ORGANIC
LETTERS

2010
Vol. 12, No. 1
124−126

Iron-Mediated Radical Nitro-Cyclization Reaction of 1,6-Dienes

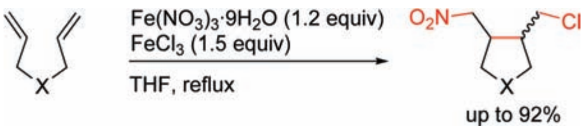
Tsuyoshi Taniguchi and Hiroyuki Ishibashi*

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan

isibasi@p.kanazawa-u.ac.jp

Received October 30, 2009

ABSTRACT



Sequential steps that involved radical addition of a nitro group to 1,6-dienes promoted by the thermal decomposition of iron nitrate(III) nonahydrate, cyclization, and trapping of the resulting terminal radicals by a chlorine atom in the presence of chloride salt afforded five-membered-ring compounds. The present reaction provides a practical method for the synthesis of nitro compounds due to its simple experimental procedure and its use of nontoxic and inexpensive iron reagents.

Recently, iron compounds have been widely employed as nontoxic and inexpensive green elements. Many chemists have focused on the use of iron complexes as replacements for rare metals such as palladium for carbon−carbon or carbon−heteroatom bond formation.[1,2] Thermal decomposition of iron(III) nitrate nonahydrate, $Fe(NO_3)_3 \cdot 9H_2O$, is well-known to generate nitrogen dioxide (NO_2),[3] which is a radical species, but little attention has been paid to synthetic applications of this method.[4] Herein, we report an efficient radical nitro-cyclization of 1,6-dienes using $Fe(NO_3)_3 \cdot 9H_2O$ to give cyclic nitro compounds. To the best our knowledge, the radical cyclization of 1,6-dienes initiated by introducing a nitro group has never been reported.[5−7]

Nitro compounds are useful for medicines, industrial materials, and fuels and are precursors of amines in organic synthesis.[8] Of the several methods available for the synthesis

---

(1) For reviews on iron-catalyzed reactions, see: (a) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, Germany, 2008. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217. (c) Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624. (d) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (e) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317. (f) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *47*, 1500. (g) Correa, A.; García Mancheño, O.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. (h) Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 1364.

(2) For selected recent examples of iron-catalyzed reactions, see: (a) Kohno, K.; Nakagawa, K.; Yahagi, T.; Choi, J.-C.; Yasuda, H.; Sakakura, T. *J. Am. Chem. Soc.* **2009**, *131*, 2784. (b) Rao Volla, C. M.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701. (c) Xu, T.; Yu, Z.; Wang, L. *Org. Lett.* **2009**, *11*, 2113. (d) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (e) Sylvester, K. T.; Chirik, P. J. *J. Am. Chem. Soc.* **2009**, *131*, 8772. (f) Ito, S.; Fujiwara, Y.; Nakamura, E.; Nakamura, M. *Org. Lett.* **2009**, *11*, 4306. (g) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 5024. (h) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 12915.

(3) (a) Hill, W. D., Jr. *Inorg. Chem. Acta* **1986**, *121*, L33. (b) Wieczorek-Ciurowa, K.; Kozak, A. J. *J. Therm. Anal. Calorim.* **1999**, *58*, 647.

(4) The synthesis of azides from hydrazines with nitrogen dioxide generated from clay-supported $Fe(NO_3)_3$ (clayfen) has been reported, see: (a) Laszlo, P.; Polla, E. *Tetrahedron Lett.* **1984**, *25*, 3701. The synthesis of β-nitrostylenes with clayfen has been also reported: (b) Varma, R. S.; Naicker, K. P.; Liesen, P. J. *Tetrahedron Lett.* **1998**, *39*, 3977.

(5) For reviews on radical reactions, see: (a) Renaud, P.; Sibi, M. P. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001. (b) Gansäuer, A., Ed. Radicals in Synthesis I and II. In *Topics in Current Chemistry*; Springer: Berlin, Germany; 2006; Vols. 263 and 264.

