Synlett R. Oishi et al. Letter

Hypervalent Iodine-Mediated Beckmann Rearrangement of Ketoximes

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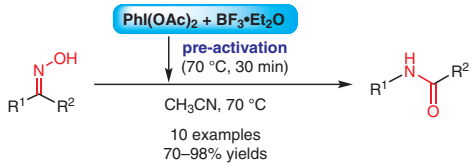


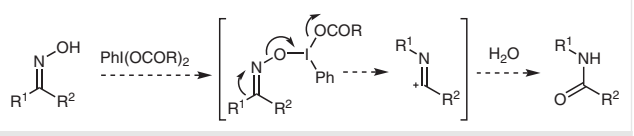
Received: 23.02.2018
Accepted after revision: 26.03.2018
Published online: 23.04.2018
DOI: 10.1055/s-0037-1609686; Art ID: st-2018-u0121-l

Abstract We developed a Beckmann rearrangement employing hypervalent iodine reagent under mild conditions. The reaction of ketoxime with hypervalent iodine afforded the corresponding ketone, but premixing of hypervalent iodine and a Lewis acid was effective for promoting Beckmann rearrangement. Aromatic and aliphatic ketoximes were converted into their corresponding amides in good to high yields.

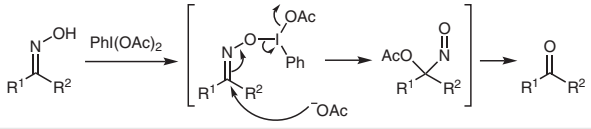
Key words hypervalent iodine reagent, Beckmann rearrangement, oxime, amide, Lewis acid

Hypervalent iodine is a mild oxidizing reagent with a reactivity similar to that of heavymetaloxidizing reagents, but with much lower toxicity. Hypervalent iodine reagents exhibit versatile and unique reactivity.[1] Phenyliodine diacetate ($PhI(OAc)_2$) and phenyl iodine bis(trifluoroacetate) ($PhI(OCOCF_3)_2$) are of particular interest.[2] We recently developed a novel decarboxylative halogenation reaction using a combination of $PhI(OAc)_2$ and LiX.[3] In this reaction, $PhI(OAc)_2$ promotes decarboxylation by reacting with the associated hydroxy group. We applied this reactivity to the activation of oximes and hypothesized that oxime groups would react with hypervalent iodine and undergo Beckmann rearrangement (Scheme 1).

Beckmann rearrangement is the most important and powerful strategy for constructing amides from oximes and is widely utilized in organic syntheses.[4] Beckmann rearrangements can be induced using a variety of methods including Lewis acid activation, although this requires relatively high temperatures.[5] The reaction of oximes with $PhI(OAc)_2$ has already been reported where the corresponding ketone is obtained by attacking the eliminated acetate ion of the activated intermediate (Scheme 2).[6]



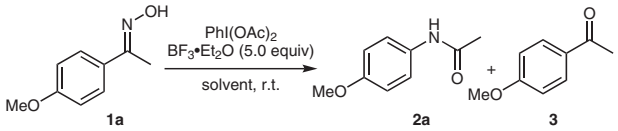
Scheme 1 Hypervalent iodine mediated Beckmann rearrangement



Scheme 2 Reported transformation of ketoxime to ketone by $PhI(OAc)_2$

We hypothesized that the addition of a Lewis acid would suppress the nucleophilic attack of acetate ion and activate a hypervalent iodine reagent, resulting in Beckmann rearrangement. We chose 4′-methoxyacetophenone oxime (**1a**) as a substrate, and the reaction was conducted using 1.2 equivalents of $PhI(OAc)_2$ and 5 equivalents of $BF_3{\cdot}Et_2O$ as the Lewis acid. In the first attempt, tetrahydrofuran (THF) was used as the solvent, but the desired reaction did not proceed; ketone **3** was obtained at a 70% yield and 15% of ketoxime **1a** was recovered (Table 1, entry 1). Running the reaction in 2,2,2-trifluoroethanol (TFE), which is often used in reactions with hypervalent iodine,[7] afforded a trace amount of amide **2a** (Table 1, entry 2). CH_3CN and CH_2Cl_2 were effective solvents for amide formation (Table 1, entries 3 and 4) and the use of CH_2Cl_2 afforded amide **2a** in 52% yield (Table 1, entry 4). The reaction without $PhI(OAc)_2$ gave poor results (Table 1, entries 5 and 6), which indicates that $PhI(OAc)_2$ plays an important role in this reaction.

