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COMMUNICATION

Iron-mediated one-pot formal nitrocyclization onto unactivated alkenes†

Tsuyoshi Taniguchi,* Tatsuya Fujii and Hiroyuki Ishibashi

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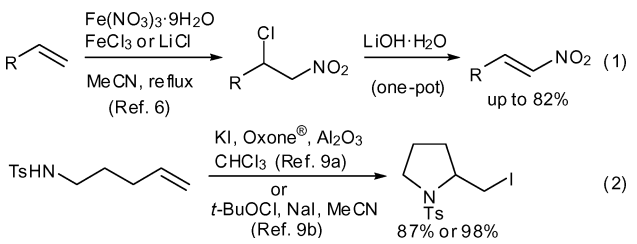
One-pot synthesis of heterocycles having a nitromethyl group was achieved by sequential steps that involved chloronitration of alkenes using iron(III) nitrate nonahydrate followed by elimination and intramolecular Michael addition. This reaction provides an efficient method for the synthesis of heterocycles due to the simple experimental procedure and the use of inexpensive reagents of low toxicity.

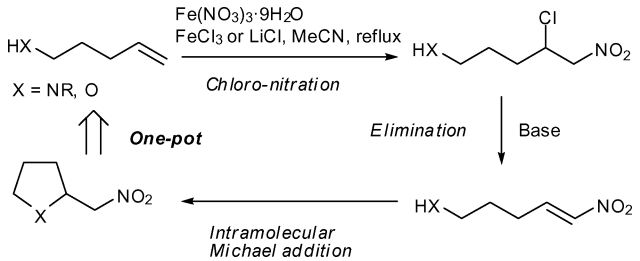
Nitro compounds are useful for medicines, industrial materials and fuels, and their compounds are also valuable synthetic intermediates in organic chemistry.[1] For example, they are transformed into various derivatives such as amines and ketones by reduction of a nitro group and the Nef reaction.[2] Moreover, C–C and C–X (X = N, O) bond formations by nitro-aldol reaction and nitro-Michael reaction have been extensively investigated.[3] To date, a number of nitration methods have been established.[4,5] Recently, we reported radical halonitration of alkenes by thermal decomposition of iron(III) nitrate nonahydrate [$Fe(NO_3)_3{\cdot}9H_2O$] (Scheme 1, eq. 1).[6] In this reaction, subsequent treatment of the reaction mixture with an appropriate base gives corresponding nitroalkenes in one-pot.[7] Herein, we report one-pot synthesis of heterocycles by iron-mediated halonitration of ω-alkenylamine (or alcohol) derivatives and subsequent elimination followed by intramolecular nitro-Michael addition (Scheme 2). Many useful difunctionalization reactions of unactivated alkenes involving cyclization reactions such as halolactonization and haloamination have been reported (Scheme 1, eq. 2).[8,9] On the other hand, electrophilic nitrocyclization of ω-alkenylamine or ω-alkenylcarboxylic acid derivatives



Scheme 1 Iron-mediated chloronitration of alkenes and intramolecular iodoamination.

School of Pharmaceutical Sciences, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kakuma-machi, Kanazawa, 920-1192, Japan. E-mail: tsuyoshi@p.kanazawa-u.ac.jp; Fax: +81-76-234-4439; Tel: +81-76-234-4439

† Electronic supplementary information (ESI) available: Spectroscopic data for all new products is available. See DOI: 10.1039/c0ob00905a

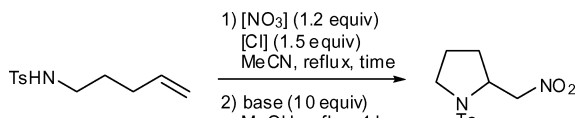


Scheme 2 Chloronitration followed by the one-pot construction of heterocycles.

using the nitronium ion (NO_2^+) has never been reported.[10] It is presumed that the extreme reactivity of NO_2^+ is the main reason for this. Our present reaction can be regarded as a formal nitroamination (or nitrooxygenation), and, to the best of our knowledge, this direct transformation from unactivated alkenes has never been explored.

