Efficient Iodine-Mediated Beckmann Rearrangement of Ketoximes to Amides under Mild Neutral Conditions

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Abstract: Aryl ketoximes readily underwent Beckmann rearrangement to give N-substituted amides in excellent yields on electrophilic activation by elemental iodine in anhydrous acetonitrile under reflux. The main advantages of this environmentally friendly protocol include a high selectivity as a result of the absence of any accompanying deprotection to form the parent ketones as byproducts, mild neutral conditions, procedural simplicity, and particularly ease of isolation of the products.

Key words: rearrangements, amides, ketoximes, catalysis, Beckmann rearrangements

The Beckmann rearrangement of ketoximes to N-substituted amides is an organic transformation of immense synthetic and mechanistic importance.[1] This rearrangement of ketoximes, which are readily prepared from the corresponding ketones, provides an atom-economic connection between the vast chemical space of ketones, with their remarkable synthetic flexibility, and that of amides and lactams. The products are widely used in drugs and pharmaceuticals, and they also have host of industrial applications as detergents, lubricants, and raw materials for polyamides such as nylon-6 and nylon-12.[2] Alternative routes to amides by the reaction of amines with activated carboxylic acid derivatives, such as acid chlorides or acid anhydrides, are less atom-economical and they involve the use of noxious chemicals and the production of hazardous waste materials. Mechanistically, the Beckmann rearrangement of ketoximes involves the migration of an aryl or alkyl moiety from carbon to nitrogen triggered by the departure of the oximic hydroxy group with concomitant cleavage of a C–C bond and formation of a C–N bond. The success of the rearrangement hinges on the electrophilic activation of the hydroxy function, which is normally a poor nucleofuge. Conventional methods for this activation are based on the use of strong Brønsted or Lewis acids, such as concentrated sulfuric acid, hydrogen chloride in acetic anhydride, or phosphorus pentachloride in diethyl ether.[1,3] These protocols are performed under harsh conditions and they are incompatible with acid-sensitive substrates. The neutralization of excess acids by a base, such as ammonia or a metal hydroxide, during the workup and isolation of the products is also somewhat problematic because of the strong affinity between the acidic reagents and basic amides.[4] This process also generates large amounts of waste, in the form of ammonium or metal sulfates, particularly in large-scale industrial processes such as the production of ε-caprolactam, in which concentrated sulfuric acid is used. To circumvent these limitations, and in response to the current concern for the development of environmentally benign chemical processes, the rearrangement has been explored in the vapor phase, in the liquid phase, and under solvent-free conditions. Vapor-phase methods, with a particular focus on the sulfate-free industrial production of ε-caprolactam, have been performed by using heterogeneous solid catalysts, such as high-silica zeolites,[5] metal oxides,[6] or clays[7] at temperatures as high as 300 °C. These methods frequently suffer from low selectivities and rapid decay of the activity of the catalyst as a result of the high temperatures that are used. Liquid-phase procedures have been attempted using chlorosulfonic acid in *N*,*N*-dimethylformamide,[8] ethyl chloroformate and boron trifluoride diethyl etherate,[9] anhydrous oxalic acid,[10] 2,2,2-trichloroethane-1,1-diol (chloral hydrate),[11] or organocatalysts such as sulfamic acid,[4] bis(2-oxo-3-oxazolidinyl)phosphinic chloride,[12] cyanuric chloride in *N*,*N*-dimethylformamide,[13] diethyl chlorophosphate,[14] triphosphazene[15] and poly(ethylene glycol)-ω-sulfonic acid,[16] an *O*-alkyl-*N*,*N*-dimethylformamidium salt,[17] iron(III) chloride impregnated silica gel (silferc catalyst),[18] iron(III) chloride and montmorillonite K-10[19] catalyst, or mercury(II) chloride.[20] Recently, attempts have been made to use room-temperature ionic liquids with Brønsted acidity[21] or supercritical water[22] as alternative green media for the reaction, but these have had mixed success. In addition to their limitations in terms of low yields and the formation of byproducts, existing approaches often require reagents that are expensive, noxious, or need to be prepared before use; they also require toxic solvents and frequently involve cumbersome procedures, such as high-vacuum operations.[11] There was therefore a need to develop a simple mild protocols for the synthesis of N-substituted amides from ketoximes.

