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Microwave-Promoted Tin-Free Iminyl Radical Cyclization with TEMPO Trapping: A Practical Synthesis of 2-Acylpyrroles

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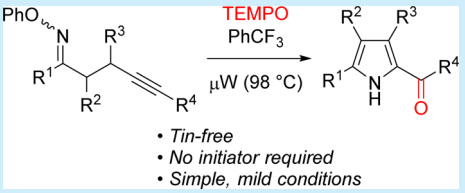
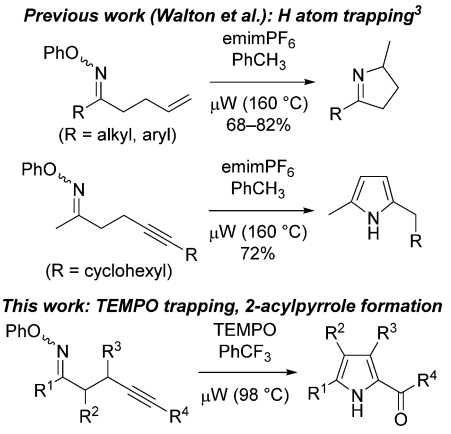
Supporting Information

ABSTRACT: Microwave-promoted iminyl radical cyclizations can be terminated by trapping with TEMPO, affording functionalized adducts. The use of alkynes as radical acceptors delivers a range of 2-acylpyrroles in good yields. Toxic and hazardous reagents, which are frequently employed in radical reactions, are not required. The *O*-phenyl oxime ether substrates are constructed in a single step from readily available ketones.



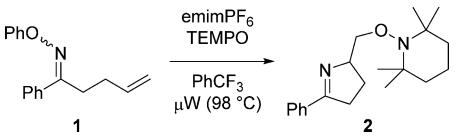
Radical processes are valued for their mild reaction conditions, excellent functional group tolerance, and ability to engage in one-pot multistep cascade transformations.[1] A current area of emphasis involves the development of radical reactions that do not require toxic or hazardous reagents (e.g., organotins, azo compounds, or peroxides).[2] In this regard, we became interested in the microwave-promoted iminyl radical cyclizations of Walton and co-workers, which furnish dihydropyrroles from alkene acceptors and pyrroles from alkyne acceptors (Scheme 1).[3−5] No radical initiators or tin reagents are required, as the weak N−O bond in the substrate is cleaved directly via thermolysis and the toluene solvent functions as a hydrogen atom donor. Attracted by the simple and environmentally friendly nature of this process, we wondered if more complex products could be generated by trapping the cyclic radical intermediate with species other than hydrogen atoms. Herein, we present our initial findings on this topic, which have led to a concise and efficient synthesis of 2-acylpyrroles.

Scheme 1. Microwave-Promoted Iminyl Radical Cyclization



We began by investigating TEMPO as a radical trapping agent due to the many examples of its successful use for this purpose.[6,7] To avoid competitive hydrogen atom trapping, a solvent other than toluene was required. We posited that trifluorotoluene might serve as a suitable substitute. Our first experiment involved microwave irradiation of *O*-phenyl oxime ether **1**[3] (Table 1), TEMPO, and the ionic liquid 1-ethyl-3-methyl-1*H*-imidazol-3-ium hexafluorophosphate (emimPF$_6$, employed by Walton and co-workers to facilitate efficient microwave heating of the reaction mixture) in this solvent at 160 °C (the temperature employed in Walton's study[3]). A complex mixture resulted, and further investigation revealed that TEMPO decomposes under microwave irradiation in PhCF$_3$ at this temperature. Fortunately, the thermolysis of **1** followed by cyclization and TEMPO trapping took place at temperatures just below 100 °C, delivering dihydropyrrole **2** rapidly and in excellent yield (Table 1, entry 1). Since PhCF$_3$ is more polar than toluene, we reasoned that the ionic liquid additive might not be necessary. Indeed, microwave heating was efficient in its absence, and the yield of **2** was essentially unchanged (Table 1, entry 2). Moreover, the amount of TEMPO could be reduced to 1.1 equiv, albeit with an increase in the reaction time from 15 to 30 min (Table 1, entry 3).

Table 1. TEMPO Trapping of Iminyl Radical Cyclization



entry	emimPF$_6$ (equiv)	TEMPO (equiv)	time (min)	yield (%)
1	1.0	1.5	15	93
2	0	1.5	15	90
3	0	1.1	30	92

Walton and co-workers found that 5-*exo* iminyl radical cyclizations onto alkyne acceptors furnished pyrroles due to

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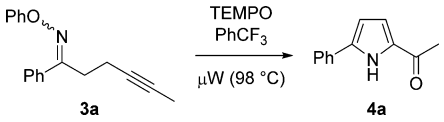
isomerization and aromatization of the initially formed adducts (Scheme 1).[3] We wondered if TEMPO-terminated cyclizations onto alkyne acceptors conducted at lower temperatures would also be accompanied by isomerization. If aromatization could be prevented, the resulting dihydropyrrole enol ethers would be valuable synthetic intermediates possessing numerous possibilities for further functionalization. Interestingly, when alkyne-containing *O*-phenyl oxime ether **3a**[8] was subjected to the conditions developed with substrate **1**, 2-acylpyrrole **4a** was obtained in moderate yield, and the presumed dihydropyrrole enol ether intermediate was not observed (Table 2, entry 1). Optimization studies revealed that 3.0 equiv of TEMPO were required to deliver **4a** in good yield (Table 2, entry 3).

