Synthetic Methods

Hydrative Aminoxylation of Ynamides: One Reaction, Two Mechanisms

Alexandre Pinto, [a] Daniel Kaiser, [a] Boris Maryasin, [a, b] Giovanni Di Mauro, [a] Leticia González, [b] and Nuno Maulide* [a]

Abstract: Organic synthesis boasts a wide array of reactions involving either radical species or ionic intermediates. The combination of radical and polar species, however, has not been explored to a comparable extent. Herein we present the hydrative aminoxylation of ynamides, a reaction which can proceed by either a polar-radical crossover mechanism or through a rare cationic activation. Common to both processes is the versatility of the persistent radical TEMPO and its oxidised oxoammonium derivative TEMPO+. The unique mechanisms of these processes are elucidated experimentally and by in-depth DFT-calculations.

Introduction

The chemistry of free radicals has shaped organic chemistry for over a hundred years, and during this time, has produced several ground-breaking innovations. Once thought uncontrollable due to high reactivity and barely predictable behaviour, the last decades have brought a deeper understanding of the role of free radicals in organic reactions and have placed them at the forefront of some major developments in organic synthesis. These range from free-radical chain reactions, all the way to photoredox catalysis, and in nitroxide-mediated living free-radical polymerisation (NMP).

Scheme 1a). Additionally, its longevity allows TEMPO to be used as a trapping agent or radical scavenger in radical carbon–carbon bond-forming reactions. Similarly, TEMPO itself has been employed in the aminoxylation of enolate derivatives, affording α-oxidised carbonyl products. It is, however, arguably most famous for its ability to oxidise primary and secondary alcohols to the corresponding carbonyl compounds, a task which it achieves via its oxidised oxoammonium counterpart TEMPO•+. Curiously, the chemistry of oxoammonium salts is not much developed beyond this synthetically useful reactivity manifold (Scheme 1b).

Scheme 1. a) Reactivity patterns of TEMPO, b) TEMPO•+, and c) our hydrative aminoxylation.

[a] A. Pinto,* D. Kaiser,* Dr. B. Maryasin,* G. Di Mauro, Prof. Dr. N. Maulide Institute of Organic Chemistry, University of Vienna Währinger Strasse 38, 1090 Vienna (Austria)
E-mail: nuno.maulide@univie.ac.at
[b] Dr. B. Maryasin,* Prof. Dr. L. Gonzalez Institute of Theoretical Chemistry, University of Vienna Währinger Strasse 17, 1090 Vienna (Austria)
[*] These authors contributed equally to this work.
[1] Supporting information and the ORCID identification number for the author of this article can be found under https://doi.org/10.1002/chem.201706063.
[2] © 2018 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

DOI: 10.1002/chem.201706063
Herein we report the TEMPO-mediated hydrative aminoxyl-
ation of ynamides (Scheme 1c), an unusual reaction that can proceed by either a polar-radical crossover mechanism or a cationic hydrative pathway and which showcases the unique versatility of the chemistries of persistent radicals and ketyl-
iminium ions, as well as a detailed mechanistic and computa-
tional study of the process.

Results and Discussion

Following our recent report on the reaction of TEMPO with ac-
tivated amides,\textsuperscript{[14]} our initial efforts focused on the combina-
tion of ynamides\textsuperscript{[15]} with TEMPO under the action of a Brønsted
acid (Scheme 2). We eventually found that it was possible to
intercept an acid-preactivated ynamide 1a with TEMPO under
mild conditions. This enabled the preparation of a hydrative
oxyamination product 2a in 80\% isolated yield.\textsuperscript{[16]} Further
modification of the conditions, including the premixing of yn-
amide and TEMPO, as well as the use of fewer equivalents of TEMPO, led to no improvement in yield (details of optimisation
experiments are compiled in the Supporting Information). The
strict requirement for 2.2 equivalents of TEMPO in order to
obtain high yields of product would prove to have significant
mechanistic implications (vide infra).

