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Tandem Radical Addition and Cyclization of ϵ-Substituted δ-Yne Ketimines†

Marta Fernández and Ricardo Alonso*

Departamento de Química Orgánica y Unidad Asociada al CSIC,
Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

qoraa@usc.es

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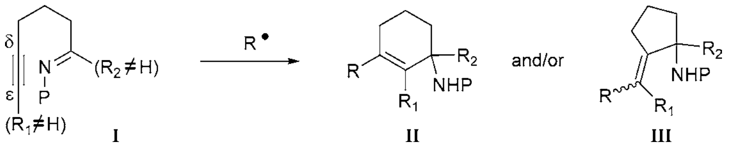
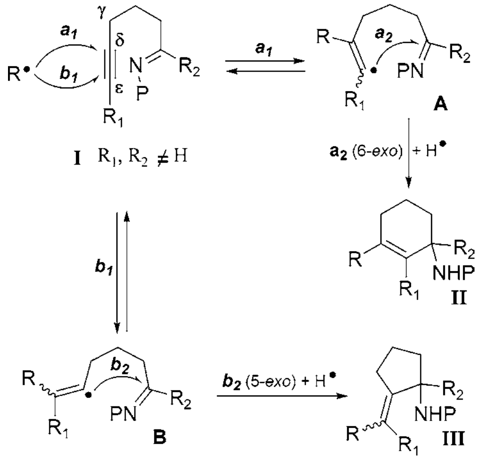
ABSTRACT



The first one-step conversions of ketimines I into cyclized allylamine derivatives of types II and III are reported.

Nitrogen-containing compounds are part of the basis of life and are one of the main classes of pharmacologically active agents. The development of new methods for their preparation is one of the main goals of synthetic organic chemistry. As the result of research in this field over the past 2 decades, the addition of radicals to C═N bonds has become a reliable procedure that is used in a growing number of syntheses of nitrogenated compounds.[1−3] However, the full synthetic potential of this reaction, especially its potential for preparing nitrogenated quaternary centers, i.e., the addition outcome when using ketimine derivatives as radical acceptors,[4] remains unrealized. In particular, it has not hitherto been clear whether systems such as **I** (R_1 and $R_2 \neq$ H, Scheme 1) could undergo tandem radical addition and cyclization sequences[5] such as those that would lead to compounds of types **II** and **III** (Scheme 1) or whether, if so, the reaction outcome could be controlled.

Scheme 1



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† Dedicated to Prof. Rafael Suau Suárez.

(1) Reviews: (a) Free Radical Cyclizations Involving Nitrogen. Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543; includes a compilation of cyclization and ring-opening rate constants for some representative cases. (b) Martínez-Grau, A.; Marco-Contelles, J. *Chem. Soc. Rev.* **1998**, *27*, 155. (c) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (d) Kim, S.; Joon, J.-Y. Novel Radical Traps. In *Radicals in Organic Synthesis*, 1st ed.; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim; New York, 2001; Vol. 2, Chapter 1. (e) Bertrand, M.; Feray, L.; Gastaldi, S. *C. R. Chimie* **2002**, *5*, 623. (f) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, *7*, 1140.

(2) Selected recent examples of the radical addition onto imine derivatives of aldehydes include the following. (i) Intramolecular: (a) Friestad, G. K.; Massari, S. E. *J. Org. Chem.* **2004**, *69*, 863. (ii) Intermolecular: (b) Halland, N.; Jorgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, *11*, 1290. (c) Friestad, G. K.; Shen, Y.; Ruggles, E. L. *Angew. Chem. Int. Ed.* **2003**, *42*, 5061. (d) Fernandez, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461. (e) Singh, N.; Anand, R. D.; Trehan, S. *Tetrahedron Lett.* **2004**, *45*, 2911. (f) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *69*, 1531.

(3) Although most examples apply to the addition to the C atom of the C═N bond, intramolecular carbon-radical addition to the nitrogen of an azomethine is also known and synthetically useful; see: (a) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163 and references therein.

