Beckmann Rearrangement of Oximes Catalyzed with Tetrabutylammonium Perrhenate and Trifluoromethanesulfonic Acid

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The Beckmann rearrangement of oximes is catalyzed by a combined use of tetrabutylammonium perrhenate (Bu_4NReO_4) and trifluoromethanesulfonic acid in nitromethane under azeotropic conditions, giving amides in high yield. By employing this catalytic system, amides can be prepared directly from ketones and hydroxylamine hydrochloride.

The Beckmann rearrangement is often used to transform oximes into amides or lactams in organic synthesis; it is also applied to the production of ε-caprolactam as an industrial process.[1] This reaction generally requires the use of excess amounts of strong Brønsted acids, such as concentrated sulfuric acid and polyphosphoric acid, which cause serious problems, such as decomposition of the products and formation of a large quantity of inorganic salts by neutralization. It has been known that the Beckmann rearrangement also proceeds by a treatment of onium salts in a weakly basic media.[2] However, the reaction does not proceed catalytically under both of acidic and basic conditions; it is strongly desired to exploit a catalytic method of this rearrangement. Although there have been reported various kinds of heterogeneous catalysts for the vapor-phase process,[3] only two catalytic methods have been developed in the liquid-phase process by using *O*-alkyl-*N*,*N*-dimethylformamidium salt[4] and antimony (V) salt.[5]

In addition, a direct transformation of ketones into amides has been investigated via a one-pot formation of oximes and a successive Beckmann rearrangement. However, in most cases, the use of large excess amounts of strong Brønsted acids is required, and there is only one catalytic process through which the reaction proceeds with a catalytic amount of trifluoromethanesulfonic acid in formic acid.[6]

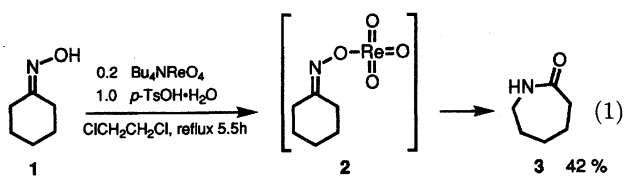
Recently, we have reported that a Beckmann rearrangement of oximes is catalyzed by tetrabutylammonium perrhenate (Bu_4NReO_4) and trifluoromethanesulfonic acid (CF_3SO_3H) in refluxing nitromethane.[7] This report describes a full account of the Beckmann rearrangement using Bu_4NReO_4 and CF_3SO_3H as catalysts, including a one-pot preparation of amides from ketones and hydroxylamine hydrochloride.

Results and Discussion

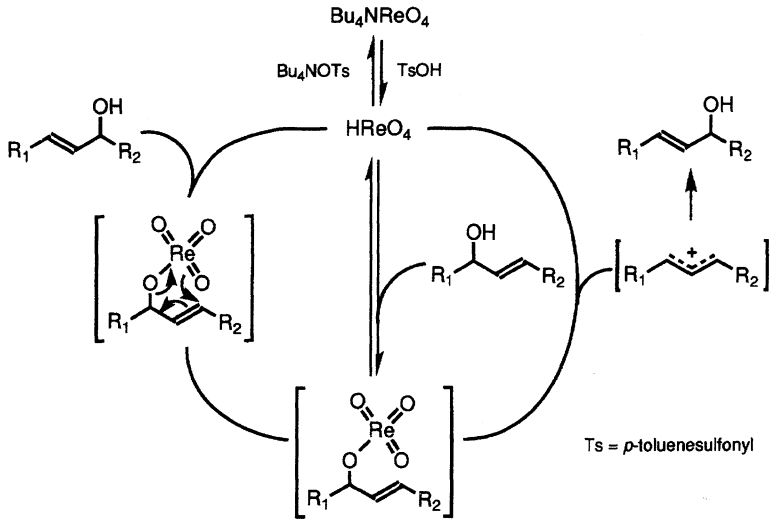
Catalytic Beckmann Rearrangement of Oximes. We have already reported on a 1,3-rearrangement of allylic and propargylic alcohols by a catalytic use of Bu_4NReO_4 and *p*-toluenesulfonic acid (*p*-TsOH·H_2O).[8] In these reactions, it was supposed that perrhenic esters were formed at first from perrhenic acid and alcohols; then, rearranged alcohols were produced via the formation of allylic cations along with an elimination of perrhenic acid or via a [3.3] sigmatropic rearrangement of the perrhenic esters (Scheme 1).

