Synthetic Methods

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Three-Component Reaction Using the Bestmann–Ohira Reagent: A Regioselective Synthesis of Phosphonyl Pyrazole Rings**

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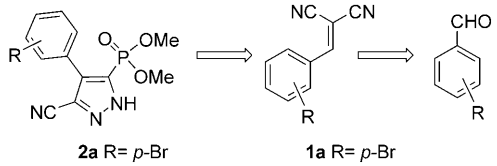
Organophosphorus compounds continue to attract much attention because of their various potent biological activities.[1] In particular, phosphonates are important synthetic derivatives which can often act as phosphate and carboxylic acid mimics, and interfere with enzymatic processes. Much of this activity has been attributed to the relatively inert nature of the C–P bond,[1] which is not as easily hydrolyzed as compared to the P–O bond found in phosphates. The synthesis and biological activities of important natural and non-natural phosphonate derivatives, including phosphonated azaheterocycles and nucleotides, has been reviewed recently.[2,3] In view of the importance of heterocycles bearing a phosphonate group, new synthetic methods that would allow straightforward access to these versatile building blocks are needed.[1,4,5] Among the various bioactive heterocycles, the pyrazole moiety remains of great interest because of its wide applications in the pharmaceutical and agrochemical industry.[6,7] In addition, pyrazoles also play a central role in coordination chemistry.[8] In the plethora of existing methodologies for the synthesis of pyrazole derivatives,[9] a vast majority relies on either the condensation of hydrazine with 1,3-difunctional compounds,[9a,b] or the 1,3-dipolar cycloadditions of diazo compounds with triple bonds.[9c,d] Although a large number of new pyrazole syntheses that complement efficiently the traditional approaches[9e–l] have been reported in recent years, relatively few examples are known for the preparation of phosphonyl pyrazoles, and the existing methods are often limited by the number of steps and the harsh conditions needed.[10] Recently, an attractive procedure has been described wherein 5-phosphonyl pyrazoles are obtained from nitroalkenes. However, the reaction is restricted to aryl and heteroaryl nitroalkenes which are usually not commercially available.[11] Therefore, there remains a need for identifying improved methods for the synthesis of phosphonyl pyrazole scaffolds employing simple building blocks and a minimal number of synthetic steps. To this end, multicomponent reactions (MCR), which allow the formation of multiple bonds in a one-pot fashion and give access to complex molecules without isolating or purifying the intermediates, represent an attractive alternative.[12] Being operationally simple and atom-economical, these processes use simple substrates and offer additional opportunities for subsequent transformations that will increase the molecular complexity and the structural diversity.

Recently, we reported the one-pot synthesis of triazoles from aldehydes using the Bestmann–Ohira reagent (BOR)[13] which is more commonly used to prepare alkynes from aldehydes under mild reaction conditions ($MeOH/K_2CO_3$).[14] Encouraged by the straightforward access to these valuable chemical motifs, we were interested in exploiting the synthetic potential offered by this unique reagent. In particular, we have been exploring the possibility of achieving the construction of diversely substituted 5-phosphonyl pyrazoles through a convergent MCR strategy. Based on a domino Knoevenagel condensation/formal 1,3-dipolar cycloaddition sequence, this three-component process involving the combination of readily available reactants (aldehyde, BOR, and cyanoacetic derivatives[15]) should generate small molecules with a high degree of skeletal and functional diversity and demonstrate for the first time that the BOR could be used in MCRs.

To achieve this goal, preliminary experiments were performed with unsaturated nitrile **1a**, which was prepared by reaction of malononitrile and 4-bromobenzaldehyde in the presence of *t*BuOK (Scheme 1, R = *p*-Br).[16] When **1a** was reacted with the BOR under the same conditions (*t*BuOK/MeOH) phosphonyl pyrazole **2a** was obtained as a single tautomer in 74% yield. This product suggested that a formal 1,3-dipolar cycloaddition took place between the in situ generated anion of the BOR and **1a** with a subsequent elimination of a cyano group.

Considering the reactivity of the BOR towards aldehydes, we needed to demonstrate that the Knoevenagel condensation of malononitrile with an aldehyde was faster than the homologation reaction. To our delight, the one-pot three-component reaction between BOR, *p*-bromobenzaldehyde,



2a R= *p*-Br **1a** R= *p*-Br

Scheme 1. Access to phosphonyl pyrazole from aldehydes.

