Diazophosphonates: Effective Surrogates for Diazoalkanes in Pyrazole Synthesis

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Abstract: Diazophosphonates, readily prepared from α-ketophosphonates by oxidation of the corresponding hydrazones in batch or in flow, are useful partners in 1,3-dipolar cycloaddition reactions to alkynes to give N-H pyrazoles, including the first intramolecular examples of such a process. The phosphoryl group imbues a number of desirable properties in the diazo 1,3-dipole. The electron-withdrawing nature of the phosphoryl stabilizes the diazo compound making it easier to handle, whilst the ability of the phosphoryl group to migrate readily in a [1,5]-sigmatropic rearrangement enables its transfer from C to N to aromatize the initial cycloadduct, and hence its facile removal from the final pyrazole product. Overall, the diazophosphonate acts as a surrogate for the much less stable diazoalkane in cycloadditions, with the phosphoryl group playing a vital, but traceless, role. The cycloaddition proceeds more readily with alkynes bearing electron-withdrawing groups, and is regiospecific with unsymmetrical alkynes. The potential for use of diazophosphonates in bioorthogonal cycloadditions is demonstrated by their facile addition to strained alkynes.

Nitrogen-containing heterocyclic compounds are of huge academic, industrial and commercial importance, and play a major role in Nature and as medicines, agrochemicals, and materials for electronics. Within this large family of ring systems, pyrazoles hold a special place in view of their presence in a wide range of bioactive compounds.[1,2] The first pyrazole derivative was prepared by Ludwig Knorr in 1883 by the reaction of phenylhydrazine with ethyl acetoacetate,[3] and the useful medicinal properties of its *N*-methyl derivative (phenazone) were very quickly discovered. In the modern era, a number of pyrazoles have become best-selling medicines, including the antiinflammatory agent celecoxib and the phosphodiesterase 5 inhibitor sildenafil (Figure 1).

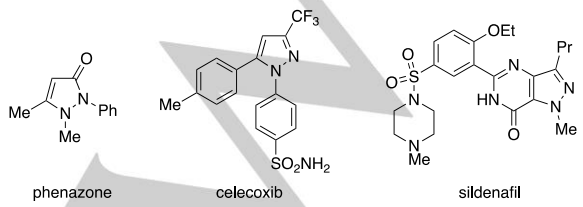
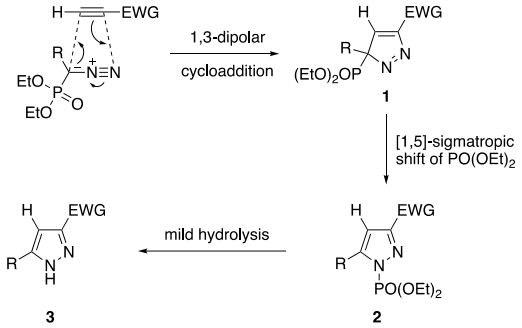


Figure 1.

However, the synthesis of pyrazoles by the reaction of 1,3-dicarbonyl compounds with hydrazines is not the only method available.[1,2] In particular, the 1,3-dipolar cycloaddition of diazo compounds to alkynes,[2,4] first discovered by Buchner in 1889,[5] is a highly effective route to pyrazoles, since no σ-bonds are broken in the process. Recently, such efficient cycloadditions have come to the fore in bioorthogonal chemistry,[6,7] a term first introduced by Bertozzi in 2003 to cover chemical reactions that can be conducted in living systems without disrupting natural processes.[8,9] Although bioorthogonal cycloadditions are mainly exemplified by the well known azide-alkyne click chemistry,[10-13] other 1,3-dipoles including diazo compounds also function, sometimes at higher rates.[14-20] In continuation of our interest in the generation and reaction of diazo compounds,[21-27] we now report that diazophosphonates are particularly suitable 1,3-dipoles in both intermolecular, and for the first time, intramolecular cycloaddition reactions with alkynes to give *N*-unsubstituted pyrazoles.

