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Cu(OTf)₂-catalyzed Beckmann Rearrangement of Ketones Using Hydroxylamine-*O*-sulfonic Acid (HOSA)

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Abstract

The Beckmann Rearrangement (BKR) of ketones to secondary amides often requires harsh reaction conditions that limit its practicality and scope. Herein, we describe the Cu(OTf)₂-catalyzed BKR of ketones under mild reaction conditions using hydroxylamine-*O*-sulfonic acid (HOSA), a commercial water soluble aminating agent. This method is compatible with most functional groups and directly provides the desired amides in good to excellent yields.

Graphical Abstract

Keywords

Hydroxylamine-*O*-sulfonic acid (HOSA); Ketone; Beckmann Rearrangement; Cu(OTf)₂; Secondary amide

The Beckmann rearrangement (BKR) is a popular method for the formation of amides from ketones and aldehydes via an oxime intermediate.¹ The conversion of an oxime into an amide was done firstly by German chemist Ernst Otto Beckmann in 1886.² Notably, the BKR enjoys a prominent industrial role including the manufacture of monomer for polymerization into nylon-6 and nylon-12.³ Also, amides are common components in drugs, natural products, agrochemicals and functional materials (Fig. 1).^{4,5}

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Supporting Information: Copies of ¹H and ¹³C NMR spectra.

The traditional BKR requires harsh conditions such as high reaction temperatures and strongly acidic media, thus restricting the variety of suitable substrates; often, the process requires isolation of the oxime intermediate which can be labile and involves a cumbersome purification process (Scheme 1a,b).⁶ More recent modifications have addressed these limitations via catalysis with transition metals,⁷ calcium complexes,⁸ organocatalysts,^{9–13} inorganic Lewis acids,¹⁴ and boronic acid.¹⁵ Nevertheless, the need for a mild, inexpensive, and environmentally friendly procedure, especially for the direct conversion from ketones¹⁶, still persists.

Hydroxylamine-*O*-sulfonic acid (HOSA) attracted our attention for the BKR because it is commercial, inexpensive, water soluble, and readily handled.¹⁷ Indeed, it has found sporadic utility in the BKR,¹⁸ but primarily with aliphatic ketones. With aromatic ketones or hindered systems, strong acid and/or high temperatures are still required.¹⁹ Fortuitously, we had observed early transition metal salts, especially Cu(OTf)₂, accelerated the condensation and rearrangement of aromatic ketones with HOSA.

To actualize our aim, an introductory study was done using 2-methoxyacetophenone (**1a**) as a representative substrate along with HOSA and Cu(OTf)₂ at rt (Table 1). Our investigation to optimize the reaction parameters to obtain amide **2a** from **1a** showed base was needed to commence the reaction. With Lithium hydroxide (LiOH), 95% of the starting material **1a** was consumed and the expected amide was obtained in 85% yield along with 10% of oxime **3a** (Table 1, entry 1). The most satisfactory result was achieved with cesium hydroxide monohydrate (CsOH·H₂O) in which the desired amide **2a** was obtained in 88% yield (entry 7) whereas other mild bases were not very effective (Table 1, entries 2–5) or in the case of K₂CO₃ proved ineffective (entry 6).

Finally, a variety of solvents were screened including hexafluoroisopropanol (HFIP), 2,2,2-trifluoroethanol (TFE), methanol, ethyl alcohol, tetrahydrofuran (THF), acetonitrile, dichloromethane and a mixture of TFE/CH₂Cl₂ (1:4) (Table 1). While HFIP and TFE delivered amide **2a** in comparable yields (83% and 84%, respectively; entries 8 and 9), a mixture of TFE/CH₂Cl₂ was best for both the yield of amide **2a** (88%, entry 7) and for solubilization of ketones. Only acetonitrile, despite its frequent use in amidation reactions, failed to support the BKR (entry 14).

Having established the optimum reaction conditions, the scope of the methodology was evaluated with a range of representative ketones (Scheme 2). Generally, acetophenones with strong aryl electron donating groups reacted smoothly at rt to deliver the derived *N*-phenylacetamides in very good yields, e.g., phenol **2b**, 4-methoxy **2c**, 3,4-dimethoxy **2d**, and 4-allyloxy **2e**. The latter example is noteworthy for its chemoselectivity, i.e., no allylic²⁰ or C-H amination²¹ or aziridination^{17c} under the reaction conditions. In contrast, 4-tolyl **2f**, phenyl **2g**, and naphthyl **2h** required heating for a reasonable reaction rate, although rt reactivity was restored in the homologous **2i**, **j**. The halogenated ketones **2l–n** were well behaved and provided good yields of amide, except for 4'-fluoroacetophenone which was less reactive, as it delivered the corresponding amide **2k** with only 25% of yield at 70 °C in 24h. The BKR of benzophenone and 3-acetylindole furnished **2o** and **2p**, respectively, albeit in modest yields. Lactams **2q–t** were readily obtained from the corresponding cyclic ketones

in high yields. Following upon well-established migratory priorities, estrone 3-methyl ether and hex-2-one led to **2u** and **2v**, respectively.

