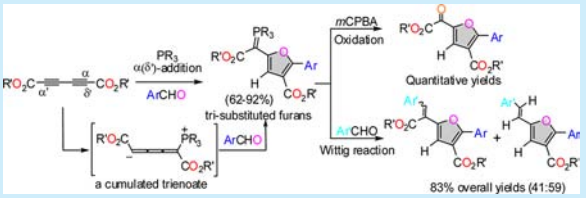
Supporting Information

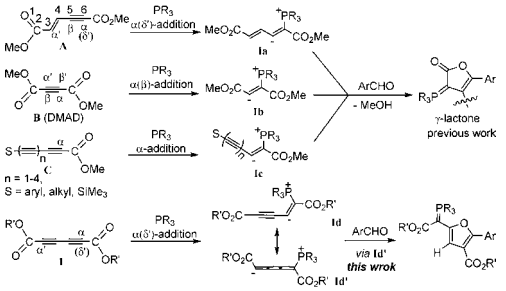
ABSTRACT: Multicomponent reactions of phosphines, diynedioates, and aryl aldehydes have been demonstrated, providing trisubstituted furans appending reactive phosphorus ylides, through cumulated trienoates as key intermediates. The proposed trienoate intermediates, 1,5-dipolar species formed via nucleophilic α-attack of phosphines toward diynedioates (α-addition-δ-evolvement of an anion, abbreviated αAδE), undergo addition to aryl aldehydes followed by 5-*endo-dig* cyclization, proton transfer, and resonance to give trisubstituted furans. Furthermore, the phosphorus ylides are oxidized to α-keto ester furans and utilized as Wittig reagents.



Conjugate addition of nucleophiles to α,β-unsaturated species is a fundamental synthetic methodology in organic chemistry.[1] Nucleophilic species such as carbonucleophiles,[2] organophosphines,[3] pyridines,[4] isocyanides,[5] and amines[6] can undergo conjugate addition toward alkenes or alkynes substituted with electron-withdrawing functionality to generate 1,3-dipolar intermediates regioselectively. In conjugate addition methodology, one possible pathway with the α-carbon of α,β-unsaturated species being the electrophilic center for direct nucleophilic attack, termed *anti*-Michael or 1,3-addition, was relatively rare and not usually used for synthetic design.[7] The first hypothesized α-addition attempt on β-trifluoromethyl-substituted alkenoates by Walborsky and Schwarz et al. was not successful due to the insufficient inductive effect on the β-carbon and resonance stabilization of the generated β-anion.[8] Soon after, Knunyants and Cheburkov demonstrated successful examples of α-addition of alkenoates substituted with two trifluoromethyl groups at the β-carbon toward nucleophiles in 1960.[9] In addition, Rapoport[10] and Klumpp[11] further showed phenyl and trimethylsilyl-substituted ynamides as other α-addition substrates, demonstrating an *anti*-Michael reaction through intra- and intermolecular addition, respectively. Afterward, trifluoromethyl-substituted alkynones have also been reported as another acceptor for α-addition reactions toward nucleophiles.[12]

Apart from the rare examples with a 1,3-addition pattern, relevant discovery in phosphine chemistry remains scarce. Recently, we have reported that (*E*)-hex-2-en-4-ynedioic acid dimethyl ester (**A**)[13] underwent α(δ′)-addition toward phosphines followed by addition to aldehydes, generating γ-lactones bearing α-phosphorus ylides in one pot through formation of 1,3-dipolar intermediates **Ia** (Scheme 1).[14] Further, dimethyl acetylenedicarboxylate (DMAD, **B**)[15] and poliynoates (**C**)[16] also proceeded through a similar reaction pathway, via **Ib** and **Ic**

Scheme 1. Various Alkynoates Systems for Nucleophilic Conjugate Addition



respectively, to give γ-lactones. In contrast to **C** undergoing an unusual 1,3-addition, the addition patterns of **A** and **B** toward phosphines are 1,6- and 1,4-addition respectively according to IUPAC nomenclature numbering rule. However, reactions of **A** and **B** toward nucleophiles could be considered an α-addition since the alkynyl carbons being attacked by nucleophiles neighbor the proximate carbonyl moiety. A common reaction feature of substrates **A**−**C** toward phosphines lies in the formation of lactone products through β-anion intermediates after α-attack of phosphines, an α-addition-β-evolvement (αAβE) of anion system. Our continuing interest in finding new addition patterns of alkynoates toward phosphines led us to examine the reactivity of symmetrical diynedioates **1** and survey opportunities for building other new structural motifs. Herein, we report that a new trisubstituted-furan motif bearing phosphorus ylides can be prepared through three-component reactions (3CRs), via α(δ′)-addition of phosphines to

