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A Direct Phosphine-Mediated Synthesis of Pyrroles from Acid Chlorides and α,*β*-Unsaturated Imines

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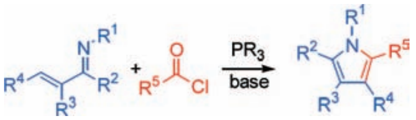
ABSTRACT



A one-step method to assemble pyrroles from α,*β*-unsaturated imines and acid chlorides has been developed. This reaction is mediated by triphenylphosphine, which eliminates phosphine oxide to allow cyclization. This reaction has been employed to access a diverse range of pyrroles via modulation of the two building blocks and applied as well to the synthesis of lukianol A.

Pyrroles have found utility in such diverse fields as medicinal chemistry, materials science, polymer synthesis, and metal-coordinating ligands and as synthetic building blocks. Examples of these include various anti-inflammatory agents,[1] antitumor agents,[2] the blockbuster drug atorvastatin calcium, commonly known as Lipitor,[3] poly(pyrrole)-based conjugated materials,[4] and numerous natural products.[5] This utility has made the design of efficient routes to prepare pyrroles an area of active research. Traditional methods for pyrrole synthesis include the Hantzsch,[6] Knorr,[7] and Paal−Knorr[8] syntheses.[9] However, these methods can be limited by the multistep syntheses often needed for their precursors and sometimes harsh conditions. As such, a range of new synthetic routes, including multicomponent coupling reactions[10] and metal-catalyzed syntheses,[11] have been devel-

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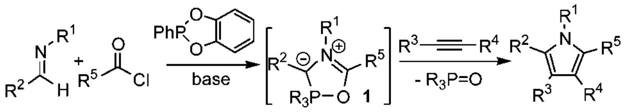
10.1021/ol900185n CCC: $40.75

Scheme 1. Phosphonite-Mediated Dipolar Cycloaddition to Pyrroles



oped, many of which can provide easy access to these products. Nevertheless, there remains a need for methods to synthesize pyrroles in an efficient fashion, especially those that employ simple building blocks and a minimal number of overall synthetic steps.

Toward this end, we have recently reported that phosphonites can mediate the multicomponent coupling of imines, acid chlorides, and alkynes to generate pyrroles in one pot and from readily available building blocks (Scheme 1).[12] Although this approach is effective, the reaction can be limited by the necessary use of electron-withdrawing units on the alkyne (e.g., the 3- and/or 4-pyrrole positions) and poor regiocontrol with similarly sized alkyne substituents. Both of these factors arise from the mechanism of pyrrole formation, which involves a 1,3-dipolar cycloaddition reaction to the in situ generated **1**. In considering approaches to address this issue, one possibility would be to change the mechanism of phosphine-mediated pyrrole formation. The role of phosphine in this chemistry is ultimately to remove oxygen from the acid chloride as phosphine oxide, which is liberated upon dipolar addition (Scheme 1). In principle, this dipolar cycloaddition pathway can be avoided by instead employing simple α,β-unsaturated imines. The latter are readily available by simple aldol reactions followed by imine formation and can potentially serve the same overall role as imines and alkynes. As described below, these studies have led to the design of a new, one-step route to generate pyrroles. Although phosphines have been previously employed to mediate cyclizations to form pyrroles,[13] to our knowledge this is the first to employ such simple building blocks: α,β-unsaturated imines and acid chlorides (Figure 1). In addition to its efficiency, the pyrroles are formed with perfect regiocontrol, with a diverse range of substituents, and employ only simple PPh_3 to mediate the reaction.

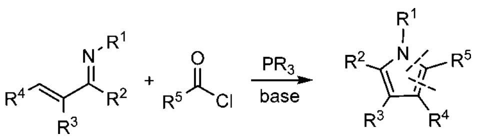
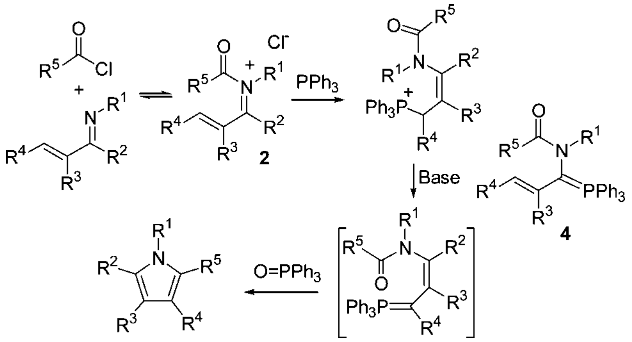


Figure 1. An approach to pyrroles from imines and acid chlorides.

