Organic etters

Electrochemical, lodine-Mediated α -CH Amination of Ketones by **Umpolung of Silyl Enol Ethers**

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Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02068 **Read Online** ACCESS III Metrics & More Article Recommendations Supporting Information **ABSTRACT:** The electrochemical, oxidative Umpolung reaction Me₃Si R^3 Nal (0.5 equiv) of silvl enol ethers utilizing simple iodide salts for the synthesis of CCE α -amino ketones is described. The products were isolated in

excellent yields of up to 100%, and various functionalized starting materials were accepted in an undivided electrochemical cell design. Moreover, a sensitivity assessment to ensure an improved reproducibility of the reaction and cyclic voltammetry experiments



were performed to postulate a plausible reaction mechanism on their basis.

 α -Amino ketones are a very important structure motif in organic chemistry because they represent the key structure of many natural products and of biological and pharmacological active compounds, such as the psychoactive cathinone and amfepramone or the antiplatelent prasugrel.¹ Moreover, they act as important building blocks for interesting structures like heterocycles or 1,2-amino alcohols, e.g., spisulosine (Figure 1).²



Figure 1. Selected examples of biologically active α -amino ketones and α -amino alcohols.

Due to the significance of this substance class the development and improvement of their synthesis has been of high interest since the 19th century.³ One method for the synthesis of these compounds is the oxidative amination reaction.⁴ For example, a Cu(II)-catalyzed amination of ketones, esters, and aldehydes was described by MacMillan.^{4a} Commonly, the formation of α -amino ketones can be achieved either by α -amination of carbonyl derivatives, e.g., silyl enol ethers, with electrophilic Ncompounds, like α -haloamines, hydroxylamines, or nitrosoformates,⁵ or by reaction of carbonyl groups with reversed polarity with nucleophilic N-compounds. 33,6-11 The Umpolung reaction can be performed with, e.g., tosylazoalkanes, nitro-soalkenes, or enamine derivatives.⁷ Guo developed a NH₄Icatalyzed method for the reaction of acetophenone derivatives with secondary amines using sodium percarbonate as external oxidant (Scheme 1, path a).8 This conversion can be accomplished as well by applying N-iodosuccinimide (NIS)

and tBuOOH as oxidant (Scheme 1, path b).⁹ Zeng and Sun were able to develop an electrochemical alternative avoiding further chemical oxidants (Scheme 1, path c).¹⁰ However, very long reaction times and an excess of electric current $(14 \,\mathrm{F \cdot mol^{-1}})$ were needed, and the reaction seems to be limited to acetophenone derivatives which could be converted to the desired products in good yields of up to 75%. A very innovative approach was described by Wirth, utilizing the Umpolung of silyl enol ethers with stoichiometric amounts of PIDA $(PhI(OAc)_2)$ and the intramolecular reaction of a preinstalled nucleophile (path d). 11

Scheme 1. Previously Reported Procedures for the Synthesis of α -Amino Ketones



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The complex prefunctionalization of the starting materials, stoichiometric or even excessive usage of co-oxidants, limited substrate scopes and/or the addition of toxic heavy metal catalysts are still drawbacks of these reactions. For this reason, we envisioned an electrochemical oxidative method, which enables the substoichiometric use of nontoxic and simple iodide salts as Umpolung reagent for silyl enol ethers. The use of silyl enol ethers is advantageous compared to ketones because they cannot condense with amines forming enamines. We intended to simplify the elaborate prefunctionalization of the starting materials as demonstrated by Wirth to regain flexibility in the approach by adding the *N*-nucleophile separately to the reaction mixture and performing an intermolecular reaction.

Accordingly, the synthesis of α -amino ketone **3a** by the reaction of silyl enol ether **1a** with dibenzylamine **2a** under electrochemical conditions was examined. We started our investigation adopting the conditions described by Zeng and Sun (NH₄I, 0.5 equiv), LiClO₄ (0.1 M), amine (3.0 equiv), and anhydrous CH₃CN as solvent)¹⁰ and were able to isolate the desired product **3a** in 59% yield. During a screening of different iodide salts, the yield could be raised to 78% by using sodium iodide (Table 1, entry 1). Based on these conditions, we started the screening program for the optimization of the reaction (Table 1).

