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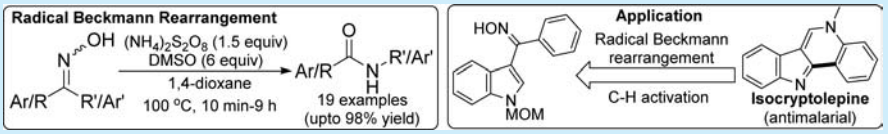
Radical Beckmann Rearrangement and Its Application in the Formal Total Synthesis of Antimalarial Natural Product Isocryptolepine via C−H Activation

Pankaj S. Mahajan, Vivek T. Humne, Subhash D. Tanpure, and Santosh B. Mhaske*

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411 008, India

Supporting Information



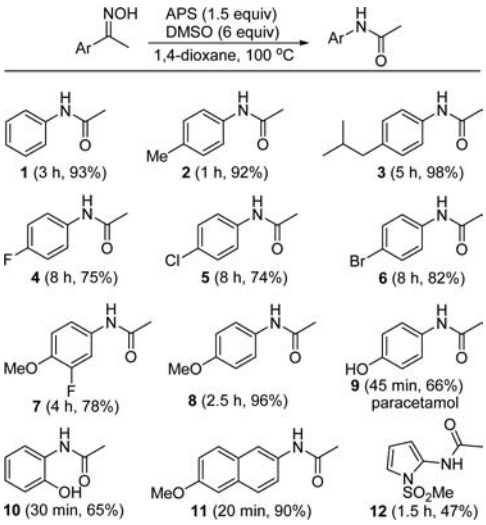
ABSTRACT: The Beckmann rearrangement of ketoximes, mediated by ammonium persulfate-dimethyl sulfoxide as a reagent, has been achieved under neutral conditions. Based on the radical trapping and ^{18}O-labeling experiments, the transformation follows a mechanism involving a radical pathway. The scope and generality of the developed protocol has been demonstrated by 19 examples. The developed protocol and Pd-catalyzed intramolecular double C−H activation were used as key steps in the formal total synthesis of antimalarial natural product isocryptolepine.

The Beckmann rearrangement was rightly termed as The Mona Lisa of molecular rearrangements by Jones.[1] Discovered[2] in 1886, it is undoubtedly one of the most important synthetic transformations in industry. It is used in the large scale production of caprolactum and the commonly used drug paracetamol and in the synthesis of several bioactive natural products.[3] Generally strong Bronsted or Lewis acids, high reaction temperatures and dehydrating conditions are necessary for this reaction, which limits its application in sensitive substrates.[4] Development of noncatalytic and catalytic methods over the past two decades have improved the efficiency of this reaction considerably.[3−5] The study of the mechanism and development of novel reagents for this important transformation has been an area of immense interest.[4] We recently reported the application of ammonium persulfate-dimethyl sulfoxide (APS-DMSO) for the synthesis of imides, methylene bisamides, diarylmethanes, and also for the Mannich reaction.[6] In continuation of our interest in finding newer applications for this interesting reagent combination, we envisaged that it could be a new reagent for the Beckmann rearrangement. A literature survey revealed that APS-silica gel has been used for the solid state deoximation to regenerate carbonyl compounds using microwave heating.[7] Aryliminyls, produced by oxidation of oximinoacetic or -propanoic acids with persulfate has been used for the synthesis of phenanthridines and quinolines.[8] However, APS-DMSO has been never reported as a general reagent for Beckmann rearrangement. In this context, reported herein is a mild and effective protocol for Beckmann rearrangement, study of its mechanism and application in natural product synthesis.

The optimization of the protocol was straightforward because of our prior experience with APS-DMSO reagent.[6] The condition was first optimized on acetophenone oxime. The reaction did not work in the absence of either reagent. The best yield of acetanilide **1** (93%) was obtained when the reaction mixture containing acetophenone oxime (1 equiv), APS (1.5 equiv), and DMSO (6 equiv) was refluxed in 1,4-dioxane for 3 h. The standard protocol was applied on various substrates with variation in the aromatic ring to demonstrate its generality (Scheme 1).