After treatment of compound **1a** with $Fe(NO_3)_3{\cdot}9H_2O$ in the presence of $FeCl_3$ in boiling MeCN, addition of K_2CO_3 and MeOH to the reaction mixture gave pyrrolidine **2a** in 21% yield (Table 1, entry 1). The use of $LiNO_3$ instead of $Fe(NO_3)_3{\cdot}9H_2O$ resulted in no improvement in yield of the product (Table 1, entry 2), whereas the use of LiCl instead of $FeCl_3$ afforded compound **2a** in improved yield (Table 1, entry 3). When KOAc was used

Table 1 Optimizations of the one-pot synthesis heterocycle **2a**[a]

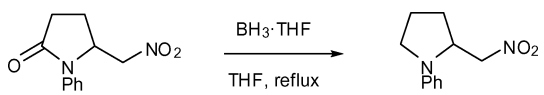


Entry	[NO_3]	[Cl]	Base	Time/h	Yield (%)[b]
1	$Fe(NO_3)_3{\cdot}9H_2O$	$FeCl_3$	K_2CO_3	1	21
2[c]	$LiNO_3$	$FeCl_3$	K_2CO_3	6	15
3	$Fe(NO_3)_3{\cdot}9H_2O$	LiCl	K_2CO_3	8	36
4	$Fe(NO_3)_3{\cdot}9H_2O$	LiCl	KOAc	8	55
5	$Fe(NO_3)_3{\cdot}9H_2O$	LiCl	$LiOH{\cdot}H_2O$	8	9
6	$Fe(NO_3)_3{\cdot}9H_2O$	LiCl	DBU	8	0
7	$Fe(NO_3)_3{\cdot}9H_2O$	LiCl	$NaHCO_3$	8	63
8[d]	$Fe(NO_3)_3{\cdot}9H_2O$	LiCl	$NaHCO_3$	8	70

[a] Reaction conditions: **1a** (0.4 mmol), [NO_3] (0.48 mmol) and [Cl] (0.60 mmol) in MeCN (2 mL), then base (4.0 mmol) and MeOH (1 mL). [b] Isolated yield. [c] 5.0 equiv. of $LiNO_3$ (2.0 mmol) and 2.0 equiv. of $FeCl_3$ (0.8 mmol) was used. [d] 1.5 equiv. of $Fe(NO_3)_3{\cdot}9H_2O$ (0.60 mmol) and 1.9 equiv. of LiCl (0.76 mmol) were used.

instead of K_2CO_3 as a base, a significantly improved result was obtained (Table 1, entry 4). $LiOH{\cdot}H_2O$, which was efficient in one-pot synthesis of nitroalkenes using this method (Scheme 1, eq. 1),[6b] gave the product in very low yield (Table 1, entry 5). The reaction using an organic base gave no desired product (Table 1, entry 6). Eventually, we found that the use of $NaHCO_3$ gave the best result (Table 1, entries 7 and 8).‡