This result suggested to us that a Beckmann rearrangement of oximes would proceed catalytically by employing Bu_4NReO_4 and Brønsted acid via the formation of perrhenic ester of oximes, such as **2** (Scheme 2).

Based on the above-mentioned assumption, the Beckmann rearrangement of cyclohexanone oxime (**1**) was tried, and the treatment of **1** with a 0.2 molar amount of Bu_4NReO_4 and an equimolar amount of *p*-TsOH·H_2O in refluxing 1,2-dichloroethane gave ε-caprolactam **3** in 42% yield (Eq. 1). In the absence of Bu_4NReO_4, the reaction did not proceed at all. When an *O*-acetyl derivative of the oxime **1** was employed instead of the oxime, itself, the Beckmann rearrangement hardly occurred with the catalysts under the same reaction conditions. Hence, the reaction is considered to proceed via the oxime perrhenate **2**, as expected.



(1)

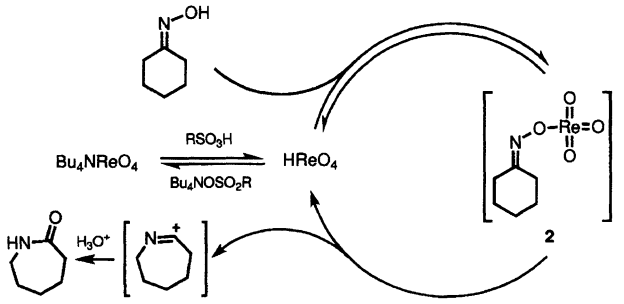


Scheme 1.

Table 1. Screening of the Reaction Conditions in the Rearrangement of **1**[a)]

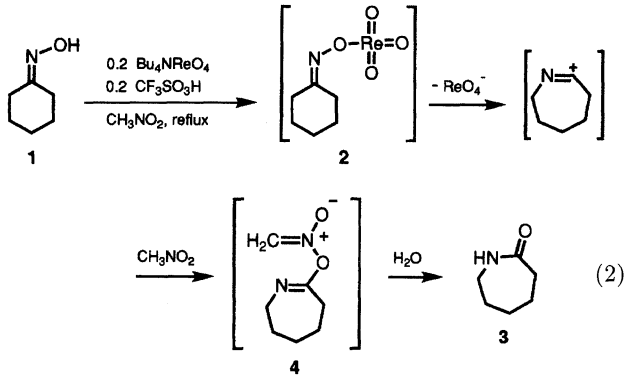
Entry	Bu_4NReO_4 (molar amount)	Acid (molar amount)	Solvent	Time (t/h)	Yield of **3** (x/%)
1	0.2	p-TsOH·H_2O (1.0)	$ClCH_2CH_2Cl$	5.5	42
2	0.2	H_2SO_4 (1.0)	$ClCH_2CH_2Cl$	5.5	13
3	0.2	CF_3SO_3H (0.4)	$ClCH_2CH_2Cl$	5	71
4	0.2	CF_3SO_3H (0.2)	$ClCH_2CH_2Cl$	8	68
5	0.2	CF_3SO_3H (0.2)	CH_3CN	7	44
6	0.2	CF_3SO_3H (0.2)	DMF[b)]	5	10
7	0.2	CF_3SO_3H (0.2)	CH_3NO_2	1	85
8	0.15	CF_3SO_3H (0.15)	CH_3NO_2	2.5	75
9	0.1	CF_3SO_3H (0.1)	CH_3NO_2	4.5	62
10	0	CF_3SO_3H (0.2)	CH_3NO_2	1	<10

a) All reactions were carried out under reflux conditions. b) The reaction was carried out at 100 °C.



Scheme 2.

By screening the reaction conditions (Table 1) it was revealed that ε-caprolactam **3** could be obtained in good yield by using only a catalytic amounts of Bu_4NReO_4 and CF_3SO_3H[9)] instead of p-TsOH·H_2O (Entry 4). The yield of the lactam **3** was considerably improved by carrying out the reaction in nitromethane (Entry 7), which was a polar solvent having a small donor number, as compared with acetonitrile (Entry 5) or *N*,*N*-dimethylformamide (DMF) (Entry 6).[10)] Presumably, nitromethane may capture the rearranged cationic intermediate effectively by forming an *aci*-nitro derivative **4** (Eq. 2), which is easily hydrolyzed to afford ε-caprolactam **3**. When the reaction was carried out using a 0.15 or 0.1 molar amount of the catalyst (Entry 8,9), the yield of the lactam **3** was decreased. Also, tetrabutylammonium perrhenate was found to be indispensable for the above reaction, because the yield of the product **3** was less than 10% when the reaction was examined only with a 0.2 molar amount of CF_3SO_3H in nitromethane (Entry 10).