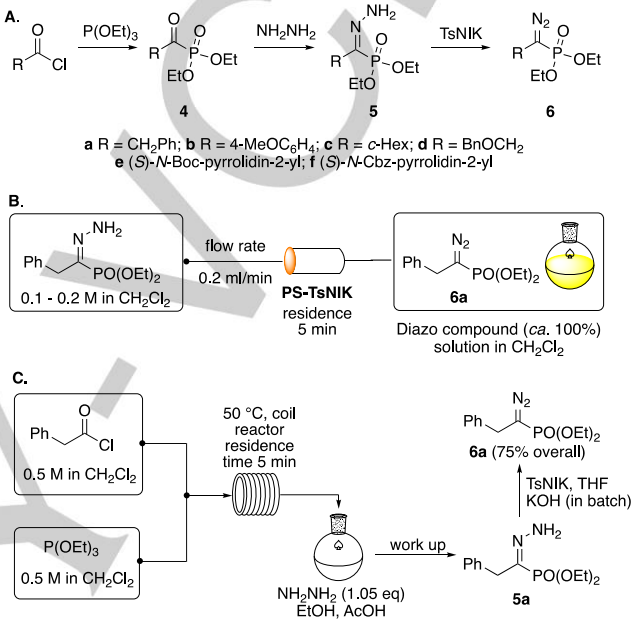
The cycloaddition of diazo compounds to alkynes to give pyrazoles is an efficient process, notwithstanding the safety issues in handling diazo compounds, although these can be alleviated by their generation *in situ* and direct conversion into pyrazoles.[28] However, we reasoned that diazophosphonates[29] would be a viable alternative given the useful properties of the phosphoryl group, wherein it would fulfill three key functions. Firstly its electron-withdrawing nature stabilizes the diazo compound making it easier to handle, but more importantly, the little known and unexploited propensity of the phosphoryl group to migrate readily in sigmatropic rearrangements facilitates its transfer from C to N in the initial cycloadduct, that, thirdly, results in its facile removal from the final pyrazole product (Scheme 1). Hence overall, the diazophosphonate, $RCN_2PO(OR)_2$, acts as a surrogate for the much less stable diazoalkane, $RCHN_2$ in cycloadditions.



Scheme 1. Diazophosphonates in pyrazole synthesis (EWG = electron-withdrawing group)

Diazophosphonates, first prepared in 1967,[30,31] are best known for use in the Seyferth-Gilbert and Bestmann-Oshira reagents that convert aldehydes into alkynes.[32-34] In some cases the resulting alkyne can undergo cycloaddition with the original diazo compound to give pyrazoles.[35,36] However, the early work on the addition of diazophosphonates to alkynes is due to Regitz.[37] The reaction proceeds by 1,3-polar cycloaddition, which is regiospecific in the case of unsymmetrical alkynes as shown in Scheme 1, to give an intermediate 3*H*-pyrazole **1**,[38] that undergoes the so-called van Alphen-Hüttel rearrangement via 1,5-sigmatropic migration of the phosphoryl group to give the pyrazole-1-phosphonate **2**. *N*-Phosphorylpyrazoles are reactive phosphorylating agents,[39,40] and hence the N-P bond in **2** is readily cleaved under mild conditions to deliver the parent pyrazole heterocycle **3** (Scheme 1) with the original phosphoryl group being traceless.[41] The key step in the formation of pyrazole **3** is the facile sigmatropic rearrangement of the phosphoryl group. Although acyl groups are well known for their high migratory aptitude, for example a formyl group migrates over 100 times faster than hydrogen in [1,5]-sigmatropic rearrangements in cyclohexa-2,4-dienes,[42] and a carboxylate migrates extremely readily in 3*H*-pyrazoles,[43] almost nothing is known about the participation of P=O containing groups in sigmatropic rearrangements. Nevertheless it is clear from Regitz.[37] and the present work that such groups have high migratory aptitudes.