The reaction worked equally well with oximes having alkyl substitution on the aromatic ring to furnish Beckmann products **2** and **3** in excellent yields. Halide substitution was tolerated to obtain corresponding products **4**−**6**. The methoxy- and fluoro-disubstituted oxime also furnished amide **7**. Oxime with methoxy

Scheme 1. Varyingly Substituted Aromatic "Ar"-Ring



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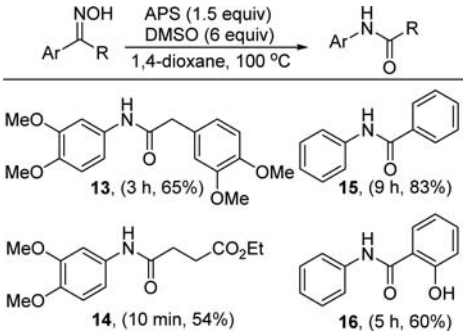
substitution provided the Beckmann product **8** in excellent yield. This observation is in accordance with the known fact that electron-rich substituents facilitate the rearrangement. Paracetamol (**9**) and its analogue **10** were synthesized by the treatment of corresponding oximes under standard protocol. A methoxy-substituted naphthalene ketoxime provided the corresponding Beckmann product **11** in very good yield. The protocol worked with a protected pyrrole oxime, which features a heterocyclic aromatic ring, to furnish amide **12** in moderate yield.

The effect of variation in the other part (-R) of the ketoxime on the Beckmann rearrangement was studied (Scheme 2).

Scheme 2. Varyingly Substituted −R



Replacement of methyl by benzyl group (R = 3,4-MeO−Ph−CH_2−) did not have much effect, and the amide **13** could be obtained in good yield. With extended aliphatic chain (R = EtO_2C−CH_2−CH_2−) the Beckmann product **14** was obtained in moderate yield. Benzophenone oxime and its derivative also worked well to furnish amide **15** and **16** in good to moderate yields.

Our protocol did not work on the five substrates shown in Figure 1. Difficulty in migration of aromatic ring due to ring

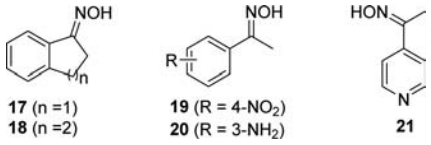


Figure 1. Protocol did not work with these substrates.

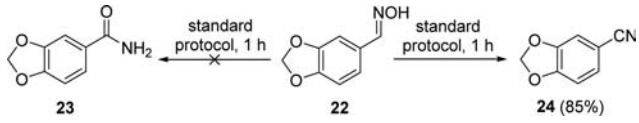
strain might be the reason behind unreactive nature of ketoximes **17** and **18**. Similarly, ketoxime **19** remained unreactive; however, the plausible reason could be the low migratory aptitude of electron withdrawing aromatic ring having $-NO_2$ group.

The ketoximes **20** and **21** decomposed quickly after 10 min heating, and the color of the reaction mixture turned to dark brown/black. The TLC did not show presence of starting substrates, but expected product could not be isolated from these complex reaction mixtures. The reactive nitrogen loan pair and high tenacity of basic nitrogen containing compounds to undergo oxidation might be the reason.

The protocol was also applied to aldoxime **22** (Scheme 3), but the amide **23** was not observed; however, the corresponding benzonitrile **24** was formed in very good yield as observed by Augustine et al.[9]

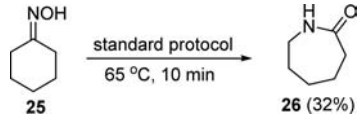
One of the most important commercial applications of Beckmann rearrangement is the synthesis of caprolactam, which is a monomer for the production of Nylon-6 polymer.[10] Application of our protocol to cyclohexanone oxime furnished

Scheme 3. Aldoxime Provided Corresponding Benzonitrile



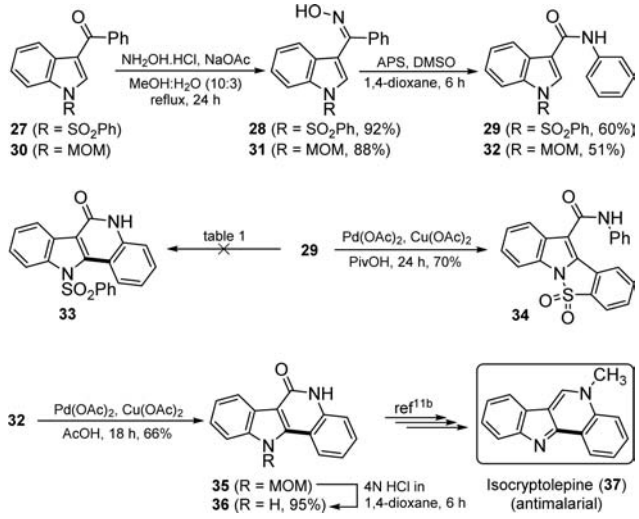
caprolactum **26** in maximum 32% yield. Our attempts to increase the yield met with failure. Further oligomer formation or polymerization under our reaction conditions might be the cause behind low yield of caprolactam (Scheme 4).