Having identified optimal reaction conditions, we were inter-
ested in investigating the scope and functional group toler-
ance of the reaction (Scheme 3).

Aromatic substituents on the ynamide were well tolerated
throughout (2a–i), affording the desired hydrative aminoxyla-
tion products in high yields. Upon changing the substitution
to aliphatic chains (2j–t), it became evident that the reaction
benefited from slightly elevated temperatures (40 °C). When
these conditions were applied, linear (2j, k) and branched (2i–
n) aliphatic substrates alike smoothly underwent hydrative
aminooxylation and good to excellent yields of the correspond-
ing products were isolated. For both aromatic and aliphatic
substrates, poor diastereocontrol was observed (2i and 2n, re-
spectively). Cyclopropyl ynamide 1o, a valuable substrate to
probe radical processes (vide infra), also underwent the reac-
tion with minimal ring cleavage.\textsuperscript{[17]} However, isolation of the
 corresponding product 2o required reductive TMP-cleavage
and TBDPS-protection, contributing to the modest 35\% yield.
 Various functional groups were tolerated under the reaction
conditions, including alkene (2p), chloride (2q), ester (2r),\textsuperscript{[18]}
and phthalimide (2t) moieties.

From the outset, we were intrigued about the role of
TEMPO in this reaction, and carried out the mechanistic experi-
ments depicted in Scheme 4.\textsuperscript{[19–21]} For instance, we initially sus-
pected that TEMPO\textsuperscript{+}, the oxoammonium counterpart of TEMPO, was involved in this process. However, substituting
TEMPO for TEMPO\textsuperscript{+} in the procedure presented above yielded
no traces of product (Scheme 4a). Similar thoughts concerning
a possible in situ disproportionation of TEMPO under reaction
conditions led us to add TEMPO-H (the reduced, protonated
form of TEMPO) instead, which also did not afford any product
(with or without added TEMPO\textsuperscript{+}, Scheme 4b).

Similarly, the addition of triflic acid to TEMPO (known to pro-
mote disproportionation\textsuperscript{[22]}) followed by subsequent introd-
uction of the ynamide into the reaction mixture afforded only
7\% NMR yield of the hydrative aminooxylation product
(Scheme 4c).
Surprisingly, however, we observed that in the absence of triflic acid, a combination of TEMPO$^+$ (1.00 equiv) and water (2.00 equiv) is competent in providing the hydrative aminoxylated product 2a in 62% yield (Scheme 4d). This unexpected observation hints at the ability of TEMPO$^+$ to activate yn- amides as a cationic O$^+$-donor reagent.\[23\]

The generality of this transformation was briefly investigated and results are compiled in Scheme 5. As can be seen, the use of TEMPO$^+$/water allows hydrative aminoxylation of several ynamides in yields comparable to those of the combined TfOH/TEMPO procedure (and with considerably shorter reaction times) for a variety of substitution patterns. In addition to select repeated examples from Scheme 3 (2a, b, d, k, m, p, s, t), ynamicides containing varying alkyl and aryl substitution (2u–x) were smoothly converted to the desired products and, pleasingly, both silyl ethers (2y) and nitriles (2z) were tolerated under the reaction conditions.

Mechanistic studies

The unusual observation that two sets of diametrically opposed conditions lead to the same product, raises significant mechanistic questions. While the procedure involving TEMPO$^+$/water appears to proceed by a “conventional” cationic activation/aqueous capture pathway (Scheme 6a), we still had no clear picture for the intriguing polar-radical combination of the TfOH/TEMPO protocol. In particular, the stringent requirement for 2 equivalents of TEMPO$^+$ in the latter set of conditions contrasts with the successful hydrative aminoxylated observed with only 1 equivalent TEMPO$^+$ in the aqueous procedure. Furthermore, the possibility that both mechanisms would overlap remained open—until the isotopic labelling experiments of Scheme 6 were carried out.

