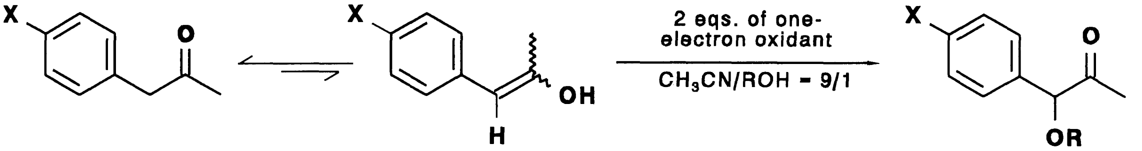
CHEMISTRY LETTERS, pp. 1935-1938, 1994.

# α-Umpolung of Ketones via Enol Cation Radicals. Mechanistic and Synthetic Aspects[1)]

Michael SCHMITTEL*,† and Michael LEVIS
Institut für Organische Chemie und Biochemie der Universität Freiburg,
Albertstr. 21, D-79104 Freiburg, Germany

The novel α-Umpolung of ketones via intermediate enol cation radicals has been explored mechanistically and tested for different nucleophiles that are compatible to the oxidative conditions. The rate of the reaction was determined indicating that enolization takes place prior to the one-electron oxidation step.

Although ketone, enol and enolate chemistry is of paramount interest for organic group transformations and C-C-bond formations,[2)] the reactions of the corresponding cation radicals have only marginally been investigated.[3-5)] Based on the recently established inversion of the thermochemical stability order upon one-electron oxidation[4)] in the keto/enol system, we[4)] and others[6)] have independently developed a one-pot strategy to functionalize ketones via selective oxidation of the enol tautomer. The following paper reports on the possibilities to vary the nucleophiles in this protocol and on kinetic experiments to clarify the mechanism.

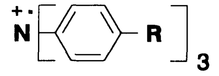


**1k** (X: OMe): $E_p^{ox} = 1.34$ V
**2k** (X: H): $E_p^{ox} = 1.87$ V

**1e** (X: OMe): $E_{1/2}^{ox} = 0.39$ V
**2e** (X: H): $E_{1/2}^{ox} = 0.73$ V

**3a - h**, **4a** with R= **a**: Me, **b**:Et, **c**:*i*-Pr, **d**:*n*-Bu, **e**: 2-Bu, **f**:*t*-Bu, **g**:*neo*-Pent, **h**:Ac.

As model compounds for this study we have investigated *p*-anisyl acetone (**1k**) and phenyl acetone (**2k**), exhibiting enol contents as low as $10^{-4}$%.[7)] For both systems the keto form is difficult to oxidize but the enol oxidation potentials are lower by about one volt.[8)] As a consequence selective oxidation of the enol tautomer should be possible through the use of the well-known one-electron oxidants tris(*p*-bromophenyl)aminium hexachloroantimonate (**TBPA**$^{+\cdot}$, $E_{1/2}$ = 0.70 V), tris(*p*-tolyl)aminium hexafluoroantimonate (**TTA**$^{+\cdot}$, $E_{1/2}$ = 0.37 V) or iron(III)phenanthroline hexafluorophosphate (**FePhen**, $E_{1/2}$ = 0.69 V).



$Fe(phen)_3(PF_6)_3$

**TBPA**$^{+\cdot}$ (R: Br)
**TTA**$^{+\cdot}$ (R: $CH_3$)

**FePhen**

---

† Present Address: Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany.

Indeed, in the presence of two equivalents of one-electron oxidants the α-Umpolung reaction of **1k** or **2k** in a solvent mixture acetonitrile/nucleophile = 9 : 1 is readily accomplished.