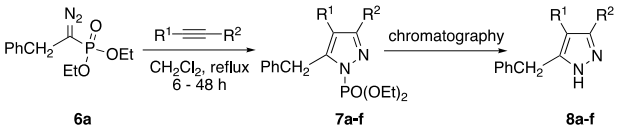
Intermolecular cycloadditions. The synthesis of a small range of diazophosphonates **6** was carried out by oxidation of the corresponding hydrazones **5** using potassium *N*-iodo p-toluenesulfonamide (TsNIK, iodamine-T), a reagent recently developed in our laboratory.[44] This conveniently prepared reagent has advantages over the heavy-metal based oxidants traditionally used for this transformation. Also, when supported on polystyrene it can be used under flow conditions and readily recycled.[24,45] The hydrazones **5** can be accessed from the corresponding ketophosphonates **4**, which are commercially available or obtained by Arbuzov-like reaction of triethyl phosphite with the corresponding acid chloride (Scheme 2A). Although, the hydrazones **5** can be isolated, normally the reaction is run in sequence from acid chloride to diazophosphonate **6** without isolation and purification of intermediates. The two proline-derived diazophosphonates **6e** and **6f** were prepared in this manner although the yield of the Boc-compound **6e** was poor The preparation of diazophosphonate **6a** by oxidation of hydrazone **5a** was also carried out in flow over polymer supported TsNIK resin in quantitative yield as previously described (Scheme 2B).[24] Flow chemistry could also be applied to the synthesis of ketophosphonate **4a** by flowing an equimolar mixture of phenylacetyl chloride and triethyl phosphite through a coil reactor at 50 °C (residence time 5 min) directly into a solution of hydrazine hydrate in acetic acid/ethanol. The resulting hydrazone was oxidized giving diazophosphonate **6a** in 75% overall yield from the acid chloride (Scheme 2C).



Scheme 2. **A**. Preparation of diazophosphonates **6** by oxidation of hydrazones **5**; **B**. Flow preparation of diazophosphonate **6a**; **C**. Flow preparation of hydrazone **5a**, and its subsequent oxidation to diazophosphonate **6a**.

The cycloaddition reactions were initially investigated using the diazophosphonate **6a** with a range of alkynes. The reaction occurred over prolonged time in dichloromethane at reflux, and after chromatography gave a mixture of the 1-phosphorylpyrazole **7**, formed by 1,5-sigmatropic rearrangement of initial cycloadduct (Scheme 1), and the NH-pyrazole **8** in which the phosphoryl had partially hydrolysed, presumably during chromatography. In all cases (Table 1, entries 1, 3, 5-8), the *N*-phosphoryl compound **7** was the major product, although it was not possible to obtain pure samples due to the aforementioned facile dephosphorylation. The reaction proceeded more readily, and in better yield, with electron-deficient alkynes as anticipated for a $LUMO_{dipolarophile}$ reaction and exhibited the expected regioselectivity with unsymmetrical alkynes. Thus trimethylsilyl- and phenyl-acetylene both exhibited poor reactivity with low conversion to product even after 48 hours (Table 1, entries 7 and 8), although both reactions were regioselective. The diazophosphonate **6a** derived from the in-flow oxidation of hydrazone **5a** was directly added to a solution of the alkyne. Under these conditions, the hydrolysis of the phosphoryl group was more complete upon work, presumably due to the presence of potassium hydroxide in the polymer supported

TsNIK resin used for the hydrazone oxidation, and gave the NH-pyrazole as the major product (Table 1, entries 2 and 4).