(6) For recent examples of radical cyclizations of 1,6-dienes, see: (a) Schmidt, B.; Pohler, M.; Costisella, B. *J. Org. Chem.* **2004**, *69*, 1421. (b) Waser, J.; Gaspar, B.; Nambu, H.; Carreira, E. M. *J. Am. Chem. Soc.* **2006**, *128*, 11693. (c) James, P.; Schenk, K.; Landais, Y. *J. Org. Chem.* **2006**, *71*, 3630. (d) Hirai, T.; Han, L.-B. *Org. Lett.* **2007**, *9*, 53. (e) Mantrand, N.; Renaud, P. *Tetrahedron* **2008**, *64*, 11860. (f) Sánchez, E. M.; Arteaga, J. F.; Domingo, V.; Quílez del Moral, J. F.; Mar Herrador, M.; Barrero, A. F. *Tetrahedron* **2008**, *64*, 5111. See also ref 5.

(7) For examples of iron-mediated radical cyclizations, see: (a) Cabri, W.; Borghi, D.; Arlandini, E.; Sbraletta, P.; Bedeschi, A. *Tetrahedron* **1993**, *49*, 6837. (b) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315. (c) Booker-Milburn, K. I.; Barker, A.; Brailsford, W.; Cox, B.; Mansley, T. E. *Tetrahedron* **1998**, *54*, 15321. (d) Jahn, P.; Hartmann, P. *Chem. Commun.* **1998**, 209. (e) Bach, T.; Schlummer, B.; Harms, K. *Chem. Commun.* **2000**, 287. (f) Booker-Milburn, K. I.; Jones, J. L.; Sibley, G. E. M.; Cox, R.; Meadows, J. *Org. Lett.* **2003**, *5*, 1107.

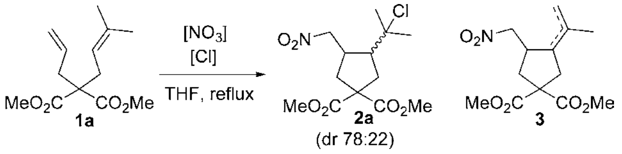
(8) (a) Feuer, H.; Nielsen, T. *Nitro compounds: Recent Advances in Synthesis and Chemistry*; VCH: New York, 1990. (b) Ono, N. *The Nitro Group in Organic Synthesis*; John Wiley-VCH: New York, 2001.

10.1021/ol902510p

of aromatic and aliphatic nitro compounds,[9,10] nitrogen dioxide gas is one of the most simple and common nitration reagents. Addition of nitrogen dioxide to a C−C multiple bond affords aliphatic nitro compounds.[11,12] There are, however, serious disadvantages associated with the use of nitrogen dioxide, due mainly to the difficulty of its handling and toxicity. Therefore, the use of nitrogen dioxide is limited to special cases in synthetic chemistry.

Compound **1a** was treated with $Fe(NO_3)_3{\cdot}9H_2O$ in the presence of several chloride salts in boiling THF to give the nitrated cyclization product **2a**,[13,14] along with a small quantity of alkene **3** (Table 1, entries 1−7). Even when $LiNO_3$ or $Mg(NO_3)_2{\cdot}6H_2O$ was used instead of $Fe(NO_3)_3{\cdot}9H_2O$ in the presence of $FeCl_3$, compound **2a** was obtained in good yield (entries 8 and 9). Since no product was obtained in this reaction in the absence of iron,[15] it is assumed that iron(III) plays an important role in the present reaction.

