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Horner−Wadsworth−Emmons Reagents as Azomethine Ylide Analogues: Pyrrole Synthesis via (3 + 2) Cycloaddition

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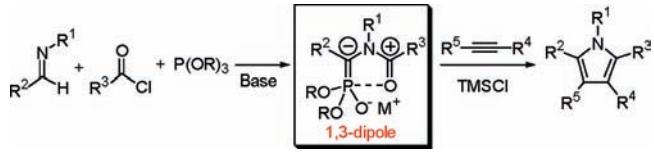
ABSTRACT



Amido-substituted Horner−Wadsworth−Emmons reagents can serve as precursors to 1,3-dipoles for use in cycloaddition. These compounds are assembled in one pot via the TMSOTf-catalyzed Arbuzov reaction of imines, acid chlorides, and phosphites. The coupling of this synthesis with alkyne cycloaddition provides a three-component synthesis of pyrroles. The dipoles can be prepared with a diverse range of imines and acid chlorides, and (3 + 2) cycloaddition with unsymmetrical alkynes is highly regiospecific, providing a modular approach to form substituted pyrroles.

1,3-Dipolar cycloaddition with azomethine ylides has found broad application in the synthesis of five-membered ring heterocycles.[1] There are a range of methods available to generate azomethine ylides, including the α-deprotonation of activated imine precursors,[2] the carbon−carbon ring opening of aziridines,[3] or the desilylation of in situ generated *N*-α-silyliminium ions.[4] While effective, these methods typically require the initial buildup of a precursor with the correct substituents prior to creating the dipole or need specific activating groups to proceed in good yields (e.g., imines with electron-withdrawing substituents). In addition, because of their symmetry, the regioselectivity of azomethine ylide cycloaddition is substituent dictated and will result in mixtures unless there is a large electronic or steric bias between the two carbon-bound units.[1,5]

A potential approach to address these issues of azomethine ylide generation and selectivity is to design synthetic equivalents.[6] One commonly employed variant of azomethine ylides is Hüisgen's 1,3-oxazolium-5-oxides (i.e., Münchnones, **2**, Figure 1),[7] though these can also be challenging to prepare unless they are derived from natural amino acids[8,9] or formed via catalysis.[10] As an alternative, we have recently reported that Wittig-type reagents **3** can serve as precursors to 1,3-dipoles via cyclization to form **4**.[11] These phosphorus-based dipoles can be synthesized in a modular fashion from imines, acid chlorides, and phosphonites. In addition, the PR_3

‡ These authors contributed equally to this work.

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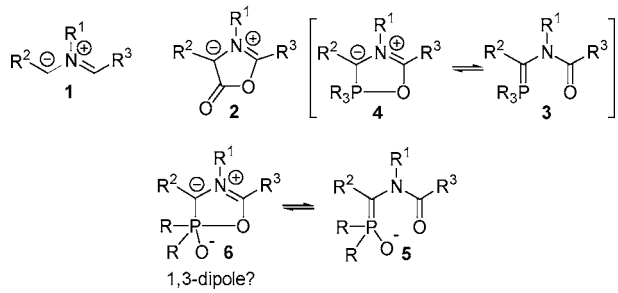
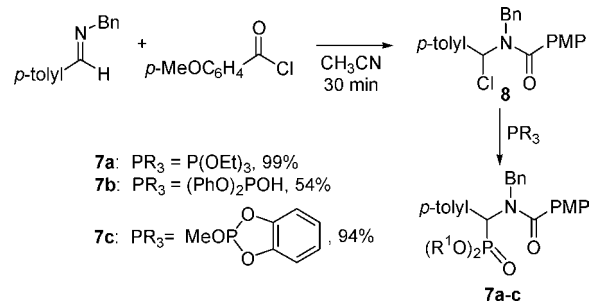


Figure 1. 1,3-Dipolar cycloaddition reagents.

unit creates a strong electronic bias across the dipole, providing a tool to control selectivity in cycloaddition reactions.[11c]

A challenge in the use of **4** is that it is generated via the equilibrium reaction of imines, acid chlorides, and P(*o*-catechyl)Ph, thereby limiting the scope of dipoles available to those derived from stabilized precursors (e.*g*., R^2 or R^3 = aryl, alkyl).[11] In considering this issue, we became interested in the potential of Horner−Wadsworth−Emmons reagents such as **5** (Figure 1) to behave as 1,3-dipoles. Horner−Wadsworth−Emmons reagents have become useful alternatives to Wittig reagents in alkene synthesis due in large part to the stability and availability of their precursors: phosphonates (e.g., **7**, Scheme 1).[12] The latter are generated via the Arbuzov reaction of phosphites and electrophiles. As described below, amido-substituted Arbuzov products can serve as attractive precursors to 1,3-dipoles. These compounds are formed in a nonequilbrium reaction of imines, acid chlorides,

Scheme 1. Synthesis of Phosphonate Precursors **1a**−**c**[a−c]



[a] $P(OEt)_3$ at 0 °C, 5 min. [b] $(PhO)_2POH$ in CH_2Cl_2 with 2,4,6-collidine, 0 °C → rt. [c] P(catechyl)OMe at rt, 15 h.

and phosphites, are airstable, and can be broadly diversified. In addition, the generation of dipole **6** can be coupled with cycloaddition, providing one-pot access to pyrroles.