 Table 1. Selected Examples of Variation of the Reaction

 Conditions*

Me ₃ Si Me	$ \begin{array}{c} O \\ HN \\ \end{array} \begin{array}{c} Ph \\ HN \\ \end{array} \begin{array}{c} Conditions^{[a]} \\ \end{array} \end{array} $	Me N Ph	
1	a 2a	3a	
no.	alterations	yield ^b (%)	
1	none	78	
2	N ₂ atmosphere, CH ₃ CN	2	
3	$CH_3CN + 5.0$ equiv. H_2O	67	
4	$CH_3CN + 20.0$ equiv. $H_2O^{[c]}$	89	
5	$CH_3CN + 50.0$ equiv. H_2O	68	
6	0 °C	34	
7	40 °C	40	
8	1.1 equiv. of amine 2a	2	
9	1.5 equiv. of amine 2a	72	
10	2.0 equiv. of amine $2a^{[d]}$	100 ^[e]	
11	15 mA	47	
12	1.1 equiv. I_2 , without electricity	64	

^{*}Reactions were performed in an undivided cell on a 0.5 mmol scale. ^aConditions: 0.5 equiv of NaI, 3.0 equiv of amine 2a, LiClO₄ (0.1 M), Pt electrodes ($1.0 \times 3.0 \text{ cm}^2$), anhydrous CH₃CN, rt, 10 mA, 4 F·mol⁻¹. ^bThe yield was determined by GC analysis of the unpurified reaction mixture with mesitylene as internal standard. ^cThis change was kept for entries 5–11. ^dThis change was kept for entry 11. ^eIsolated yield.

When the reaction was performed under inert conditions the yield of **3a** dropped to 2%. Notably, the water amount seemed to have a profound effect on the yield and was therefore varied subsequently (0.5-50 equiv. H₂O, anhydrous CH₃CN). The addition of 20.0 equiv of H₂O increased the yield to 89%; consequently, this parameter was maintained for the following

experiments. The variation of the reaction temperature (0 °C, 40 °C), electrolyte (nBu_4NBr , nBu_4NBF_4 , none), or of the solvent (dichloromethane, methanol, THF) led to no further improvements. By varying the amount of the amine (1.1–2.5 equiv) **3a** was isolated in quantitative yield when 2.0 equiv of amine **2a** was applied. Further variations of the amount of NaI (0.1–0.3 equiv) and the electrode material (glassy carbon, graphite) downgraded the yield for which reason the former determined reaction conditions were chosen (for more information, see the SI). At last, a comparative experiment was done by using equimolar amounts of iodine instead of electricity. The product **3a** could be isolated in 64% yield (Table 1, entry 12), which exemplified the great potential of this reaction.

Despite the many advantages of electroorganic synthesis (e.g., less waste, the use of renewable energy and electrons as reagent)¹² its application is underrepresented, which might be rooted in reproducibility issues. To avoid this problem and assess systematic and random errors, a sensitivity test was performed which is based on the assumption that already small variations of the reaction parameters, that might occur accidentally by reproduction of the experiment by other researchers, could have an impact on the reproducibility.¹³ The sensitivity of the reaction to fluctuations of typical reaction parameters (e.g., concentration or scale) but also a discrepancy of the setup was investigated. Especially the setup is a major factor in electrochemical reactions because most working groups use their individually manufactured equipment. The amination reaction was insensitive against many parameters but showed a medium sensitivity toward a lower concentration, higher temperatures and increased currents (Figure 2). The reduction of the electrode distance (-30%) led to the bisection of the yield. An undersized electrode distance seems to lead to a "chemical shortcut". Meaning, that the oxidized iodine species is directly reduced at the cathode without undergoing the desired reaction. So special attention should be paid to this parameter.



Figure 2. Sensitivity assessment of the electrochemical amination (see the SI for more information).

After the optimization of the reaction conditions and the sensitivity assessment, the starting materials were varied to examine scope and limitations of the electrochemical amination reaction (Scheme 2). First, the tolerance of the reaction against functional groups should be tested by applying different substituted dibenzylamines. Fortunately, electron-deficient as well as electron-rich arene moieties were tolerated, but the introduction of electron-deficient groups was associated with lower yields. While the 4-methoxy derivative **3b** was generated

quantitatively, the 4-cyano and 4-bromo derivatives 3c and 3d were isolated in moderate yields (51-55%). As expected, compound 3e was isolated with the lowest yield (27%) probably due to the highly deactivation and redox lability of the nitro group. Subsequently, the substituents of the nitrogen were varied. N-Methylbenzylamine as well as the sterically highly demanding N-benzylcyclohexylamine could be converted to the products 3h and 3i (90% and 39%). The conversion of the primary amine N-benzylamine 2j failed. Moreover, amine 2k (with a substituent in 1-position) was converted successfully and the product was isolated in a good yield of 91%. Also, cyclic amines were tested as well: While the tetrahydroisoquinoline product 31 was isolated in 82% yield, the application of morpholine 2n only led to 3n in 38% yield and the transformation with piperidine for the synthesis of **3m** failed completely for no obvious reason. The same was observed for N-methylbenzamide (20), which was anticipated due to the lower nucleophilicity of amides. Nevertheless, di-n-butylamine and diallylamine yielded the products 3p and 3q in 53–56%, respectively. After variation of the amines, different silvl enol ethers were reacted. The conversion of sterically more demanding alkyl-substituted silyl enol ethers to products 3r and 3s succeeded in 71-73% yield, respectively. But the reaction failed with cyclic silyl enol ethers toward the α -amino ketone 3t.¹⁴ Fortunately, the generation of product 3u, where a tertiary carbon atom was generated, worked excellently (97% yield). At last, the diastereomeric product 3v (dr = 1.4:1, 22%) could be isolated.

In the same manner, different substituted aromatic silyl enol ethers could be converted. While no product was observed in the reaction of α -trimethylsilyloxystyrene with *N*-methylbenzylamine (Table 2, entry 1), the conversion of ((1-(4-methoxyphenyl)vinyl)oxy)trimethylsilane gave the amination product **3x**

Scheme 2. Substrate Scope of the Electrochemical Amination of Silyl Enol Ethers a



^aYields refer to isolated, purified products.

in 75% (Table 2, entry 2). The utilization of other functionalized styrene-type silvl enol ethers led to overoxidation and generation of the α -amidated products 4y, 4z, and 4aa (entries 3–5). The reaction was repeated and stopped after a consumption of 2 F· mol⁻¹ utilizing ((1-mesitylvinyl)oxy)trimethylsilane. Although the reaction was not complete only the α -ketoamide 4y was isolated (40% yield). In the literature, the same observation was made in case of the direct oxidative conversion ($tBuOOH/I_2$ or electrochemical) of acetophenone derivatives.^{9,15} By introduction of a substituent in α -position of the carbonyl group, the isolation of α -amino ketones was enabled. This approach also worked well for the electrochemical conversion, since the reaction of 1-phenyl-1-trimethylsilyloxypropene led to product 3aa which was isolated in 62% yield (Table 2, entry 5). Finally, the psychoactive drug amfepramone 3ab could be generated as well although only in moderate yield (Table 2, entry 6).

Table 2. Aromatic Silyl Enol Ethers as Starting Materials

Me ₃	^{Si} 0 R ²	amine 2 (Nal (0. LiClO ₂ CH ₃ Pt ele 10 mA,	(2.0 equiv.) 5 equiv.) ₄ (0.1 M) CN, rt ctrodes 4 F ⋅ mol ⁻¹		$ \begin{array}{c} $		
no.	\mathbb{R}^1	R ²	amine	3	4		
1	Н	Н	Me I HN Ph	3w 0%	4w 0%		
2	4-MeO	Н	Me ⊢ HN Ph	3x 75%	4x 0%		
3	2,4,6-Me ₃	Η	Me ⊢ HN Ph	3y 0%	4y 57% (40%) ^[a]		
4	4-NO ₂	Н	Me ⊢ HN Ph	3z 0%	4z 24%		
5	Н	Me	Me I HN Ph	3aa 62%	4aa 0%		
6	Н	Me	HNEt ₂	3ab 36%	4ab 0%		
Consumption of 2 $\text{F} \cdot \text{mol}^{-1}$.							

