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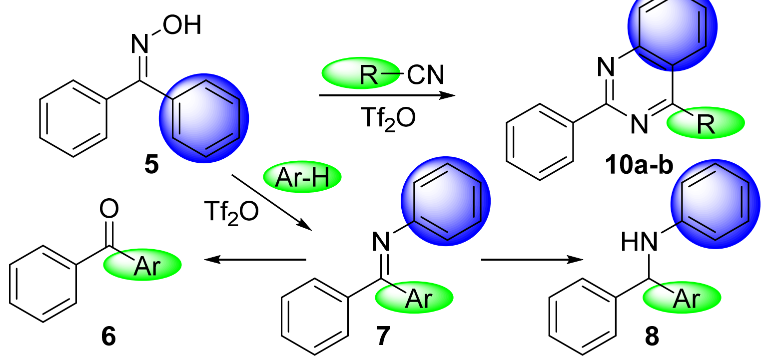

Metal-Free Tandem Beckmann-Electrophilic Aromatic Substitution Cascade Affording Diaryl Imines, Ketones, Amines and Quinazolines

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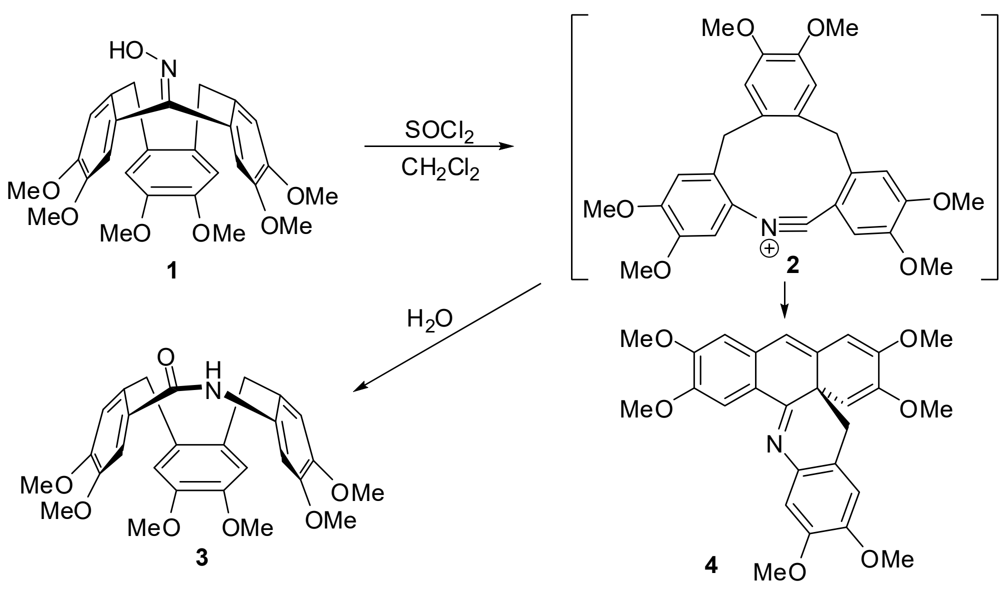
Abstract

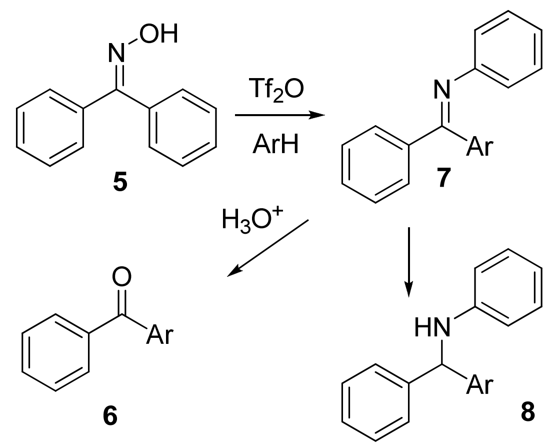
A cascade reaction sequence involving a Beckmann rearrangement on benzophenone oxime followed by an electrophilic aromatic substitution (EAS) on the intermediate nitrilium ion affords N-phenyl diaryl imines that may then be hydrolyzed to ketones, or reduced to the corresponding amines. Reaction with benzonitrile afforded 2,4-diphenylquinazoline through a Beckmann-Ritter-EAS cascade.