Amido-substituted phosphonates can be generated by the reaction of in situ formed α-chloroamides with phosphites.[13] For example, the reaction of *p*-tolyl(H)C═NBn and anisoyl chloride in acetonitrile leads to the formation of α-chloroamide **8** within minutes at ambient temparature (Scheme 1). The subsequent addition of $P(OEt)_3$ results in a rapid Arbuzov reaction, generating phosphonate **7a** in near quantitative yield. Other phosphites can also participate in this reaction, yielding variously phosphorus-substituted products (**7b** and **7c**).

Amido-substituted phosphonate **7a** can be deprotonated with LiHMDS to generate the corresponding ylide **5a** (Table 1). This product has the potential to cyclize in a fashion similar to Wittig-type reagents **3** (Figure 1). However, in situ ^{31}P and ^{13}C NMR data suggest **5a** exists predominately in an acyclic ylide structure. For example, ^{31}P NMR analysis reveals a signal at 34.4 ppm, which is typical of Horner−Wadsworth−Emmons structures,[14] while the amide ^{13}C NMR resonance (δ 176.8 ppm) is not perturbed as expected for the 1,3-dipole.[11] Despite these structural features, the addition of the alkyne DMAD to **5a** does result in a slow cycloaddition reaction to form pyrrole (Table 1).[15] **5b** and **5c** react in a similar fashion, with the less sterically encumbered catechyl-substituted **5c** leading to the rapid formation of pyrrole (<5 min, entry 3).

While the reaction in Table 1 provides a method to generate pyrroles, there are several challenges in this approach. First, the most effective phosphonate precursor, the catechyl-substituted **7c**, is formed slowly from P(*o*-catechyl)OMe and **8**, making it difficult to diversify this reagent to other imines/acid chlorides. This can be addressed

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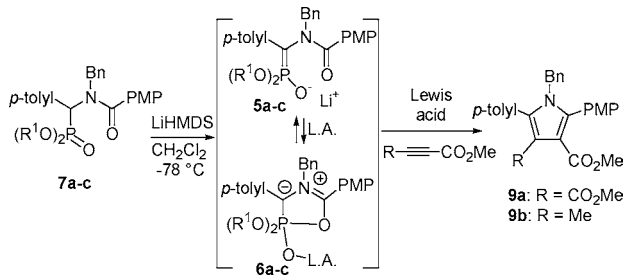
(15) **5a** also undergoes standard Wadsworth−Emmons reactions with aldehydes. See Supporting Information and: (a) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron Lett.* **1993**, *34*, 1479. (b) Hendrickson, J. B.; Rodriguez, C. *J. Org. Chem.* **1983**, *48*, 3344.

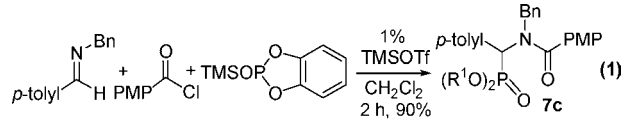
Table 1. Phosphonates in Alkyne Cycloaddition and Pyrrole Synthesis[a]



entry	compd	R	Lewis acid	time (h)	yield (%)
1	**7a**	CO_2Me	–	24	50
2	**7b**	CO_2Me	–	0.5	70
3	**7c**	CO_2Me	–	<5 min	80
4	**7c**	Me	–		–
5	**7c**	Me	$BF_3{\cdot}Et_2O$		–
6	**7c**	Me	TsCl		–
7	**7c**	Me	^{t}BuPh$_2$SiCl	17	73
8	**7c**	Me	$SiCl_4$	17	56
9	**7c**	Me	TBSCl	17	68
10	**7c**	Me	TESCl	3	91
11	**7c**	Me	TMSCl	3	95

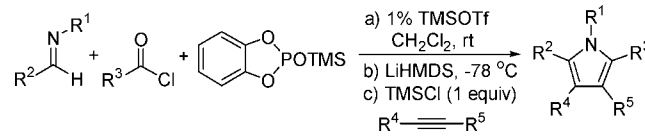
[a] 0.2 mmol of **7** in 0.5 mL of CH_2Cl_2, −78 °C, 0.2 mmol of LiHMDS solution; then 0.22 mmol of L.A. at rt, followed by 0.6 mmol of alkyne.

