

A New Use of Wittig-Type Reagents as 1,3-Dipolar Cycloaddition Precursors and in Pyrrole Synthesis

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1,3-Dipolar cycloaddition has become one of the central approaches employed to construct heterocycles.¹ One useful class of these substrates is 1,3-oxazolium-5-oxides, commonly known as Münchnones (**1**).² The cycloaddition of **1** is usually followed by CO₂ loss and provides an efficient route to synthesize a number of biologically relevant products, including such common cores as pyrroles, imidazoles, β -lactams, pyrrolidines, and others.^{2b} While effective, as with many highly substituted 1,3-dipoles, Münchnones are most generally prepared via a multistep synthesis themselves (via α -amido acids).² The latter can not only complicate syntheses to create the correctly substituted precursor but also can make it challenging to diversify products. In this regard, there have been alternative routes developed to construct **1**,³ including our report of the palladium-catalyzed coupling of iminium salts and carbon monoxide.⁴ However, these approaches do tend to be more limited in scope.

In efforts to develop more efficient routes to heterocycles, we have become interested in generating alternative cycloaddition reagents, which display the reactivity of Münchnones, yet are both easily generated and diversified. Toward this end, we describe here the development of a new class of phosphorus-based 1,3-dipolar substrate in the form of **2** (Figure 1). These compounds undergo cycloaddition to form products analogous to those from **1**, yet can be generated in one pot, in a modular fashion, and directly from phosphines, imines, and acid chlorides. This suggests their potential general utility as new 1,3-dipoles for heterocycle synthesis. The latter is illustrated in the synthesis of pyrroles from simple imines, acid chlorides, and alkynes.

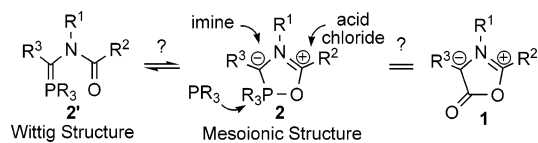


Figure 1. Modular approach to Wittig-type cycloaddition substrates.

Our design of **2** is shown in Figure 1 and is based upon its structural analogy to Münchnones. On examining **1**, we noted that the carbonyl moiety is ultimately liberated as CO₂ after cycloaddition. This suggests this C=O might be replaced with another fragment capable of leaving with oxygen. Phosphines are well-established to abstract oxygen from strong multiple bonds to form phosphine oxides (e.g., Wittig reagents).⁵ The replacement of the carbonyl in **1** with a PR₃ unit would create the organophosphorus heterocycle **2**. While appearing somewhat complex, **2** is in principle simply an isomeric form of commonly employed Wittig reagents **2'**. The latter can be potentially generated by the one-pot reaction of phosphines with imines and acid chlorides. However, this would still require an unknown reaction for phosphorus ylides: 1,3-dipolar cycloaddition.⁶

Our initial studies toward this chemistry probed the reaction of PPh₃ with imine **3** and acid chloride **4**. This leads to the in situ formation of phosphorus salt **6a**, which can be deprotonated with BuLi to generate **2a** in 84% yield. However, under no conditions

does this substrate undergo 1,3-dipolar cycloaddition (Table 1). We postulated that the inhibited dipolar reactivity in **2a** might result from a lack of chelation of oxygen to the relatively electron-rich phosphorus center (e.g., form **2a'**). This is consistent with ¹³C NMR data, which show the carbonyl resonance of **2a'** at δ 175.7 and a ³¹P NMR resonance at δ 10.2, both of which are similar to typical amides and Wittig reagents, respectively. Thus, range of less electron-rich phosphite and phosphonites was examined in this reaction. As shown in entries 3–6, these substrates not only participate in the reaction with imines and acid chlorides but also can undergo the desired 1,3-dipolar addition with **5**. In the case of the catechyl-substituted **2b**, this reaction is rapid (30 min) and results in the near quantitative pyrrole formation.

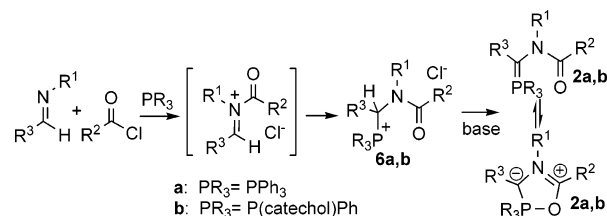
Table 1. A Phosphonite-Mediated Pyrrole Synthesis^a

entry	PR ₃	temp (°C)	time (h)	yield ^b (%)
1	PPh ₃	80		0
2	Ph ₂ P(OPh)	80		0
3	PhP(OPh) ₂	65	48	80
4	PhP(O- <i>p</i> -CNPh) ₂	50	11	81
5	P(OPh) ₃	23	15	53
6	PhP(catechyl)	23	0.5	95

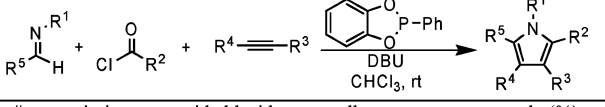
^a **3**, **4**, **5** (3 equiv), PR₃ (1.5 equiv), and DBU (2 equiv) were mixed in 20 min intervals. ^b Determined by ¹H NMR analysis versus a standard.