(2)

Although by the reaction in nitromethane the ox-

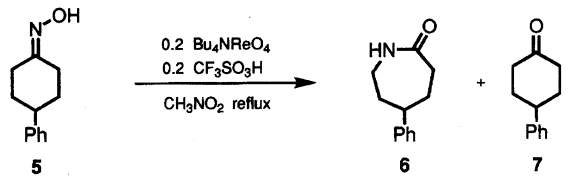


Table 2. Effect of Hydroxylamine Hydrochloride

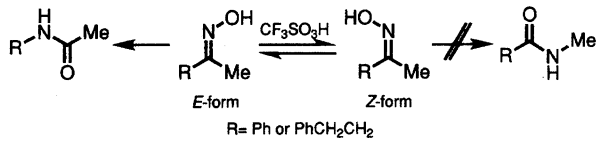
Entry	NH_2OH·HCl	Condition	Time (t/h)	Yield (x/%) 6	7
1	None	Reflux	1	79	16
2	0.5 molar amount	Reflux	2.5	91	0
3	0.5 molar amount	Azeotropic	1	91	0

ime **1** was entirely consumed, the yield of **3** was less than 90%. Since the hydrolysis of the oxime **1** to cyclohexanone was supposed to proceed as a side reaction, the reaction of 4-phenylcyclohexanone oxime (**5**) was tried under the same reaction conditions to detect the hydrolyzed product. In fact, the treatment of the oxime **5** with the catalysts in refluxing nitromethane afforded 4-phenylcyclohexanone (**7**) in 16% yield along with the corresponding lactam **6** in 79% yield (Table 2, Entry 1).

The hydrolysis could not be suppressed by adding dehydrating agents, such as sodium sulfate, magnesium sulfate, acetic anhydride, trifluoroacetic anhydride, or triethyl orthoformate. Expecting the in situ conversion of the resulting ketone **7** to the oxime **5**, the reaction of **5** was tried in the presence of a 0.5 molar amount of hydroxylamine hydrochloride (H_2NOH·HCl). The yield of the lactam **6** was increased to 91% and the ketone **7** was not detected (Table 2, Entry 2). Furthermore, the reaction was found to be accelerated by an azeotropic removal of water (Table 2, Entry 3).

The catalytic Beckmann rearrangement of several oximes was investigated under the above-mentioned reaction conditions; the results are summarized in Table 3. In most cases, the reactions proceeded smoothly under azeotropic conditions to give the corresponding amides in high yield (Entries 1—6). An aldoxime and an α-tertiary alkyl ketone oxime did not rearrange to amides, and nitriles were obtained in moderate yield by Beckmann fragmentation (Entries 7 and 8). The reaction of α,β-unsaturated ketone oxime resulted a complex mixture (Entry 9).

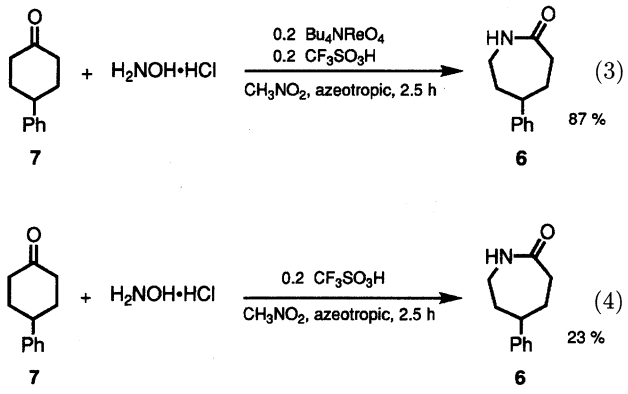
In the reactions of unsymmetrical ketone oximes, such as acetophenone oxime and benzylacetone oxime, the oximes having (E)-geometry were employed as the starting materials, and each product comprised a single amide (Table 3, Entries 4 and 6). When the rearrangement reaction of the (E)-oximes was stopped after a short reaction time, the recovered oximes were mixtures of the (E)- and (Z)-isomers (acetophenone oxime, $E:Z=3:1$; benzylacetone oxime, $E:Z=4:1$).[11] In addition, the isomerization of benzylacetone oxime



Scheme 3.