As shown, when using $^{18}$O-water in conjunction with TEMPO$^+$, unambiguous incorporation of the label into the car- bonyl oxygen was observed (Scheme 6a). This strongly suggests that the reaction proceeds by cationic activation of the ynamide coupled to hydrolysis. Unexpectedly, the use of $^{18}$O-la- belled TEMPO for the TfOH/TEMPO procedure led to significant double incorporation of the label (Scheme 6b), indicating that both oxygens inserted into the final product originate from

---

Scheme 4. Mechanistic experiments.

Scheme 5. Scope of the electrophilic TEMPO$^+$/H$_2$O addition to ynamides. Yields refer to isolated products.

Scheme 6. a) Proposed mechanistic outline and isotopic labelling validation for the TEMPO$^+$-mediated hydrative aminoxylation of ynamides. b) Double incorporation of the $^{18}$O-label for the reaction with TEMPO.
the persistent aminoxyl radical reagent. Notably, quenching the TFOH/TEMPO reaction with ¹⁷O-labelled water did not lead to incorporation of the label into the final product, thereby further corroborating a difference in mechanism for the two transformations. At this juncture, we resorted to quantum chemical calculations at the DFT level of theory (see the Supporting Information for the computational details) to shed more light on the intricacies of this unusual polar-radical cross-over process.

DFT studies

As shown previously,[24] the treatment of ynamide 1a with TFOH leads to the transient formation of an E/2-mixture of the triflated species A-OTf, which exists in equilibrium with the keteniminium ion A. For this reason, calculations of the formation mechanism for the formation of products 2a were performed starting from A (Scheme 7).

At the outset of our calculations, we were mindful of the labelling studies that effectively established the prerequisite for incorporation of two oxygen atoms from TEMPO in the final product; this prerequisite was reflected in the calculations.

The computed reaction profile is shown in Figure 1. The starting point (intermediate A') presents two TEMPO radicals and the keteniminium cation A. In the first step, one of the TEMPO radicals attacks the cation A leading to the imidate intermediate B (Pinner-type).[25] The intermediates A' and B, as well as the corresponding transition state TS A,X a cationic diradicals and therefore exist both in triplet and singlet states, both of which were considered in the calculations (shown in red and blue, Figure 1).[26] Intersystem crossing (ISC) of the triplet and the singlet states occurs on the phase between the transition state TS A,X and the intermediate B (Figure 1). The computed resonance structure of B (a N,O-ketene acetal derivative) also accounts for the stability of the cationic radical species and thereby can be reconciled with the low amounts of the corresponding ring-opening product detected in the case of cyclopropyl product 2o (vide supra).

The next steps of the reaction occur in the closed-shell state. Intermediate B and the second TEMPO radical recombine, forming intermediate C. This explains the experimental fact that both oxygen atoms within the final product are derived from TEMPO (cf. Scheme 6b). The final step C→D is very favourable thermodynamically (−95.0 kcal mol⁻¹). In this step, one of the O–N bonds is cleaved heterolytically, leading to the neutral final product 2a, and a cation originating from rearrangement of the TMP⁺ fragment (two possible cations are depicted in Figure 1).[27]

We have also computationally considered the reaction of the keteniminium intermediate with TEMPOH or TEMPO⁺ as alternative non-radical mechanism of the studied processes.

The quantum chemical calculations at the DFT level of theory suggest that the necessary closed-shell (non-radical) transition state does not exist as a stationary point on the potential energy surface. This means that this process has a large kinetic barrier and therefore is highly unlikely to take place. This is consistent with the aforementioned experimental observations (cf. Scheme 4).