Cascade or domino reactions enable the assemblage of complex molecules through a sequence of reactions where one reaction step prepares a reactive intermediate that is immediately employed in a subsequent reaction.[1] Examples of cascade reactions include the tandem Aldol-Tishchenko reaction[2,3] and the Banert cascade.[4] The Beckmann rearrangement[5] is a synthetic workhorse that is still of current theoretical interest regarding the concerted or stepwise nature of its mechanism.[6] As part of our program to investigate apex-modified derivatives[7] of the bowl-shaped supramolecular scaffold cyclotriveratrylene (CTV),[8] we employed the Beckmann rearrangement to afford a ring expansion via the oxime **1**[9] derived from CTV to afford the corresponding 10-membered CTV lactam **3,** which depending upon the experimental conditions, was also accompanied by the product of an intramolecular electrophilic addition reaction affording an unexpected helical pentacycle **4** (Scheme 1).[10] We realized that this by-product must have arisen from a cascade process wherein the intermediate nitrilium ion **2** formed in the Beckmann reaction was intercepted by one of the electron-rich veratrole rings of the macrocycle in a trans-annular process. We questioned whether this tandem Beckmann-electrophilic aromatic addition reaction could be generalized to an intermolecular variant with electrophilic aromatic substitution arising from the Beckmann intermediate, and were encouraged by similar cascade processes. Schinzer previously employed nucleophilic allylsilanes to intramolecularly trap the cationic Beckmann rearrangement intermediate in the preparation of various heterocycles.[11-13] Amidines have been synthesized by trapping the Beckmann iminocarbocation intermediates derived from oximes by Katritzky[14] while Mukaiyama conveniently formed amidines and enamines by trapping Beckmann carbocation intermediates with amines and resonance-stabilized carbanion nucleophiles, respectively using trifluoromethanesulfonic anhydride as the electrophilic initiator,[15] but trapping of the cationic Beckmann rearrangement intermediate by an intermolecular electrophilic aromatic addition has not been previously reported to our knowledge. We describe herein the intermolecular tandem Beckmann-electrophilic aromatic substitution cascade utilizing benzophenone oxime and a variety of aromatic nucleophiles to afford the corresponding imines which could be isolated, hydrolyzed, or reduced to the corresponding amines.



Scheme 1: Intramolecular Tandem Beckman-Electrophilic Aromatic Addition from CTV Oxime

In the original intramolecular case, the reaction is favored both by the very electron-rich nature and close proximity (3.4-3.6Å)[10] of the dimethoxy ring to the Beckmann nitrilium intermediate. We therefore initially employed neat conditions and electron rich π-nucleophiles to probe the viability of the intermolecular variation, employing benzophenone oxime as the Beckmann substrate. Initiating the Beckmann with thionyl chloride did not afford the tandem product, as it led only to the formation of the simple Beckmann product, benzanilide, as rapid attack of the chloride anion precluded attack by the π-nucleophile. Thus, an intermediate chloroimine presumably formed which was hydrolyzed upon workup. Switching to trifluoromethanesulfonic anhydride to initiate the Beckmann rearrangement[15] in the absence of a nucleophilic leaving group allowed time for the nitrilium ion to react with the π-nucleophilic aromatic to give good to excellent yields of the TB-EAS products (Table 1). In the first case with the π-nucleophile veratrole employed as solvent, a 95% isolated yield of the hydrolyzed ketone **6a** was obtained. We continued to explore the generality of the TB-EAS sequence employing various electron rich and electron poor π-nucleophiles, first under neat conditions, followed by hydrolyzing the intermediate imine **7** directly to the ketone products (**6**). We examined reducing the ratio of π-nucleophile to two equivalents relative to benzophenone oxime in 1,2-dichloroethane at reflux (Table 2). Once validated through isolation of the ketone, the imines **7** were isolated, and the subsequent imines were reduced to the corresponding α,N-arylbenzenemethanamines **8**, as these molecules as a class are important in pharmaceuticals[16].