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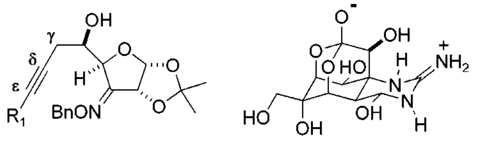
To study this issue we initially used compound **Ia**,[6] a choice dictated by our interest in the total synthesis of tetrodotoxin (**1**,[7] Figure 1) and other targets with nitrogenated quaternary centers.[8] However, our attempts to cyclize **Ia** using $Ph_3Sn^{\bullet}$ or $PhS^{\bullet}$ radicals (Ph_3SnH/Et_3B, Ph_3SnH/AIBN, PhSH/AIBN, or PhSH/300 W tungsten sunlamp) all met with failure, **Ia** remaining essentially unaltered.



Ia R_1 = $CH(OEt)_2$
Ib R_1 = CO_2Me
Ic R_1 = Ph

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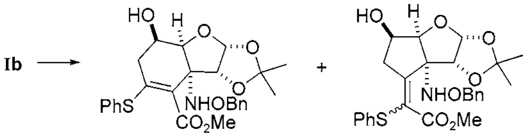
Figure 1. Structures of the γ-alkynyl ketimine derivatives of type **I** selected for this study and of natural tetrodotoxin (**1**).

We then prepared **Ib**, which bears a methoxycarbonyl group as the R_1 alkynyl substituent instead of the diethoxymethyl unit present in **Ia** (Figure 1). Although triphenyltin radicals generated with Et_3B or AIBN were again unable to induce any reaction (Table 1, entries 1 and 2), the phenylthiyl radical did promote reaction under otherwise similar conditions (AIBN, refluxing toluene; see Table 1, entry 3) to give a mixture of the cyclized amine derivatives **IIb** and **IIIb**. Formation of these products could be explained according to the tandem processes outlined in Scheme 1; specifically, addition of $PhS^{\bullet}$ to the δ-carbon of **Ib** (path $\boldsymbol{a_1}$), followed by 6-*exo* cyclization of the resulting type **A** vinyl radical would have given **IIb**, whereas **IIIb** would have been formed by addition of the $PhS^{\bullet}$ radical to the ϵ-carbon (path $\boldsymbol{b_1}$) and subsequent 5-*exo* cyclization of the intermediate type **B** radical.

Table 1. Reactivity of γ-Alkynyl Ketoxime Ether Derivative **Ib** with Ph_3SnH and PhSH under Radical-Forming Conditions[a]



IIb **IIIb**

entry	radical generation system RH/initiator/energy source (equivalents, RH add. time)	solvent[b] [M][c]	time (h)	**IIb** %[e] (%)[f]	**IIIb** %[d] (%)[f]
1	$Ph_3SnH/Et_3B/\Delta^g$ (2.6 equiv, 1 equiv, 2.5 h)	PhMe [0.015]	14		
2	$Ph_3SnH/AIBN^h/\Delta^g$ (1.5 equiv, 2 equiv, 3.5 h)	PhMe [0.015]	14		
3	$PhSH/AIBN^h/\Delta^g$ (1.3 equiv, 0.2 equiv, 3.5 h)	PhMe [0.08]	9.5	14 (18)	41 (52)
4	$PhSH^i/AIBN^h/sunlamp^{j,k}$ (0.6 equiv + 0.6 equiv, 0.6 equiv)	PhMe [0.08]	19	11 (26)	29 (68)
5	$PhSH^i$/450-W Hg lamp^{k,l} (1.1 equiv + 0.4 equiv)	PhH [0.04]	6	24^m	20^m
6	PhSH/450-W Hg lamp^{k,l} (1.1 equiv)	PhH [0.02]	3	16^m (21)	12^m (16)