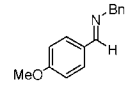
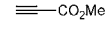
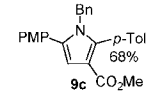
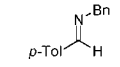
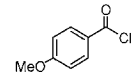
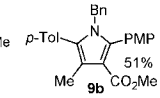
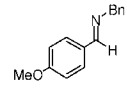
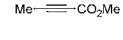
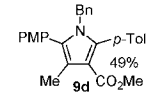
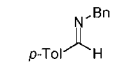
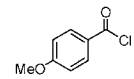
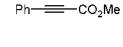
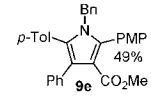
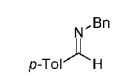
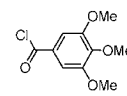
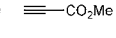
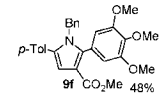
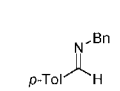
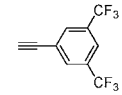
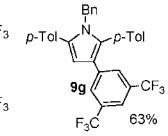
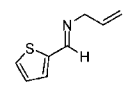
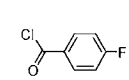
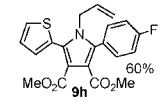
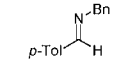
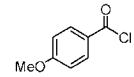
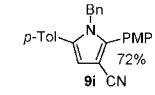
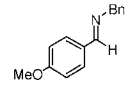
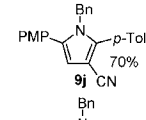
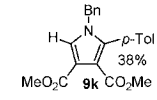
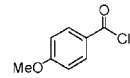
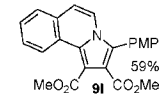
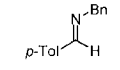
by the use of the slightly more nucleophilic P(*o*-catechyl)-OTMS and addition of catalytic TMSOTf (eq 1). Under these conditions, **7c** is generated within 2 h at ambient temperature, presumably via the in situ formation of a more electrophilic *N*-acyl iminium triflate salt intermediate. This approach can also be readily adapted to less reactive imines and acid chlorides (vide infra).



A second issue with **5c** is its inability to undergo cycloaddition with less activated dipolarophiles (e.g., Table 1, entry 4). The low reactivity presumably arises from the relatively electron-rich phosphorus unit in **5**, which disfavors a P−O interaction to generate the dipole. One approach to favor cyclization of **5** is to neutralize the formal oxygen anionic charge. As shown in Table 1, a number of Lewis acids can serve this purpose (entries 7−11), with TMSCl proving to be the most effective. In situ NMR analysis is consistent with the Lewis acid favoring a dipolar form (**6c**). This shows a significant perturbation of the amide carbonyl resonance of **6c** in the presence of TMSCl (at δ 146.8 ppm), as well as an upfield shift in the ^{31}P NMR resonance (δ −28.2 ppm, relative to **5c** at 47.6 ppm). This latter is within the range expected for pentacoordinate organophosphorus struc-

Table 2. Scope of Three-Component Pyrrole Synthesis[a]



No.	Imine	Acid chloride	Alkyne	Pyrrole (%)
1		*p*-TolCOCl		 68% **9c**
2				 51% **9b**
3		*p*-TolCOCl		 49% **9d**
4[b,c]				 49% **9e**
5[d]				 48% **9f**
6		*p*-TolCOCl		 63% **9g**
7[e]			DMAD	 60% **9h**
8[f]				 72% **9i**
9[f]		*p*-TolCOCl		 70% **9j**
10[d,g]		*p*-TolCOCl	DMAD	 38% **9k**
11			DMAD	 59% **9l**
12[h]			DMAD	65% **9m**
13[h,i]				50% **9n**
14			DMAD	44% **9o**

[a] (a) 0.20 mmol of imine/acid chloride, 0.5 h; TMSOP(Cat) (0.22 mmol), TMSOTf (0.002 mmol), 2 h; (b) 0.20 mmol of LiHMDS; (c) TMSCl (0.20 mmol), alkyne (0.60 mmol). [b] (c) 55 °C. [c] Major isomer (66:34 ratio). [d] (a) 24 h. [e] 5% TMSOTf. [f] 0.80 mmol of LiHMDS. [g] 0.22 mmol of TMSOTf, CH_3CN, DBU. [h] (a) 12 h,55 °C. [i] (c) 0.40 mmol of TMSOTf.