Scheme 2: Preparation of diarylketones **6** and amines **8** via imines **7**

Table 1. TB-EAS Results with π-Nucleophiles[a]

Entry	π-Nuc	Ar	Ketone **6**[b] Yield (% neat/soln)	Imine **7**[c] Yield (%)	Amine **8** Yield (%)
a	veratrole	3,4-dimethoxyphenyl	95/91	58[f]	51[d]
b	1,4-dimethoxy-benzene	2,5-dimethoxyphenyl	97/72	56	57[d]
c	anisole	4-methoxyphenyl (plus ortho)	95/96	91[f]	90[e]
d	*p*-xylene	2,5-dimethyl phenyl	95/70	90	63[e]
e	$PhCH_3$	4-methylphenyl (plus ortho)	75/93	66[f]	73[e]
f	PhCl	4-chlorophenyl (plus ortho)	68/19	56[f]	45[e]
g	PhBr	4-bromophenyl (plus ortho)	75/34	60[f]	59[e]
h	PhCN	3-cyanophenyl	0[g]/0[g]	39[g]	…

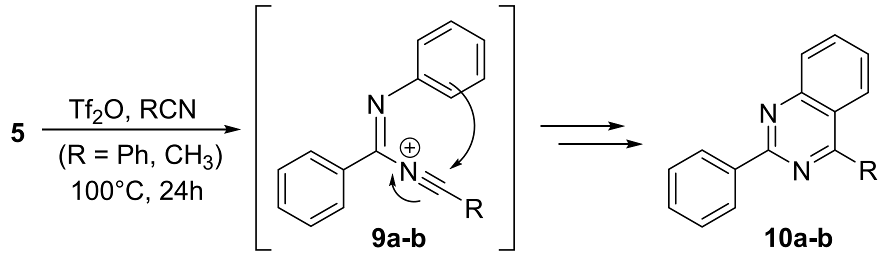
[a]Benzophenone oxime in 1,2-dichloroethane was treated with triflic anhydride under reflux for 16-24h in the presence of 2 equivalents of π-nucleophile with the exception for PhCl and PhBr which used 4 eq and 8 eq, respectively. [b]Hydrolytic workup with acid afforded ketones **6**; [c] aqueous sodium bicarbonate quench afforded imines **7**; [d]Crude imines were treated with $NaBH_4$ in MeOH or THF to form amines **8**; [e]Reflux with lithium aluminum hydride in THF/2h followed by Fieser workup afforded amines **8**; [f]The imine contained traces of ketone after workup; [g]Reaction with benzonitrile gave the

imine even after acidic hydrolytic workup, along with 2,4-diphenylquinazoline (**10** in 47% yield).

Encouraged by the success with neat veratrole, but wishing to avoid the inconvenience of using neat π-nucleophiles as solvent, we obtained a 91% yield of ketone **6a** employing 2 equivalents of veratrole in 1,2-dichloroethane. In a separate experiment, veratrole afforded a 58% yield of imine **7a** after column chromatography, generally as a mixture of E and Z isomers, and contaminated in most cases with some ketone **6a**. The imines were difficult to isolate as they suffered hydrolysis during purification, and were best reduced directly. Direct reduction of the imine **7a** after the TB-EAS sequence furnished a 51% yield of α,N-arylbenzenemethanamine **8a** (R=H). Ketone products **6a-g** could also be obtained by acid hydrolysis of the isolated imine, but as expected, the yields were lower than the direct hydrolysis. Amine products (**8a-g**) were obtained by direct reduction of the crude imines from the TB-EAS sequence without isolation. Employing *p*-dimethoxybenzene gave a high yield of ketone **6b** (97%) after hydrolysis but attempted isolation of the imine was problematic due to very rapid hydrolysis even with an aqueous bicarbonate workup. Direct reduction of the imine with sodium borohydride gave amine **8b** in 57% yield. Neat anisole provided a 95% yield of ketone **6c** (7:1 *para*:*ortho*) and reaction with 2 equivalents of anisole in 1,2-dichloroethane at reflux gave a comparable high isolated yield of ketone **6c** (96%). A mild basic quench enabled isolation of imine **7c** in 91% yield. Direct reduction of the imine to α,N-(4-methoxyphenyl)-benzenemethanamine with sodium borohydride proceeded in 90% yield. The sigma donor, *p*-xylene, furnished a 95% isolated yield of diaryl ketone **6d** employing *p*-xylene as the solvent, although the use of 2 equivalents of *p*-xylene resulted in a moderately lower yield (70%). The imine **7d** derived from *p*-xylene was isolated in 90% yield, whereas reduction of imine **7d** gave amine **8d** in 63% yield. Performing the TB-EAS reaction with toluene afforded a more modest yield under neat conditions (75%) but surprisingly a higher yield (93%) when using 2 equivalents of toluene in 1,2-dichloroethane. The imine **7e** from toluene was isolated in 66% yield, and was reduced to aryl amine **8e** in 73% yield. The TB-EAS reactions with halobenzenes were more sluggish and gave lower yields. Chlorobenzene and bromobenzene gave ketones **6f** and