We propose the Cu(OTf)₂ has a dual role in catalyzing the BKR (Figure 2). Firstly, as a mild Lewis acid, it assists in the formation of the transient ketoxime intermediate **A** that could be observed in some cases. Secondly, by way of the five membered transition state **B**, the copper catalyzes the migration of the R' group to the nitrogen from which the Beckmann product is finally obtained.

In conclusion, we have developed an operationally simple, one pot BKR route to secondary amides directly from ketones using inexpensive, easily handled HOSA as aminating agent via Cu(II)-catalysis.

Reactions, unless otherwise stated, were carried out with magnetic stirring open to the atmosphere in oven dried glassware. Reagents were used as received, unless otherwise noted. TLC used precoated plates (Merck silica gel 60, F₂₅₄) and was visualized with UV light and/or charring after dipping in PMA or KMnO₄ solution. The compounds were purified by triturating the crude reaction mixture under hexane or by flash column chromatography using silica gel (100–200 mesh) with ethyl acetate:hexane as eluent. ¹H and ¹³C NMR spectra were recorded at 400 and 100 MHz, respectively, in CDCl₃ or DMSO-*d*₆ as solvent. Chemical shifts δ are reported in parts per million (ppm) relative to residual undeuterated solvent as an internal reference (¹H δ 7.26 and ¹³C δ 77.0 for CDCl₃, δ 2.50 and 39.52 for DMSO-*d*₆ respectively). The following abbreviations are used to indicate NMR peak multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br s = broad singlet.

General procedure for synthesis of amides from ketones

To a stirring rt solution of Cu(OTf)₂ (0.05 mmol, 10mol%) in TFE/CH₂Cl₂ (1:4) (2–3 mL) were added ketone (0.5 mmol, 1.0 equiv), HOSA (2.0 equiv) and CsOH·H₂O (2.0 equiv). The reaction mixture was maintained at the temperature and for the time indicated in Table 2. After completion, the reaction mixture was diluted with CH₂Cl₂ (10 mL) and washed with saturated aqueous Na₂CO₃ (3×5 mL). The organic layer was washed with brine solution (5 mL) and dried over anhydrous Na₂SO₄. The crude product obtained after removal of all volatiles in vacuo was purified via SiO₂ (100–200 mesh) chromatography using ethyl acetate/hexane as eluent.

N-(2-methoxyphenyl)acetamide (**2a**)²²

Yield: 73 mg (88%); solid, mp 72–74 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.35 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.77 (s, 1H), 7.03 (td, *J* = 7.8, 1.7 Hz, 1H), 6.95 (td, *J* = 7.8, 1.5 Hz, 1H), 6.87 (dd, *J* = 8.1, 1.5 Hz, 1H), 3.88 (s, 3H), 2.20 (s, 3H).

N-(4-Hydroxyphenyl)acetamide (2b)²³

Yield: 60 mg (80%); brown solid, mp 170–171 °C.

¹H NMR (400 MHz, DMSO-d₆): δ = 9.64 (s, 1H), 9.13 (s, 1H), 7.33 (d, *J* = 8.9 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 1.98 (s, 3H).

N-(4-Methoxyphenyl)acetamide (2c)¹⁵

Yield: 82 mg (86%); white solid, mp 129–130 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.41–7.35 (m, 2H), 6.87–6.81 (m, 2H), 3.78 (s, 3H), 2.14 (s, 3H).

N-(3,4-Dimethoxyphenyl)acetamide (2d)²⁴

Yield: 78 mg (80%); white solid, mp 126–127.7 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.30 (d, *J* = 2.3 Hz, 1H), 6.87–6.70 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 2.15 (s, 3H).

N-(4-(Allyloxy)phenyl)acetamide(2e)²⁵

Yield: 82 mg (86%); white solid, mp 94–95 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.37 (d, *J* = 8.7 Hz, 2H), 7.14 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.04 (ddd, *J* = 21.8, 10.4, 5.2 Hz, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 4.51 (d, *J* = 5.1 Hz, 2H), 2.15 (s, 3H).

N-(p-tolyl)Acetamide (2f)²³

Yield: 63 mg (85%); white solid, mp 151–152 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.37 (d, *J* = 8.3 Hz, 2H), 7.25 (br s, 1H), 7.11 (d, *J* = 8.1 Hz, 2H), 2.31 (s, 3H), 2.15 (s, 3H).

N-Phenylacetamide (2g)²⁶

Yield: 54 mg (80%); white solid, mp 114–115 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.49 (d, *J* = 7.7 Hz, 2H), 7.31 (t, *J* = 7.9 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 2.17 (s, 3H).

N-(Naphthalen-2-yl)acetamide(2h)²⁷

Yield: 65 mg (70%); off white solid, mp 133–135 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.18 (br s, 1H), 7.80–7.77 (m, 3H), 7.48–7.37 (m, 4H), 2.24 (s, 3H).

N-Phenylpropionamide (2i)¹³

Yield: 63 mg (85%); white solid, mp 107–108 °C.

¹H NMR (CDCl₃, 400 MHz): δ = 7.52 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.26 (br, 1H), 7.10 (t, J = 7.4 Hz, 1H), 2.38 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H).

N-Phenylisobutyramide (2j)⁹

Yield: 88 mg (81%); white solid, mp 109–111 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.53 (d, J = 8.0 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.09 (t, J = 7.3 Hz, 1H), 2.51 (sept, J = 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 6H).

N-(4-Fluorophenyl)acetamide (2k)²⁸

Yield: 19 mg(25%);white solid; mp 153–154.6 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.45 (dd, J = 8.8, 4.8 Hz, 2H), 7.31 (br s, 1H), 7.00 (t, J = 8.6 Hz, 2H), 2.16 (s, 3H).

N-(4-Bromophenyl)acetamide (2l)²⁸

Yield: 65 mg (60%); white solid, mp 167–169 °C

¹H NMR (400 MHz, CDCl₃): δ = 7.47–7.36 (m, 4H), 7.23 (br s, 1H), 2.17 (s, 3H).

N-(3-Bromophenyl)acetamide (2m)²⁹

Yield: 75 mg (70%); white solid, mp 81–83 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.81 (s, 1H), 7.69 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 16.1, 4.4 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 2.22 (s, 3H).

N-(2,4-Dichlorophenyl)acetamide (2n)³⁰

Yield: 38 mg (70%); brown solid, mp 142–144 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.34 (d, J = 8.7 Hz, 1H), 7.55 (s, 1H), 7.38 (d, J = 1.7 Hz, 1H), 7.28–7.22 (m, 1H), 2.24 (s, 3H).

N-Phenylbenzamide (2o)¹³

Yield: 49mg (50%); white solid, mp 164–165 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, J = 7.8 Hz, 2H), 7.80 (s, 1H), 7.64 (d, J = 8.1 Hz, 2H), 7.56 (t, J = 7.0 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.16 (t, J = 7.2 Hz, 1H).

N-(1-Tosyl-1H-indol-3-yl)acetamide(2p)¹⁵

Yield: 82 mg (50%); white solid, mp 193–194 °C.

¹H NMR (400 MHz, CDCl₃): δ = 8.20 (s, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.41–7.32 (m, 2H), 7.28–7.26 (m, 1H), 7.25–7.22 (m, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H).

7-Phenylazepan-2-one (2q)³¹

Yield: 76 mg (80%); white solid, mp 134–136 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.41–7.21 (m, 5H), 6.18 (br s, 1H), 4.46 (d, *J* = 9.3 Hz, 1H), 2.66–2.49 (m, 2H), 2.11–1.83 (m, 4H), 1.76–1.57 (m, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 177.93, 141.92, 129.18, 128.22, 126.24, 58.85, 36.91, 36.79, 29.78, 22.91.

1,3,4,5-Tetrahydro-2H-benzo[b]azepin-2-one (2r)²⁷

Yield: 61 mg (75%); white solid, mp 137–139 °C.

¹H NMR (400 MHz, CDCl₃): δ = 7.56 (br s, 1H), 7.25–7.20 (m, 2H), 7.16–7.10 (m, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 2.80 (t, *J* = 7.2 Hz, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.27–2.21 (m, 2H).

Azacyclotetradecan-2-one (2s)³²

Yield: 96 mg (89%); white solid, mp 155–157 °C.

¹H NMR (400 MHz, CDCl₃): δ = 5.57 (br s, 1H), 3.36–3.26 (m, 2H), 2.25–2.15 (m, 2H), 1.76–1.61 (m, 2H), 1.54–1.44 (m, 2H), 1.43–1.20 (m, 16H).

