Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 3909–3912

Sequenced cyclizations involving intramolecular capture of alkyl-oxyaminyl radicals. Synthesis of heterocyclic compounds

Luz Marina Jaramillo-Gómez,[a,*] Alix Elena Loaiza,[a] Jaime Martin,[b] Luz Amalia Ríos[c] and Peng George Wang[d]

[a]*Departamento de Química, Universidad del Valle, Apartado 25360, Cali, Colombia*
[b]*Departamento de Química, Universidad del Cauca, Popayán, Colombia*
[c]*Departamento de Química, Universidad de Caldas, Manizales, Colombia*
[d]*Department of Chemistry, Ohio State University, Columbus, OH 43210, USA*

Received 10 March 2006; revised 23 March 2006; accepted 27 March 2006
Available online 27 April 2006

Abstract—A cascade radical cyclization process involving oxime ethers tethered to a brominated phenyl and an activated olefin moiety is described. The generated aryl radicals using tri-*n*-butyltin hydride react with the C=N bond to yield neutral alkyl-oxyaminyl radicals, which were then simultaneously captured by the activated double bond to provide heterocyclic systems with a pyrrolidinic nucleus.

Cascade radical reactions have become a powerful tool to synthesize polycyclic frameworks, since they allow the efficient construction of a number of bonds in a single reaction.[1] Although most of the efforts in this area have focused on carbon centered radicals, nitrogen radicals have attracted attention because they provide access to a variety of important heterocyclic systems.[2] Several methods have been reported for the generation and capture of nitrogen centered radicals, for example, neutral dialkylaminyl radicals ($R_1R_2N^{\bullet}$), for the synthesis of alkaloids and related heterocycles.[3] In contrast, no reports involving the trapping of neutral alkyl-oxyaminyl radicals [$(R_1)(R_2O)N^{\bullet}$] have been published, although alkoxyaminium radical cations [$(R_1)(R_2O)$-$(H)N^{\bullet+}$] have been generated by direct anodic oxidation of δ-alkenylmethoxy hydroxilamines and cyclized on olefin moieties.[4] Neutral alkyl-oxyaminyl radicals are generated via the reductive intermolecular or intramolecular addition of carbon radicals to the C=N bond of oxime ethers, which allows to anticipate their eventual capture by other functionalities (e.g., double bonds). Oxime ethers are easily prepared and relatively stable compounds compared to imines. Important applications of radical cyclizations onto carbon–nitrogen π bonds (C=N), including the oxime ethers has been well documented.[5] Besides, the cyclization rates for *O*-benzyl oximes ($k_{c(5\text{-}exo)} = 4.2 \times 10^7\ s^{-1}$ and $k_{c(6\text{-}exo)} = 2.4 \times 10^6\ s^{-1}$) are two orders of magnitude higher[6] than the analogous cyclization rates of alkenyl radicals,[7] indicating the excellent ability of the oxime ether function to act as an acceptor of alkyl radicals.

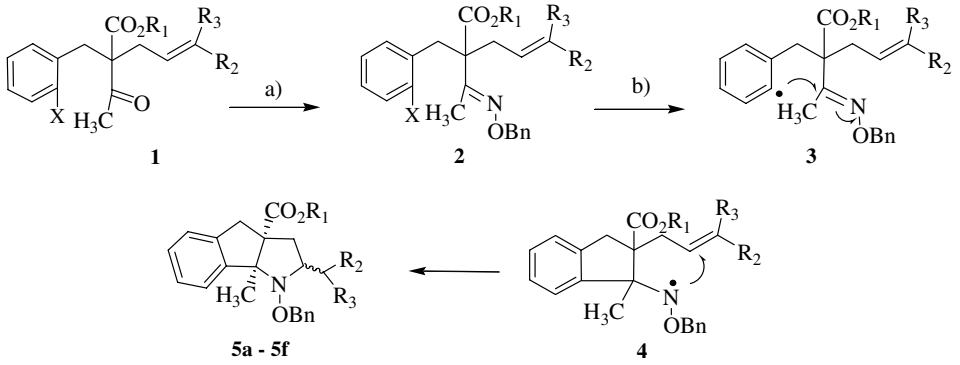
Although the kinetic constants for the intramolecular addition of vinyl[8] and aryl[9] radicals to oxime ethers have not been reported, high cyclization constants could be expected.

