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Phosphonite mediated 1,3-dipolar cycloaddition: a route to polycyclic 2-pyrrolines from imines, acid chlorides and alkenes†

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2-Pyrrolines can be generated by the PhP(2-catechyl) mediated coupling of alkene-tethered imines and acid chlorides. This reaction proceeds *via* phosphorus-containing 1,3-dipoles, which undergo cycloaddition with alkenes with high stereo- and regioselectivity. The modularity of this reaction can be used to assemble a range of polysubstituted pyrrolines in one pot transformations.

2-Pyrrolines, and their fully reduced counterpart pyrrolidines, are common structural motifs in biologically relevant products. Examples of these range from natural products,[1] structures of pharmaceutical utility[2] (*e.g.* anti-cancer agents,[3] antibiotics,[4] hepatitis C inhibitors[5] or antitubercular agents[6]), amino acid derivatives,[7] and others. One challenge in the use of pyrrolines is their synthesis. A common approach to 2-pyrrolines is *via* the cyclization of amine-containing precursors, such as hydroamination,[8] iodoamination,[9] ring expansion,[10] or catalytic cyclization[11] reactions. While effective, these require the build-up of the correctly substituted substrate for subsequent cyclization.

A more convergent approach to 2-pyrrolines is *via* [4+1][12] or [3+2][13] cycloaddition reactions. The latter has been exploited with 1,3-oxazolium-5-oxides (Münchnones),[14] metallated azomethine ylides,[15] isocyanoesters,[16] and aziridines[17] in reactions with alkenes or alkynes. While alkenes and alkynes are readily available, a requirement in this case is the generation of the polysubstituted 1,3-dipole or dipole precursor. As an alternative, we have recently reported a modular approach to phosphorus-dipoles of the form **1** (*i.e.* phospha-Münchnones). **1** is generated *via* the equilibrium tautomerization of amide-substituted Wittig ylides (Fig. 1). By coupling the multicomponent generation of **1′** with spontaneous cyclization, **1** can be formed in one pot, with imines, acid chlorides and phosphines as the building blocks.[18]

Considering their ease of synthesis, we became interested in the potential utility of **1** in pyrroline synthesis. We describe the results of these studies below. These show that the correctly substituted dipole **1** can participate in alkene cycloaddition with high selectivity. This has allowed the design of a general approach to assemble polycyclic 2-pyrrolines directly from olefin-tethered imines and acid chlorides (Fig. 2).

Our initial studies examined the reaction of the imine **2a** (Table 1). **2a** is readily accessible from salicylaldehyde, and alkene cycloaddition would provide a route to polycyclic pyrrolines[2] uncomplicated by the multiple alkene cycloadditions sometimes observed with Münchnones.[14] PPh_3 can react with **2a**, toluoyl chloride, followed by a base to form **1**/**1′**. However no cycloaddition is observed, and this compound simply decomposes at high temperatures (entry 1). Similar behaviour is observed with PCy_3 and $P(NMe_2)_3$ (entries 2 and 3). We have previously noted that electron rich phosphines do not favor the amide chelation necessary for cyclization of the acyclic Wittig-type structure **1′** to its 1,3-dipole form (Fig. 1),[18b] which could slow down the cycloaddition to the unactivated alkene in **2a**. Consistent with this, the more electron poor phosphite $P(OPh)_3$ reacts with these same substrates to both generate **1**, and undergo cycloaddition to form 2-pyrroline **3a** in a 46% yield (entry 4). A similar reaction occurs with $P(OCH_2CF_3)_3$ (entry 5). The moderate yield of **3a** under these conditions arises from the poor nucleophilicity of phosphites, which reacts slowly with the *in situ* generated α-chloroamide **4** (Scheme 1). The latter can be enhanced by the addition of TMSOTf to activate **4** towards nucleophilic attack (X = OTf, entries 6 and 7). Alternatively, the more nucleophilic phosphonite PhP(2-catechyl) avoids the need for this additive, and with DBU base leads to the high yield and rapid formation of **3a** (entry 10).

Pyrroline **3a** is formed as a single observable diastereomer and alkene regioisomer. In considering the reaction mechanism,

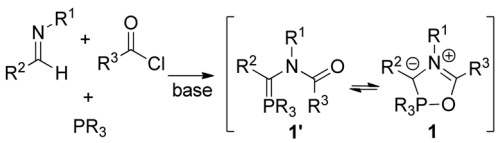

Fig. 1 Multicomponent assembly of phospha-Münchnones.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for all new compounds. See DOI: 10.1039/c2cc38274a

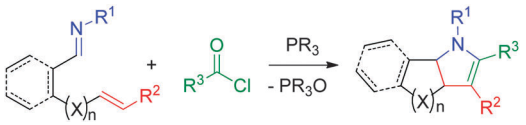
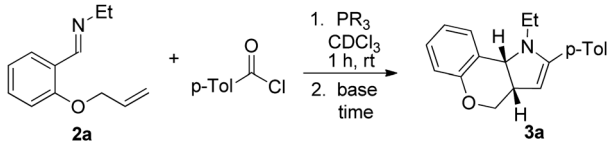


Fig. 2 Phosphine mediate approach to pyrrolines.