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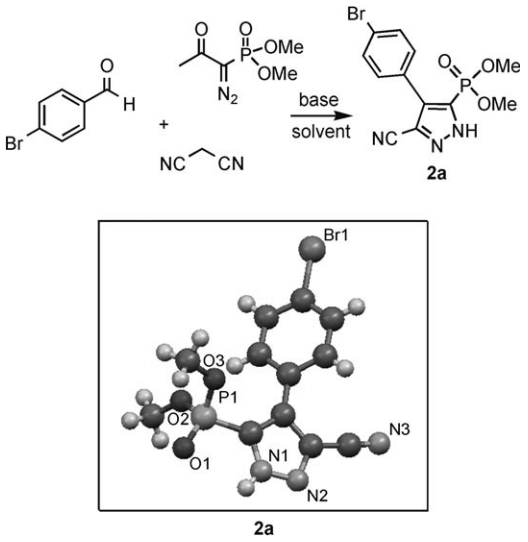
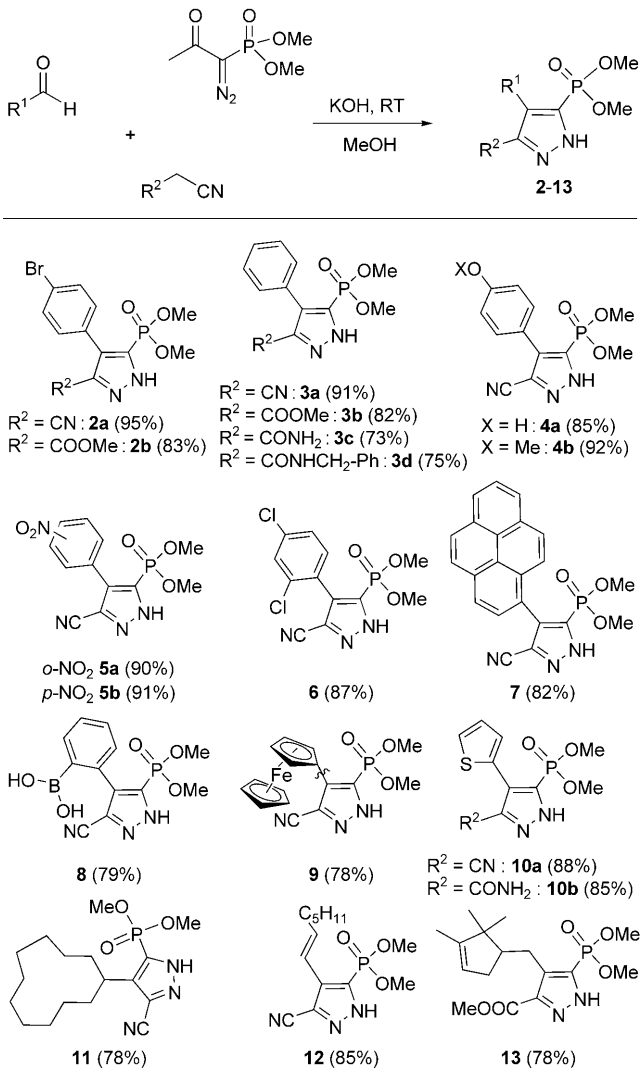
and malononitrile in the presence *t*BuOK in anhydrous methanol at room temperature afforded 3-cyano-4-*p*-bromophenyl-5-dimethoxyphosphonyl pyrazole (**2a**) in 88% yield (Scheme 2), whereas the two-step sequence gave only 57%



Scheme 2. One-pot access to phosphonyl pyrazoles and X-ray structure of **2a**.

overall yield. As 1.2 equivalents of malononitrile are used in both experiments, the modest yield obtained in the two-step sequence might come from consecutive reactions of the initially formed Knoevenagel adduct and the excess of nucleophile.[17] The structure of **2a** was unambiguously established by NMR and single-crystal X-ray analysis.[18] Notably, the ^{1}H NMR spectrum of the crude reaction mixture did not reveal the presence of any major side product. This reaction was therefore selected to establish optimum experimental conditions. An initial base and solvent screen revealed that the use of KOH and MeOH led to the best results, thereby generating phosphonyl pyrazole **2a** in 95% yield (see Table S1 in the Supporting Information). Interestingly, K_2CO_3 led mostly to the unwanted alkyne.

The scope of this unique one-pot three-component phosphonyl pyrazole synthesis was next investigated. As depicted in Scheme 3, the reaction proceeded effectively with several substituted aromatic derivatives and was not found to be dependent upon the electronic features of the substituents. In many cases, the phosphonyl pyrazoles could be isolated in greater than 90% yield after column chromatography on silica gel. The flexibility of the process allows the strategic placement of functional groups. For instance, examples **6** and **8** which contain chlorine atoms and a boronic acid group respectively, were easily prepared and could be additionally derivatized thereby providing a convenient alternative for the generation of a broad range of analogues.[9d] The scope of the MCR was additionally surveyed by probing the changes on the aldehydes; for example **9, 10a**, and **11** demonstrate that ferrocenyl, heteroaromatic, and aliphatic aldehydic substrates respectively, could also be used. Interestingly, when the α,β-unsaturated octenaldeyde was treated under identical con-

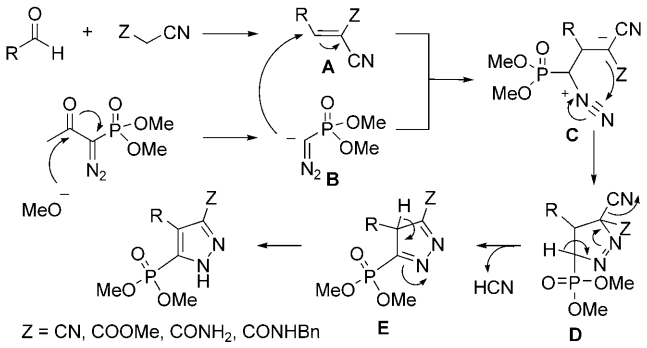


Scheme 3. Three-component synthesis of phosphonyl pyrazoles. The yields are for the isolated product.