Conclusions

In conclusion, we have documented an unusual hydrative amination of ynamides that can proceed by two different mechanisms. Crucial to each pathway is the presence of either the persistent aminoxyl radical TEMPO or its oxidised oxoammonium variant TEMPO⁺. The first process involves addition of a radical species to a keteniminium intermediate, a transformation which is underrepresented in synthesis and which was elucidated by extensive DFT calculations. The second pathway dispenses with acidic pre-activation and proceeds by a classical nucleophile/electrophile cooperative process. Both processes highlight the versatility of TEMPO as a truly chameleonic reagent in synthesis.

Acknowledgements

Financial support of this research by the ERC (CoG 682002 to N.M.) and the FWF (Grant P30226) is acknowledged. D.K. is a
DOC-fellow of the Austrian Academy of Sciences. A.P. acknowledges a Grant from the Ministerio de Economía, Industria y Competitividad (BES-2013-064292 and EEBB-I-17-11898). Calculations were partially performed at the Vienna Scientific Cluster (VSC). Generous continued support of our research by the University of Vienna is gratefully acknowledged.

Conflict of interest

The authors declare no conflict of interest.

Keywords: aminooxylation · density functional calculations · heterocycles · radicals · reaction mechanisms

[1] C. R. J. Stephenson, A. Studer, D. P. Curran, Beilstein J. Org. Chem. 2013, 9, 2778–2780.
[2] A. Studer, D. P. Curran, Nat. Chem. 2014, 6, 765–773.
[3] For comprehensive reviews on free radical chain reactions, see: a) D. P. Curran, Synthesis 1988, 417–439; b) D. P. Curran, Synthesis 1988, 489–513; c) B. Quiclet-Sie, S. Z. Zard, Pure. Appl. Chem. 2011, 83, 519–551.
[4] For reviews on photoredox catalysis, see: a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, Chem. Rev. 2013, 113, 5322–5363; b) M. H. Shaw, J. Twilton, D. W. C. MacMillan, J. Org. Chem. 2016, 81, 6898–6926.
[5] D. Griller, K. U. Ingold, Acc. Chem. Res. 1976, 9, 13–19.
[6] M. Gomberg, J. Am. Chem. Soc. 1900, 22, 757–771.
[7] a) O. L. Lebedev, S. N. Kazarnovski, Tr. Khim. Khim. 1959, 2, 649–665; b) A. Studer, T. Schulte, Chem. Rec. 2005, 5, 27–35; c) T. Vogler, A. Studer, Synthesis 2008, 13, 1979–1993; d) O. Garcia Manchego, T. Stopka, Synthesis 2013, 45, 1602–1611.
[8] a) S. Coseri, K. U. Ingold, Org. Lett. 2004, 6, 1641–1643; b) J. E. Babiarz, G. T. Cunkle, A. D. DeBellis, D. Eveland, S. D. Pastor, S. P. Shum, J. Org. Chem. 2002, 67, 6831–6834.
[9] a) H. Fischer, Chem. Rev. 2011, 111, 3581–3610; b) K. O. Siegenthaler, A. Studer, Macromolecules 1995, 28, 8722–8728.
[10] M. Hartmann, Y. Li, A. Studer, J. Am. Chem. Soc. 2012, 134, 16516–16519.