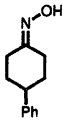
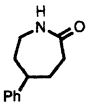
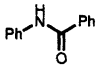
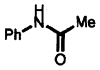
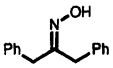
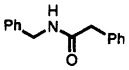
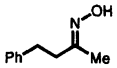
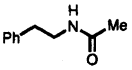
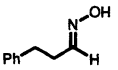
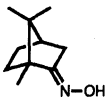
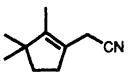
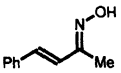
was observed by a treatment with trifluoromethanesulfonic acid in nitromethane at room temperature. These results indicated that a substituent having a higher migration ability rearranges preferentially to the nitrogen atom, regardless of the geometry of the starting oximes (Scheme 3).

One-Pot Preparation of Amides from Ketones and Hydroxylamine Hydrochloride. In the above-mentioned catalytic Beckmann rearrangement, the by-production of ketones was effectively suppressed by carrying out the reaction in the presence of H_2NOH·HCl. This result prompted us to examine the one-pot preparation of amides from ketones and hydroxylamine hydrochloride via an in situ formation of oximes. 4-Phenylcyclohexanone (**7**) was treated with a 0.2 molar amount of Bu_4NReO_4 and a 0.2 molar amount of CF_3SO_3H in the presence of a 1.2 molar amount of H_2NOH·HCl in nitromethane under azeotropic conditions. The reaction proceeded smoothly to give the lactam **6** in 87% yield, as expected (Eq. 3). In the absence of Bu_4NReO_4, the lactam **6** and the oxime **5** were obtained in only 23 and 18 %, respectively, along with recovery of the ketone **7** (Eq. 4); the yield of the lactam **6** was not improved even after a prolonged reaction time (4 h).



A catalytic direct preparation of amides from several acyclic ketones was examined to give the corresponding amides in moderate-to-good yield, as shown in Table 4. Although a small amount of the starting material was recovered in every case, the yield of the amide was not improved after a longer reaction time. Accordingly, the formation of oximes seems to be the rate-determining step in this method, and the rhenium catalyst is gradually decomposed before completing the oximation of ketones.

Table 3. Beckmann Rearrangement of Oximes[a)]

Entry	Substrate	NH_2OH·HCl (molar amount)	Time	Product	Yield (x/%)
1		0.5	1 h		84
2		0.5	1 h		91
3		0.5	20 min		98
4		0.2	1 h		94
5		0.2	40 min		88
6		0.2	2 h		88
7		0	45 min		60
8		0	30 min		69
9		0	Complex mixture		

a) All reactions were carried out using a 0.2 molar amount of Bu_4NReO_4 and a 0.2 molar amount of CF_3SO_3H in nitromethane under azeotropic conditions (MS4A).

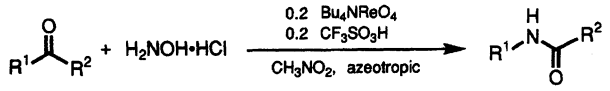


Table 4. One-Pot Preparation of Amides[a)]

R^1	R^2	Time (t/h)	Yield (x/%)
Ph	Ph	2	66
Ph	Me	2	77
$PhCH_2$	$PhCH_2$	2	58
$Ph(CH_2)_2$	Me	4	52

a) A small amount of ketone was recovered in every case.

Experimental

General. IR spectra were measured with a Horiba FT-300S spectrometer. ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker AM500 spectrometer in $CDCl_3$ using $CHCl_3$ (δ=7.24) as an internal standard. Preparative TLC was carried out on silica gel (Wakogel B-5F). Tetrabutylammonium perrhenate (Bu_4NReO_4) was purchased from Aldrich Chemical Co., Inc. and was purified by recrystallization from methanol– ether. Trifluoromethanesulfonic acid was used without purification. Hydroxylamine hydrochloride was recrystallized from water and dried under reduced pressure. Nitromethane was distilled from CaH_2 and kept under an argon atmosphere.

General Procedure for the Beckmann Rearrangement of Oximes. To a solution of dibenzyl ketone oxime (225 mg, 1.00 mmol), Bu_4NReO_4 (99.5 mg, 0.20 mmol) and trifluoromethanesulfonic acid (32.8 mg, 0.21 mmol) in CH_3NO_2 (6 ml) was added H_2NOH·HCl (15.2 mg, 0.21 mmol) at room temperature. The mixture was refluxed for 40 min under the azeotropic condition using Molecular Sieves 4A as a dehydrating agent, and was quenched with saturated aqueous sodium hydrogencarbonate. After the mixture was extracted three times with dichloromethane, the combined extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo, and the crude materials were purified by thin-layer chromatography (silica gel, benzene : methanol=95 : 5) to give *N*-(benzyl)phenylacetamide (198 mg, 88% yield).