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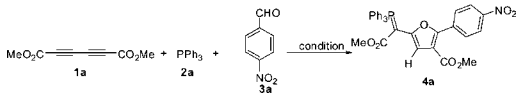
diynedioates **1** followed by addition to aryl aldehydes. This novel 3CR proceeded through initial formation of reactive intermediates **Id** and resonance-derived cumulated trienoate intermediates **Id′** (α-addition-δ-evolvement of anion, abbreviated αAδE), followed by the addition of **Id′** to aldehydes. The resulting furans appending phosphorus ylides underwent Wittig reaction with aldehydes to give 5-furyl olefins and can be oxidized by *m*CPBA to give 2,3,5-trisubstituted furans with α-keto ester functionality. These structurally related substituted furans were useful structure motifs[17] since they were bioactive and useful building blocks in the pharmaceutical industry;[18] for example, disubstituted furans and furans-derived tetracyclic azepines and oxazocines possessed potential utilization as MAPKAP-K2 (MK2) inhibitors for the treatment of rheumatoid arthritis, Crohn's disease, inflammatory bowel syndrome, and cancer.[19]

To commence this work, dimethyl hexa-2,4-diynedioate (**1a**), triphenylphosphine (**2a**), and 4-nitrobenzaldehyde (**3a**) were chosen as the reaction substrates for optimizing the reaction conditions (Table 1). We carried out the reactions stepwise technically by adding a solution of **1a** to a mixture of **2a** and **3a**. In preliminary studies, reactions with the molar ratio **1a**:**2a**:**3a** = 1:1:1 ([**3a**] = 0.026 M) in chlorinated solvents were found to perform better than those in THF and toluene at rt for 1 h (entries 1−5). Further, reactions in *ortho*-dichlorobenzene (*o*-DCB) gave 10% and 15% higher yields than those in dichloromethane (DCM) and 1,2-dichloroethane (DCE) at rt, respectively (entries 3−5). We realized that increasing the reaction temperature, from rt to 50 and 60 °C respectively, did not improve the formation of **4a** due to the increasing instability of **1a** at higher temperature, giving 40% and 42% yields, respectively (entries 6 and 7). Yet, lowering the temperature to 0 °C gave poor yields (32%), even with prolonging the reaction time to 7 h (entry 8). However, reactions carried out at elevated temperature upon finishing injection of **1a** at 0 °C provided a remarkable improvement in yields (entries 9−10), likely due to providing sufficient energy for subsequent reactions after generating intermediates **Id′** at low temperature. Further adjustments such as shortening the injection time of **1a** to 10 min, modification of the molar ratio of reactants, and control of reaction times provided the best yield of 71% (entries 11−13). The improvements were attributed to a lesser preference for side reactions of zwitterions **Id′** with **1a** at 0 °C and the higher efficiency of furanization at higher temperature (60 °C). To further improve yields, we attempted to extend the reaction time to 3 h for full consumption of **3a**, but it gave a comparable yield (68%, entry 14). Substrate **1a** was relatively unstable since it tended to polymerize at higher solution concentration. To our delight, 83% and 90% yields were achieved in high-dilution conditions with [**3a**] = 0.0026 and 0.0013 M respectively (entries 15−16). A control experiment with the concentration doubled, 0.052 M, decreased the reaction yield to 57% (entry 17). Under this circumstance, intense baseline materials were observed likely due to polymerization.

Table 1. Condition Optimization for Reaction of Diynedioate 1a, Phosphine 2a, and Aldehyde 3a To Give Furan 4a[a]