While the mechanism of this reaction is still under investigation, the unusual reactivity of **2b** likely results in part from the balanced nature of the phosphonite, which is sufficiently nucleophilic to react with the in situ generated *N*-acyl iminium salt, yet can still accept chelation of the amide oxygen to form a five-membered mesoionic ring. Consistent with this argument, monitoring the reaction by in situ NMR spectroscopy shows that PhP(catechol) forms phosphonium salt **6b** (Scheme 1) within 10 min at ambient temperature,

Scheme 1. A One-Pot Synthesis of Mesoionic **2**



while the ¹³C NMR data on the deprotonated **2b** show the carbonyl unit (δ 149.9) shifted far upfield from a typical amide and that of **2a'** (δ 175.7) and instead consistent with a Münchnone-type structure (140–150 ppm).^{2,7} The lower steric encumbrance and ring strain of the catechyl unit could help favor formation of a trigonal

Table 2. Diversity of PhP(catechyl) Mediated Pyrrole Synthesis^a


#	imine	acid chloride	alkyne	pyrrole (%)
1				 85%
2				 89%
3				 4%
4				 60%
5 ^{b,d}				 44%
6 ^{b,c}				 61%
7 ^b				 67%
8 ^e				 42%
9 ^f				 24%
10				 69%
11				 R ⁵ =Tol R ² =p-An: 88% R ⁵ =p-An R ² =Tol: 91%

^a Table 1 procedure. ^b LiHMDS at -78°C . ^c Imine/acid chloride at -78°C ; AgOTf (1 equiv) added. ^d Imine/acid chloride/PR₃ for 16 h prior to base. ^e At 50°C . ^f For 33 h.

bipyramidal structure,⁸ at least as a reactive intermediate. Overall, this can allow the rapid intramolecular abstraction of oxygen from the former acid chloride unit upon reaction with dipolarophiles.

These cycloaddition reagents **2** are both easily generated and formed from available materials.⁹ As such, they provide the potential to access heterocyclic products in a modular fashion. These are illustrated in Table 2, where the formation of **2** and its cycloaddition has been used to design a one-pot, phosphonite-mediated coupling of imines, acid chlorides, and alkynes to synthesize pyrroles.¹⁰ As shown, in addition to the reagents employed in Table 1, these 1,3-dipoles can be generated with an array of imines and acid chlorides. This includes stabilized C-aromatic and -heteroaromatic imines, as well as less stable enolizable and formaldehyde-based substrates (entries 5 and 6).¹¹ A similar range of substituents can be used on the acid chloride, while alkyl, aryl, and common protecting groups can be incorporated onto the nitrogen. The cycloaddition capability of **2** also appears to be broad, with electron-poor and even the more electron-rich alkynes (acetylene, propargyl ethers) generating pyrrole, albeit in lower yield, as well as chloroalkenes. Together, this can allow the build up of diverse families of pyrroles.

Interestingly, these reagents also show a high regioselectivity upon reaction with unsymmetrical alkynes. The latter can be a

challenge in employing 1,3-dipolar cycloaddition to construct heterocycles (e.g., with Münchnones), which often generate mixtures of isomers. In contrast, these phosphorus-based reagents have a large steric discrimination between the carbons at R² and R⁵ due to the PR₃ unit. This can allow, for example, the selective synthesis of isomeric 2,5-substituted pyrroles simply by choice of the correct imine and acid chloride (entries 2, 3, 7, and 11).¹² Overall, considering the accessibility, generality, and selectivity of **2**, this provides a straightforward pyrrole synthesis, where any of the five substituents can be selectively modified.

In conclusion, a new class of 1,3-cycloaddition substrate can be synthesized from phosphonites, imines, and acid chlorides. These substrates undergo cycloaddition in a similar fashion to classic 1,3-dipoles, yet can be generated in a one-pot, modular fashion from available reagents, suggesting their potential utility in the synthesis of various heterocycles. Experiments directed toward the latter are underway.

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Supporting Information Available: Synthesis of **2** and pyrroles. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Wittig reagents have been found to react with 1,3-dipoles.⁵ In addition, for the closest related example, a trifluoromethyl-substituted [1,4,2]-oxazaphospholine has been shown to behave as a dipole precursor (Burger, K.; Fehn, J.; Moll, E. *Chem. Ber.* **1971**, *104*, 1826). However, a simple phosphorus ylide (e.g., **2'**) has not been used as a 1,3-dipole.
- All other data are consistent with the structure shown, including an upfield ³¹P NMR signal ($\delta -16.9$, *Handbook of Phosphorus-31 NMR Data*; Tebby, J. C., Ed.; CRC Press: Boston, 1991). Nevertheless, a Wittig-type **2b'** cannot be ruled out, with the reactive form as the 1,3-dipole **2b**.
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- In contrast, the palladium-catalyzed pyrrole synthesis from these reagents is limited to stabilized imines and acid chlorides (ref 4a).
- A 2:1 mixture of these pyrroles is generated via Münchnones.

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