Table 1 Development of PR_3 mediated pyrroline synthesis[a]

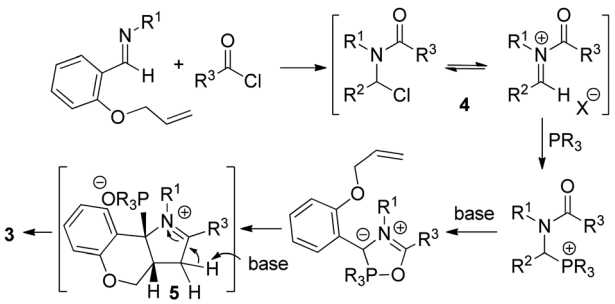


Entry	PR_3	Base	Additive	Time	Yield[b] (%)
1	PPh_3	LiHMDS[c]	—	—	0
2	PCy_3	LiHMDS[c]	—	—	0
3	$P(NMe_2)_3$	LiHMDS[c]	—	—	0
4	$(PhO)_3P$	DBU	—	24 h	46
5	$(CF_3CH_2O)_3P$	DBU	—	10 h	46
6	$(PhO)_3P$	DBU	TMSOTf	5 h	80
7	$(CF_3CH_2O)_3P$	DBU	TMSOTf	2 h	67
8	PhP(2-catechyl)	Et_3N	—	6 h[d]	66
9	PhP(2-catechyl)	$Et(^iPr)_2N$	—	6 h[d]	36
10	PhP(2-catechyl)	DBU	—	2 h	85

[a] **2a** (38 mg, 0.2 mmol), TolCOCl (34 mg, 0.22 mmol), 0.5 mL $CDCl_3$, 30 min; then PR_3 (0.22 mmol), 1 h; base (0.36 mmol), rt. [b] NMR yield. [c] Added at −78 °C. [d] 65 °C.

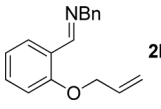
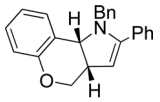
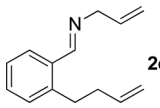
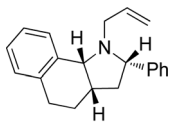
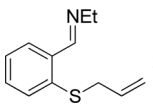
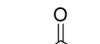
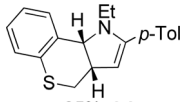
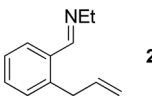
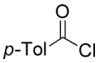
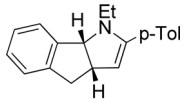
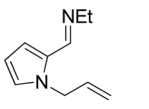
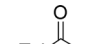
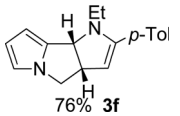
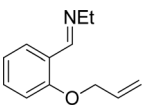
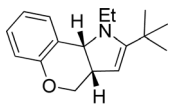
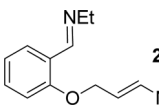
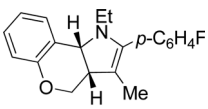
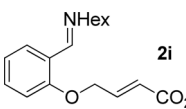
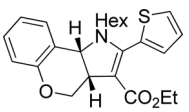
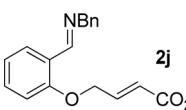
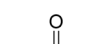
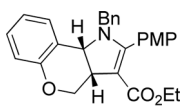
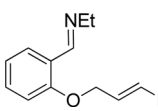
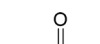
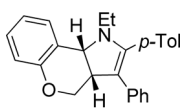
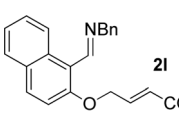
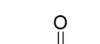
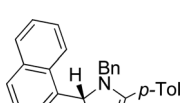
these both likely arise from the generation of the phosphorus-bound intermediate **5** (Scheme 1). The large steric profile of the PR_3 unit presumably favors the *cis*-ring fusion upon alkene cyclization, while slow phosphine oxide loss from **5** would allow the selective deprotonation at C4, and lead to a single pyrroline alkene isomer.