As part of our continuing program aimed at developing synthetic protocols based on the use of elemental iodine as a mild, water-compatible, Lewis acid in catalytic or substoichiometric amounts,[23] we became interested in evaluating it as a reagent for the Beckmann rearrangement. We were encouraged in this search by recent reports in the literature on the use of iodine as a catalyst in the coupling of homoallylic alcohols with aldehydes to give tetrahydro-

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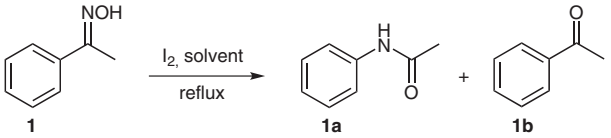
pyrans (the Prins cyclization)[24] and in hydroperoxidations of carbonyl compounds with *tert*-butyl hydroperoxide.[25]

We chose acetophenone oxime (**1**) as a representative substrate, and subjected it to reactions with various amounts of finely pulverized iodine in various solvents under reflux. The results of our initial exploratory experiments are summarized in Table 1. It is pertinent to mention here that attempts to conduct the reaction at lower temperatures, even with prolonged exposure, were dismal failures. Our experiments showed that the conversion to amide is markedly dependent on the nature of the solvent used. Anhydrous acetonitrile proved to be the medium of choice, whereas nonpolar dichloromethane or coordinating polar or hydroxylic solvents such as tetrahydrofuran, *N*,*N*-dimethylformamide, or methanol were unsuitable as reaction media.

Table 1 Optimization of the Iodine-Mediated Beckmann Rearrangement of Acetophenone Oxime (**1**)



1 **1a** **1b**

Entry	I_2 (mol%)	Solvent (mL)	Time (h)[a]	Yield of **1a** (%)[b]	Yield of **1b** (%)
1	10	MeCN (4)	3	65	10
2	20	9:1 MeCN–H_2O (4)	2	30	45
3	20	anhyd MeCN (4)	2	90	–
4	50	anhyd MeCN (4)	1	98	–
5	100	anhyd MeCN (4)	1	96	–
6	50	CH_2Cl_2 (4)	3	–	–
7	50	anhyd MeOH (4)	4	25	10
8	50	anhyd THF (4)	4	–	–
9	50	DMF (4)	3[c]	20	–

[a] Reactions were performed on a 1-mmol scale, and the amounts of I_2 and solvent used refer to 1 mmol of substrate.
[b] Isolated yields after column chromatography.
[c] The reaction was carried out at 100 °C.

The special facilitating role of acetonitrile is presumably linked to the absence of any significant interaction between it and iodine, thereby allowing the latter to assist in the departure of hydroxy groups by electrophilic activation, whereas hydroxylic solvent such as methanol, or strongly coordinating solvents such as tetrahydrofuran and *N*,*N*-dimethylformamide, deactivate iodine and inhibit its activity as a catalyst. This explanation is confirmed by an analogous effective partnership between iodine and acetonitrile in the iodine-catalyzed elimination of a hydroxy group during the hydroperoxidation of carbonyl compounds.[25] Selectivity was seriously compromised by the presence of water in the acetonitrile, resulting in substantial deoximation to acetophenone. Notably, there is precedent in the literature for catalytic deoximation by iodine in water in the presence of an anionic surfactant (sodium dodecylsulfate),[26] which provides micellar solubilization as well as activation of the iodonium ion.[27] Water presumably impedes the rearrangement process by coordinating with iodine, thereby encouraging the competitive deoximation process. A reaction using 50 mol% of iodine in anhydrous refluxing acetonitrile gave excellent results in terms of the yield and reaction time (98%, 1 h), and these conditions proved to be optimal.[28] To establish the scope and generality of the method, a wide range of ketoximes of various degrees of reactivity were treated with iodine under the optimized reaction conditions (Table 2).