Table 1 Investigation of Reaction Conditions for Beckmann Rearrangement

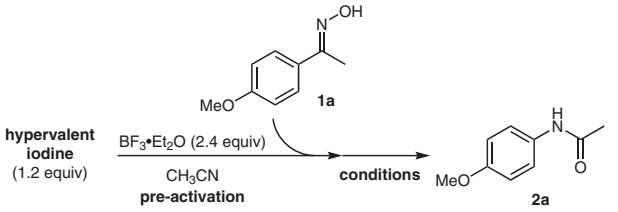


Entry	$PhI(OAc)_2$ (equiv)	Solvent	Time (h)	Yield of **2a** (%)	Yield of **3** (%)
1	1.2	THF	21	–	70
2	1.2	TFE	21	3	37
3	1.2	CH_3CN	20	27	13
4	1.2	CH_2Cl_2	3	52	30
5	–	CH_3CN	24	3	3
6	–	CH_2Cl_2	21	15	3

Intriguingly, pre-activation of $PhI(OAc)_2$ with $BF_3{\cdot}Et_2O$ before the addition of ketoxime enhanced the Beckmann reaction, and the product was obtained at a high yield (Table 2). After pre-activation of 1.2 equivalents of $PhI(OAc)_2$ with 2.4 equivalents $BF_3{\cdot}Et_2O$ in CH_3CN at room temperature for 24 h, the Beckmann rearrangement proceeded to give the corresponding amide **2a** at a 64% yield after 8 h at room temperature (Table 2, entry 1) whereas the use of CH_2Cl_2 as a solvent afforded poor result (Table 2, entry 2). When pre-activation was conducted at 70 °C for 30 min, amide **2a** was successfully obtained at a 91% yield at room temperature after 8 h (Table 2, entry 3). These are mild reaction conditions for a Beckmann rearrangement. Most previously reported methods employing Lewis acids have required high reaction temperatures, usually reflux conditions. In addition, the rearrangement reaction was greatly accelerated at 70 °C, and the reaction was complete after 5 min (Table 2, entry 4). The reaction also proceeded with other hypervalent iodine reagents, such as $PhI(OCOCF_3)_2$ or PhI(OH)OTs, but the yields were decreased to 67% and 27%, respectively (Table 2, entries 5 and 6). Reactions employing other Lewis acids, such as $SnCl_4$ and $ZnCl_2$, gave high yields but required 5 h and 24 h, respectively, for completion (Table 2, entries 7 and 8).

Optimized reaction conditions and substrate scope were also investigated. Although the reaction of *p*-methoxyacetophenone oxime (**1a**) at room temperature afforded a 91% yield (Table 3, entry 1), the reaction of *o*-methoxyacetophenone oxime (**1b**) at room temperature resulted in a moderate yield (52%, Table 3, entry 3). Raising the reaction temperature to 70 °C greatly enhanced the reactivity in both cases and the reactions were complete after only 5 min with improved yields (Table 3, entries 2 and 4). These data warranted further exploration of heating conditions. Non-substituted acetophenone oximes **1c** also underwent Beckmann rearrangement and afforded a 98% yield after 30 min (Table 3, entry 5). Reactions of acetophenone oxime with electron-withdrawing groups, such as Cl and NO_2, required more time than with substrates bearing electron-donating groups, but afforded the corresponding amides **2d** and **2e** in 97% and 79% yields after 4 h and 19 h, respectively (Table 3, entries 6 and 7). Indole ketoxime protected with a benzenesulfonyl group **1f** was also converted into the amide **2f** in 90% yield (Table 3, entry 8). Under the same conditions, aliphatic ketoxime **1g** gave amide **2g** in moderate yield (70%) after 5 h (Table 3, entry 9). The reaction of benzophenone oxime **1h** gave the corresponding amide **2h** at a 94% yield within 15 min (Table 3, entry 10).

Table 2 Optimization of Reaction Conditions for Beckmann Rearrangement



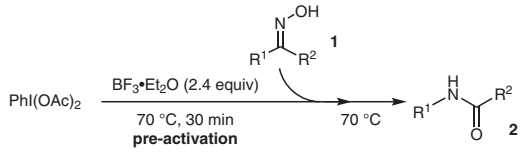
Entry	Hypervalent iodine	Pre-activation	Conditions	Yield (%)
1	$PhI(OAc)_2$	r.t., 24 h	r.t., 8 h	64
2[a]	$PhI(OAc)_2$	r.t., 24 h	r.t., 8 h	trace
3	$PhI(OAc)_2$	70 °C, 30 min	r.t., 8 h	91
4	$PhI(OAc)_2$	70 °C, 30 min	70 °C, 5 min	97
5	$PhI(OCOCF_3)_2$	70 °C, 1.5 h	70 °C, 5 h	67
6	PhI(OH)OTs	70 °C, 1.5 h	70 °C, 5 h	27
7[b]	$PhI(OAc)_2$	70 °C, 15 min	70 °C, 5 h	88
8[c]	$PhI(OAc)_2$	70 °C, 24 h	70 °C, 24 h	88