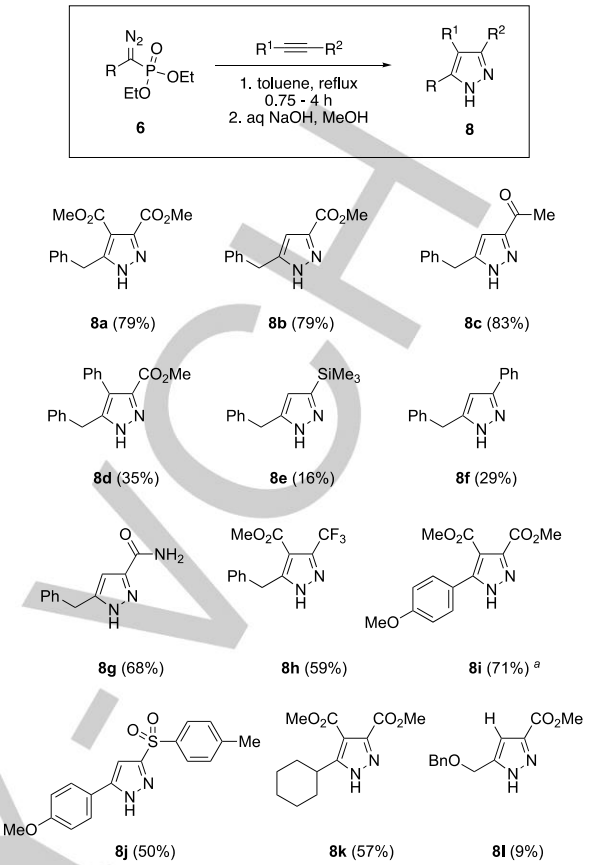
6a **7a-f** **8a-f**

Table 1. 1,3-Dipolar cycloaddition of diazophosphonate **6a** to alkynes.

Entry	R^1	R^2	**7/8**	**7** + **8** Yield (%)	**7** + **8** Ratio
1	CO_2Me	CO_2Me	**a**	83	77:23
2	CO_2Me	CO_2Me	**a**	79 [a]	0:100
3	H	CO_2Me	**b**	85	86:14
4	H	CO_2Me	**b**	86 [a]	22:78
5	H	COMe	**c**	75	78:22
6	Ph	CO_2Me	**d**	15	72:28
7	H	$SiMe_3$	**e**	12	99:1
8	H	Ph	**f**	8	81:19

[a] Diazophosphonate generated in flow.

At this juncture, we elected to simplify the process by the addition of a hydrolysis step. Thus after the cycloaddition, the solution was evaporated to dryness and redissolved in methanol with the addition of aqueous sodium hydroxide. Hydrolysis was rapid and gave the NH-pyrazole **8b** in 79% yield from the reaction of diazophosphonate **6a** with methyl propiolate. Subsequently this method was used in the cycloadditions of diazophosphonates **6a-6d** with alkynes, including two additional alkynes, carried out in toluene at reflux to accelerate the reaction, to give pyrazoles **8a-8l** (Scheme 3). Unsymmetrical alkynes were regioselective in their additions. Again, both trimethylsilylacetylene and phenylacetylene gave the corresponding pyrazoles **8e** and **8f** regioselectively but in low yield, with competing Bamford-Stevens reaction to diethyl (*E*)-styrylphosphonate occurring at the higher temperature. Attempted cycloaddition with 1-octyne and 3-hexyne failed to produce pyrazole products, with only the formation of the Bamford-Stevens product being observed. Interestingly methyl 3-trifluoromethylpropiolate exhibited opposite regiochemistry in the pyrazole **8h** to methyl propiolate and methyl 3-phenylpropiolate, in accord with the strongly inductively electron withdrawing nature of the CF_3-group. Such regioselectivity with CF_3-substituted alkynes has been observed previously.[46] The regiochemistry of pyrazole **8h** was unambiguously assigned on the basis of the 36 Hz J_2 (F-C) coupling seen to C-3 (143.0 ppm) in the ^{13}C NMR spectrum. In the case of 3-toluenesulfonylpyrazole **8j**, the structure of the product was confirmed by *X*-ray crystallography (Figure 2) corroborating the regiochemistry of the cycloaddition. The yield from the reaction of diazo compound **6d** was poor, and the two proline-derived diazophosphonates **6e** and **6f** gave no isolable cycloadducts. The 1*H*-pyrazoles synthesized are shown in Scheme 3.