Acetophenone oxime or its derivatives bearing activating (methoxy, *O*-allyl, or amino), moderately activating (acetoxy, acetoxamido), or electroneutral (methyl) groups were smoothly converted into the corresponding N-substituted amides exclusively in yields of 88% to near-quantitive, without any accompanying cleavage of the ketones. The structure of the amide formed was not perceptibly influenced by the sterochemical identity (*E*/*Z*) of the oxime, and aryl moieties always migrated in preference to methyl groups. Presumably, *E* or *Z* oximes interconvert under the conditions of the reaction.[13b,28] Hydroxy derivatives of acetophenone oxime showed greater reluctance to undergo rearrangment than did their less-activated methoxy or acetoxy counterparts, which is contrary to what would be expected on electronic grounds. This was particularly the case for *ortho*-hydroxy derivatives. It is possible that the presence of a free hydroxy group impedes the reaction by providing an alternative coordination site for iodine and this, coupled with a steric factor, decreases the reaction rate for *ortho*-hydroxy derivatives. An unfavourable effect of a hydroxy group on the aromatic ring was also evident in the case of (4-hydroxyphenyl)(phenyl)methanone oxime (entry 12).

The current procedure was successfully extended to oximes of cyclic ketones or 1-(2-thienyl)ethanone and to aliphatic and α,β-unsaturated ketones. The conversion of cyclohexanone into ε-caprolactam constitutes the most important industrial application of the Beckmann rearrangement. Unfortunately, our procedure proved unsuccessful with cyclohexanone oxime under the optimized conditions, yielding ε-caprolactam in a disappointingly low yield of 6% along with intractable products. To our delight, however, the conversion was clean and smooth with 20 mol% of iodine, giving ε-caprolactam in 90% yield within one hour. In all the cases investigated, the migration of the aryl moiety was unidirectional and a single product was always isolated. Aryl aldoximes, such as oximes of 1,3-benzodioxole-5-carbaldehyde or 4-hydroxy-3-methoxybenzaldehyde (vanillin) (entries 18 and 19), remained mostly unchanged and gave only about 15–22% of the parent aldehydes upon sluggish deoximation. Dehydration of aldoximes to aryl nitriles, which frequently occurs under the influence of strong acids[10] or bases,[16]

was excluded here because of the mild neutral nature of the reagent.

To explain the role of iodine in the Beckmann rearrangement of aryl ketoximes, we propose the following tentative catalytic cycle (Scheme 1); this, however, is purely hypothetical at the current stage of investigation.

In conclusion, we have developed a greener procedure for the Beckmann rearrangement of ketoximes mediated by iodine, as a nonmetallic Lewis acid, in anhydrous acetonitrile. Among the attractive features of this protocol are its use of and inexpensive readily available reagent under mild and neutral reaction conditions that are tolerated by several common functional groups, its simple trouble-free operational conditions, and its freedom from demanding separation procedures for the isolation of products.

Table 2 Iodine-Mediated Beckmann Rearrangements of Oximes in Anhydrous Acetonitrile

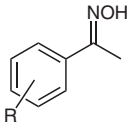
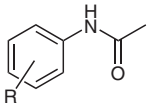
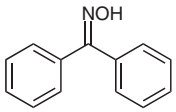
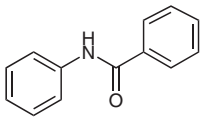
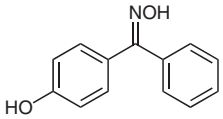
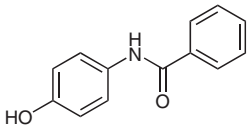
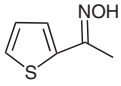
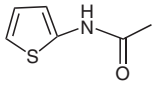
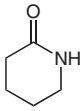
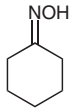
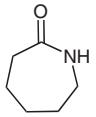
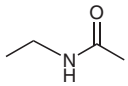
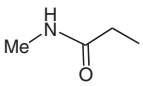
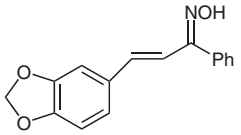
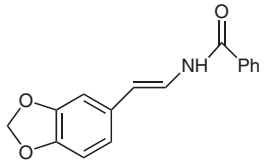
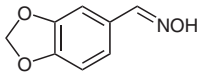
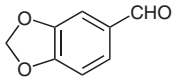
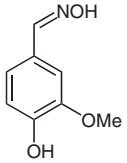
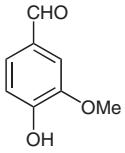
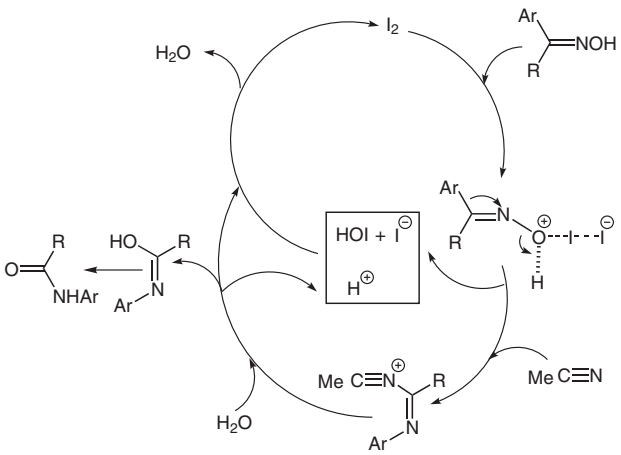
Entry	Substrate	Product	Time (h)[a]	Yield (%)[b]
				
