Direct methylation and carbonylation of in situ generated arynes via HDDA-Wittig coupling†

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A highly efficient HDDA-Wittig coupling strategy for the synthesis of fully functionalized benzenes, such as ethyl 2-methylbenzoates and o-tolylethanones, is reported. The formation of four new C–C bonds via a one-pot, multicomponent cascade proceeded through the formation of a benzyne intermediate by self-cyclization, which then reacted with a phosphorus ylide. The target bicyclic aromatic compounds were prepared by the reaction of tetranyne with (acetylmethylene)triphenylphosphorane/(carbomethoxy-methylene)triphenylphosphorane, and trace water allowed direct methylation and played a pivotal role in the construction of the natural carbonylated 2,3-dihydro-1H-indene cores, which were highly substituted. This report describes a robust method for the production of fused polyfunctional aromatic hydrocarbons.

Results and discussion

Herein, we developed a mild, catalyst-free procedure for the synthesis of polyfunctional fused aromatics in good to excellent yields. This method was simple and met the requirements of atom economy for green chemistry. It was verified that H2O played a crucial role in this reaction. With this novel method, the simultaneously methylation and carbonylation of the aro-
matic ring was achieved. The polyfunctionalized fused aromatic derivatives were generated by cascade HDDA reactions of different P-ylide and tetrayne substrates. We proposed a possible mechanism for the reaction: the tetrayne substrates form benzyne intermediates by self-cyclization and then react with the P-ylides to yield the fused aromatics compounds via an HDDA reaction. This method, which does not require a directing group, exhibits precise regioselectivity and can generate fused methyl 4-methyl-2,3-dihydro-1H-indene-5-carboxylates and ethyl 4-methyl-2,3-dihydro-1H-indene-5-carboxylates via a one-pot, multiterminal cycloaddition reaction (1a–1q) with excellent yields (Table 1). Consequently, this reaction provides an economical, efficient, and direct method for the synthesis of highly substituted ethyl 2-methylbenzoate and o-toly lethane compounds. A reaction scheme for accessing carbon-bridged tetraynes with ylides in a catalyst-free manner was designed. The optimum reaction conditions in terms of water addition, temperature, solvent, and reaction time are discussed. Initially, with dry toluene as the solvent, substrate 1a was reacted with (carbomethoxymethylene)triphenylphosphorane at 100 °C. TLC was performed to monitor the reaction, and the starting material disappeared after 9 h. After separation and purification of the products, the reaction with a toluene : water ratio of 100 : 1 using (carbomethoxymethylene)triphenylphosphorane for 9 h at 100 °C yielded 10% of the desired product, and when the temperature was 90 °C (with a reaction time of 9 h), the yield was 80%. Because TLC did not fully reflect raw materials, the actual yield was 72%. Then, the temperature was increased to 110 °C and 120 °C with the same 9 h reaction time. TLC-based monitoring showed that the raw materials had been consumed, and the reaction had reached completion. We investigated the reactions in acetonitrile, toluene and cyclohexane and found that toluene was the most effective. The optimum reaction conditions for the tetrayne substrate (1 equiv.) with (carbomethoxymethylene)triphenylphosphorane (1.05 equiv.) and water (2 equiv.) were as follows: toluene 1.5 mL, 100 °C, 9 h.

First, the effect of the structure of the tetrayne substrate on the yield was investigated. As shown in Table 1, a series of products (3a–3p) were obtained from the reactions of tetraynes with (carbomethoxymethylene)triphenylphosphorane or ethyl 2-(triphenylphosphoranylidene)acetate, and the yields ranged from 75% to 85%. The effect of different tetrayne substrate on the product yield was examined. When OPr, OEt and OMe were connected to the carbonyl carbon in the alkyne substrates, the yields were almost the same (3a (80%) and 3d (80%), 3i (79%), 3n (77%) and 3p (77%)). While the yields of 3c and 3h were 78% and 75%, respectively. Compounds containing benzene rings with fluorine, chlorine or other electron-withdrawing substituents exhibited lower yields than those with unsubstituted rings, for example, the yield of chloride-containing substrate 3c was 78%, while that of the molecule with an unsubstituted benzene ring was 80% (3a); the yield of the substrate with a benzene ring bearing a fluoride (3o) was 73%, while the molecule with an unsubstituted benzene ring has offered a yield of 77% (3n).

| Reaction scale: tetraynes 1 (1.0 equiv.), (carbomethoxymethylene)triphenylphosphorane 2 (1.05 equiv.), water (2.0 equiv.), toluene 1.5 mL, 100 °C. | Isolated yield. |
As shown in Table 2, yields of 76–87% were obtained from the reactions of tetraynes with [(acetylmethylene)triphenylphosphorane. When OiPr, OEt and OMe were connected to carbonyl carbon of the tetrayne substrates, the yields were similar, such as those of 3q (80%), 3x (81%), 3r (82%) and 3v (81%). The yields with benzene ring-containing tetraynes with alkyl groups as electron donors were slightly higher than those of tetraynes directly bearing alkyl groups as electron donors. For example, the yields of 3r and 3s were 82% and 85%, respectively (Table 2), while the yields of 3t and 3u were 80% and 79%, respectively. The yields of benzene rings with alkyl substituents were higher than those of benzene rings without substituents. For example, the yield of 3s, with an n-propyl group on the benzene ring, was 87%, and the yield of 3r, with a methyl group on the benzene ring, was 82%, while the yield of the unsubstituted benzene ring was 80% (3a). The structures of 3h and 3y were confirmed by X-ray diffraction.16

Scheme 2 shows a possible mechanism of the reaction. Tetrayne substrate 1 formed a benzyne intermediate by self-cyclization and then reacted with a Wittig reagent to yield fused aromatic compounds B via nucleophilic addition reaction. The tetrayne substrate first undergoes an HDDA reaction to form benzyne intermediate A, and then, the carbanion in the phosphorus ylide attacks benzyne intermediate A to form four-membered ring intermediate B.17 Triphenyl oxyphosphorous C is produced after the self-cyclization performance of intermediate B, affording the intermediate D via a 4π-electrocyclic ring opening process.18 With the elimination of phosphine oxide,19 E, which is the different resonance structure of D then transformed to product 3f. Deuterated benzene was initially used as the solvent to explore the source of the methyl hydrogen in the product. 1H NMR spectroscopy confirmed that deuterated benzene was not the source of the hydrogen in the product, demonstrating the importance of D$_2$O in this process.

Conclusions

In summary, we describe the first method for the synthesis of fully substituted benzenes, such as ethyl 2-methylbenzoates...
and o-tolylethane, via the reaction of acetyl methyl-enediarylphosphorane/acylphosphorane or carbomethoxyphosphorane and trace water with polynes. The formation of four new C–C bonds via a one-pot, multicomponent cascade led to the formation of benzyne intermediates by self-cyclization, and these intermediates then reacted with phosphorus ylides. The reactions produced highly substituted targets with excellent regioselectivity. Rare, fully substituted benzene derivatives were obtained in high yields under aerobic conditions. Future studies will be focused on the construction of polyfunctional aromatic hydrocarbons.

Conflicts of interest

There are no conflicts to declare.

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