[a] For a procedure for the thermally induced tandem addition−cyclization of **Ib**, entry 3, see Supporting Information. [b] Except for entry 1, the solvent was deoxygenated by bubbling argon for 10 min. [c] Molar concentration of the substrate. [d] Compound **IIIb** was obtained as an approximately 1:1 mixture of geometric isomers. [e] Isolated yields. [f] Isolated yields corrected for recovered **Ib** (21%, 58%, and 23% for entries 3, 4, and 6, respectively). [g] The reaction was carried out in refluxing solvent. [h] AIBN was added portionwise throughout the reaction to ensure continuous radical initiation. [i] PhSH was added in two portions, the second (0.6 equiv for entry 4, 0.4 equiv for entry 5) after a reaction period of 16 h (entry 4) or 4 h (entry 5). [j] A 300-W tungsten-filament sunlamp and Pyrex reaction flasks were employed. [k] Temperature was maintained below 40 °C. [l] A 450-W medium-pressure Hg UV lamp and Pyrex reaction vessels were employed. [m] An insoluble orange solid, the identity of which remains undetermined, was formed during the irradiation.

Light-induced initiation (300-W tungsten sunlamp, $T <$ 40 °C) also proved effective though slower, achieving 40% conversion of **Ib** into **IIb** and **IIIb** after 19 h of irradiation versus 55% after 9.5 h in refluxing toluene when recovered **Ib** is not taken into account (Table 1, entries 4 and 3, respectively).

UV light (450-W medium-pressure mercury lamp) accelerated the reaction rate, so that **Ib** was completely consumed within 6 h, but reduced the combined yields of **IIb** and **IIIb** to 44% (Table 1, entry 5), a result that was undoubtedly related to the formation of an orange solid that precipitated from the reaction mixture.[9] Halving both the irradiation time and the initial molar concentration of **Ib** and adding 1.1 equiv of PhSH all in one portion at the beginning

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(4) Although more difficult and by far less developed than for aldimines, the radical addition onto ketimine derivatives is also useful; examples include the following. (i) Intramolecular: (a) Noya, B.; Alonso, R. *Tetrahedron Lett.* **1997**, *38*, 2745. (b) Noya, B.; Paredes, M. D.; Ozores, L.; Alonso, R. *J. Org. Chem.* **2000**, *65*, 5960 and references therein. (ii) Intermolecular: (c) Torrente, S.; Alonso, R. *Org. Lett.* **2001**, *3*, 1985 and references therein.

(5) For a review on *Heteroatom Radical Addition-Cyclization and its Synthetic Application*, see: Naito, T. *Heterocycles* **1999**, *50*, 505. For a recent example involving a C═N radical-cyclization step, see: Friestad, G. K.; Jiang, T.; Fioroni, G. M. *Tetrahedron*: *Asymmetry* **2003**, *14*, 2853.

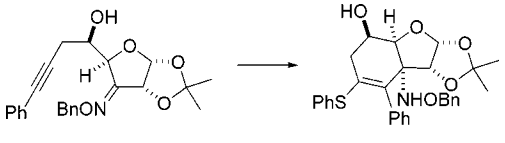
(6) Synthesis of the radical cyclization precursors, the γ-alkynyl ketoxime ethers **Ia**−**c**, will be described in a forthcoming full paper. They were fully characterized (^{1}H NMR, ^{13}C NMR, DEPT, and MS).

(7) For synthetic studies on tetrodotoxin, see: (a) Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772. (b) Ohyabu, N.; Nishikawa, T.; Isobe, M. *J. Am. Chem. Soc.* **2003**, *125*, 8798. (c) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (d) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782 and references therein.