Table 1. Iron-Mediated Radical Nitro-Cyclization

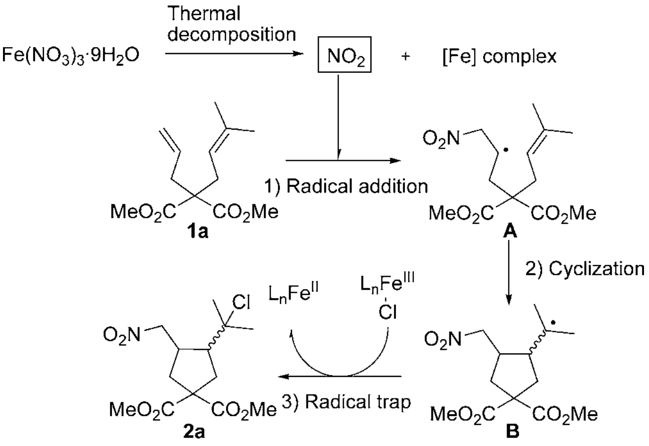


entry	$[NO_3]$ (equiv)	[Cl] (equiv)	time (h)	yield (%)[a,b] 2a	3
1	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	LiCl (1.5)	6.5	59	9
2	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	$MgCl_2$ (1.5)	14	38	6
3	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	$CuCl_2$ (1.5)	4.5	56	11
4	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	$CoCl_2$ (1.5)	9	54	10
5	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	$ZnCl_2$ (1.5)	4	40	16
6	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	$ZrCl_4$ (1.5)	6.5	63	10
7	$Fe(NO_3)_3{\cdot}9H_2O$ (1.2)	$FeCl_3$ (1.5)	2.5	65	9
8	$LiNO_3$ (5.0)	$FeCl_3$ (2.0)	6.5	60	7
9	$Mg(NO_3)_2{\cdot}6H_2O$ (5.0)	$FeCl_3$ (2.0)	8	61	5

[a] Isolated yields. [b] Diastereoisomer ratio of **2a** was determined by ^1H NMR analysis.

A plausible mechanism for the formation of **2a** from **1a** is shown in Scheme 1. Addition of nitrogen dioxide (NO_2), generated by thermal decomposition of $Fe(NO_3)_3{\cdot}9H_2O$, onto **1a** followed by cyclization of the resulting radical intermediate **A** gives the cyclized radical **B**. The radical intermediate **B** is then trapped by the chlorine atom to give **2a**. The possibility that the formation of **2a** involves oxidation of the radical intermediate **B** followed by addition of chloride anion to the resulting cation intermediate cannot be ruled out, because a small amount of alkene **3** has been formed.

Scheme 1. Plausible Mechanism



The advantages of the present reaction are as follows: (1) all reagents herein employed have low toxicity and are inexpensive and (2) the experimental procedure is very simple and safe.[16]

On the basis of the results of these exploratory experiments, we decided to use a combination of $Fe(NO_3)_3{\cdot}9H_2O$ and $FeCl_3$ (Table 1, entry 7) for further reactions.[17]

Table 2 shows the results of radical cyclizations of various precursors **1b**−**m**. The precursors **1b**−**d** afforded 5-*exo* cyclization products **2b**−**d** in good yield (entries 2−4). The diallylic precursors **1e**−**h** also provided the corresponding 5-*exo* products **2e**−**h** in good yield (entries 5−8). In the cases of **1e**−**h**, no formation of a six-membered compound was observed, indicating that the possibility of a cationic cyclization (Scheme 1) can be ruled out. The reaction of precursor **1i** bearing a 2-methylallyl group also gave cy-

---

(9) For reviews on nitration of aromatic compounds, see: (a) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanisms*; VCH Publishers Inc.: New York, 1989. (b) Mori, T.; Suzuki, H. *Synlett* **1995**, 383. (c) Suzuki, T.; Noyori, R. *Chemtracts* **1997**, *10*, 813.

(10) For nitration of alkanes, see: (a) Olah, G. A.; Ramaiah, P.; Rao, C. B.; Graham, S.; Golam, R.; Trivedi, N. J.; Olah, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 7246. (b) Suzuki, H.; Nonoyama, N. *J. Chem. Soc., Chem. Commun.* **1996**, 1783. (c) Nishiwaki, Y.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5663. See also ref 9a.