Scheme 4. Caprolactam Synthesis



Usefulness of the developed protocol in the synthesis of natural product was demonstrated by a formal synthesis of antimalarial natural product isocryptolepine (**37**, Scheme 5). Studies toward the synthesis of isocryptolepine have been a subject of interest due to its antimalarial properties.[11]

Scheme 5. Formal Synthesis of Isocryptolepine



The synthesis began with *N*-(phenylsulfonyl)indole, which was benzoylated to obtain ketone **27** according to the literature procedure.[12] It was converted to oxime **28** by usual method. Ketoxime **28** was treated with APS-DMSO to furnish amide **29** in good yield. It is important to note that the direct preparation of amide **29** from the corresponding indole-3-carboxylic acid and aniline gives low yield[13] and that the substrate indole-3-carboxylic acid is expensive. Several reaction conditions were tried on amide **29** for the envisaged intramolecular double C−H activation (Table 1); however, none of them could furnish the expected product **33**. Interestingly, under one of the conditions (Table 1, entry 11) the formation of product **34** in very good yield was observed. Laha et al. have recently reported such intramolecular oxidative coupling of phenyl sulfone-protected indoles.[14]

We decided to change the indole protecting group. 3-Benzoylindole was prepared[15] and protected with MOM group to obtain compound **30**. It was converted to oxime **31** in high

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Table 1. Optimization of the C−H Activation Protocol on 29 and 32 at 120 °C on 50 mg Scale

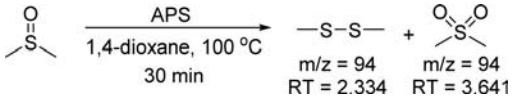
No.	Pd-catalyst (equiv)	oxidant/base (equiv)	solvent	**33** (%)	**35** (%)
01	$Pd(OAc)_2$ (0.1)	CsOAc (2.8)	DMAc	NR	NR
02	$Pd(OAc)_2$ (0.05)	K_2CO_3 (3)	toluene	NR	NR
03	$PdCl_2$ (0.05)	$Cu(OAc)_2$ (1.2)	*p*-xylene	NR	NR
04	$Pd(TFA)_2$ (0.05)	AgOAc (3)	PivOH	NR	NR
05	$Pd(TFA)_2$ (0.05)	$AgCO_3$ (3)	PivOH	NR	NR
06	$Pd(OAc)_2$ (0.2)	BQ (0.1), Ag_2CO_3 (0.2)	DCE	NR	NR
07	$Pd(OAc)_2$ (0.15)	$Cu(OAc)_2$ (1)	AcOH	NR	53
08	$Pd(OAc)_2$ (0.2)	$Cu(OAc)_2$ (1)	AcOH	NR	66
09	$Pd(OAc)_2$ (0.05)	$Cu(OAc)_2$ (1)	AcOH	NR	25
10	$Pd(OAc)_2$ (0.1)	$Cu(OAc)_2$ (1)	AcOH	NR	46
11[a]	$Pd(OAc)_2$ (0.2)	$Cu(OAc)_2$ (1)	PivOH	70 (**34**)	56

[a]Unexpected product **34** obtained.

yield. The standard protocol was applied on the oxime **31** to furnish amide **32** in good yield. Various conditions (Table 1) were tried on amide **32** for the envisaged intramolecular double C−H activation, and the reaction condition (Table 1, entry 8) employing $Pd(OAc)_2$ (20 mol %) and $Cu(OAc)_2$ (1 equiv) in acetic acid at 120 °C was the best to obtain compound **35**. To the best of our knowledge, such C−H activation is not known on this system. The synthesis of the antimalarial natural product isocryptolepine (**37**) from compound **35** has been previously reported by Hibino et al.[11b] Additionally, the compound **35** was deprotected to obtain a well-known bioactive scaffold indoloquinolinone[16] **36** in excellent yield. This class of compounds are effective DNA intercalators and cytotoxic against leukemia and ovarian, breast, colon, and central nervous system cancer.[17] The above-mentioned study demonstrates the scope, application, and limitation of the developed protocol.