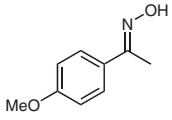
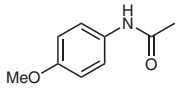
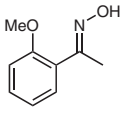
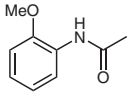
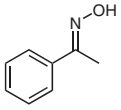
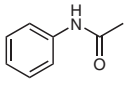
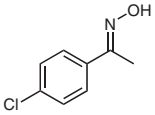
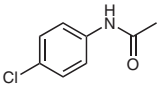
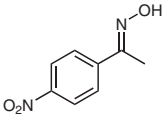
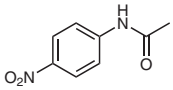
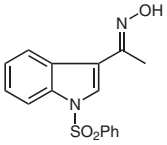
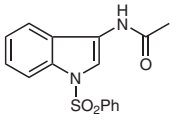
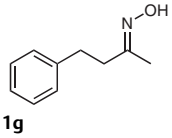
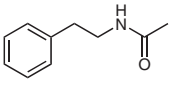
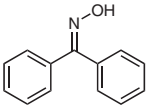
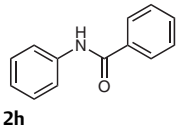
[a] CH_2Cl_2 was used as a solvent instead of CH_3CN.
[b] 2.4 equiv of $SnCl_4$ was used instead of $BF_3{\cdot}Et_2O$.
[c] 2.4 equiv of $ZnCl_2$ was used instead of $BF_3{\cdot}Et_2O$.

A plausible reaction mechanism is indicated below (Scheme 3). First, $PhI(OAc)_2$ activates the hydroxy group of the oxime by substitution with an acetoxy group. The rearrangement occurs concomitantly with the elimination of iodosobenzene and the acetoxy group. Pre-activation of $PhI(OAc)_2$ with $BF_3{\cdot}Et_2O$ form the active species[8] which may accelerate the substitution of the hydroxy group of the oxime or generate active species *in situ*. In addition, $BF_3{\cdot}Et_2O$ may suppress the nucleophilicity of the acetoxy anion, thereby preventing conversion to the corresponding ketone.[6] Then, one of the substituents of oxime **1** transfers to the nitrogen atom and the generated cation reacts with H_2O to afford the amide **2**.

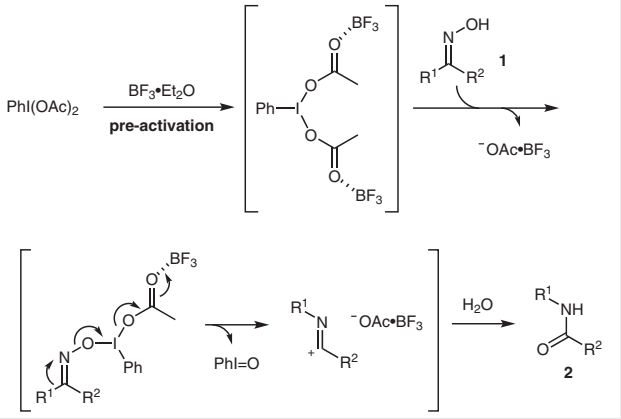
In conclusion, we developed a novel Beckmann rearrangement employing $PhI(OAc)_2$ and $BF_3{\cdot}Et_2O$. Pre-activation of $PhI(OAc)_2$ and $BF_3{\cdot}Et_2O$ was an effective means of promoting the reaction without resorting to reflux conditions.[9] Both aromatic and aliphatic ketoximes were convert-

Table 3 Substrate scope



Entry	Ketoxime **1**	Amide **2**	Time	Yield(%)
1[a]	 **1a**	 **2a**	8 h	91
2	**1a**	**2a**	5 min	97
3[a]	 **1b**	 **2b**	24 h	52
4	**1b**	**2b**	5 min	97
5	 **1c**	 **2c**	30 min	98
6	 **1d**	 **2d**	4 h	97
7[b]	 **1e**	 **2e**	19 h	79
8	 **1f**	 **2f**	1 h	90
9	 **1g**	 **2g**	5 h	70
10	 **1h**	 **2h**	15 min	94

[a] The reaction was conducted at r.t.
[b] 4.8 equiv of BF_3·Et_2O was used.