6g in moderate yields (68% and 75%, respectively), but yields were lower in solution, despite employing 4 and 8 equivalents of the halobenzene, respectively (19% and 34%), whereas the 4-chlorophenylimine **7f** and 4-bromophenylimine **7g** intermediates were isolated in moderate yields (56% and 60%, respectively). Thus, the bromo and chlorobenzene nucleophiles were considerably more concentration dependent and relatively higher temperatures are needed to achieve moderate yields; reaction at 2M concentration of nucleophile proved to be unsuccessful whereas reaction at 4M produced low yields and 8M gave the yields shown. The amines **8f** and **8g** were isolated in 45 and 59% yield, respectively. Utilization of nitrobenzene as the π-nucleophile (not shown) gave low yields of as-yet unidentified products and was not pursued.

Employing neat benzonitrile as the π-nucleophile in the TB-EAS sequence did not give the expected ketone **6h** upon acidic hydrolysis, but rather imine **7h** was isolated in 39% yield, along with a 47% yield of 2,4-diphenylquinazoline **10a** (Scheme 3), which arises from a Ritter type reaction[17-18] involving attack of the Beckmann nitrilium ion by benzonitrile followed by an EAS reaction by the N-phenyl group on the resulting nitrilium ion **9a/b**, comprising a Beckmann-Ritter-EAS cascade sequence. Ritter iminium ions have been trapped previously by intramolecular EAS to afford dihydroisoquinolines,[19] and Kofanov reported a similar cascade sequence starting with an N-aryl amide to prepare 2,4-diarylquinazolines.[20] The intermediate in this sequence should be the same cation proposed by Meerwein in his early synthesis of quinazolines where he treated the corresponding chloroiminium species with aluminum trichloride.[21] When we employed benzonitrile in solution (8M in 1,2-dichloroethane) rather than in the neat reaction, a much improved (88%) yield of 2,4-diphenylquinazoline **10a** (R = Ph) was obtained. On the other hand, employing acetonitrile as the solvent at 75°C afforded 2-phenyl-4-methylquinazoline **10b** (R = CH_3) in 37% isolated yield, but acetonitrile as a solution in 1,2-dichloroethane afforded **10b** in only 13% yield). Thus, the Beckmann-Ritter-EAS cascade affording quinazolines is higher yielding with the aryl nitrile versus the aliphatic nitrile under the present conditions, but the generality with more substituted derivatives in both categories remains to be explored.



Scheme 3: Preparation of quinazolines **10a** (R = Ph) and **10b** (R = CH_3)

In summary, the intermolecular TB-EAS reaction commencing with benzophenone oxime affords N,α,α-triarylimine derivatives which may be hydrolyzed to unsymmetrical diarylketones or reduced to α,N-arylbenzenemethanamines. Reaction with benzonitrile proceeded via a Beckmann-Ritter-EAS cascade sequence to afford 2,4-diphenylquinazoline (**10a**) in very good (88%) yield. Current efforts are focused on expanding the scope of the TB-EAS and Beckmann-Ritter-EAS cascade sequences, particularly toward the synthesis of more highly substituted quinazolines under metal-free conditions.

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Supplementary data

Supplementary data associated with this article can be found in the online version.

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