Based on these precedents we carried out two sequenced cyclizations on the oxime ethers **2** bearing a suitably placed alkenyl moiety. The reaction started with the formation of aryl radicals **3** which added to the electrophilic carbon C=N–OR. Our main objective was the capture of the generated neutral alkyl-oxyaminyl radical **4** by the double bond, before its reduction by Bu_3SnH, in a tandem process, which would lead to the construction of tricyclic systems **5** (Scheme 1).

Each precursor of the synthesis started from ethyl or methyl acetoacetate, which were dialkylated with 2-bromo or 2-iodobenzylbromide and allyl bromides,

Keywords: Trapping of alkyl-oxyaminyl radicals; Cascade radical cyclizations; Synthesis of *N*-heterocyclic compounds.
* Corresponding author. Tel.: +57 2 321 21 48; fax: +57 2 339 24 40; e-mail addresses: luzmaja@univalle.edu.co; luzmaja@usa.net

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.03.161



X = Br, R_1 = Et: **2a** $R_2 = CO_2Me$, R_3 = H; **2b** R_2 = CN; R_3 = H; **2d** R_2 = Ph; R_3 = H; **2e**; $R_1 = R_2$ = Me; **2f** $R_2 = R_3$ = H **X** = I, R_1 = Me: **2c** R_2 = Ph, R_3 = H

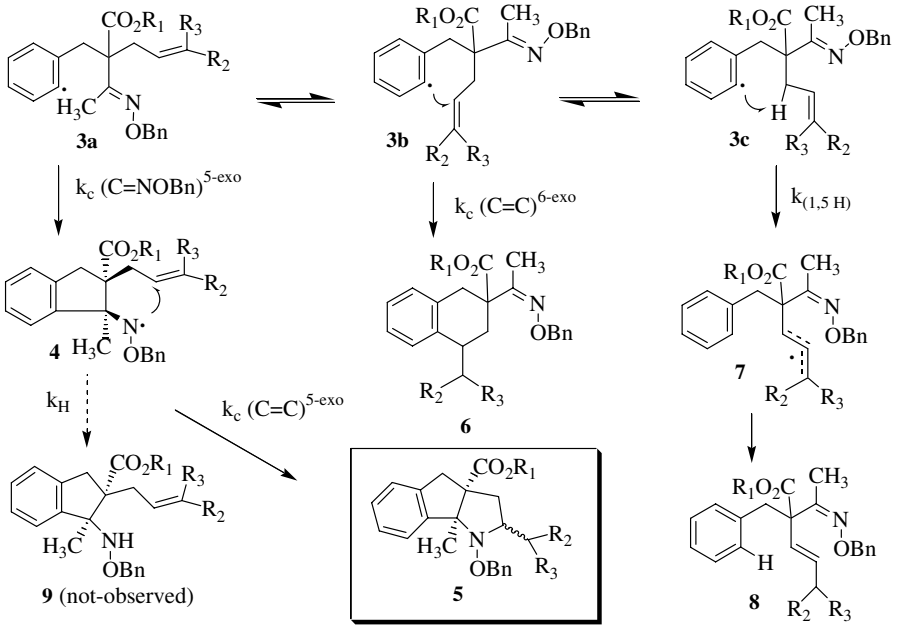
Scheme 1. Reagents and conditions: (a) $HCl{\cdot}H_2NOBn$, pyridine/MeOH, 50 °C; (b) Bu_3SnH, AIBN, Cy, 80 °C or Bu_3SnH, Et_3B/O_2, Cy, rt.

yielding dialkyl oxo-esters **1**. The reaction of these oxo-esters with *O*-benzyl hydroxylamine hydrochloride in the presence of pyridine produced the required oxime ether derivatives **2**.

The sequential radical cyclization was carried on the oxime ethers **2** with Bu_3SnH and AIBN in cyclohexane, under argon, and the mixture stirred at 80 °C for 6–8 h.[10] Comparable yields were obtained when the cyclization was carried out at room temperature using Et_3B/O_2 as initiator.

Quantitative conversion of the starting materials into several compounds was observed. The expected tricyclic products **5** were distinguished from the ^1H NMR spectra of the crude mixtures as a 1:1 diastereomeric mixture along with two side products **6** and **8** (Scheme 2). Products **5a**–**e**, **6a**,**c**,**d**, and **8a**,**b**,**d**–**f** were purified by column chromatography and their structures characterized by NMR and HRMS.[10,11] Products **5f**, **6b**,**f**, and **8c** could not be isolated and then were detected and quantified from the ^1H NMR of the crude mixture. The approximate yields shown in Table 1 were calculated by integrating the benzyloxy methylene signals in the ^1H NMR spectra of the crude mixtures after KF workup.

