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Photochemistry of acyloximes: synthesis of heterocycles and natural products

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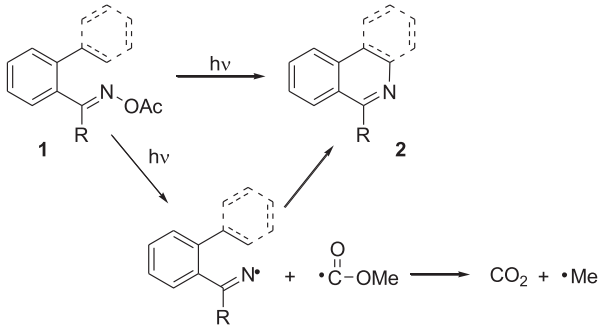
ABSTRACT

New applications of the photochemically generated iminyl radicals ring closure onto phenyl, thiophenyl, and pyridinyl rings are presented. The influence on the reactivity of different substituent throughout the acyloxime structure is discussed. Some observed effects are interpreted from computational studies. This reaction provides a new, simple, and straightforward method for the preparation of several polycyclic heteroaromatic compounds and it has been applied to the synthesis of some natural products.

1. Introduction

The rich potential of iminyl radicals, generated by both thermal and photochemical methods, is manifested in cyclization reactions. However, the literature on iminyl radical cyclizations is scarce. In most cases, formation of five-membered nitrogen heterocyclic rings takes place.[1] We described, for the first time, the use of iminyl radicals, generated from irradiation of acyloximes, to the preparation of six-membered rings such as phenanthridines or isoquinolines (Scheme 1).[2] The formation of one or another cycle has been rationalized by ab initio calculations[3] and observed experimentally,[3,4] and the generation of methyl radical has been detected by EPR spectroscopy.[4d] Bearing in mind that aza heterocycles are recurrent structures in important natural products, we found of interest to extend our methodology to the synthesis of such heterocycles.

In our previous work, we explored simple substitution patterns (mainly phenyl, vinyl, and ethynyl) on the basic structure with a phenyl group as a spacer, thus producing compounds **2a**–**2f** (Chart 1).[2] In the present study, more complex acyloximes were synthesized in an effort to broaden the scope of this photoreaction to the synthesis of different heterocycles and natural products.



Scheme 1.

2. Results and discussion

2.1. Influence of the spacer

First, we tried to use a naphthyl group, rather than a phenyl group, as a spacer. When subjected to irradiation in acetonitrile through Pyrex glass, **3** gave a 55% yield of benzo[*i*]phenanthridine **4**, after cyclization of the iminyl radical onto the phenyl ring and the loss of an H-atom to restore the aromaticity (Scheme 2). However, the irradiation of indolyl derivative **5** led to the formation of the nitrile **6**, instead of the expected cyclization product (Scheme 3). Formation of nitriles has also been observed for the previously described reactions.[2]

These results suggested that ring closure of intermediate iminyl radical onto phenyl ring supported on a five-membered spacer should be slower than that of six-membered one and unable to

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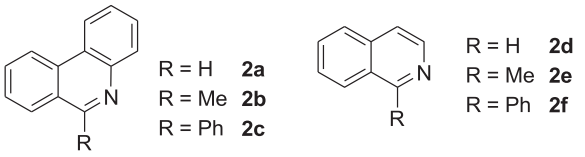
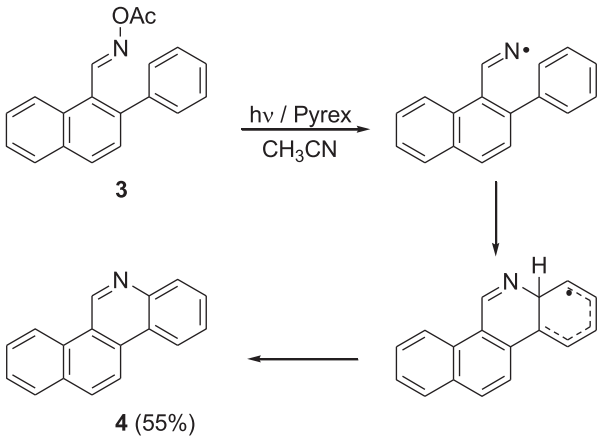
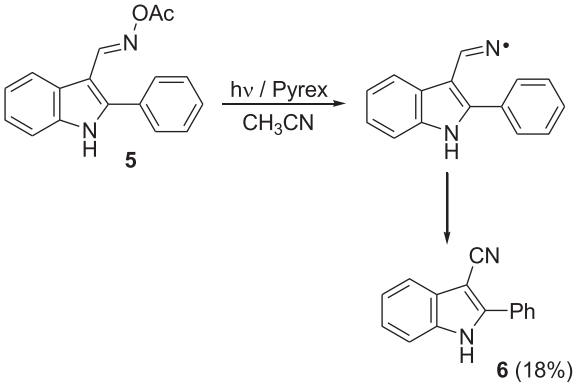