Scheme 3. 1,3-Dipolar cycloaddition of diazophosphonates **6** to alkynes and structures of resulting 1*H*-pyrazoles. [a]Reaction carried out in dichloromethane.

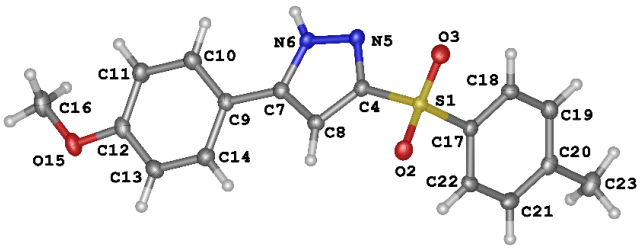
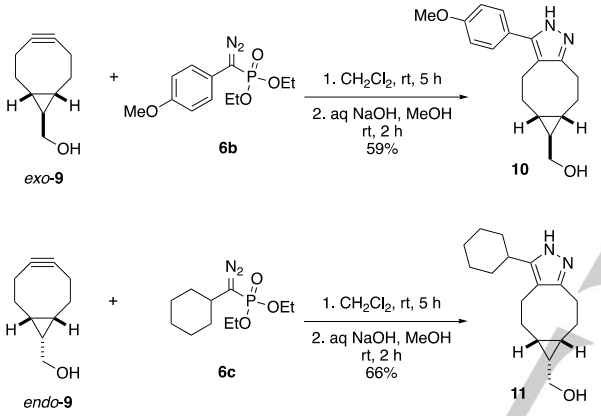


Figure 2. *X*-ray crystal structure of 5-(4-methoxyphenyl)-3-(4-toluenesulfonyl)-1*H*-pyrazole **8j**. Deposition number 2082983 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the Cambridge Crystallographic Data Centre (http://www.ccdc.cam.ac.uk/structures).

Although the above cycloadditions to generate pyrazoles are catalyst-free, they require elevated temperatures in order to proceed at a reasonable rate. If diazophosphonates were to be applied in bioorthogonal cycloadditions,[7] the reactions should be able to take place at room temperature. Based on an early observation by Wittig that the strained, cyclic alkyne cyclooctyne reacted violently with phenyl azide to give the triazole cycloadduct,[47] Bertozzi developed the use such alkynes in bioothogonal chemistry.[48,49] Subsequently a number of cyclic alkynes have been developed for use in

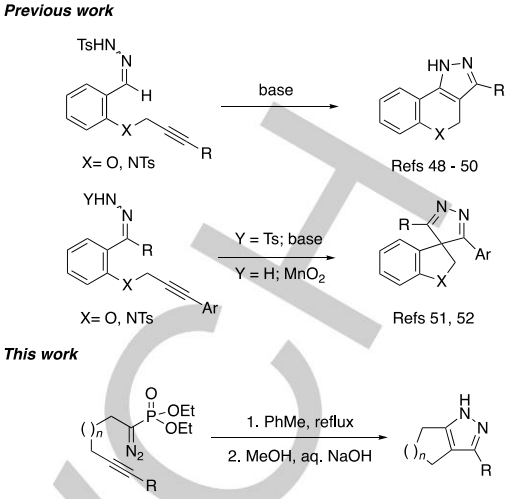
strain-promoted cycloadditions and used to label azide-containing proteins and other biomolecules in live cells.[50,51]