ditions, phosphonyl pyrazole **12** was formed in 85% yield with no detectable formation of the Michael addition side product. The scope of the reaction was expanded by varying the nature of the active cyanoacid derivative. In this context, ethylcyanoacetate was found to be a good substrate allowing access to 3-carbomethoxy-5-phosponyl pyrazoles **2b**, **3b**, and **13** after transesterification under the reaction conditions. Notably, in these specific cases we found that longer reaction times were needed to reach completion, however the yields remained unaffected. Another way to extend the scope of the present MCR was to apply the reaction to cyanoacetamide derivatives. Interestingly, the reactions between aldehydes, the BOR, and cyanoacetamide or *N*-benzyl-2-cyanoacetamide were successful as the expected phosphonylpyrazoles **3c**, **3d**, and **10b** were obtained in very good yields. In these cases, the substituents on the cyanoacetamide did not seem to have an influence on the reactivity. Hence, by varying both the aldehyde and the cyanoacid components, a wide variety of substituted phosphonylpyrazoles could be readily

prepared. As expected the use of (phenylsulfonyl)acetonitrile with benzaldehyde and the BOR led only to **3a** as a result of the higher stability of the phenylsulphinate anion compared with that of cyanide (pK_a values of phenylsulphinic acid and hydrogen cyanide in water are 2.1 and 9.2, respectively).[19] The only unmatched results were obtained with less activated cyanoacetic derivatives. Indeed, under the reaction conditions phenylbutyronitrile, benzylcyanide, and trimethylsilylacetonitrile led to the formation of the homologated alkyne. Nonetheless, these examples confirm that the Knoevenagel condensation is indeed the first step in this reaction sequence. As demonstrated by ^{1}H and ^{31}P NMR analysis, pyrazoles **2**–**13** did not exhibit tautomerism in solution.

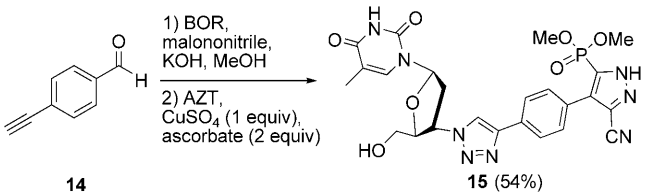
Our postulated mechanism for this reaction is shown in Scheme 4. This proposal accounts for the facts that the reaction rate is solvent-dependent whereas it is almost unaffected by electron-withdrawing or electron-donating groups on the starting aldehyde. Therefore, we assume that this formal 1,3-cycloaddition is based on a Michael-type 1,4-addition of the dimethyl (diazomethyl)phosphonate anion **B**



Scheme 4. Proposed mechanism for the formation of pyrazoles. Bn = benzyl.

to the unsaturated nitrile **A**, both of which are generated in situ. The resulting intermediate **C** undergoes cyclization leading to an unstable pyrazoline intermediate (**D**).[20] Elimination of HCN then gives **E**, which after intramolecular proton transfer lead to the corresponding pyrazole, with complete regioselectivity.

As an illustration of the significance of this unprecedented reactivity, we devised a MCR/copper-catalyzed azide–alkyne 1,3-dipolar cycloaddition (CuAAC) sequence.[21] As shown in Scheme 5, aldehyde **14** was submitted to the optimized MCR reaction conditions using BOR, and was then subjected to the copper-catalyzed click reaction with azidothymidine (AZT) to afford the modified thymidine 3′-pyrazolyl phosphonate **15** in 54% yield. In this case, one equivalent of copper sulfate was needed to access the 1,2,3-triazole derivative. The need of this unusual amount of copper(II) might be explained by the chelation of Cu^{II} ions by the pyrazole ring.[22] Nevertheless, this constitutes a straightforward approach for the construction of highly functionalized molecules considering that five new bonds and two heterocyclic rings are formed in a one-pot fashion.



Scheme 5. One-pot MCR/CuAAC sequence.

In summary, we have developed a simple and completely regioselective one-pot Knoevenagel condensation/formal 1,3-dipolar cycloaddition reaction which generates 5-phosphonyl pyrazole scaffolds through the formation of two C–C bonds and one C–N bond. To the best of our knowledge this represents the first example in which the Bestmann–Ohira reagent is used: 1) in a multicomponent reaction and 2) in the presence of an aldehyde without leading to the expected homologated alkyne. Attractive features of this domino process are its versatility, the readily available starting material needed, and the efficiency in creating a complex core in a single operation. The scope of the reaction was expanded with the development of an efficient MCR/CuAAC reaction sequence in single step. This highly flexible methodology should provide a quick and easy access to libraries of molecules of pharmaceutical or agrochemical interests.

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