entry	equiv[b]	solvent	injection condition[c]	reaction condition[d]	yield (%)[e]
1	1:1:1	THF	1 h; rt	1 h; rt	19 (35)
2	1:1:1	toluene	1 h; rt	1 h; rt	29 (39)
3	1:1:1	DCM	1 h; rt	1 h; rt	30 (33)
4	1:1:1	DCE	1 h; rt	1 h; rt	35 (38)
5	1:1:1	*o*-DCB	1 h; rt	1 h; rt	45 (54)
6	1:1:1	*o*-DCB	1 h; 50 °C	1 h; 50 °C	40 (54)
7	1:1:1	*o*-DCB	1 h; 60 °C	1 h; 60 °C	42 (58)
8	1:1:1	*o*-DCB	1 h; 0 °C	7 h; 0 °C	32 (32)
9	1:1:1	*o*-DCB	1 h; 0 °C	2 h; rt	41 (54)
10	1:1:1	*o*-DCB	1 h; 0 °C	1 h; 60 °C	45 (54)
11	1:1:1	*o*-DCB	10 min; 0 °C	1 h; 60 °C	48 (54)
12	3:3:2	*o*-DCB	10 min; 0 °C	1 h; 60 °C	63 (67)
13	2:2:1	*o*-DCB	10 min; 0 °C	1 h; 60 °C	71 (75)
14	2:2:1	*o*-DCB	10 min; 0 °C	3 h; 60 °C	68 (71)
15[f]	2:2:1	*o*-DCB	10 min; 0 °C	1 h; 60 °C	83 (91)
16[g]	2:2:1	*o*-DCB	10 min; 0 °C	1 h; 60 °C	90 (94)
17[h]	2:2:1	*o*-DCB	10 min; 0 °C	1 h; 60 °C	57 (61)

[a]All reactions were performed with **3a** (0.21 mmol, [**3a**] = 0.026 M) in anhydrous solvents unless otherwise noted. [b]Molar ratio of **1a**:**2a**:**3a**. [c]Injection conditions denoted for addition of **1a** solution by a digital syringe pump. [d]Reaction condition after injection of **1a**. [e]Yields were determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard, and yields in parentheses were based on converted **3a**. [f]**3a** (0.066 mmol, [**3a**] = 0.0026 M). [g]**3a** (0.066 mmol, [**3a**] = 0.0013 M). [h]**3a** (0.21 mmol, [**3a**] = 0.052 M).

To gain insight into the tolerance of this reaction, we next studied the reaction scope with various phosphines (**2a**−**k**), diynedioates (**1a**−**d**), and aldehydes (**3a**−**e**) with [**3**] = 0.0013 M in *o*-DCB, as shown in Table 2.[20] In general, reactions with electron-donating phosphines (**2b**−**d**) afforded their corresponding furans (**4b**−**d**) in good yields (81−85%, entries 2−4). In contrast, those with electron-withdrawing phosphines (**2e**−**f**) performed slightly poorly, 65% and 77% yields for tri(4-chlorophenyl)phosphine (**2e**) and tri(4-fluorophenyl)-phosphine (**2f**), respectively (entries 5 and 6). Heteroaryl or dimethylamino phosphines (**2g**−**h**), on the other hand, also generated products **4g**−**h** in comparable yields to those with electron-withdrawing phosphines (62% and 66%, entries 7 and 8). It was worth mentioning that reactions with hexamethylphosphorus triamide (**2h**) resulted in a lower yield (66%) due to the complexity of reaction mixtures and that dark baseline bands were observed during column chromatography upon isolating unstable **4h**. Furthermore, this reaction could be performed with other substituted benzaldehydes **3b**−**c** and 4-pyridinecarboxaldehyde (**3d**), giving moderate to good yields of **4i**−**q** (69−92%; entries 9−17). Under this survey, the reaction of **1a** and 4-cyanobenzaldehyde (**3c**) with highly nucleophilic tricyclohexylphosphine (**2i**) gave good yields of **4o** (78%, entry 15). Further, reactions with 4-pyridinecarboxaldehyde (**3d**) also provided furans **4p**−**q** with relatively lower yields (69% and 74%, entries 16 and 17). Last, we performed reactions with diethyl hexa-2,4-diynedioate (**1b**), di-*n*-butyl hexa-2,4-diynedioate (**1c**), and dibenzyl hexa-2,4-diynedioate (**1d**) and obtained their corresponding products **4r**−**t** in moderate to good yields (70%, 82%, and 64%, entries 18−20). It was noteworthy that reactions with highly nucleophilic phosphines, PMe_3 or PBu_3, did not provide corresponding isolable products, likely due to the presence of electron-donating phosphines which rendered the formed phosphorus ylide products highly reactive (entries 21−22). Reaction with either hexanal or benzaldehyde gave no corresponding product (entries 23−24). In these entries, aldehydes were mostly recovered and dark black materials were observed in the baselines upon chromatography (SiO_2),

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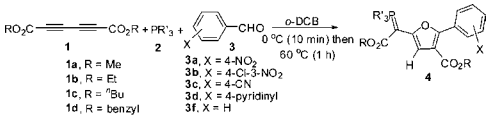
Table 2. Reaction Scope of Diynedioates 1, Phosphines 2, and Aldehydes 3 To Give Furans 4[a]