In order to investigate the reaction of diazophosphonates with strained alkynes, we elected to use the bicyclo[6.1.0]nonyne derivative **9** developed by Dommerholt *et al*.[50] The compound is readily prepared, and is symmetrical ensuring that upon cycloaddition only one regioisomer is formed. The cycloooctyne *exo*-**9** was then reacted with the diazophosphonate **6b** to give pyrazole **10** in good yield (Scheme 4). This cycloaddition reaction was performed at room temperature in less than 5 h and, again, the phosphoryl group fulfilled its role by undergoing facile [1,5]-sigmatropic migration to nitrogen, followed by its cleavage under mild conditions. The *endo*-cyclic alkyne **9** reacted similarly and gave pyrazole **11** (66%) upon reaction with diazophosphonate **6c** for 5 h at room temperature, followed by hydrolysis. These results illustrate that appropriate water-compatible diazophosphonates might be applicable in bioorthogonal cycloaddition reactions.



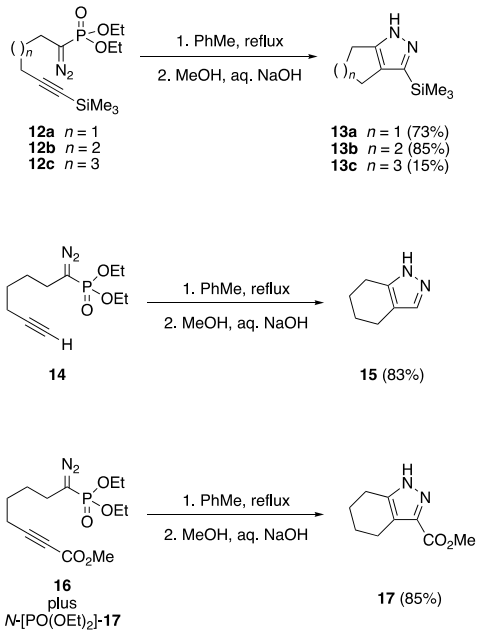
Scheme 4. Addition of diazophosphonates to strained bicyclo[6.1.0]nonynes.

Intramolecular cycloadditions. In the vast panoply of intramolecular cycloaddition reactions, the addition of diazo 1,3-dipoles to alkynes has only featured rarely. Most examples employ aryl diazo compounds generated *in situ* from the corresponding *ortho*-substituted benzaldehyde tosylhydrazones, and give fused pyrazoles or spiro-4*H*-pyrazoles according to whether the intermediate diazo species is mono- or di-substituted (Scheme 5).[52-57] In contrast, we chose to exploit the electron-withdrawing properties of the phosphoryl group to enable the first utilization of such diazo compounds in a range of intramolecular 1,3-dipolar cycloadditions to give carbocyclic fused pyrazoles (Scheme 5).



Scheme 5. Intramolecular cycloaddition of diazo compounds to alkynes.

The synthesis of the substrates for our proposed intramolecular cycloaddition reactions was achieved from the known terminal trimethylsilyl alkynoic acids $Me_3SiC{\equiv}C(CH_2)_nCO_2H$, which were in turn readily prepared from lithium trimethylsilylacetylide and the corresponding bromoalkanoic acid. The acids were converted into the hydrazones by a three-step sequence carried out without isolation of intermediates as shown in the Supporting information. Thus reaction with oxalyl chloride gave the acid chloride that was immediately reacted with triethyl phosphite in an Arbuzov reaction to give the ketophosphonates, readily converted into the hydrazones $Me_3SiC{\equiv}C(CH_2)_nC(=NNH_2)PO(OEt)_2$, isolated as a mixture of *E*/*Z*-isomers, in good overall yield. Finally, TsNIK oxidation of the hydrazones gave the desired diazophosphonates **12** isolated as yellow oils in excellent yield (see Supporting Information). Preliminary studies with diazophosphonate **12b** established that the cycloaddition occurred extremely slowly in dichloromethane at room temperature, and even after prolonged heating at reflux, the product pyrazole **13b** was formed in mixture with its *N*-phosphoryl derivative (*ca.* 1:4, 40% combined). Subsequently, the intramolecular cycloadditions of diazophosphonates **12** were effected by heating in toluene at reflux (2.5 – 48 h), followed by addition of aqueous sodium hydroxide to achieve complete cleavage of the phosphoryl group to give the fused pyrazoles **13** (Scheme 6). The cyclopenta- and cyclohexa- derivatives **13a** and **13b** were formed in good yield whereas the cycloheptapyrazole **13c** formed much more slowly, and was isolated in poor yield, presumably reflecting the increased difficulty in forming 7-membered rings in intramolecular cycloaddition reactions.