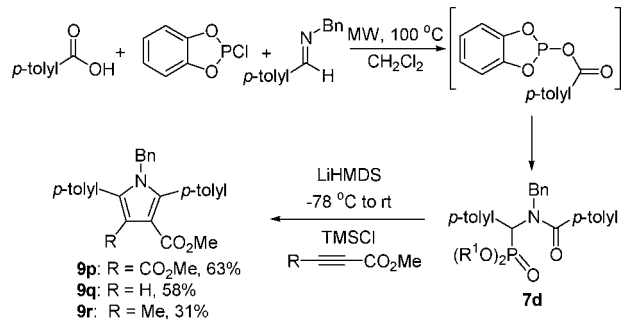
tures[16] and similar to crystallographically characterized phosphorus dipoles.[11]

The coupling of these optimized conditions for phosphonate formation, deprotonation, and dipolar cycloaddition allows for a series of very rapid and selective reactions and the assembly of polysubstituted pyrroles within hours at ambient temperature (Table 2).[17] Because of the stability of the phosphonate intermediates, this transformation is straightforward to generalize. A range of *C*-aryl, -functionalized aryl, and -heteroaryl-substituted imines can be used in this reaction (entries 1−7), as can various aryl-substituted acid chlorides. Electron-poor dipolarophiles are the most reactive with **6**, though aryl-acetylenes are also viable substrates (entry 6). Alkynes can be replaced with electron-deficient alkenes, which undergo acid loss to generate pyrroles upon cycloaddition (entries 8 and 9). In addition to forming pyrroles, the cycloadditions with unsymmetrical alkynes typically result in a single isomeric product, where the electron-withdrawing unit is directed away from the formerly phosphorus-bound carbon. This is consistent with a phosphorus-induced electronic bias in these dipoles controlling regioselectivity.[11c]

The irreversibility of phosphonate formation can also allow the use of less stable imine/acid chloride reagents. For example, formaldimines can be employed in the coupling, followed by subsequent cyclization and dipolar addition to form 5-H substituted pyrroles (entry 10). Alternatively, imines can be replaced with aromatic heterocycles such as isoquinoline, which can be efficiently trapped to yield a polycyclic pyrrole (entry 11).[18] The acid chlorides can even be replaced with chloroformates and chlorothioformates. While these latter create less electrophilic analogues to **8**, their trapping can occur with P(*o*-catechyl)OTMS, providing a route to 2-heteroatom-substituted pyrroles (entries 12−14).

The Arbuzov intermediates in this reaction can be exploited to create alternative routes to these dipoles. Burnaeva and co-workers have reported that the reaction of imines with benzoate-substituted phosphonites leads to amido-substituted phosphonates.[19] Performing this reaction with a catechyl-substituted phosphorus reagent can provide a single-step synthesis of **7d** from commercial (*o*-catechyl)PCl, *p*-toluic acid, and imine (Scheme 2). Notably, this approach avoids both the need to generate (*o*-catechyl)P(OTMS) and the use of sensitive acid chloride (and iminium salt) precursors. Coupling this synthesis with subsequent cycloaddition can allow the overall synthesis of pyrroles in one pot from carboxylic acids, imines, and alkynes.

Scheme 2. Pyrrole Synthesis from Carboxylic Acids[a]



[a] 0.2 mmol of imine, 0.22 mmol of carboxylic acid, 0.22 mmol of (*o*-catechyl)PCl, 1 mL of CH_2Cl_2, MW, 100 °C 2 h; 0.45 mmol of LiHMDS solution,−78 °C to rt; 0.4 mmol of TMSCl, 0.6 mmol of alkyne, rt.

In conclusion, amido-substituted Horner−Wadsworth−Emmons reagents can serve as precursors to 1,3-dipoles and participate in cycloaddition reactions with alkynes to form pyrroles. Coupling the generation of these reagents with cycloaddition can provide a modular method to construct pyrroles directly from available building blocks. Studies directed toward the reaction of these reagents with other dipolarophiles, and the development of alternative approaches to generate **6**, are under investigation.

Acknowledgment. We thank NSERC, FQRNT, and the CFI for their financial support.

Supporting Information Available: Synthesis and spectral data for pyrrole products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102075Y

(16) (a) *Ylides and Imines of Phosphorus*; Johnson, A. W.; Wiley-Interscience: New York, New York, 1993. (b) *Handbook of Phosphorus-31 NMR Data*; Tebby, J. C., Ed.; CRC Press: Boston, 1991.

(17) TMSCl is the formal byproduct of **7** formation with P(*o*-catechyl)-OTMS; however, excess TMSCl is beneficial to the reaction (Table 2, entry 2 is in 37% yield without additional TMSCl).

(18) Van der Jeught, S.; Stevens, C. V. *Chem. Rev.* **2009**, *109*, 2672.

(19) Mironov, V. F.; Gubaidullin, A. T.; Burnaeva, L. M.; Litvinov, I. A.; Ivkova, G. A.; Romanov, S. V.; Zyablikova, T. A.; Konovalov, A. I.; Konovalova, I. V. *Russ. J. Gen. Chem.* **2004**, *74*, 32.