¹³C NMR (101 MHz, CDCl₃): δ = 173.10, 38.46, 36.27, 28.31, 26.49, 25.79, 25.71, 25.63, 25.41, 25.26, 23.95, 23.70, 23.13.

5-(tert-Butyl)azepan-2-one (2t)³³

Yield: 73 mg (85%); semi solid.

¹H NMR (400 MHz, CD₃OD): δ = 3.33–3.25 (m, 2H), 2.58–2.48 (m, 1H), 2.16 (td, *J* = 13.4, 4.9 Hz, 1H), 2.07–1.94 (m, 2H), 1.84 (td, *J* = 13.9, 5.4 Hz, 1H), 1.37–1.14 (m, 3H), 0.90 (s, 9H); ¹³C NMR (101 MHz, CD₃OD) δ 167.50, 48.46, 33.23, 32.60, 28.76, 27.91, 27.64, 26.76.

(4aS, 4bR, 10bS, 12aS)-8-methoxy-12a-methyl-3,4,4a,4b,5,6,10b,11,12,12a-decahydronaphtho[2,1-f]quinolin-2(1H)-one (2u)³⁴

Yield: 126 mg (85%); white solid, mp 220–222 °C

¹H NMR (400 MHz, CDCl₃): δ = 7.18 (d, *J* = 8.6 Hz, 1H), 6.76–6.46 (m, 3H), 3.77 (s, 3H), 2.93–2.79 (m, 2H), 2.56–2.34 (m, 4H), 2.15–1.99 (m, 2H), 1.89–1.81 (m, 1H), 1.77–1.66 (m, 1H), 1.58–1.25 (m, 5H), 1.19 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 171.96, 157.65, 137.57, 131.79, 126.17, 113.52, 111.69, 55.21, 54.49, 46.49, 43.28, 39.85, 39.34, 30.65, 29.88, 26.67, 26.21, 22.19, 19.83.

***N*-Butylacetamide (2v)³⁵**

Yield: 82 mg (50%); clear oil.

¹H NMR (400 MHz, CDCl₃): δ = 5.66 (s, 1H), 3.26–3.18 (m, 2H), 1.95 (s, 3H), 1.52–1.41 (m, 2H), 1.38–1.28 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Amide bonds in drug molecules.

(a) Traditional approach **(b) Recent developments in amide synthesis** **(c) This work** **Scheme 1.**

Beckmann rearrangement of ketones and recent variations.

Scheme 2.

One pot synthesis of secondary amides from ketones

Scheme 3.

Proposed mechanism for $\text{Cu}(\text{OTf})_2$ catalyzed Beckmann rearrangement

Table 1:

Optimization of reaction conditions^a

Entry	Base	Solvent	Yield (%)	
			2a	3a
1 ^b	LiOH	TFE/CH ₂ Cl ₂ (1:4)	85	10
2 ^c	Na ₂ CO ₃	TFE/CH ₂ Cl ₂ (1:4)	10	0
3 ^d	Et ₃ N ^e	TFE/CH ₂ Cl ₂ (1:4)	60	40
4 ^d	Pyridine	TFE/CH ₂ Cl ₂ (1:4)	60	40
5 ^d	DMAP ^f	TFE/CH ₂ Cl ₂ (1:4)	40	60
6 ^g	K ₂ CO ₃	TFE/CH ₂ Cl ₂ (1:4)	NR	
7 ^d	CsOH·H ₂ O	TFE/CH ₂ Cl ₂ (1:4)	88	0
8 ^d	CsOH·H ₂ O	HFIP	83	0
9 ^d	CsOH·H ₂ O	TFE	84	0
10	CsOH·H ₂ O	MeOH	10	90
11 ^h	CsOH·H ₂ O	EtOH	0	50
12 ⁱ	CsOH·H ₂ O	THF	0	30
13	CsOH·H ₂ O	CH ₂ Cl ₂	10	90
14 ^g	CsOH·H ₂ O	CH ₃ CN	NR	

^aReaction Conditions: Cu(OTf)₂ (0.1equiv), HOSA (2 equiv.), CsOH·H₂O (2equiv.), TFE/CH₂Cl₂ (1:4), rt, 14h. TFE = 2,2,2-trifluoroethanol.^b5% **1a** recovered.^c90% **1a** recovered.^d100% **1a** consumed.^eTriethylamine.^f4-Dimethylaminopyridine.^gNR = no reaction.^h50% **1a** recovered.ⁱ70% **1a** recovered.