Scheme 6. Intramolecular cycloaddition of diazophosphonates to alkynes to give cycloalkapyrazoles.

Given that use of trimethylsilylacetylene resulted in very poor yield in the aforementioned intermolecular cycloadditions (Table 1, entry 7), we investigated the effect that removal of this bulky electron-releasing group would have on the intramolecular process. Thus the alkynoic acid $Me_3SiC{\equiv}C(CH_2)_4CO_2H$ was treated with methanolic potassium carbonate to give the desilylated material, heptynoic acid in near quantitative yield. Conversion into the diazophosphonate **14** proceeded without incident by way of the corresponding hydrazone (see Supporting Information). On heating in toluene, diazophosphonate **14** underwent intramolecular cycloaddition reaching completion in 1.5 h and gave tetrahydroindazole **15** in high yield. Finally, we investigated the effect of introduction of an electron-withdrawing ester group onto the alkyne dipolarophile in anticipation that its LUMO-lowering effect would increase the rate of reaction. In the event, this proved to be the case. However, attempted preparation of the diazophosphonate **16** by oxidation of the corresponding hydrazone, prepared as shown in the Supporting Information, gave the expected diazophosphonate **16** together with the phosphorylated version of pyrazole **17** (68% combined), the cycloaddition occurring during attempted isolation and purification of the diazophosphonate **16** due to the reactive nature of the electron-deficient dipolarophile. Subjecting the mixture of diazophosphonate **16** and the phosphorylpyrazole to the normal conditions gave the pyrazole **17** in excellent yield after aqueous work-up (Scheme 6).

These first examples of intramolecular 1,3-dipolar cycloaddition reactions of the diazophosphonates again emphasize the beneficial influence of the phosphoryl group on the properties and subsequent reactions of the diazo 1,3-dipole, wherein its facile sigmatropic rearrangement from C to N in the initial cycloadduct is key. In addition, the stabilizing influence of the electron-withdrawing phosphoryl group, highlights the role that diazophosphonates can play as surrogates for less stable diazoalkanes.

Experimental Section

For full details of all experimental procedures and copies of ^{1}H and ^{13}C NMR spectra, see the Supporting Information.

Acknowledgements

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Keywords: pyrazole • diazophosphonate • dipolar cycloaddition • 1,5-sigmatropic rearrangement

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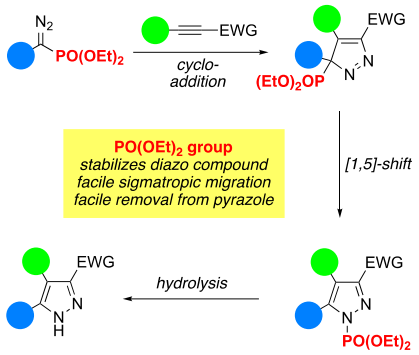

Diazophosphonates are excellent 1,3-dipoles in both inter- and intra-molecular cycloaddition reactions with alkynes to give *N*-H pyrazoles. The phosphoryl group has three key roles: its electron-withdrawing nature stabilizes the diazo compound, its unexploited propensity to migrate readily in sigmatropic rearrangements facilitates its transfer from C to N in the initial cycloadduct, and hence its facile removal from the final pyrazole product.