(8) Other targets, besides tetrodotoxin (ref 7), having nitrogenated quaternary centers include the following. (−)-Huperzine A: (a) Yamada, F.; Kozikowski, A. P.; Reddy, E. R.; Pang, Y.; Miller, J. H.; McKinney, M. *J. Am. Chem. Soc.* **1991**, *113*, 4695. (−)-Cephalotaxine: (b) Isono, N.; Mori, M. *J. Org. Chem.* **1995**, *60*, 115. Immunosuppressant FR901483: (c) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442. (+)-Halichlorine: (d) Trauner, D.; Schwarz, J. B. Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (e) Wright, D. L.; Schulte J. P., II; Page, M. A. *Org. Lett.* **2000**, *13*, 1847. Lactacystin: (i) Donohoe, T. J.; Sintim, H. O.; Sisangia, L.; Harling, J. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2293. Myriocin: (j) Lee, K.-Y.; Oh, C.-Y.; Kim, Y.-H.; Joo, J.-E.; Ham, W.-H. *Tetrahedron Lett.* **2002**, *43*, 9361.

(9) The identity of the orange solid formed when **Ib** is irradiated with a 450-W medium-pressure Hg Hanovia UV lamp in the presence of PhSH remains undetermined.

Table 2. Reactivity of γ-Alkynyl Ketoxime Ether Derivative **Ic** with PhSH under Radical-Forming Conditions[a]



Ic **IIc**

entry	PhSH/ AIBN[b] equiv	initiator	additives	solvent[c] [M][d]	reaction time (h)	**IIc** (%)[e,f]
1	1.3[h]/0.1	Δ^{i}		PhMe [0.08]	9	50
2	1.28[h]/0.45	300 W		PhMe [0.075]	7.5	45–54
3	1.5/0.3	300 W	*p*-TsOH [0.2 equiv]	PhMe [0.08]	9	36
4	1.8/0.45	300 W	$MgBr_2$ [0.4 equiv]	PhMe [0.08]	15.5	45
5	1.45/-	$h\nu^{j,k}$		PhH [0.045]	2	63[g]
6	1.05/-	$h\nu^{j,k}$		PhH [0.02]	3	75[g]
7	1.28[e]/0.1	Δ^{i}		*o*-xylene [0.077]	5.5	38[l]
8	2.1/0.66	)))[m,n]		PhMe [0.036]	9.5	61

[a] For a procedure for the photochemically induced tandem addition–cyclization of **Ic**, entry 6, see Supporting Information. [b] AIBN was added portionwise throughout the reaction to ensure continuous radical initiation. [c] The solvent was deoxygenated by bubbling argon for 10–20 min. [d] Molar concentration of **Ic**. [e] Isolated yields. [f] Besides **IIc**, several other minor spots were visualized on TLC plates in almost all cases, but they were not isolated or identified. [g] See ref 13. [h] PhSH was added either slowly via syringe (entry 1, 3.5 h) or in three portions (entry 2). [i] The reaction was carried out in refluxing solvent. [j] A 450-W medium-pressure Hanovia Hg UV lamp and Pyrex reaction vessels were employed. [k] Temperature was maintained below 40 °C. [l] Starting **Ic** was partially recovered (24%) [m] The reaction mixture was sonicated by introducing the reaction flask into an ultrasound water bath. [n] No reaction took place in the absence of AIBN.

of the reaction failed to improve matters (Table 1, entry 6 and footnote f): the formation of the orange solid was not avoided and the total yield of **IIb** + **IIIb** + recovered **Ib** (23%) was only 51%, compared to 76% for the thermally promoted reaction and 98% when a sunlamp was used.

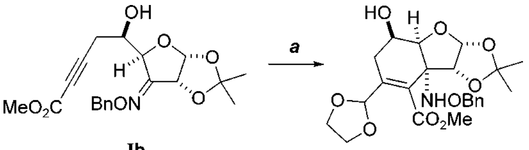
Having found that **I** does indeed undergo synthetically useful tandem processes under appropriate conditions (R_1 = CO_2Me, $R^\bullet$ = $PhS^\bullet$, AIBN, Δ or sunlamp), we next considered whether modification of structural factors, specifically the nature of R_1 and $R^\bullet$, might allow control over whether the major product was **II** or, as hitherto (Table 1, entries 3 and 4),[10] **III**. When compound **Ic**, in which R_1 is a phenyl (Figure 1), was treated with PhSH (1.3 equiv) and AIBN (0.1 equiv) in refluxing toluene, the major product was, as hoped, the cyclohexenylamine derivative **IIc**[11] (yield 50%) instead of the corresponding cyclopentylamine **III** (Table 2, entry 1).