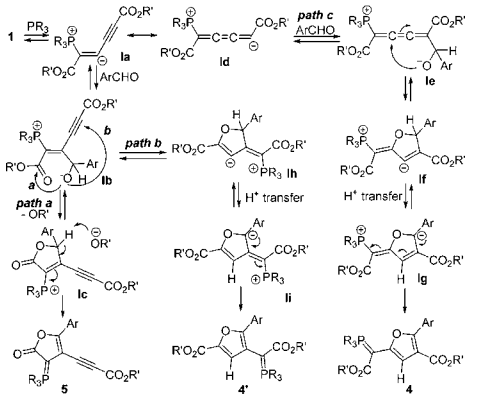
entry	1	2, PR'_3	3	4	yield (%)[b]
1	**1a**	**2a**, PPh_3	**3a**	**4a**	90 (94)
2	**1a**	**2b**, $P(p\text{-tolyl})_3$	**3a**	**4b**	83 (84)
3	**1a**	**2c**, $PPh_2(p\text{-tolyl})$	**3a**	**4c**	81 (83)
4	**1a**	**2d**, $P(4\text{-OMe-Ph})_3$	**3a**	**4d**	85 (89)
5	**1a**	**2e**, $P(4\text{-Cl-Ph})_3$	**3a**	**4e**	65 (81)
6	**1a**	**2f**, $P(4\text{-F-Ph})_3$	**3a**	**4f**	77 (81)
7	**1a**	**2g**, $P(2\text{-thienyl})_3$	**3a**	**4g**	62 (84)
8[c]	**1a**	**2h**, HMPT	**3a**	**4h**	66 (67)
9	**1a**	**2a**, PPh_3	**3b**	**4i**	72 (74)
10	**1a**	**2d**, $P(4\text{-OMe-Ph})_3$	**3b**	**4j**	70 (74)
11	**1a**	**2a**, PPh_3	**3c**	**4k**	92 (97)
12	**1a**	**2b**, $P(p\text{-tolyl})_3$	**3c**	**4l**	85 (90)
13	**1a**	**2c**, $PPh_2(p\text{-tolyl})$	**3c**	**4m**	79 (81)
14	**1a**	**2d**, $P(4\text{-OMe-Ph})_3$	**3c**	**4n**	79 (83)
15	**1a**	**2i**, PCy_3	**3c**	**4o**	78 (87)
16	**1a**	**2b**, $P(p\text{-tolyl})_3$	**3d**	**4p**	69
17	**1a**	**2d**, $P(4\text{-OMe-Ph})_3$	**3d**	**4q**	74
18	**1b**	**2a**, PPh_3	**3a**	**4r**	70 (71)
19	**1c**	**2a**, PPh_3	**3a**	**4s**	82 (87)
20	**1d**	**2a**, PPh_3	**3a**	**4t**	64 (65)
21	**1a**	**2j**, PMe_3	**3a**	**4u**	ND[d]
22	**1a**	**2k**, PBu_3	**3a**	**4v**	ND
23	**1a**	**2a**, PPh_3	**3e**[e]	**4w**	ND
24	**1a**	**2a**, PPh_3	**3f**	**4x**	ND

[a]Reactions were carried out under anhydrous conditions with [**3**] = 0.0013 M in *o*-DCB unless otherwise noted: at 0 °C for injection (10 min) of **1** and 60 °C for reaction (1 h). [b]Yields (%) in parentheses were determined based on converted aldehydes. [c]Injection at 0 °C for 10 min and reaction at rt for 1 h after injection. [d]ND denotes not detected. [e]Hexanal was used.

indicating that self-polymerization could take place with diynedioates in the presence of phosphines. A control experiment also displayed similar dark baseline materials in the absence of aldehydes. The scope study indicated that only reactions with highly electron-withdrawing aromatic aldehydes provided furans **4**, reflecting the necessity of more acidic benzylic protons during the reaction course.