Our postulated mechanism for this reaction is shown in Scheme 2. This is based upon the potential of phosphines to undergo Micheal-type 1,4-addition to in situ generated α,β-unsaturated iminium salts **2**,[14] rather than the 1,2-addition we have previously noted with simple imines. Upon in situ deprotonation, an intramolecular Wittig-type reaction would allow cyclization and the generation of pyrroles.

Scheme 2. Postulated Mechanism for PPh_3-Mediated Pyrrole Synthesis



The results of our first attempt at this reaction were promising. When the reaction of imine **3** and aroyl chloride was carried out with PPh_3 and NEt_3 base, pyrrole was formed within 15 min (Table 1, entry 1), albeit in 52% yield. Monitoring this reaction by ^1H and ^{31}P NMR spectroscopy reveals that the low yield of pyrrole resulted from two issues: the incomplete reaction between the iminium salt and PPh_3 (resulting in **2** at the end of the reaction) and the formation of ca. 20% of a phosphorus-containing byproduct. The latter is preliminarily characterized to be the phosphorus-ylide

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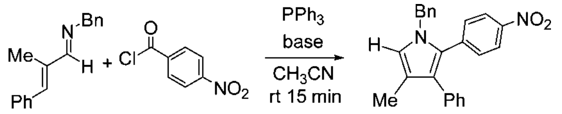
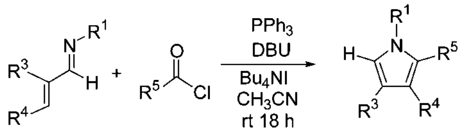
Table 1. Development of a PPh_3-Mediated Pyrrole Synthesis[a]

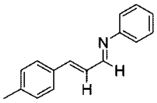
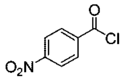
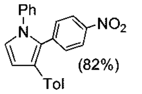
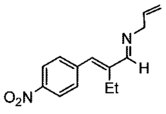
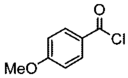
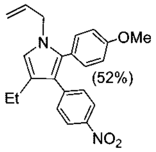
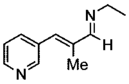
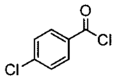
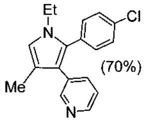
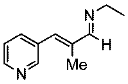
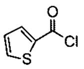
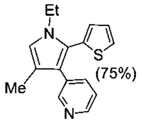
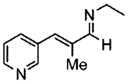
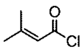
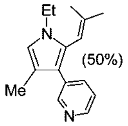
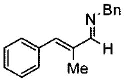
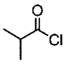
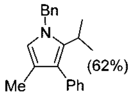
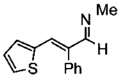
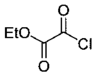
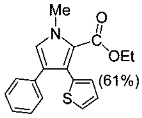
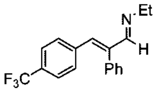
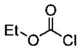
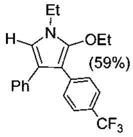
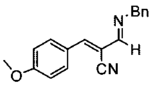
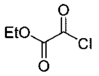
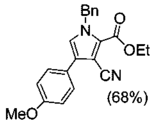
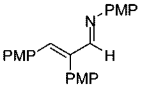
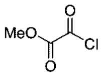
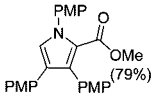


entry	base	additive	yield (%)
1[b]	NEt_3		52
2	NEt_3		71
3	NEt_3	Bu_4NI	86
4	DBU	Bu_4NI	85
5	NEt_3	Bu_4NBr	78
6	NEt_3	NaI	52
7	NEt_3	KI	61

[a] Imine (94 mg, 0.40 mmol), 4-nitro-benzoychloride (89 mg, 0.48 mmol), PPh_3 (157 mg, 0.60 mmol), base (0.60 mmol), and additive (0.40 mmol) in 1 mL of CH_3CN. [b] 0.40 mmol PPh_3.

Table 2. Diversity of Pyrroles Available from Imines and Acid Chlorides[a]



no.	imine	acid chloride	product (%)
1			 (82%)
2[b]			 (52%)
3			 (70%)
4			 (75%)
5			 (50%)
6[b]			 (62%)
7			 (61%)
8[b]			 (59%)
9			 (68%)
10			 (79%)

[a] Imine (0.40 mmol), acid chloride (0.40 mmol), Bu_4NI (148 mg, 0.40 mmol), PPh_3 (156 mg, 0.60 mmol), and DBU (90 mg, 0.60 mmol) in 1 mL of CH_3CN, rt, 18 h. [b] 65 °C for 18 h.

resulting from 1,2-addition to the α,β-unsaturated imine (**4**),[15] which cannot undergo intramolecular cyclization. Although the use of a slight excess of PPh_3 can eliminate **2** and increase pyrrole yield (entry 2, 71%), this still results in the formation of **4**.