Next, the synthesis of various heterocycles using optimized conditions (Table 1, entry 8) was examined (Table 2). Reactions of substrates **1b** and **1c** bearing dimethyl and diphenyl groups on the tether moiety gave corresponding pyrrolidine derivatives **2b** and **2c** in good and moderate yields, respectively (Table 2, entries 2 and 3). Substrate **1d** bearing a phenyl group on the tether moiety gave pyrrolidine derivative **2d** in good yield, but the diastereomeric selectivity was low (Table 2, entry 4). Substrate **1e** bearing a cyclohexyl group gave spiro cycles **2e** in good yield (Table 2, entry 5). In the case of α-phenylamine derivative **1f**, diastereoselective cyclization proceeded to give *cis*-2,5-disubstituted pyrrolidine derivative **2f** as a sole product in good yield (Table 2, entry 6).[11,12] The reaction of 2,2-disubstituted alkene **1g** gave cyclized product **2g** in lower yield than that of the reaction of **1b**, probably because of the steric effect in the intramolecular Michael addition (Table 2, entry 7). The use of a Cbz (benzyloxycarbonyl) group as a protecting group caused a significant decline in the yield of cyclized product **2h** (Table 2, entry 8). This smaller yield might be due to the lower nucleophilicity of a nitrogen atom of a carbamate than that of a sulfonamide. When pentenamide derivatives **1i** and **1j** were used as substrates, cyclization on the nitrogen atom took place to give γ-lactams **2i** and **2j**, respectively (Table 2, entries 9 and 10).[13,14] This was confirmed by reduction of γ-lactams **2i** by borane to give pyrrolidine compound **3**, and no O-cyclized product was detected (Scheme 3). The present reaction could be applied to the construction of piperidine ring **2k** and tetrahydrofuran ring **2l**, respectively (Table 2, entries 11 and 12). Reactions of *cis*- and *trans*-2-allylcyclohexylamine derivatives **1m** and **1n** resulted in nitrations and diastereoselective cyclizations to give bicyclic compounds **2m** and **2n**, respectively, in good yields (Table 2, entries 13 and 14). *N*-Tosyl-2-allylaniline (**1o**) never gave a cyclized product because nitration of an electron-rich aromatic ring occurred the as a significant competitive reaction (Table 2, entry 15). However, we soon found that use of electron-drawing protecting groups on the nitrogen atom gave dihydroindole derivatives **2p–r** (Table 2, entries 16–18).

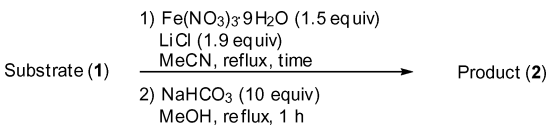


2i **3** (88%)

Scheme 3 Reduction of **2i**.

In summary, we have developed a method of one-pot formal nitrocyclizations for synthesis of heterocycles using a subsequent process involving iron-mediated chloronitration followed by elimination and intramolecular Michael addition under at basic conditions. Inexpensive reagents of low toxicity are used in the reaction, and the experimental procedure is very simple. The present reaction will provide a new practical method for the synthesis of heterocyclic compounds. Further studies directed

Table 2 One-pot synthesis of various heterocycles



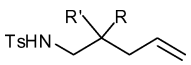
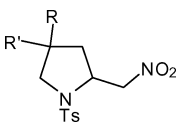
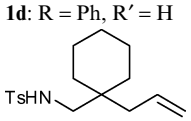
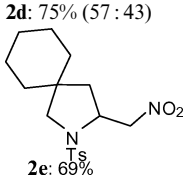
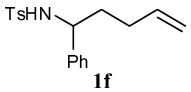
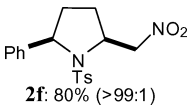
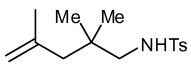
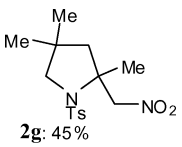
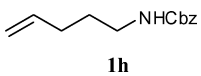
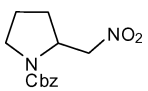
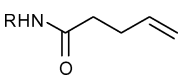
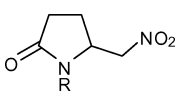
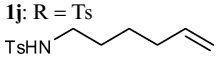
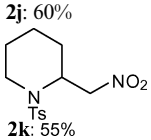
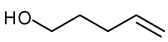
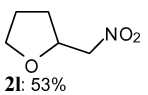
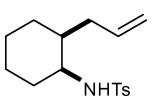
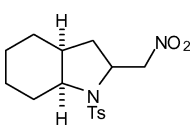
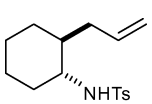
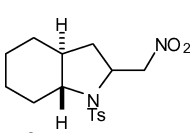
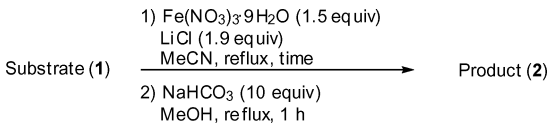
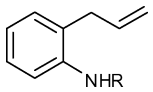
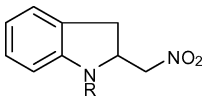
Entry	Substrate	Time/h	Product[a,b]
			