Chart 1.



Scheme 2.



Scheme 3.

compete with the formation of nitrile. This effect may be understood by taking into account the theoretical DFT calculated structures and energies.[5,6] As shown in Fig. 1, according to our calculations, the ring closure from radical **8** must surpass a barrier of 10.2 kcal/mol to reach the transition state **8TS**, while this barrier increases to 14.6 kcal/mol from **7** to **7TS**, which implies a higher reaction rate for the first. The key to explain this barrier energy difference could be found looking at both iminyl radical structures. The five-membered ring places the substituent angles C–C–C at 129.6° and 132.9° and the distance N–C at 2.993 Å, while these values are reduced to 124.1°, 123.9°, and 2.896 Å, respectively, in the six-membered structure. For the sake of comparison, Fig. 1 also shows the calculations for the ring closure onto ethynyl, which led to the formation of isoquinoline **2d** in 64% yield.[2] Although model **9** has an N–C distance of 3.262 Å, our calculations indicate a barrier of 7.2 kcal/mol. Once again, the substituent angles C–C–C are reduced to 122.6° and 122.0°, which supports its significance on the reaction course. Finally, in order to study the influence of some substituents on the reactivity of the intermediate radicals, we carried out

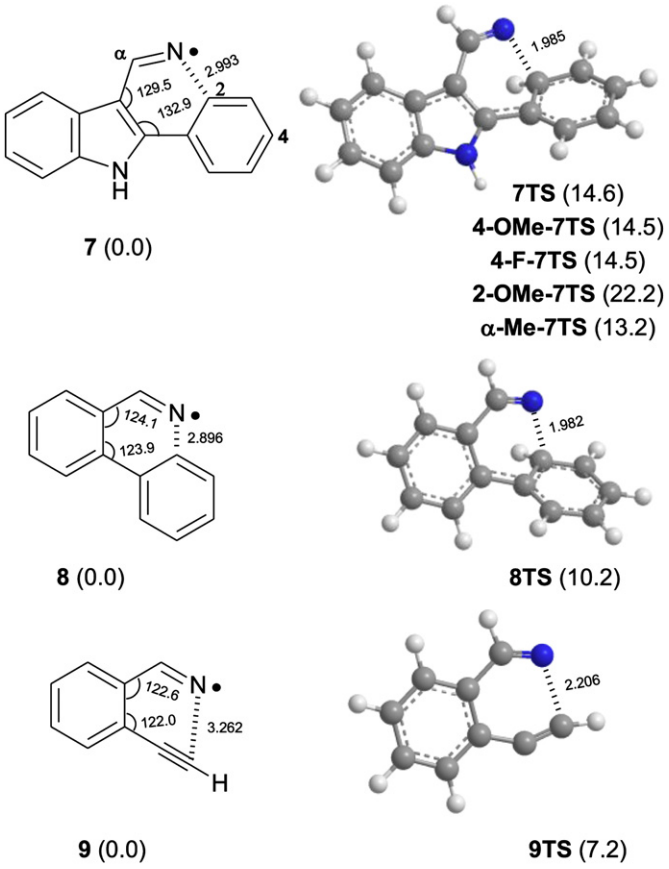
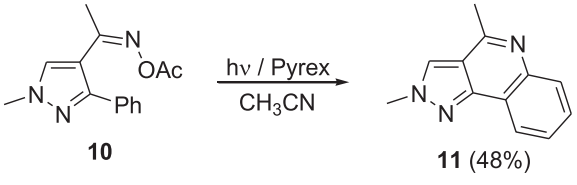