As shown in Table 1, the tricyclic products **5** were formed predominantly in the case of olefins bearing an electron withdrawing group. Whereas, in the case of the precursor **2e** with an olefin bearing an electron releasing substituent, both tricyclic compound **5e** and isomerization product **8e** were obtained in almost equal amounts. With the precursor **2f**, containing a terminal double bond, the reduced open chain compound **8f** was obtained as major product (40%), while the expected compound **5f** was only afforded in 8% yield.



Scheme 2.

Table 1. Radical cyclization of oximes **2a–f**

Oxime	R_2	R_3	Initiator	% **5**	% **6**	% **8**
2a	CO_2Me	H	AIBN	60	10	15
			Et_3B	58	9	18
2b	CN	H	AIBN	52	13	20
			Et_3B	46	11	16
2c	Ph	H	AIBN	42	11	8
2d	Ph	H	AIBN	36	10	6
			Et_3B	40	9	10
2e	Me	Me	AIBN	24	13	19
			Et_3B	22	7	18
2f	H	H	AIBN	8	6	40

Scheme 2 depicts the different pathways followed by three rotamers or conformers (**3a**,**b**, and **3c**) of the aryl radical, which led to the formation of products **5**, **6**, and **8**. Side products **8a–f** were formed via a favored intramolecular 1,5-hydrogen atom transfer followed by olefin isomerization and the monocyclized products **6a–f** were formed by 6-*exo* ring closure of the aryl radical on the C=C double bond. No clear evidences of compound **9**, which would be generated from reduction of the intermediates *alkyl-oxyaminyl radicals* **4**, were found in any of the tested systems during this work.

It is important to note that in spite of the side reactions, the expected bicyclization was significant in four of the tested systems, which suggests that the first cyclization of the aryl radical **3** onto the oxime, takes place at a higher rate than the other routes. Aryl radicals display higher reactivity than primary alkyl radicals toward 5-*exo* closures on C=C double bonds,[12] and a similar effect could be expected for aryl radicals through intramolecular addition to the oxime ether moiety. As a consequence, this event predominates over the 1,5-hydrogen transfer and 6-*exo*-cyclization processes whose respective rate constants 1.2×10^9 and 6.5×10^8 were calculated by Curran and Fairweather[13] in allyl 2-iodobenzyl malonate systems.

In summary, a methodology for the intramolecular capture of neutral alkyl-oxyaminyl radicals by alkenes has been described for the first time. The best results were obtained with precursors containing olefins substituted with electron withdrawing groups, suggesting a nucleophilic nature of the alkyl-oxyaminyl radicals. Current work is focused on improving the efficiency of this process and the exploration of the scopes of this novel bicyclization methodology for the synthesis of analogous or intermediates of natural products with pharmacological potential.

Acknowledgements

We thank COLCIENCIAS–(Bogotá-Colombia), for the financial support through the project 1106-05-10108, Universidad del Valle (Colombia). This work was supported in part by NSF (CH-0316806) to P.G.W.