In addition to generating **3a**, since this reaction relies on imines and acid chlorides, it is straightforward to diversify these products. As shown in Table 2, a number of *N*-alkyl substituents can be employed in the reaction, including common protecting groups (entries 2, 9, and 11). Carbon-, sulfur- and oxygen-containing tethers can all be employed in this chemistry (entries 1–3), as can various aromatic spacers, including simple phenyl, naphthyl (entry 11) and even pyrrole units (entry 5). However, amine tethered variants of **2b** are not compatible with these conditions. The alkene can be similarly diversified, with terminal and internal olefins both affording

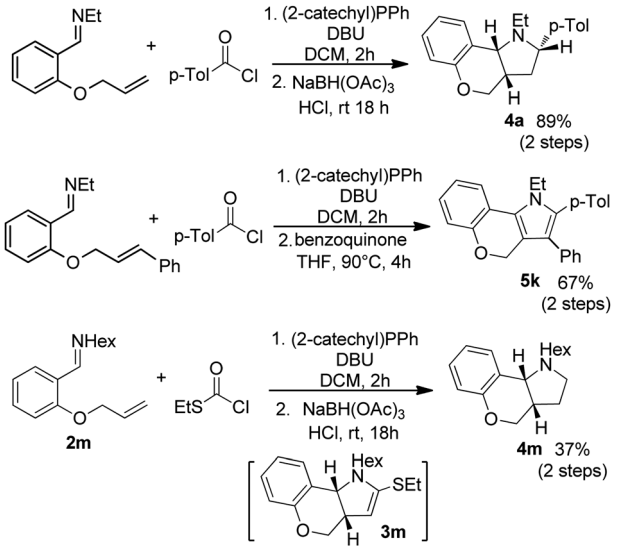


Scheme 1 Mechanism of formation of **3**.

Table 2 Diversity of one pot 2-pyrroline synthesis[a]

Entry	Imine	Acid chloride	Product (% yield)
1	 **2b**		 85% **3b**
2[b]	 **2c**		 75% **4c**
3[c]	 **2d**		 95% **3d**
4	 **2e**		 74% **3e**
5[d]	 **2f**		 76% **3f**
6	 **2a**		 64% **3g**
7[e]	 **2h**		 88% **3h**
8[f]	 **2i**		 80% **3i**
9[f]	 **2j**		 89% **3j**
10[e]	 **2k**		 91% **3k**
11[f]	 **2l**		 75% **3l**

[a] Imine (0.20 mmol), acid chloride (0.21 mmol), 0.5 mL $CHCl_3$, 30 min; (2-catechyl)PPh (47.5 mg, 0.22 mmol), 1 h; DBU (45.7 mg, 0.30 mmol), rt, 10 min. [b] Reduced with $NaBH(OAc)_3$ (0.30 mmol), 1 M HCl–ether (0.40 mmol), 18 h. [c] 2 h. [d] CD_3CN. [e] 60 °C, 1 h. [f] 0.40 mmol DBU.



Scheme 2 One-pot synthesis of pyrrolidines and pyrroles.

pyrrolines in good yields, and with similar selectivity (entries 7–11). This includes electron poor (entries 8 and 9), styrenyl (entry 10) and even weakly donating alkyl-substituted alkenes (entry 7). 5,5-Fused ring products are also accessible (entries 4, 5). The acid chloride unit can be similarly varied to form a number of 5-aryl, -thiophenyl and even tertiary alkyl substituted products (entries 5–9). Overall, this provides a modular route to prepare polycyclic 2-pyrrolines from accessible alkene-tethered imines and acid chlorides, where in one pot each substituent is tuned by the choice of appropriate building blocks.

Pyrrolines have been demonstrated to serve as useful building blocks for a variety of products. For example, coupling the generation of **3** with *in situ* reduction with $NaBH(OAc)_3$ results in a stereoselective route to prepare pyrrolidine **4a**, with five separate bonds generated in one pot (Scheme 2). Alternatively, the generation of **3** with subsequent benzoquinone oxidation allows the overall synthesis of polycyclic pyrrole **5k**. This reaction platform can also be expanded to chlorothioformates. In this case, cycloaddition and subsequent reduction leads to a dethiolated product **4m**. The dethiolation presumably occurs upon reduction of **3m**,[19] and allows the assembly of 5-unsubstituted pyrrolidines: a structure unavailable from normal acid chloride chemistry.

In conclusion, alkene-tethered imines and acid chlorides can undergo phosphonite mediated cyclization to generate polycyclic pyrrolines with high regio- and stereoselectivity. This reaction exploits the modular formation of phosphorus-containing dipoles **1**, which undergo rapid cycloaddition with alkenes. When coupled with the reactivity of the 2-pyrroline core itself, this can allow the synthesis of a range of heterocycles (pyrrolines, pyrroles, pyrrolidines) in efficient, one pot reactions.

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