1	**1a**: R = H, R′ = H	5	**2a**: 70%
2	**1b**: R = Me, R′ = Me	9	**2b**: 75%
3[c]	**1c**: R = Ph, R′ = Ph	4	**2c**: 48%
4	**1d**: R = Ph, R′ = H	5	**2d**: 75% (57 : 43)
5	 **1e**	9	 **2e**: 69%
6	 **1f**	5	 **2f**: 80% (>99:1)
7	 **1g**	2	 **2g**: 45%
8	 **1h**	6	 **2h**: 31%
			
9[c]	**1i**: R = Ph	12	**2i**: 47%
10[c]	**1j**: R = Ts	1	**2j**: 60%
11	 **1k**	4	 **2k**: 55%
12	 **1l**	6	 **2l**: 53%
13	 **1m**	5	 **2m**: 78% (95:5)
14	 **1n**	9	 **2n**: 72% (>99:1)

Table 2 *(Contd.)*



Entry	Substrate	Time/h	Product[a,b]
			
15[c]	**1o**: R = Ts	3	**2o**: no detected
16[c]	**1p**: R = Ac	1.5	**2p**: 69%
17[c]	**1q**: R = TFA	3	**2q**: 56%
18[c]	**1r**: R = Cbz	1	**2r**: 42%

[a] Isolated yields. [b] Diastereomeric ratio was determined by ^{1}H NMR analysis. [c] $FeCl_3$ was used instead of LiCl because the reaction did not complete.

toward the application of this method to the synthesis of bioactive compounds are currently underway in our laboratory.

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Notes and references

‡ **Typical procedure:** To a solution of **1a** (95.7 mg, 0.40 mmol) and LiCl (31.8 mg, 0.76 mmol) in MeCN (2 mL) was added $Fe(NO_3)_3{\cdot}9H_2O$ (242 mg, 0.60 mmol), and the mixture was heated at reflux for 5 h. To the reaction mixture was added $NaHCO_3$ (336 mg, 4.00 mmol) and MeOH (1 mL) and the mixture was heated at reflux for 1 h. After cooling to room temperature, the resultant suspension was diluted with Et_2O and filtered. Solvent of filtrate was removed under reduced pressure and the residue was purified by silica gel chromatography (hexane–EtOAc, 5 : 1) to give **2a** (80.0 mg, 70%) as a colourless oil.

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10 Electrophilic nitration of alkenes using NO_2Cl has been reported, see: H. Shechter, F. Conrad, A. L. Daulton and R. B. Kaplan, *J. Am. Chem. Soc.*, 1952, **74**, 3052.

11 It has been reported that 5-*exo*-trig intramolecular Michael addition of a 2-substituted toluenesulfonamide derivative gave a *cis*-pyrrolidine compound in good diastereomeric selectivity, see: R. E. Dolle, C.-S. Li and A. N. Shaw, *Tetrahedron Lett.*, 1989, **30**, 4723.

12 A relative configuration of compound **2f** was presumed by comparison with reported spectroscopic data of known similar compounds, *cis*- or *trans*-1-(4-methylphenylsulfonyl)-2-hydroxymethylphenyl-5-phenylpyrrolidine (**4**). ^{1}H NMR signals of 5-H of these compounds are 4.71 (1H, app. t, J = 6.6 Hz, for **2f**), 4.79 (1H, dd, app. t, J = 7.0 Hz, for *cis*-**4**) and 5.06 (1H, d, J = 8.5 Hz, for *trans*-**4**), see: P. Evans, T. McCabe, B. S. Morgan and S. Reau, *Org. Lett.*, 2005, **7**, 43.

13 Synthesis of a β-lactam derivative by intramolecular Michael addition of unsaturated amides has been reported, see: Y.-H. W. J. R. Corrigan and R. F. Feldkamp, *J. Org. Chem.*, 1961, **26**, 1531.

14 For a recent study of selectivity in O-cyclizations or N-cyclizations of unsaturated amides using electrophiles, see: T. Hu, K. Liu, M. Shen, X. Yuan, Y. Tang and C. Li, *J. Org. Chem.*, 2007, **72**, 8555 and references therein.