	R = H			
1	R = 4-OMe		1	98
2	R = 4-Me		0.5	97
3	R = 4-OAc		1	>99
4	R = 4-OAllyl		4	88
5	R = 4-OH		2.5	96
6	R = 4-NH_2		1.5	95
7	R = 4-NHAc		4	90
8	R = 2-OH		3	88
9	R = 2-OAc		6	85
10			3	90
11			2	98
12			5	85
13			4 h	86
14			1 h	88
15			1 h[c]	90
				
		70%		
16			2 h	95
				
		30%		

Table 2 Iodine-Mediated Beckmann Rearrangements of Oximes in Anhydrous Acetonitrile (continued)

Entry	Substrate	Product	Time (h)[a]	Yield (%)[b]
17			4 h	97
18			5 h	15
19			5 h	22

[a] Reaction conditions: I_2 (50 mol%), anhyd MeCN (4 mL), reflux.
[b] Refers to isolated yield after chromatographic purification; the amide or lactam products are known compounds with physical and spectral properties that agreed closely with those reported in the literature.
[c] Reaction conditions: I_2 (20 mol%), anhyd MeCN (4 mL), reflux.



Scheme 1 Tentative catalytic cycle for the iodine-mediated Beckmann rearrangement

$H_2NOH{\cdot}HCl$ and I_2 were obtained from Merck, Germany and SRL, India, respectively. IR spectra were recorded on a Perkin-Elmer FTIR L120-000A, NMR spectra were recorded on Bruker AM-300L (300 MHz), and mass spectra were recorded on an Applied Biosystems MDS Sciex API 3200. Silica gel (60–120 mesh; Spectrochem, India) was used for column chromatographic separations and purifications. PE refers to the fraction boiling at 60–80 °C. The amide and lactam products are known compounds with physical and spectral properties that agreed closely with those reported in the literature.

N-(4-Hydroxyphenyl)benzamide (Table 2, Entry 12); Typical Procedure

Finely pulverized I_2 (131 mg, 0.516 mmol) was added to a soln of (4-hydroxyphenyl)(phenyl)methanone oxime (220 mg, 1.032 mmol) in anhyd MeCN (5 mL), and the mixture was refluxed for 5 h (TLC monitoring). The solvent was removed at reduced pressure (water suction), and the residue was treated with 10% aq $Na_2S_2O_3$ (5 mL). The mixture was extracted with EtOAc (3 × 5 mL), and the combined extracts were washed with brine (2 × 3 mL), dried (Na_2SO_4), and concentrated. The residue was filtered through a short pad of silica gel (60–120 mesh, Spectrochem, India) using EtOAc–PE (2:3) as an eluent to afford a white crystalline solid; yield: 187 mg (85%); mp 210–212 °C (lit.[29] 214–216 °C).

IR (KBr): 3335, 1651, 1611, 1597, 1580, 1537, 1514, 1439, 1376, 1323, 1251, 1175, 827 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 6.7 (d, J = 9.2 Hz, 2 H), 7.44–7.52 (m, 5 H), 7.88 (d, J = 9.2 Hz, 2 H), 9.21 (s, 1 H), 9.97 (s, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 115.0, 122.3, 127.5, 128.4, 130.8, 131.3, 135.3, 153.8, 161.9.

DEPT-135 NMR: δ = 115.0, 122.3, 127.5, 128.4, 131.3.

MS (ESI): m/z = 236.1 $[M + Na]^+$.

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