Scheme 3 Plausible reaction mechanism of $PhI(OAc)_2$–BF_3·Et_2O mediated Beckmann rearrangement

ed into their corresponding amides in good to high yields. Further investigation of the reaction mechanism and the development of a pre-activation system for $PhI(OAc)_2$ are in progress.

Funding Information

This work was partially supported by the MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2014-2018 (S1411037) and also by Grant-in-Aid for Young Scientists (B) (15K18840) from the Japan Society for the Promotion of Science (JSPS).

Acknowledgment

We thank for the fruitful and helpful comment from the reviewers.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609686.

References and Notes

(1) For recent reviews see: (a) *Hypervalent Iodine Chemistry Modern Developments in Organic Synthesis*, In *Top. Curr. Chem., Wirth, T*; Springer: Berlin, **2003**, 224. (b) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111. (c) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (d) Wirth, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3656. (e) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (f) Ochiai, M. *Synlett* **2009**, 159. (g) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073. (h) Duschek, A.; Kirsch, S. F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1524. (i) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, 517. (j) Silva, L. F.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722. (k) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.

(2) (a) Nakamura, A.; Tanaka, S.; Imamiya, A.; Takane, R.; Ohta, C.; Fujimura, K.; Maegawa, T.; Miki, Y. *Org. Biomol. Chem.* **2017**, *15*, 6702. (b) Miki, Y.; Fujita, R.; Matsushita, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2533. (c) Miki, Y.; Kobayashi, N.; Ogawa, N.; Hachiken, H. *Synlett* **1994**, 1001.

(3) (a) Hamamoto, H.; Umemoto, H.; Umemoto, M.; Ohta, C.; Fujita, E.; Nakamura, A.; Maegawa, T.; Miki, Y. *Heterocycles* **2015**, *91*, 561. (b) Miki, Y.; Umemoto, H.; Dohshita, M.; Hamamoto, H. *Tetrahedron Lett.* **2012**, *53*, 1924. (c) Hamamoto, H.; Hattori, S.; Takemaru, K.; Miki, Y. *Synlett* **2011**, 1563. (d) Hamamoto, H.; Umemoto, H.; Umemoto, M.; Ohta, C.; Dohshita, M.; Miki, Y. *Synlett* **2010**, 2593.

(4) (a) Croig, D.; Trost, B. M.; Fleming, I.; Ley, S. V. In *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, **1991**, 689. (b) Gawley, R. E. *Org. React.* **1988**, *35*, 1.

(5) (a) Ghiaci, M.; Imanzadeh, G. H. *Synth. Commun.* **1998**, *28*, 2275. (b) Thomas, B.; Sugunan, S. *Microporous Mesoporous Mater.* **2006**, *96*, 55. (c) Sugamoto, K.; Matsushita, Y.; Matsui, T. *Synth. Commun.* **2011**, *41*, 879. (d) Na, A.; Hongjun, P.; Lifeng, L.; Wenting, D.; Weiping, D. *Chin. J. Chem.* **2011**, *29*, 947.

(6) Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R. *Synth. Commun.* **1986**, *16*, 1247.

(7) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775.

(8) Izquierdo, S.; Essafi, S.; Rosal, I.; Vidossich, P.; Pleixats, R.; Vallribera, A.; Ujaque, G.; Lledós, A.; Shafir, A. *J. Am. Chem. Soc.* **2016**, *138*, 12747.

(9) **The experimental Procedures and Characterization Data**

The solution of $PhI(OAc)_2$ (0.48 mmol) and $BF_3{\cdot}Et_2O$ (0.96 mmol) in CH_3CN (1.0 mL) was stirred at 70 °C for 30 min. Then *p*-methoxyacetophenone (**1a**, 0.40 mmol) was added to the above mixture and stirred 70 °C for 5 min. Cooling to r.t., 0.5% aq Na_2SO_3 was added to the reaction mixture and extracted with $CHCl_3$. Combined organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (*n*-hexane/AcOEt = 1:1) and preparative TLC (*n*-hexane/AcOEt = 5:1) to give *N*-(4-methoxyphenyl)acetamide (**2a**, 97%) as white solid.

***N*-(4-Methoxyphenyl)acetamide (2a)**

White solid. ^{1}H NMR ($CDCl_3$): δ= 2.14 (3 H, s), 3.78 (3 H, s), 6.85 (2 H, d, J = 8.8 Hz), 7.28 (1 H, br), 7.38 (2 H, d, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ = 24.1, 55.4, 113.9, 122.0, 131.1, 156.3, 168.7.