Fig. 1. Calculated structures (parameters in Å and degrees) and relative energies (in brackets, kcal/mol) at the B3PW91/6-31G* level for the cyclization of iminyl radicals.

calculations on structures of **7** substituted by Me, OMe or F. As shown in Fig. 1, the influence of OMe and F on 4 is almost null, while the presence of OMe on 2 increases the energy barrier to 22.2 kcal/mol, probably due to steric hindrance. On the contrary, the presence of Me on α position decreases the energy barrier to 13.2 kcal/mol, which reveals that a methyl group on the iminic carbon not only prevents the formation of nitrile but also favors the cyclization, probably due to electronic effects.

Consistently, the next step was to extend the exploration of the cyclization to acyloximes with a five-membered spacer but bearing a methyl group on the iminic carbon. Thus, more complex acyloxime **10** was synthesized and irradiated, which allowed the preparation of compound **11** in 48% yield (Scheme 4).

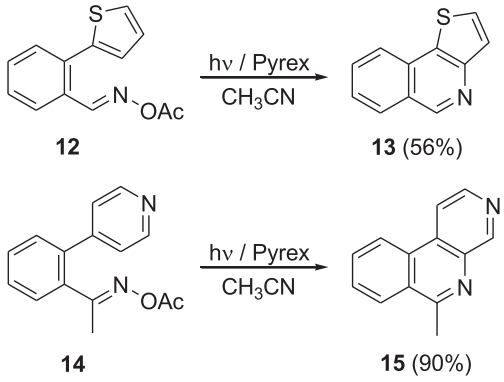


Scheme 4.

2.2. Influence of substitution

We also explored the iminyl radical ring closure onto heteroaromatic rings. The use of a thiophenyl ring as iminyl radical acceptor led to the preparation of thieno[3,2-*c*]isoquinoline **13** in 56% yield (Scheme 5). Next, we planned to use our methodology to the iminyl radical closure onto the pyridine ring. Reports of ring closure of C-centered radicals onto pyridine rings are rare[7] and there are not many examples describing the analog reaction for

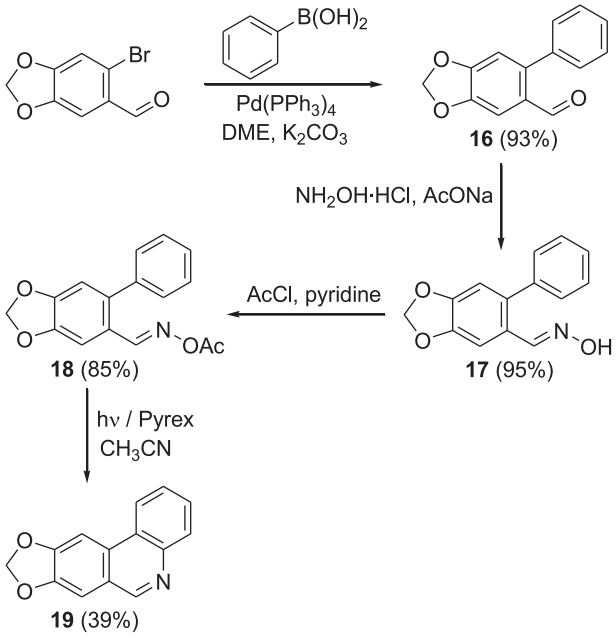
N-centered radicals either.[8] Scheme 5 also shows our result for this process. Iminyl radical, generated from irradiation of **14** in CH_3CN, did cyclize onto pyridine ring, enabling 6-methylbenzo[*c*][1,7] naphthyridine **15** to be prepared in 90% yield.



Scheme 5.