In this case, sunlamp irradiation was as effective as thermal initiation in terms of yield and reaction time (Table 2, entries 1 and 2). The efficiency of sunlamp initiation was not improved by the addition of either a protic acid (*p*-TsOH, 0.2 equiv, entry 3) or a Lewis acid ($MgBr_2$, 0.4 equiv, entry 4),[12] but irradiation with a 450-W medium-pressure mercury lamp using a lower concentration of **Ic** (0.045 M) afforded a 63% yield of **IIc** (Table 2, entry 5). As expected, running the reaction at even lower **Ic** concentration (0.02 M) reduced the amount of **C** (12%) in favor of **IIc** (75%, Table 2, entry 6).[13]

Other attempts at increasing the yield of the reaction included thermal initiation at higher temperatures in *o*-xylene (Table 2, entry 7), which afforded a corrected yield of 51% of **IIc**, and the use of ultrasound as the initiation energy source, which was slower but almost as effective as the mercury lamp (Table 2, cf. entries 8 and 5).

Finally, to evaluate the effect of the nature of $R^\bullet$ on the process, we decided to replace the electrophile-centered $PhS^\bullet$ for the nucleophile-centered 1,3-dioxolan-2-yl radical. When this radical was generated in the presence of **Ib** by UV irradiation of a solution of **Ib** and benzophenone (1 equiv) in 1,3-dioxolane, the only cyclized product isolated was compound **3** (65%, Scheme 2).

Scheme 2



Ib **3** (65%)

a. 1,3-dioxolane, Ph_2CO (1 eq), hν (450 W medium-pressure Hg lamp), PYREX® vessel; for details see the Supporting Information.

Summing up, we have shown that ϵ-substituted δ-yne ketimine derivatives can undergo tandem radical addition and cyclization reactions that result in the formation of

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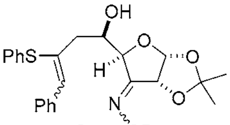
(10) Although the final yield of **IIb** is greater than that of **IIIb** in entries 5 and 6 of Table 1, we believe that **IIIb** is still the major cyclization product but, unlike **IIb**, is converted into the above-mentioned orange solid under the reaction conditions of entries 5 and 6 (450-W UV lamp). That **IIb** is stable under these conditions is suggested by its corrected yield (24% or 21%) being very similar to those obtained under the conditions of entries 3 and 4.

(11) Compound **IIc** could be crystallized and its structure confirmed by X-ray crystallography. See Supporting Information for details.

(12) Protic and Lewis acids were previously shown to favor the radical addition to ketoxime ethers; see for example ref 4c.

(13) Cyclization of **Ic** under UV irradiation (Table 2, entries 5 and 6) was clean enough to allow the isolation of side-product **C**, two chromatographic fractions, four diastereoisomers, tentative structural assignment by ^1H NMR and MS; 20% and 12% for entries 5 and 6, respectively. See Supporting Information.



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cyclized allylamine derivatives. The terminal alkyne and the attacking radical R$^\bullet$ greatly influence the reaction course. In light of established knowledge in the area, it is clear that a wide variety of cyclic allylamine derivatives could be obtained through similar tandem reactions by varying the C═N radical acceptor, the chain connecting the alkyne and C═N, and/or the reaction initiating free radical R$^\bullet$. It should also be stressed that because of their radical character and the diversity of possible reaction conditions (Δ, $h\nu$, ultrasound), these processes can be expected to proceed in the presence of a wide range of functional and protecting groups and hence are well suited for the synthesis of highly functionalized compounds such as those illustrated here.

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Supporting Information Available: Procedures for the thermal and light-induced tandem radical addition and cyclization of **Ib** and **Ic** and characterization data for the resulting allylamine derivatives, including crystallographic data for **IIc** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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