These isolated furyl ylides **4** were reactive and decomposed gradually upon isolation; characterization had to be carried out in a quick manner. Growing solid state structures of these ylides **4** for X-ray diffraction analysis was not possible since they were all isolated as oils. Therefore, we initially characterized **4a**–**t** with MS, IR, and ^{1}H, ^{13}C, ^{31}P, 2D-HMQC, and 2D-HMBC NMR spectroscopic methods. However, the correct structure of **4** remained undetermined without assertive single crystal structures of their derived products. Prior to our unambiguous characterization, we deduced three possible structures via reaction pathways *a*–*c* (Scheme 2). The first proposed products were γ-lactones **5** via 1,3-dipoles **Ia** followed by addition to aldehydes, lactonization (path *a*), and subsequent deprotonation through **Ic**. However, the physical properties displayed by isolated compounds did not resemble those of typical lactones **5**.[13−16] First, the polarity of isolated products seemed to be unexpectedly lower according to thin-layer chromatography

Scheme 2. Proposed Possible Product Structures, Furans 4 and 4′, and Lactones 5, via Pathways *a*–*c*

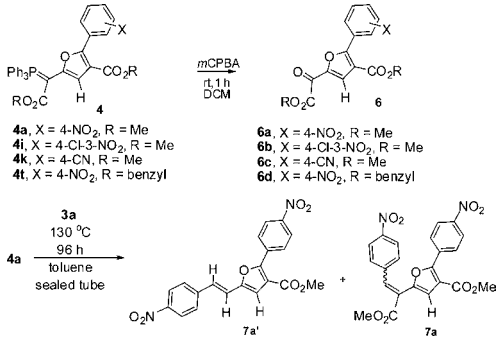


(TLC) analysis. Further, only one set of alkoxy carbonyl with ^3J (^{1}H−^{13}C) coupling should be observed in 2D-HMBC spectral analysis if lactones **5** were the products. However, two sets of couplings were observed (Figure S60; C2 with H_a and C8 with H_b), indicating that the alkoxyl groups were not released during the reaction course. Thus, structure **5** was excluded. The second possible product furans **4′** could result through intermediates **Ih** and **Ii** (path *b*), via 5-*endo*-*dig* cyclization followed by proton transfer. Both structures **4′** and **5** came from a common intermediate **Ib**. The third proposed structure, furans **4**, were formed through addition of a resonance-derived trienoate 1,5-dipole **Id** to aromatic aldehyde followed by 5-*endo*-*dig* cyclization of **Ie** to provide intermediate **If**. After proton transfer and resonance through **Ig**, furans **4** bearing phosphorus ylide were formed. However, we were not able to distinguish **4** from **4′** merely based on spectroscopic data. Further transformation of isolated products to structurally unambiguous compounds would be necessary to clarify the reaction pathways.

Notably, nearly all isolated products exhibited fast *E*/*Z* isomerism and only averaged signals were observed at rt, except for **4r** showing trace amounts of the other isomer in the ^{1}H NMR spectrum (Figure S39).

Due to their chemical reactivity toward oxidation, the selected furans **4a**, **4i**, **4k**, and **4t** were oxidized by *m*CPBA (2.4 equiv) to give α-keto esters **6a**–**d** respectively in quantitative yields (Scheme 3).[21] Compound **6c** was confirmed with single crystal structure analysis (Figure S61).[22] Further, **4a** reacted with aldehyde **3a** to give **7a** (34%) and a decarboxylated **7a′** (49%; see Scheme S2 for the proposed mechanism). To this point, the

Scheme 3. Reactions of Furans 4 with *m*CPBA To Give α-Keto Ester 6a–d and with Olefins To Give Wittig Reaction Product 7a and Decarboxylated 7a′



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studied reaction was confirmed to proceed through path *c* in Scheme 2. This pathway required acidic benzylic protons to allow proton transfer from **If** to **Ig**, consistent with the observed scope with electron-withdrawing aryl aldehydes. Although we did not observe lactones **5**, we could not exclude reactions through pathway *a*. Lactones **5** possessed a reactive alkynoate moiety toward phosphines and could be consumed upon formation. Other pathways through β-attack of phosphines to **1**, as shown in Scheme S1, were unlikely since the developed structures were inconsistent with the experimental data. Further, other relevant approaches toward tri- and tetrasubstituted furans involved PBu_3-mediated acylation and an intramolecular Wittig reaction sequence with phosphorus ylides as intermediates.[23]

In conclusion, we have demonstrated multicomponent reactions of diynedioates, phosphines, and aryl aldehydes to give trisubstituted furans appending phosphorus ylides. This reaction goes through novel initial $\alpha(\delta')$-addition of phosphines to diynedioates followed by addition of resonance-derived trienoate intermediates to aryl aldehydes as a key step. The α-addition-δ-evolvement of a carbanion, abbreviated αAδE, has been proposed for the first time in the chemistry of phosphine-mediated reactions. Furthermore, the isolated furans equipped with phosphorus ylide functionality can be readily oxidized to α-keto esters and utilized as Wittig reagents to give 2,3,5-trisubstituted furans. These furans could possess potential pharmaceutic applications in the future.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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