Table 2. TEMPO-Terminated Iminyl Radical Cyclization of Alkyne 3a



3a **4a**

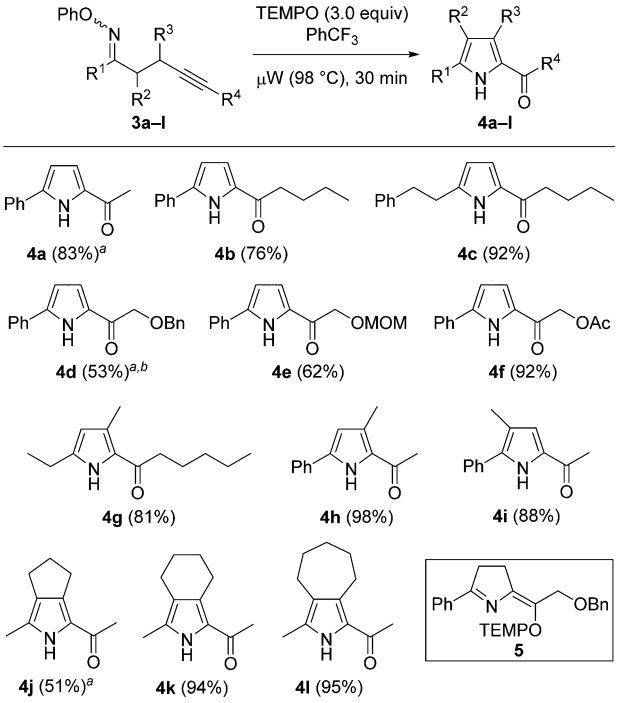
entry	TEMPO (equiv)	time (min)	yield (%)
1	1.5	30	41
2	2.5	30	43
3	3.0[a]	60	83

[a]1.5 equiv of TEMPO was added at the beginning of the reaction, and a second portion was added after 30 min.

Given the importance of pyrroles and the high level of interest in developing new methods for their synthesis,[9,10] we examined TEMPO-terminated microwave-promoted radical cyclizations of various alkyne-containing *O*-phenyl oxime ethers **3**[11] (Scheme 2). The reaction exhibited a broad substrate scope, delivering a variety of different 2-acylpyrroles. Acyl groups larger than acetyl could be easily installed (**4b**), and both aryl and alkyl groups were tolerated at the C-5 position (cf. **4b** vs **4c**). Acyl groups bearing alcohols protected with either acid-labile (**4d**, **4e**) or base-labile (**4f**) protecting groups were compatible with the mild procedure. Interestingly, a small amount of TEMPO-containing dihydropyrrole enol ether **5** was obtained alongside pyrrole **4d**. In addition to the acyl group present at C-2 and the alkyl or aryl group located at C-5 of the pyrrole, substituents at either C-3 or C-4 were also tolerated (**4g–i**). Cyclic substrates were viable, furnishing bicyclic pyrroles possessing fused five- (**4j**), six- (**4k**), and seven-membered rings (**4l**). While most of the iminyl radical cyclizations were conducted by adding the entire 3.0 equiv of TEMPO in a single portion, the sequential addition of two 1.5 equiv portions afforded slightly better results in a few cases (**4a**, **4d**, **4j**).

In addition to conducting the microwave-promoted reactions, we briefly investigated TEMPO-terminated iminyl radical cyclizations under conventional conditions. Heating a solution of oxime ether **1** and TEMPO in $PhCF_3$ at 98 °C in an oil bath for 3 h afforded dihydropyrrole **2** in 84% yield. The cyclization of **3a** under identical conditions required more time (12 h) and delivered 2-acylpyrrole **4a** in modest (52%) yield. These experiments demonstrate that microwave irradiation is beneficial but not required for these iminyl radical cyclizations to take place. It is unlikely that microwave-specific acceleration is operative, since this effect has only been documented in cases where microwave-absorbing polar or ionic solutes are selectively heated in nonpolar solvents that are essentially

Scheme 2. Scope of TEMPO-Terminated Iminyl Radical Cyclization

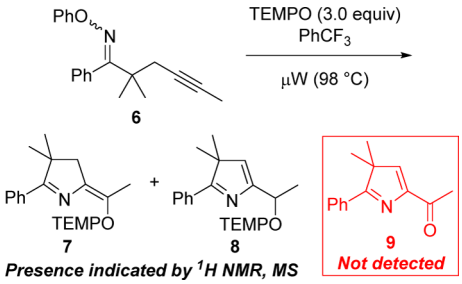


[a]TEMPO added in two 1.5 equiv portions, 60 min reaction time. [b]11% of the dihydropyrrole enol ether **5** was also obtained.

transparent to microwaves.[12] Our reactions employ a microwave-absorbing polar solvent, so it is likely that the entire solution is heated in relatively uniform fashion upon microwave irradiation.