(11) For examples of addition of nitrogen dioxide to the C−C multiple bond, see: (a) Stevens, T. E.; Emmons, W. D. *J. Am. Chem. Soc.* **1958**, *80*, 338. (b) Suzuki, H.; Mori, T. *J. Org. Chem.* **1997**, *62*, 6498. (c) Grossi, L.; Montevecchi, P. C.; Strazzari, S. *Eur. J. Org. Chem.* **2001**, 741. (d) Grossi, L.; Montevecchi, P. C. *Chem.*−*Eur. J.* **2002**, *8*, 380. See also ref 9.

(12) Radical nitration of styrene derivatives with cerium(IV) ammonium nitrate and sodium nitrite has been reported, see: (a) Hwu, J. R.; Chen, K.-L.; Ananthan, S.; Patel, H. V. *Organometallics* **1996**, *15*, 499. (b) Jayakanthan, K.; Madhusudanan, K. P.; Vankar, Y. D. *Tetrahedron* **2004**, *60*, 397.

(13) It was assumed that a cis isomer was the major product. Radical cyclizations of 1,6-dienes in general afforded cis products, see: Tripp, J. C.; Schiesser, C. H.; Curran, D. P. *J. Am. Chem. Soc.* **2006**, *127*, 5518.

(14) A classical method for nitro-chlorination of olefins with nitryl chloride has been reported, see: (a) Shechter, H.; Conrad, F.; Daulton, A. L.; Kaplan, R. B. *J. Am. Chem. Soc.* **1952**, *74*, 3052. Nitro-iodination of olefins with nitrogen dioxide and iodine has also been reported by Emmons and co-worker, see ref 11a. Jäger and Günther have also reported nitro-iodination of 1,5-, 1,6-, and 1,7-dienes using a NO_2/I_2 condition, but no cyclization product was obtained, see: (b) Jäger, V.; Günther, J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 246.

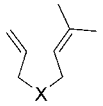
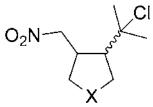
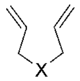
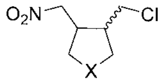
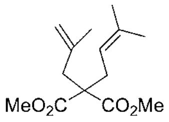
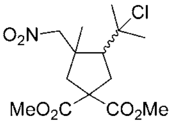
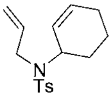
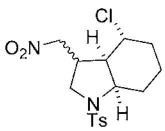
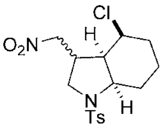
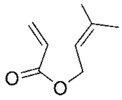
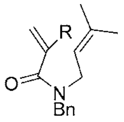
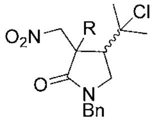
(15) When **1a** was treated with $LiNO_3$ in the presence of LiCl instead of $FeCl_3$, no reaction was observed.

(16) Leakage of toxic nitrogen dioxide gas to the outside from the reaction mixture was scarcely observed.

(17) **Typical procedure:** To a solution of **1a** (72.1 mg, 0.3 mmol) and $FeCl_3$ (73.0 mg, 0.45 mmol) in THF (3 mL) was added $Fe(NO_3)_3{\cdot}9H_2O$ (146 mg, 0.36 mmol), and the mixture was heated at reflux for 2.5 h. After cooling to room temperature, the resulting suspension was diluted with Et_2O and filtered. After removal of solvent under reduced pressure, the residue was purified by silica gel chromatography (hexane/EtOAc, 5:1) to give **2a** (62.7 mg, 65%) and **3** (7.7 mg, 9%) as a colorless oil, respectively.