For clarification of the reaction mechanism, electroanalytical measurements were performed. The cyclic voltammogram (CV) of NaI showed two reversible oxidation peaks (peak potentials: +341 and +677 mV vs Ag/AgCl as reference electrode). The first peak can be assigned to the oxidation of iodide to triiodide and the second one to the oxidation of triiode to iodine.¹⁶ When another cyclic voltammogram of NaI in the presence of silyl enol ether **1a** was run a great peak enhancement of the second oxidation peaks diminished. This indicates that a reaction of the silyl enol ether with iodine takes place forming a α -iodoketone and iodide. The peak enhancement can be explained by the fact, that the iodide is directly oxidized with triiodide generating new iodine.



Figure 3. (Left) Cyclic voltammogram of: black, NaI (5 mM); red, NaI (5 mM) and silyl enol ether 1a (2.0 equiv) in $CH_3CN/LiClO_4$ (10 mL, 0.1 M). (Right) Key: black, NaI (5 mM); red, NaI (5 mM), silyl enol ether 1a (2.0 equiv) and amine 2a (4.0 equiv); blue, NaI (5 mM) and amine 2a (4.0 equiv) in $CH_3CN/LiClO_4$ (10 mL, 0.1 M). Reference electrode: Ag/AgCl (3 M NaCl), scan rate: 200 mV/s.

The CV of NaI and amine 2a showed an enhancement and a small shift of all peaks, but form and appearance stayed the same (Figure 3, right CV). In particular, the second oxidation peak is shifted and the CV looks more reversible. This indicates the reversible formation of a complex between the iodine and the amine, which has been described in literature before.¹⁷ By generating this complex, iodide is formed, which can be reoxidized and leads to the peak enhancement. At last, the cyclic voltammogram of NaI, amine 2a, and silyl enol ether 1a showed only a small enhancement of the second oxidation peak, but all reduction peaks disappeared completely. This indicates the reaction of silyl enol ether 1a with the cationic iodonium species and the further S_N reaction of the in situ generated compound with amine 2a. To prove this assumption, 1-iodopropan-2-one was reacted with dibenzylamine 2a. Fortunately, the product 3a was formed in 93% yield. On the basis of these results a reaction mechanism was postulated (Scheme 3).



We postulate the anodic oxidation of iodide as the first step of the reaction. On one hand, the generated iodine can directly react with silyl enol ether **2a** to form α -iodoketone **B**. On the other hand, the iodine can react with amine **2a** and the complex **A** is generated. Afterward, the silyl enol ether **1a** reacts with **A** to form the α -iodoketone **B** as well. Finally, the amine **2a** attacks the intermediate **B** via nucleophilic substitution and product **3a** is generated. The nascent iodide can be reoxidized at the anode, and the proton is reduced to molecular hydrogen at the cathode.

In conclusion, an electrochemical, NaI-assisted oxidative Umpolung reaction of silyl enol ethers for the formation of α -amino ketones is described. The scope and limitations of the reaction were investigated, and to enable an improved reproducibility of the amination reaction a sensitivity assessment was done. Moreover, the synthesis of the psychoactive drug amfepramone succeeded. Compared to the work of Zeng and Sun, where only propiophenone derivatives could be converted to α -amino ketones, ^{10,18} we were able to enlarge the substrate scope so that different alkyl-substituted amino ketones were generated in addition to aromatic ones. Moreover, a distinct reduction of the reaction time from 14 to 4 F/mol was achieved. Lastly, cyclic voltammetry measurements and control experiments led to the formulation of a plausible reaction mechanism.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02068.

Synthesis, sensitivity assessment, analytical data, NMR, and CV spectra (PDF)

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Notes

The authors declare no competing financial interest.

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