References and notes

1. (a) Mc Carroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224–2248; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136; (c) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206; (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177–194; (e) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306.
2. (a) Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885–2902; (b) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747–2762.
3. (a) Guindon, I.; Guérin, B.; Landry, S. R. *Org. Lett.* **2001**, *3*, 2293–2296; (b) Senboku, H.; Hasegawz, H.; Orito, K.; Tokuda, M. *Heterocycles* **1999**, *50*, 333–340; (c) Maxwell, B. J.; Tsanaksidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276–4283; (d) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron* **1996**, *52*, 11445–11462; (e) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275–1294; Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 777–778; (f) Esker, J. L.; Newcomb, M. *Adv. Het. Chem.* **1993**, *58*, 1–45.
4. (a) Tokuda, M.; Miyamoto, T.; Fujita, H.; Suginome, H. *Tetrahedron* **1991**, *47*, 747–756; (b) Karady, S.; Corley, E. G.; Weinsntock, L. M. *Tetrahedron Lett.* **1989**, *30*, 2191–2194.
5. (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, 17543–17594; (b) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461–5496.
6. (a) Tauh, P.; Fallis, A. G. *J. Org. Chem.* **1999**, *64*, 6960–6968; (b) Kim, S.; Kim, Y.; Yoon, K. S. *Tetrahedron Lett.* **1997**, *38*, 2487–2490.
7. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373–376; (b) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 6071–6075.
8. (a) Marco-Contelles, J.; Destabel, C.; Gallego, P.; Chiara, J. L.; Bernabe, M. *J. Org. Chem.* **1996**, *61*, 1354–1362; (b) Enholm, E.; Jaramillo, L. M.; Burroff, J. *Tetrahedron Lett.* **1990**, *31*, 3727–3730.
9. (a) Booth, S.; Jenkins, P. R.; Swain, Ch. J.; Sweeney, J. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3499–3508; (b) Grissom, J. W.; Klingberg, D.; Meyenburg, S.; Stallman, B. L. *J. Org. Chem.* **1994**, *59*, 7876–7888.
10. *Experimental details. 3-Benzyloxy-2-methoxy-carbonyl-methyl-3a-methyl-2,3,3a,8-tetrahydro-1H-3-azacyclopenta-[a]indene-8a-carboxylic acid ethyl ester* (**3a**): A solution of oxime **2a** (300 mg, 0.6 mmol), AIBN (25 mg, 0.15 mmol), and TBTH (0.2 mL, 0.72 mmol) in cyclohexane (30 mL) was degassed for 1 h by bubbling dry argon, and stirred at 80 °C for 6–8 h. After cooling to rt, the solution was evaporated to dryness to yield a clear oil. The ^{1}H NMR spectrum of the crude mixture, after treatment with KF (10% aq), and filtration over silica gel showed a range of compounds (**4a**, **5a**, and **6a**). The tricyclic heterocyclic compounds **3a** were determined as the major products (60%), ratio 1:1 of the two diastereomers calculated by integrating the signals corresponding to the methylene of benzyloxy group. Purification by flash column chromatography with 15–25% AcOEt/hexanes afforded the two diastereomer mixture of compounds **3a** (102 mg, 51%) as a clear oil. A second chromatographic purification allowed separating each individual diastereomer. The yields of the other side compounds **4a** (15%) and **5a** (10%) were determined from the ^{1}H NMR of the crude spectrum after the first filtration.
Diastereomer A of **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (3H, t, $J = 7.2$ Hz, CH_3), 1.47 (3H, s, CH_3), 1.60 (1H, dd, $J = 12.8$, 10.4 Hz, CH_2), 2.26 (1H, dd, $J = 15.0$, 7.8 Hz, CH_2CO_2Me) 2.59 (1H, dd, $J = 14.8$, 6.0 Hz, CH_2CO_2Me),

2.90 (1H, dd, $J = 13.0$, 7.4 Hz, CH_2), 2.96 (1H, d, $J = 16.0$ Hz, CH_2–Ar), 3.62 (3H, s, OCH_3), 3.65 (1H, d, $J = 16.0$ Hz, CH_2–Ar), 3.97–4.05 (1H, m, CH–N), 4.09–4.17 (2H, m, OCH_2), 4.50 (1H, d, $J = 10.8$ Hz, OCH_2Ph), 4.53 (1H, d, $J = 10.8$ Hz, OCH_2Ph), 7.10–7.36 (m, 9H, CH Ar) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.39, 18.43, 28.58, 38.72, 39.74, 43.90, 51.72, 61.12, 61.82, 64.45, 77.39, 124.34, 124.73, 126.81, 128.39, 128.39, 128.85, 128.89, 137.33, 139.78, 172.54, 175.05; MS (ESI) 446.19 $[M+Na]^+$, HRMS (EI) calcd for $C_{25}H_{29}NO_5$ 423.20457, found 423.20421. *Diastereomer B of* **5a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.26 (3H, t, $J = 7.2$ Hz, CH_3), 1.51 (3H, s, CH_3), 1.82 (1H, dd, $J = 12.8$, 7.2 Hz, CH_2), 2.47 (1H, dd, $J = 15.6$, 9.0 Hz, CH_2CO$_2$Me), 2.60 (1H, dd, $J = 13.0$, 5.6 Hz, CH_2), 2.78 (1H, dd, $J = 15.6$, 4.8 Hz, CH_2CO$_2$Me), 2.90 (1H, d, $J = 16.8$ Hz, CH_2–Ar), 3.01–3.07 (1H, m, CH–N), 3.57 (3H, s, OCH_3), 3.84 (1H, d, $J = 17.2$ Hz, CH_2–Ar), 4.20 (2H, q, $J = 7.2$ Hz, OCH_2), 4.83 (1H, d, $J = 10.8$ Hz, OCH_2Ph), 4.88 (1H, d, $J = 10.8$ Hz, OCH_2Ph), 7.10–7.46 (m, 9H, CH Ar); HRMS (ESI-FT-ICR) calcd for $[C_{25}H_{29}NO_5+Na]^+$ 446.1938, found 446.1937.

2-(1-Benzyloxyimino-ethyl)-4-methoxy carbony methyl-1,2,3,4-tetrahydro-naphthalene-2-carboxylic acid ethyl ester (**6a**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.24 (t, 3H, $J = 6.5$ Hz, OCH$_2$CH_3), 1.81 (s, 3H, CH$_3$–C=N), 1.89 (dd, 1H, $J = 14.0$, 2.4 Hz, CH$_2\beta$ ar), 2.47 (dd, 1H, $J = 16.0$, 10.0 Hz, CH_2CO$_2$CH$_3$), 2.57 (ddd, 1H, $J = 13.6$, 6.4, 2.4 Hz, CHCH_2), 2.89 (dd, 1H, $J = 16.0$, 4.0 Hz, CH_2–Ar), 3.08–3.19 (m, 1H, CH–Ar), 3.32 (dd, 1H, $J = 16.1$, 2.4 Hz, CH_2–Ar), 3.69 (s, 3H, OCH_3), 4.08–4.24 (m, 2H, OCH_2), 4.94 (s, 2H, OCH_2Ph), 7.04–7.39 (m, 9H, CH Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.12, 14.36, 32.70, 34.87, 35.88, 40.98, 52.05, 52.36, 61.76, 76.22, 126.8, 127.04, 127.60, 127.83, 128.12, 128.38, 128.77, 129.07, 135.16, 137.44, 154.82, 173.17, 174.85; HRMS (ESI-FT-ICR) calcd for $[C_{25}H_{29}NO_5+Na]^+$ 446.1938, found 446.1928.

2-Benzyl-2-(1-benzyloxyimino-ethyl)-hex-3-enedioic acid 1-ethyl ester 6-methyl ester (**8a**): ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.19 (3H, t, $J = 7.2$, CH_3), 1.77 (3H, s, CH$_3$), 3.09 (2H, dd, $J = 6.8$, 1.6 Hz, CH_2CO$_2$CH$_3$), 3.16 (1H, d, $J = 14.0$ Hz, CH_2Ph) 3.41 (1H, d, $J = 14.0$ Hz, CH_2Ph), 3.69 (3H, s, OCH_3), 4.08–4.17 (2H, m, OCH_2), 5.18 (2H, s, OCH_2Ph), 5.51 (1H, dt, $J = 16.4$, 7.0 Hz, CH=CHCH$_2$), 5.98 (1H, dt, $J = 16.4$, 1.6 Hz, CH=CHCH$_2$), 7.02–7.06 (m, 3H, CH Ar), 7.17–7.18 (2H, m, CH Ar), 7.37 (5H, s, CH Ar); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.25, 14.65, 36.13, 42.69, 52.09, 61.57, 76.09, 124.08, 126.78, 127.78, 127.85, 128.02, 128.18, 130.39, 133.61, 137.04, 138.54, 156.06, 172,10, 172.20; HRMS (ESI-FT-ICR) calcd for $[C_{25}H_{29}NO_5+Na]^+$ 446.1938, found 446.1932.

11. The mixtures could not be separated by a single silica gel column chromatography but it was possible to isolate analytically pure samples of **5a**–**e**, **6a**,**c**,**d**, and **8a**,**b**,**d**–**f**, whose NMR and HRMS spectra corroborated the assigned structures, which were correlated with the crude mixture NMR spectra for the quantification.
12. Abeywickrema, A. N.; Beckwith, A. L. J.; Gerba, S. J. *J. Org. Chem.* **1987**, *52*, 4072–4078.
13. Curran, D. P.; Fairweather, N. *J. Org. Chem.* **2003**, *68*, 2972–2974.