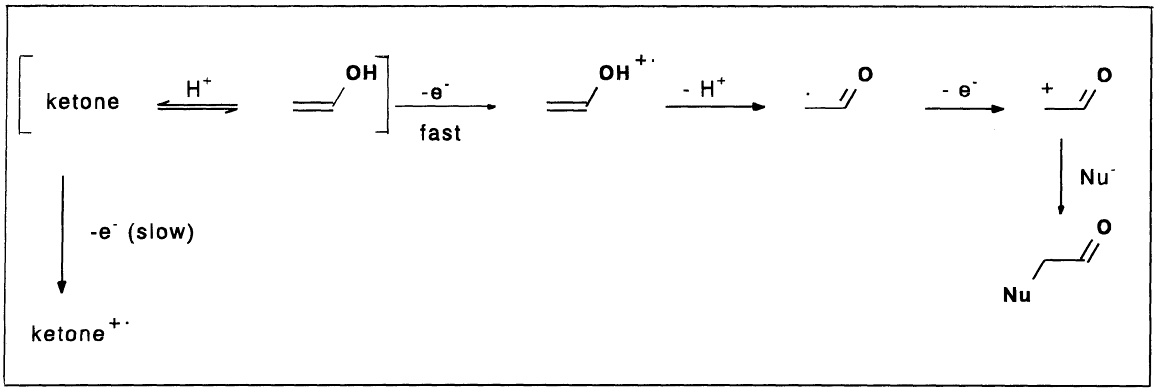
Table 1. Yields in the α-Umpolung of Arylacetones **1k** and **2k** in Anhydrous Acetonitrile Using Different Nucleophiles and One-Electron Oxidants

| Ketone | Nucleophile ROH | One-electron oxidant | Time[a] | Product | Yields |
|---|---|---|---|---|---|
| **1k** | MeOH | $\mathbf{TBPA}^{+\cdot}$ | 20 min | **3a** | 59% |
| **1k** | MeOH | $\mathbf{TTA}^{+\cdot}$ | 3 h | **3a** | 77% |
| **1k** | MeOH | **FePhen** | 20 min | **3a** | 43% |
| **1k** | EtOH | $\mathbf{TTA}^{+\cdot}$ | 2.5 h | **3b** | 76% |
| **1k** | *i*-PrOH | $\mathbf{TTA}^{+\cdot}$ | 6.3 h | **3c** | 68% |
| **1k** | *n*-BuOH | $\mathbf{TTA}^{+\cdot}$ | 3.3 h | **3d** | 71% |
| **1k** | *s*-BuOH | $\mathbf{TTA}^{+\cdot}$ | 5.5 h | **3e** | 75% |
| **1k** | *t*-BuOH | $\mathbf{TBPA}^{+\cdot}$ | 30 min | **3f** | 15% |
| **1k** | *neo*-PentOH | $\mathbf{TBPA}^{+\cdot}$ | 25 min | **3g** | 78% |
| **1k** | HOAc | $\mathbf{TBPA}^{+\cdot}$ | 14 min | **3h** | 40% |
| **2k** | MeOH | **FePhen** | 1 h | **4a** | 43% |

a) Reaction time; for $\mathbf{TTA}^{+\cdot}$ and $\mathbf{TPBA}^{+\cdot}$ time until decolorization of the oxidant.

Importantly, the reaction time could be shortened by addition of 200 mol% of trifluoromethanesulfonic acid without changing yields. While aliphatic alcohols and acetic acid worked well as nucleophiles in this approach, we were unsuccessful to react benzyl alcohol, water, anisole, methyl-2-butene, trimethylsilyl-isocyanide, trimethylsilylazide and various fluorides.[9)] For example, with water as nucleophile the decolorization of the oxidant took so much longer, that the oxidant was used up by the slow reaction with the solvent itself. Readily oxidizable nucleophiles, e.g. amines, do not work in this strategy either.

Based on our recent work on the one-electron oxidation of stable enols,[10)] a mechanism for the overall transformation (Scheme 1) may be proposed. Obviously, the selective oxidation of the enol tautomer present only at a small equilibrium concentration represents a critical point in this multi-step sequence. Thus, under conditions of rapid one-electron oxidation of the enol tautomer, enolization should constitute the rate-determining step. However, comparison of the rate of enolization of **2k** ($k_{\text{enol}} = 5 \cdot 10^{-5}\ M^{-1}s^{-1}$, 1 M = 1 mol dm$^{-3}$), as determined by Kresge,[7)] with the time for decolorization of the oxidant revealed an obvious discrepancy, since much longer reaction time would be expected. Hence, the question emerged, whether the quoted rate of enolization measured in aqueous solution ($HClO_4$/water) has any bearing on our system operating in acetonitrile. While a vast body of enolization rates[7)] has been collected over decades, basically no data are known in anhydrous solvents.[11)] Since, however, addition of water to our reaction system successfully impeded the α-Umpolung, we supposed that in anhydrous acetonitrile enolization of **1k**, **2k** or other ketones should be much faster than anticipated from literature values measured in water.



Scheme 1.

From the results above it seemed promising to use the discharge of a colored one-electron oxidant, e.g. **FePhen**,[12)] to follow the overall kinetics in rigorously dried acetonitrile. In order to avoid autocatalytic effects by the acid liberated in the overall process, we have studied the reaction rates using the ketones **1k**, **2k** and a strong acid added in excess over **FePhen**. It should be emphasized, that all kinetic traces exhibited the expected clean pseudo-zero-order behavior indicative of enolization being the rate-determining step thus confirming the mechanistic hypothesis outlined in scheme 1. As a consequence, this procedure constitutes a novel strategy to measure enolization rates[13)] in anhydrous solvents.

Table 2. Second-Order Rate Constants for the Enolization $k_{enol}$(HA) of **1k** and **2k** in Acetonitrile Containing $LiPF_6$ (0.1 M) at 25 °C

| ketone | conc. of the ketone/ mM | acid | conc. of the acid/ mM | $pK_a$[a)] | n[b)] | $k_{enol}$(HA)[c)] / $M^{-1} \cdot s^{-1}$ |
|---|---|---|---|---|---|---|
| **1k** | 19 - 28 | $CF_3SO_3H$ | 22 - 27 | 2.60 | 16 | $(1.2 \pm 0.3) \cdot 10^{-1}$ |
| **1k**[d)] | 19 - 20 | $CF_3SO_3H$ | 27 | 2.60 | 2 | $(1.22 \pm 0.06) \cdot 10^{-2}$ |
| **1k** | 28 | $FSO_3H$ | 26 | 3.38 | 3 | $(8.2 \pm 0.6) \cdot 10^{-3}$ |
| **2k** | 20 - 26 | $CF_3SO_3H$ | 27 | 2.60 | 5 | $(4.9 \pm 0.7) \cdot 10^{-2}$ |

a) Taken from reference[14]. b) Number of independent kinetic runs. c) Second-order rate constants $k_{enol}$(HA) were calculated from the observed zero-order enolization rate constants since they proved reasonably proportional to the acid and ketone concentration (least-square analysis). d) Acetonitrile/methanol = 9:1.

Interestingly, the rate constant $k_{enol}$(HA) thus determined for enolization of **2k** in anhydrous acetonitrile is about *3 orders of magnitude* higher than the one reported by Kresge in $HClO_4$/water, although $HClO_4$ is a stronger acid than $CF_3SO_3H$.[14)] Most likely, the rate increase in our system can be ascribed to the lower basicity of acetonitrile and a less pronounced leveling effect. In contrast, the acceleration of the acid-catalyzed enolization in acetonitrile/water = 99/1 is much less pronounced when compared to water, as demonstrated for the enolization of acetone in presence of $HClO_4$, where a rate increase of 23 was reported.[11)]

In summary, the kinetic study confirmed our mechanistic proposal that enolization is indeed the first step of the α-Umpolung reaction. It is noteworthy, that only the largely accelerated enolization rate in rigorously dried acetonitrile renders the reaction time of the α-Umpolung sufficiently short to prevent side reactions of the oxidant with the solvent. In comparison with other α-Umpolung strategies,2) this methodology allows the introduction of even complex nucleophiles in a one-pot reaction.

Financial support by the Stiftung Volkswagenwerk, the Wissenschaftliche Gesellschaft Freiburg and the Fonds der Chemischen Industrie is gratefully acknowledged. In particular, we are indebted to Prof. C. Rüchardt for his continued support of our research.

References

1) Dedicated to Prof. M. Schulz on the occasion of his 65th birthday: Enol Cation Radicals in Solution, 7, for part 6 see M. Schmittel, G. Gescheidt, and M. Röck, *Angew. Chem., Int. Ed. Engl.*, (1994), accepted for publication.

2) R. C. Larock, "Comprehensive Organic Transformations", VCH, New York (1989).

3) M. M. Green, G. J. Mayotte, L. Meites, and D. Forsyth, *J. Am. Chem. Soc.*, **102**, 1464 (1980); J. Y. Becker, L. R. Byrd, L. L. Miller, and Y. H. So, *ibid.*, **97**, 853 (1975).

4) M. Schmittel and U. Baumann, *Angew. Chem.*, **102**, 571 (1990); *Angew. Chem., Int. Ed. Engl.*, **29**, 541 (1990); M. Schmittel, A. Abufarag, O. Luche, and M. Levis, *Angew. Chem.*, **102**, 1174 (1990); *Angew. Chem., Int. Ed. Engl.*, **29**, 1144 (1990).

5) Electrooxidation strategies with various mediators did not involve enol cation radicals; Y. Matsumura, and T. Shono, *Bull. Electrochim.*, **6**, 89 (1990); T. Shono, Y. Matsumura, S. Katoh, T. Fujita, and T. Kamada, *Tetrahedron Lett.*, **30**, 371 (1989).

6) M. Schulz, R. Kluge, L. Sivilai, and B. Kamm, *Tetrahedron*, **46**, 2371 (1990).

7) J. R. Keeffe, A. J. Kresge, and Y. Yin, *J. Am. Chem. Soc.*, **110**, 8201 (1988); J. R. Keeffe and A. J. Kresge, in *The Chemistry of Enols*, Ed. Z. Rappoport, Wiley, Chichester 1990, p. 399.

8) All potentials are referenced to the ferrocene/ferrocenium couple ($Fc/Fc^{+\cdot}$): to obtain potentials vs. SCE simply add +0.39 V. $E_p^{ox}$ of the ketones were measured by cyclic voltammetry at $v = 100\ mV \cdot s^{-1}$ in 0.1 M $n$-$Bu_4NPF_6$ in acetonitrile. $E_{1/2}^{ox}$ of the enols were estimated by AM1-calculated adiabatic ionization potentials and a correlation of $E_{1/2}^{ox}$ with $IP_a$ that employed structurally very closely related substrates: D. D. M. Wayner, B. A. Sim, and J. J. Dannenberg, *J. Org. Chem.*, **56**, 4853 (1991).

9) With these the yields of α-Umpolung products were lower than 5 %.

10) M. Schmittel and M. Röck, *Chem. Ber.*, **125**, 1611 (1992); M. Röck and M. Schmittel, *J. Prakt. Chem.*, **336**, 325 (1994).

11) Y. Chiang, A. J. Kresge, and N. P. Schepp, *J. Am. Chem. Soc.*, **111**, 3977 (1989).

12) We have decided for **FePhen** because it exhibits a much lower extinction coefficient than $\mathbf{TBPA}^{+\cdot}$ or $\mathbf{TTA}^{+\cdot}$ thus allowing higher concentrations (ca. 2 mM) for the VIS-spectroscopic study.

13) The calculated $k_{ET}$ for oxidation of **1e** by **FePhen** is $5.2 \cdot 10^8\ M^{-1} \cdot s^{-1}$, which is much faster than the rate of ketonization $k_{ket} = 3 \cdot 10^5\ M^{-1} \cdot s^{-1}$ derived from $k_{enol}$ and the equilibrium constant7).

14) K. Izutsu, "Acid-Base Dissociation Constants in Dipolar Aprotic Solvents", Blackwell, Oxford (1990).

(Received July 8, 1994)