To probe the mechanism of 2-acylpyrrole formation, we conducted the iminyl radical cyclization of alkyne **6**, which is unable to afford an aromatic product (Scheme 3). This reaction

Scheme 3. Microwave-Promoted Cyclization of Alkyne 6



furnished a complex mixture from which we were unable to isolate the products. ^{1}H NMR and mass spectrometry analysis of the crude reaction mixture indicated the presence of enol ether **7** and its isomer **8**. Ketone **9**, which would have formed via fragmentation of **8**, was not detected. While it is premature to draw conclusions from this result, it does suggest that formation of an aromatic pyrrole ring system is necessary for the TEMPO group to fragment and generate a ketone.

We then subjected dihydropyrrole enol ether **5** to microwave heating in the absence of TEMPO (Scheme 4). Isomerization to generate the pyrrole was facile, as **10** was the major product visible in the ^{1}H NMR spectrum of the reaction mixture. However, 2-acylpyrrole **4d** was not detected, indicating that the

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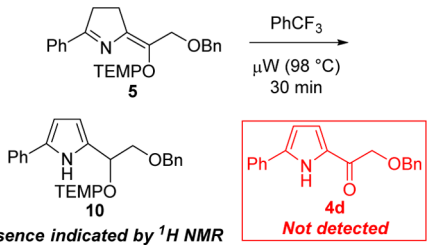
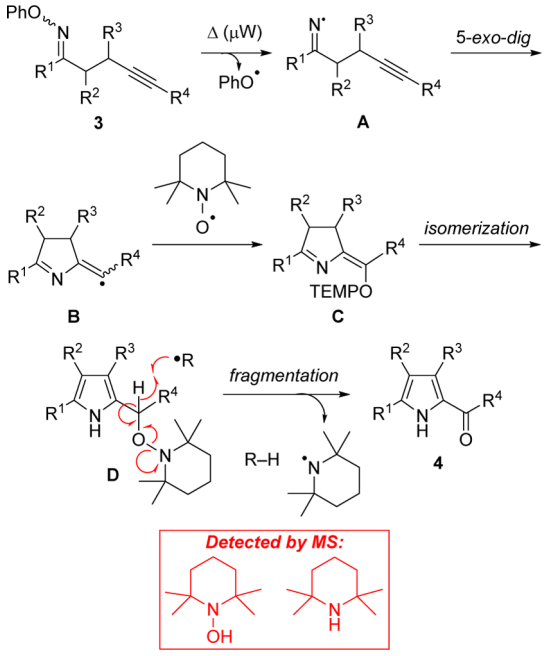
Scheme 4. Heating of 5 in the Absence of TEMPO



presence of radicals facilitates fragmentation of **10** and related adducts.

A plausible mechanism for the formation of 2-acylpyrroles **4** is shown in Scheme 5. Microwave irradiation of *O*-phenyl

Scheme 5. Proposed Reaction Mechanism



oxime ether **3** causes homolytic cleavage of the N−O bond, producing iminyl radical **A** along with the phenoxy radical as a byproduct. Radical **A** then undergoes 5-*exo*-*dig* cyclization to furnish vinyl radical **B**, which is subsequently trapped by TEMPO[13] to afford enol ether **C**. Isomerization of **C** gives pyrrole **D**, and formation of the heteroaromatic ring system presumably weakens the adjacent C−H bond sufficiently to allow a fragmentation to be triggered by abstraction of this hydrogen atom. This fragmentation could be mediated by several of the radicals that are present in the reaction mixture (i.e., PhO•, TEMPO,[14] or tetramethylpiperidinyl radical), and it proceeds with N−O bond cleavage[15,16] to produce 2-acylpyrrole **4** and the tetramethylpiperidinyl radical. The observation of enol ether **5** as a minor product of the cyclization of **3d** is consistent with this mechanism, as is the failure of *O*-phenyl oxime ether **6** to give a ketone-containing product and the inability of **10** to undergo fragmentation in the absence of TEMPO. The detection of *N*-hydroxytetramethylpiperidine and tetramethylpiperidine in the reaction mixture by mass spectrometry provides further support for the proposed pathway.

In summary, we have found that microwave-promoted iminyl radical cyclizations can be terminated by trapping with TEMPO. The use of alkynes as radical acceptors furnishes 2-acylpyrroles by a process involving isomerization and fragmentation. The *O*-phenyl oxime ether cyclization substrates are easily prepared in a single step from ketones, which are themselves readily available. 2-Acylpyrroles have traditionally been synthesized by Friedel−Crafts acylations[17] or Vilsmeier reactions.[18] When compared to these methods and others that are used to construct substituted pyrroles,[9,10] this protocol is attractive for its mild conditions that tolerate the presence of both acid- and base-sensitive functional groups. Its scope, simplicity, and good yields are also noteworthy. Moreover, toxic or hazardous reagents such as organotins, azo compounds, and peroxides are not required. Further applications of microwave-promoted iminyl radical cyclizations are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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