It is established that anions can play a role in addition to iminium salts, with soft ions favoring conjugate addition.[16] As such, a range of softer halide additives were examined in the reaction, for their ability to stabilize the positive charge at the β-position of **2**. Whereas metal iodide salts did not improve the yield, the addition of soluble Bu_4NI led to the elimination of **4** (<5%) and the formation of pyrrole in near quantitative yield. In addition to triethylamine, the stronger base DBU is also viable in this reaction (entry 4). Overall, this provides a high yield, one-step synthesis of pyrroles from α,β-unsaturated imines and acid chlorides.

This reaction employs substrates (imines and acid chlorides) and reagents (triphenylphosphine and DBU) that are all readily available. As such, it is a reaction that is both straightforward to perform and readily diversified. For example, as shown in Table 2, various aryl (electron-rich or -poor), heteroaryl, hydrogen, and alkyl substituents can be incorporated into R^3 or R^4 on the imine (entries 1−7). A similar range of alkyl, aryl, or protecting groups (benzyl, allyl) can also be employed on the imine nitrogen. In addition to aryl- and alkyl-acid chlorides, α-ester-substituted acid chlorides (entries 9 and 10) and even chloroformates (entry 8) can be used in this chemistry. The latter allows the generation of 2-alkoxy-substituted pyrroles. A range of functional groups can be used in each of these positions, such as nitro, ester, ether, and halo units. Together, this provides straightforward access to a diverse range of pyrroles, with phosphine oxide and amineHCl salt the only byproducts.

Substituents can have a dramatic influence on the rate of the coupling. For example, with electron-rich R^4 or electron-poor R^5, the products are formed at ambient temperature, whereas the opposite (electron-poor R^4 or -donating R^5) significantly slows the reaction and requires high temperature to go to completion (entries 2, 6, 8). These are likely the effect of the intramolecular Wittig reaction,

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(15) Complex **4** cannot be isolated from the reaction mixture; however, its spectroscopic data (e.g., ^{31}P NMR δ 12.6 ppm) is directly analogous to that noted for similar α-amide-substituted phosphorus-ylides.[12]

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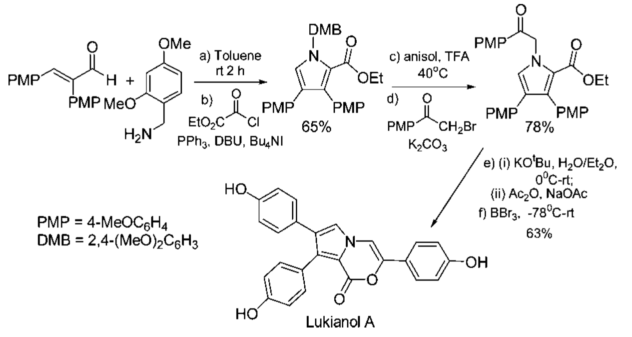
Scheme 3. Synthesis of Lukianol A



where electron-poor carbonyl and electron-rich ylides accelerate coupling.[17]

As an illustration of the potential utility of this reaction, we have examined its application to the synthesis of lukianol pyrroles. These products, such as lukianol A, have been found to have activity against human epidermatoid carcinoma.[5c,18,19] As shown in Scheme 3, this imine/acid chloride approach can be directly applied to these products, allowing the assembly of the pyrrole core **5** in one pot from the α,β-unsaturated aldehyde (65% yield), which can be subsequently converted to the target.[20] As far as we are aware, this represents one of the most straightforward approaches to these products and is also well-suited for the construction of new variants of lukianol derivatives.

In conclusion, we have described a new synthesis of pyrroles directly from simple α,β-unsaturated imines and acid chlorides, mediated by triphenylphosphine. This reaction proceeds via an intramolecular Wittig reaction pathway and provides one-step access to a diverse range of pyrrole products. The application of this chemistry to access biologically relevant pyrrole-based products, as well as other classes of heterocycles, is currently underway.

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

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(20) Steps c−f follow the protocol developed by Fürstner in ref 19a.