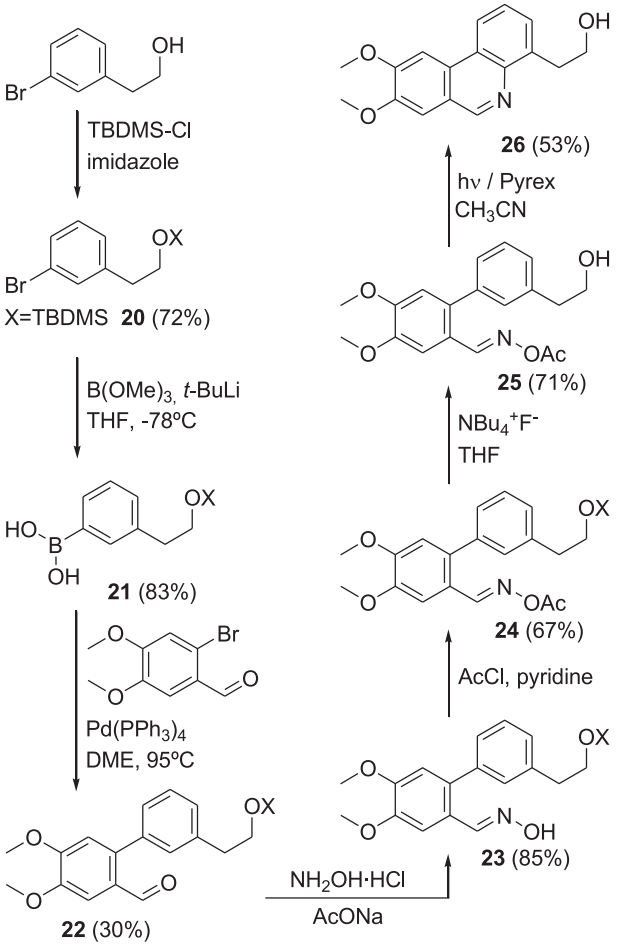
2.3. Application to natural products preparation

The synthesis of some interesting natural products was approached. Alkaloid trisphaeridine **19** was prepared in four steps starting with a Suzuki coupling of commercial 6-bromopiperonal with phenylboronic acid followed by the synthesis of the oxime and acyloxime derivatives. Irradiation of acyloxime **18** allowed the preparation of **19** in 39% yield (Scheme 6).



Scheme 6.

Our methodology was also used for the preparation of the vasconine precursor **26** (Scheme 7). The treatment of **26** with PBr_3 led to vasconine, which can also be used for the preparation of assoanine, oxoassoanine, and pratosine.[9] The hydroxy group of commercial 3-bromophenethyl alcohol was protected by reaction with *tert*-butyl(chloro)dimethylsilane (TBDMS-Cl) and treated with trimethyl borate and *t*-BuLi to obtain the boronic acid **21**. The Suzuki coupling reaction of **21** with 6-bromoveratraldehyde led to aldehyde **22**, therefrom oxime **23** and acyloxime **24** were obtained. Irradiation after deprotection of hydroxy group led to 2-(8,9-dimethoxyphenanthridin-4-yl)ethanol **26** in 53% yield after purification by column chromatography.[10]



Scheme 7.

3. Conclusions

A general framework for the use of ring closure of iminyl radicals, generated by photolysis of acyloximes, as a tool in organic synthesis has been outlined. Iminyl radicals did cyclize onto vinyl, ethynyl, phenyl, thiophenyl and pyridinyl rings. This reaction provides a new, simple, and straightforward method for the preparation of several polycyclic heteroaromatic compounds and has been applied to the synthesis of some natural products.

4. Experimental section

4.1. General

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as internal standard. Melting points are uncorrected. All solvents were purified by standard procedures. Reagents were of commercial grades.

4.2. Typical procedure for the irradiation of acyloximes

The acyloxime (0.6 mmol) was dissolved in dry acetonitrile (60 mL) and irradiated at room temperature under an Ar atmosphere through Pyrex glass with a 400 W medium pressure-mercury lamp

until the acyloxime was consumed (1–3 h, TLC, hexane/AcOEt, 4:1). The solvent was removed with a rotary evaporator and the products were separated by column chromatography (silica gel, hexane/AcOEt).

4.3. Benzo[*i*]phenanthridine (4)[11]

Yield: 76 mg, 55%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=10.25 (s, 1H), 8.95 (d, J=9.0 Hz, 1H), 8.69 (d, J=6 Hz, 1H), 8.64 (d, J=9.0 Hz, 1H), 8.30 (d, J=9.0 Hz, 1H), 8.22 (d, J=9.0 Hz, 1H), 8.05 (d, J=9.0 Hz, 1H), 7.84–7.33 ppm (m, 4H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=147.8, 145.2, 132.1, 132.0, 130.1, 130.0, 129.0, 128.9, 128.8, 128.0, 127.1, 127.1, 124.2, 122.6, 122.1, 121.7, 119.8 ppm; ES (+) m/z: 230 (M+1).

4.4. 2-Phenyl-1*H*-indole-3-carbonitrile (6)[12]

Yield: 24 mg, 18%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=8.86 (s, 1H), 7.93–7.84 (m, 2H), 7.77 (dd, J=6.27, 2.83 Hz, 1H), 7.58–7.43 (m, 4H), 7.32–7.28 ppm (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=144.7, 134.9, 132.6, 129.4, 128.8, 128.7, 128.2, 126.8, 124.4, 122.4, 119.6, 116.8, 111.6 ppm; GC–MS m/z: 218 (M, 100), 190 (24).

4.5. 2,4-Dimethyl-2*H*-pyrazolo[4,3-*c*]quinoline (11)

Yield: 95 mg, 48%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=7.93 (s, 1H), 7.66–7.63 (m, 2H), 7.42–7.40 (m, 2H), 3.95 (s, 3H), 2.31 ppm (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=192.2, 152.6, 135.0, 132.7, 129.2, 128.5, 128.05, 121.3, 39.2, 29.2 ppm; exact mass ($C_{12}H_{11}N_3$+H) calculated 198.1031, measured 198.1026.

4.6. Thieno[3,2-*c*]isoquinoline (13)[13]

Yield: 62 mg, 56%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=9.20 (s, 1H), 8.08 (d, J=8.2 Hz, 2H), 7.78 (t, J=7.6 Hz, 1H), 7.69 (dd, J_1=16.9 Hz, J_2=5.4 Hz, 2H), 7.62 ppm (t, J=7.6 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=151.2, 131.9, 131.2, 129.4, 129.0, 126.8, 126.7, 126.7, 126.4, 125.4, 122.9 ppm; ES (+) m/z: 186 (M+1).

4.7. 6-Methylbenzo[*c*][1,7]naphthyridine (15)

Yield: 105 mg, 90%. Mp: 107–109 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=9.43 (s, 1H), 8.73 (d, J=5.51 Hz, 1H), 8.60 (d, J=8.05 Hz, 1H), 8.26 (d, J=6.32 Hz, 2H), 7.87 (td, J=15.02, 7.23 Hz, 2H), 3.06 ppm (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=160.7, 152.6, 144.9, 138.7, 131.0, 130.4, 129.5, 128.7, 126.7, 126.6, 122.8, 115.1, 23.4 ppm; exact mass ($C_{13}H_{10}N_2$+H) calculated 195.0922, measured 195.0917.

4.8. Trisphaeridine (19)[4c]

Yield: 52 mg, 39%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=9.08 (s, 1H), 8.35 (d, 1H, J=8.2 Hz), 8.14 (d, 1H, J=8.2 Hz), 7.88 (s, 1H), 7.7–7.6 (m, 2H), 7.31 (s, 1H), 6.15 ppm (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=151.8, 151.7, 148.3, 144.0, 130.4, 130.0, 128.2, 126.8, 124.4, 123.2, 122.1, 105.6, 102.1, 100.1 ppm; ES (+) m/z: 224 (M+1).

4.9. 2-(8,9-Dimethoxyphenanthridin-4-yl)ethanol (26)

Yield: 90 mg, 53%. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=9.13 (s, 1H), 8.35 (dd, J=7.91, 1.92 Hz, 1H), 7.91 (s, 1H), 7.6–7.5 (m, 2H), 7.34 (s, 1H), 4.16 (s, 3H), 4.07 (s, 3H), 4.04 (t, J=6.52 Hz, 2H), 3.52 ppm (t, J=6.53 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ=153.5, 150.6, 150.4, 142.8, 140.5, 129.4, 128.9, 126.8, 124.4, 121.8, 120.7, 107.9, 102.3, 64.5, 56.4, 56.3, 37.3 ppm; exact mass ($C_{17}H_{17}NO_3$+H) calculated 284.1287, measured 284.1281.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.09.078. These data include MOL files and InChiKeys of the most important compounds described in this article.

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