General Procedure for the One-Pot Preparation of Amides from Ketones and Hydroxylamine Hydrochloride. To a solution of 4-phenylcyclohexanone **7** (99.6 mg, 0.57 mmol), Bu_4NReO_4 (56.3 mg, 0.12 mmol), and trifluoromethanesulfonic acid (17.1 mg, 0.12 mmol) in

CH_3NO_2 (9 ml) was added $H_2NOH \cdot HCl$ (45.1 mg, 0.65 mmol) at room temperature. The mixture was refluxed for 2.5 h under the azeotropic conditions using Molecular Sieves 4A as a dehydrating agent, and was then quenched with saturated aqueous sodium hydrogencarbonate. After the mixture was extracted three times with dichloromethane, the combined extracts were washed with brine and dried over anhydrous sodium sulfate. The solvent was then removed in vacuo, and the crude materials were purified by thin-layer chromatography (silica gel, benzene : methanol=95 : 5) to give lactam **6** (93.8 mg, 87% yield).

Spectral Data. All of the products are known compounds, and their spectral data are in good agreement with those of the literatures or the authentic samples.

Hexahydro-5-phenyl-2*H*-azepin-2-one (6) :[12] IR (KBr) 1662 cm^{-1}; ^1H NMR δ=1.67—1.82 (2H, m), 1.96—2.01 (2H, m), 2.52—2.64 (2H,m), 2.74 (1H, tt, J=3.4 and 12.1 Hz), 3.25—3.31 (1H, m), 3.37 (1H, ddd, J=4.7, 11.0 and 15.2 Hz), 6.64 (1H, bs), 7.14—7.15 (3H, m), 7.26—7.27 (2H, m); ^{13}C NMR δ=30.5, 35.6, 37.3, 42.1, 48.6, 126.5, 126.6. 128.6, 146.3, 178.5.

Benzanilide :[5] ^{1} NMR δ=7.12—7.86 (10H, m), 7.80 (1H, bs).

Acetanilide :[5] ^1H NMR δ=2.15 (3H, s), 7.08 (2H, t, J=7.4 Hz), 7.29 (2H, dd, J=7.9 and 7.4 Hz), 7.36 (1H,bs), 7.48 (1H, d, J=7.9 Hz).

***N*-(Benzyl)phenylacetamide :**[5] ^1H NMR δ=3.61 (2H, s), 4.39 (2H, d, J=5.8 Hz), 5.67 (1H, bs), 7.15—7.34 (10H, m).

***N*-Phenethylacetamide :**[13] ^1H NMR δ=1.91 (3H, s), 2.78 (2H, t, J=7.0 Hz), 3.50 (2H, dt, J=6.5 and 6.9 Hz), 5.44 (1H, bs), 7.17—7.31 (5H, m).

3-Phenylpropiononitrile :[13] ^1H NMR δ=2.60 (2H, t, J=8.5 Hz), 2.94 (2H, t, J=8.5 Hz), 7.20—7.35 (5H, m); ^{13}C NMR δ=19.3, 31.5, 119.1, 127.3, 128.3, 128.8, 138.0.

(2,3,3-Trimethylcyclopent-1-en-1-yl)acetonitrile : IR (neat) 2249 cm^{-1}; ^1H NMR δ=0.95 (6H,s), 1.51 (3H, s), 1.66 (2H, t, J=7.2 Hz), 2.32 (2H, bs), 3.05 (2H, s); ^{13}C NMR δ=9.55, 17.32, 26.13, 26.13, 32.39, 38.26, 47.18, 117.76, 121.50, 144.67.

We thank Sumitomo Chemical Co., Ltd. for the kind gift of tetrabutylammonium perrhenate.

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9) In the absence of Bu_4NReO_4, the reaction hardly proceeded even by the use of trifluoromethanesulfonic acid in dichloroethane.

10) Donor number: $ClCH_2CH_2Cl$ 0, CH_3NO_2 2.7, CH_3CN 14.1, DMF 26.6. Concerning donor ability of solvents, see : V. Gutmann, "The Donor–Acceptor Approach to Molecular Interactions," Plenum, New York (1978).

11) Geometry of the oximes and the ratio of *E* and *Z* were determined by ^1H NMR analysis. For assignment of the geometry, see : E. Pretsch, T. Clerc, J. Seibl, and W. Simon, "Tables of Spectral Data for Structure Determination of Organic Compounds," 2nd ed, Springer-Verlag, New York (1989).

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13) The spectral data were in good agreement with those of the authentic sample.