A few controlled experiments were performed for the mechanistic aspect studies of this interesting protocol. Jones et al. originally proposed a mechanism involving radical intermediates for Beckmann rearrangement, which was further supported by Wallis et al.[18] A photochemical Beckmann rearrangement involving radical intermediates is also well documented in the literature.[19] Nevertheless, even after a century of its discovery the mechanism of Beckmann rearrangement is still uncertain.[20] We believe that our protocol works through a radical pathway. A blank reaction, without any substrate was performed to observe the formation of reactive intermediates by GC−MS. The major peaks detected were for dimethyl disulfide and dimethyl sulfone as confirmed by GC−MS library (Scheme 6). The presence of dimethyl disulfide in the reaction mixture indicates formation of radical intermediates in our protocol.[21]

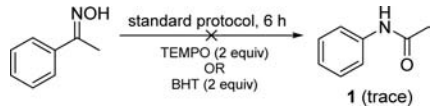
Scheme 6. Blank Reaction To Detect Reactive Intermediates



Radical scavenging experiments were also performed to support our hypothesis. The reaction of acetophenone oxime was done under the developed protocol in the presence of radical scavengers TEMPO and BHT in separate experiments. As expected, only a trace amount of acetanilide (**1**) was observed (Scheme 7).

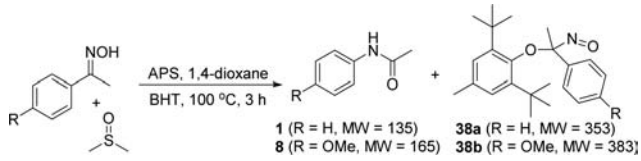
In attempt to determine a tentative mechanism of our protocol we tried to detect an intermediate trapped by BHT in yet another

Scheme 7. Radical Scavenging Studies



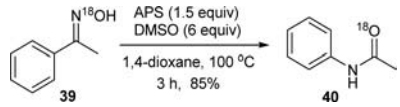
experiment. We could successfully do that and observed the adduct **38** by ESI−LCMS, which was also confirmed by ESI−HRMS.[21] Trapping of the adduct **38** formed by the combination of ketoxime and BHT once again confirms that our protocol follows a radical mechanism (Scheme 8).

Scheme 8. Trapping of Intermediates with BHT



An ^{18}O-labeling experiment was carried out to identify the source of oxygen in the Beckmann product (Scheme 9). ^{18}O-

Scheme 9. Isotopic Labelling Experiment



Labeled $NH_2{}^{18}OH$ was prepared starting from $H_2{}^{18}O$ and ammonia following the reported procedure.[22] It was used for the preparation of ^{18}O-labeled acetophenone oxime **39**.[22b] Treatment of the oxime **39** under our standard protocol furnished ^{18}O-labeled acetanilide (**39**) in very good yield. More than 50% of acetanilide (**40**) had incorporated the heavy oxygen atom. It suggests that the source of oxygen in the Beckmann product is not external but that it comes from the ketoxime itself, thus indicating an intramolecular rearrangement probably via oxaziridine intermediate.[23]

Based on all the above controlled experiments and literature precedence,[1,21,23] a putative mechanism is depicted in Figure 2.

In summary, we have achieved a general and efficient radical Beckmann rearrangement. The inexpensive, environmentally benign and safe reagents "APS-DMSO" and mild neutral reaction conditions make this protocol an efficient alternative to the existing noncatalytic methods. The scope is wide and strong acids

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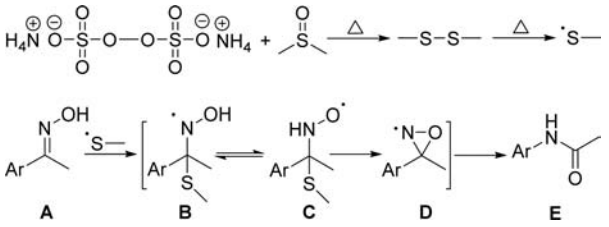

Figure 2. Putative mechanism.

or transition-metal catalysts are avoided. The controlled experiments indicate involvement of radical mechanism and intramolecular nature of the rearrangement under this protocol. Application of the developed protocol and Pd-catalyzed double C−H activation as important steps have been demonstrated in the formal total synthesis of the antimalarial natural product isocryptolepine.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01634.

Experimental procedures, spectral and analytical data, and copies of NMR spectra of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sb.mhaske@ncl.res.in.

Notes

The authors declare no competing financial interest.

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