[11] a) A. D. Allen, B. Cheng, M. H. Fenwick, W.-w. Huang, S. Missiha, D. Tahmassabi, T. T. Tidwell, Org. Lett. 1999, 1, 693–696; b) A. D. Allen, J. Porter, D. Tahmassabi, T. T. Tidwell, J. Org. Chem. 2001, 66, 7420–7426; c) M. Pouliot, P. Renaud, K. Schenk, A. Studer, T. Vogler, Angew. Chem. Int. Ed. 2009, 48, 6037–6040; Angew. Chem. 2009, 121, 6153–6156; d) Y. Li, M. Pouliot, T. Vogler, P. Renaud, A. Studer, Org. Lett. 2012, 14, 4474–4477; e) P. J. Mabe, A. Zakarian, Org. Lett. 2014, 16, 516–519; f) A. Gómez-Palomino, M. Pellicena, J. M. Romo, R. Solá, P. Romea, F. Urpi, M. Font-Bardia, Chem. Eur. J. 2014, 20, 10153–10159; g) P.-P. Ruan, C.-H. Shen, L. Li, C.-Y. Liu, L.-W. Ye, Org. Chem. Front. 2016, 3, 989–993; h) C. Heras, A. Gómez-Palomino, P. Romea, F. Urpi, J. M. Bofill, I. de P. R. Mor-eira, J. Org. Chem. 2017, 82, 8909–8916; i) X. Li, F. Lin, K. Huang, J. Wei, X. Li, X. Wang, X. Geng, N. Jiao, Angew. Chem. Int. Ed. 2017, 56, 12307–12311; Angew. Chem. 2017, 129, 12475–12479.
[12] a) Z. Ma, J. M. Bobbitt, J. Org. Chem. 1991, 56, 6110–6114; b) J. M. Bobbitt, J. Org. Chem. 1998, 63, 9367–9374; c) M. S. Shibuya, M. Tomizawa, Y. Iwabuchi, J. Org. Chem. 2008, 73, 4750–4752.
[13] a) J. M. Bobbitt, C. L. Flores, Heterocycles 1988, 27, 509–533; b) T. Breton, D. Liaigre, E. M. Belgisir, Tetrahedron Lett. 2005, 46, 2487–2490; c) Y. Liu, T. Ren, O. Guo, Chin. J. Chem. 1996, 14, 252–258.
[14] A. de la Torre, D. Kaiser, N. Maulide, J. Am. Chem. Soc. 2017, 139, 6578–6581.
[15] For a review on ynamide chemistry, see: K. A. DeKorver, H. Li, A. G. Lohse, R. Hayashi, Z. Lu, Y. Zhang, R. P. Huong, Chem. Rev. 2010, 110, 5064–5106.
[16] The product can be further functionalised through oxidative/reductive cleavage of the O–TMP bond (see Supporting Information section 4.4).
[17] No more than trace amounts of olefinic peaks, resulting from possible radical fragmentation of the cyclopropane, were detected in the crude NMR.
[18] The slightly reduced yield of 2r is likely due to partial cycloisomerisation of the ester carbonyl onto the transient keteniminium ion, competing with TEMPO addition. For a related reaction, see: D. Kaiser, A. de la Torre, S. Shaaban, N. Maulide, Angew. Chem. Int. Ed. 2017, 56, 5921–5925; Angew. Chem. 2017, 129, 6015–6019.
[19] V. D. Sen, V. A. Golubev, J. Phys. Org. Chem. 2009, 22, 138–143.
[20] Trace amounts of product were detected by HRMS; this can be explained by small quantities of TEMPO radical present, formed by oxidation of TEMPOH (5).
[21] Additionally, the low yield could also be caused by unreacted TEMPO radical and TfOH following the proposed reaction mechanism.
[22] a) V. A. Golubev, I. I. Zhdanov, V. M. Gida, E. G. Rozantsiev, Russ. Chem. Bull. 1971, 20, 768–770; b) Y. Ma, C. Loyns, P. Price, V. Chechik, Org. Biomol. Chem. 2011, 9, 5573–5578.
[23] T. Takata, Y. Tsujino, S. Nakanishi, K. Nakamura, E. Yoshida, T. Endo, Chem. Lett. 1999, 28, 937–938.
[24] L. L. Baldassari, A. de la Torre, J. Li, D. S. Lüdtke, N. Maulide, Angew. Chem. Int. Ed. 2017, 56, 15723–15727; Angew. Chem. 2017, 129, 15929–15933.
[25] a) A. Pinner, F. Klein, Ber. Dtsch. Chem. Ges. 1877, 10, 1889–1897; b) R. Roger, D. G. Neilson, Chem. