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New Light-Induced Iminyl Radical Cyclization Reactions of Acyloximes to Isoquinolines

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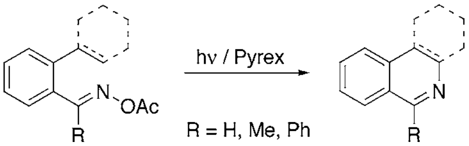
ABSTRACT



An efficient photochemical approach for the unusual generation of six-membered heterocyclic rings is reported. Iminyl radicals, generated by the irradiation of acyloximes, participate in intramolecular cyclization processes and in intermolecular addition–intramolecular cyclization sequences.

The behavior of iminyl radicals generated from *S*-arylimines, oxime benzoates, xanthyl hydrazones, *S*-benzothiazole sulfenylimines, and *N*-benzotriazolimines for the synthesis of diverse pyrrolidine systems has been reported.[1] The reactions can be promoted by both thermal and photochemical methods. More recently, the groups of Zard[2] and Narasaka[3] reported the photochemical radical cyclization of γ,δ-unsaturated ketone oxime derivatives to give 3,4-dihydro-2*H*-pyrroles. Although intramolecular cyclization between an iminyl radical and an olefin seems an attractive strategy to construct nitrogen heterocycles, as far as we know, these photochemical processes have not been utilized in the preparation of six-membered heterocyclic rings. In this letter, we report our results from investigations in this area.

In the context of our studies on the photochemistry of compounds containing a carbon−nitrogen double bond,[4] we focused our attention on acyloximes. Acyloximes can be used as photoinitiators for UV-curable coatings.[5] When they are irradiated, nitrogen−oxygen bond cleavage occurs, and this initiates the polymerization process.[6] The simplicity of the iminyl radical formation prompted us to investigate the ability of these systems to generate six-membered heterocyclic rings.

We started our investigation of the reaction conditions by irradiating a solution of 2-phenylbenzaldehyde *O*-acetyloxime[7] (**1**, 0.5 mmol) in 50 mL of hexane, with a 400 W mercury lamp through Pyrex, under an Ar atmosphere, until the acetyloxime was consumed. After the usual workup procedure, we isolated the desired six-membered ring

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[1] For a review, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543.

[2] Gagosz, F.; Zard, S. *Synlett* **1999**, 1978.

[3] (a) Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron* **1999**, *55*, 8915. (b) Mikami, T.; Narasaka, K. *Chem. Lett.* **2000**, 338. (c) Kitamura, M.; Mori, Y.; Narasaka, K. *Tetrahedron Lett.* **2005**, *46*, 2373.

[4] See, for example: (a) Ortega, M.; Rodríguez, M. A.; Campos, P. J. *Tetrahedron* **2005**, *61*, 11686. (b) Soldevilla, A.; Sampedro, D.; Campos, P. J.; Rodríguez, M. A. *J. Org. Chem.* **2005**, *70*, 6976. (c) Sampedro, D.; Caro, M.; Campos, P. J.; Rodríguez, M. A. *J. Org. Chem.* **2005**, *70*, 6705. (d) Sampedro, D.; Soldevilla, A.; Rodríguez, M. A.; Campos, P. J.; Olivucci, M. *J. Am. Chem. Soc.* **2005**, *127*, 441.

[5] For reviews on photoinitiated polymerization, see: (a) Fouassier, J. P. *Photoinitiation, Photopolymerization and Photocuring: Fundamentals and Applications*; Carl Hanser Verlag: Munich, 1995. (b) Roffey, C. G. *Photogeneration of Reactive Species for UV Curing*; J. Wiley: New York, 1997. (c) Neckers, D. C.; Jager, W. *Photoinitiation for Polymerization: UV & EB at the Millenium*, Sita Series in Surface Coatings Technology 7; J. Wiley: New York, 1999. (d) *Photoinitiated Polymerization*; ACS Symposium Series 847, Belfield, K. D., Crivello, J. V., Eds.; American Chemical Society: Washington, DC, 2003.

[6] Okada, T.; Kawanisi, M.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1969**, *42*, 2981.

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phenanthridine (**2**) in 19% yield.[8] In addition to **2**, nitrile **3** (47%) was also obtained (Scheme 1). The yields of **2** and **3** were dependent on the solvent employed (Table 1, entries 1−5). The use of *tert*-butyl alcohol afforded the highest yield of **2** (58%, entry 5).

Scheme 1

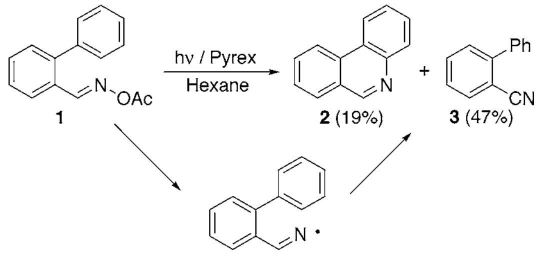
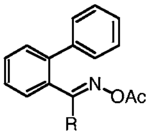
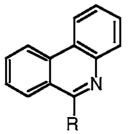


Table 1. Synthesis of Phenanthridines by Irradiation of *O*-Acyloximes

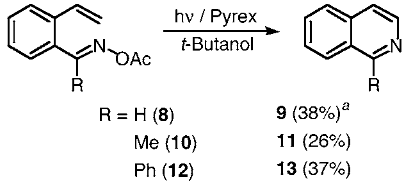
entry	solvent		yield (%)[a] 	yield (%)[a] **3**
1	hexane	R = H (**1**)	19 (**2**)	47
2	Et_2O	**1**	14 (**2**)	42
3	acetonitrile	**1**	38 (**2**)	25
4	2-propanol	**1**	25 (**2**)	8
5	*t*-butanol	**1**	58 (**2**)	28
6	*t*-butanol	R = Me (**4**)	91 (**5**)	---
7	*t*-butanol	R = Ph (**6**)	40 (**7**)	---

[a] Yields of isolated product.

We also explored the effect on the yield of the reaction of ketone *O*-acyloximes. Irradiation of 2-phenylacetophenone or 2-phenylbenzophenone *O*-acetyloxime in *tert*-butyl alcohol gave the corresponding phenanthridine in 91 and 40% yield, respectively (Table 1, entries 6 and 7).

We subsequently focused our attention on evaluating the participation of unsaturated systems other than phenyl. We assayed the irradiation of 2-vinylbenzaldehyde *O*-acetyloximes. As indicated in Scheme 2, irradiation of compounds bearing a carbon−carbon double bond (**8**, **10**, and **12**) is useful for the preparation of six-membered heterocyclic compounds.[8]

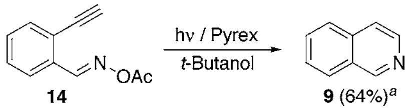
Scheme 2



[a] The corresponding nitrile was obtained in 2% yield.

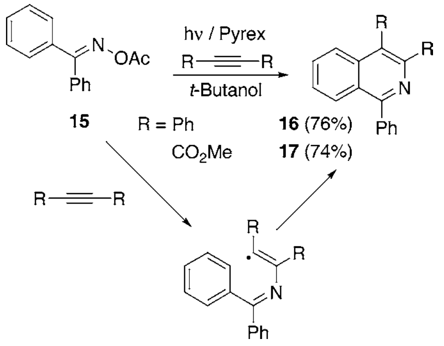
The same approach was employed in the irradiation of 2-ethynylbenzaldehyde *O*-acetyloxime (**14**). The reaction led to the formation of isoquinoline in 64% yield (Scheme 3).[9]

Scheme 3



We also investigated the intermolecular attack of the iminyl radical on a carbon−carbon triple bond. We chose benzophenone *O*-acetyloxime (**15**) as the starting material because, after an initial addition reaction, one of the phenyl groups could sequentially participate in an annulation process. Irradiation was initially performed in the presence of tolane. As shown in Scheme 4, a tandem (cascade) intermolecular addition/intramolecular cyclization took place, with isoquinoline **16** formed in 76% yield. This reaction sequence was also applied to dimethyl acetylenedicarboxylate, which led to the formation of **17**.

Scheme 4



In summary, we have developed an efficient photochemical approach for the unusual generation of six-membered heterocyclic rings from iminyl radicals, generated from acyloximes, through intramolecular cyclization or intermo-

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(7) 2-Phenylbenzaldehyde oxime, prepared according to Cullen, K. E.; Sharp, J. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2961, was used as precursor.

(8) The addition of nitrogen-centered radical should form an azacyclohexadienyl radical, from which a hydrogen atom may be abstracted by another radical to gain aromaticity: Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell: Oxford, 2000; p 68.

(9) The addition of nitrogen-centered radical should generate an isoquinolyl radical, which may evolve by hydrogen atom abstraction since the use of 2-propanol-d_7 as solvent led to 4-deuteroisoquinoline, while the use of methanol-d_1 led to nondeuterated isoquinoline.

lecular addition/intramolecular cyclization sequences. A systematic and extensive study of the scope and limitations of this process is currently under investigation in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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