Table 2. Nitro-Cyclization of Various Precursors

substrate (**1a-m**) $\xrightarrow[\text{THF, reflux}]{Fe(NO_3)_3\cdot 9H_2O\ (1.2\ equiv),\ FeCl_3\ (1.5\ equiv)}$ products (**2a-m**)

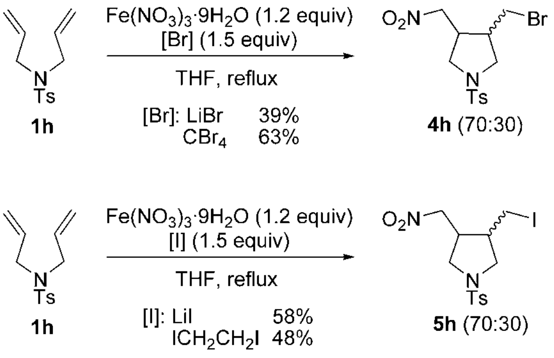
entry	substrate	time (h)	products (%)[a,b]
			
1	**1a**: X = C(CO_2Me)$_2$	2.5	**2a**: 65% (78:22)
2	**1b**: X = C(SO_2Ph)$_2$	2	**2b**: 84% (55:45)
3	**1c**: X = O	3.5	**2c**: 56% (50:50)
4	**1d**: X = NTs	3	**2d**: 53% (55:45)
			
5	**1e**: X = C(CO_2Me)$_2$	5	**2e**: 59% (85:15)
6	**1f**: X = C(SO_2Ph)$_2$	2	**2f**: 92% (73:27)
7	**1g**: X = O	4	**2g**: 46% (70:30)
8	**1h**: X = NTs	4	**2h**: 91% (70:30)
9	 **1i**	1.5	 **2i**: 73% (50:50)
10	 **1j**	2	 **2j**: 40% (α:β, 30:70) **2j'**:34% (α:β, 93:7)
11	 **1k**	12	decomposed
			
12	**1l**: R = H	2.5	**2l**: 38% (75:25)[c]
13	**1m**: R = Me	1.5	**2m**: 76% (60:40)[c]

[a] Isolated yields. [b] Diastereomer ratio was determined by ^{1}H NMR analysis. [c] The trans isomer was the major product.

clization product **2i** in good yield (entry 9). The cyclization of precursor **1j** afforded bicyclic products **2j** and **2j′** in good yield (entry 10). Acryloyl ester **1k** gave no cyclized product (entry 11),[18] but amide **1*l*** and **1m** afforded the desired γ-lactams **2*l*** and **2m**, respectively, in good yield (entries 12 and 13).[19]

Finally, brominated or iodinated cyclization compounds were also accessible by using appropriate radical trapping reagents. Treatment of **1h** with $Fe(NO_3)_3\cdot 9H_2O$ in the presence of lithium bromide or carbon tetrabromide afforded brominated product **4h**. The use of lithium iodide or 1,2-diiodoethane as a radical trapping reagent afforded iodinated product **5h** (Scheme 2).[14]

Scheme 2. Radical Trap by Other Halogen Atoms



In summary, we have developed an iron-mediated nitro-cyclization reaction of 1,6-diene to give cyclic nitro compounds. The reaction consists of treatment with low-toxic and inexpensive reagents. The present reaction will provide a new practical method for the synthesis of nitro compounds. Further study directed toward the scope and limitations of this method is currently underway in our laboratory.

Acknowledgment. This research was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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

OL902510P

---

(18) It is well-known that the synthesis of γ-lactones by radical cyclization is difficult due to a conformational disfavor of precursors. Limited successful examples have been reported, see: (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041. (b) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389. (c) Clive, D. L. J.; Zhang, J.; Subedi, R.; Boutard, V.; Hiebert, S.; Ewanuk, R. *J. Org. Chem.* **2001**, *66*, 1233.

(19) For an example of the synthesis of γ-lactams by radical cyclization of the similar 1,6-dienes, see: Miyata, O.; Kajisa, S.; Ueda, M.; Yamauchi, M.; Naito, T. *Chem. Pharm. Bull.* **2005**, *53*, 995.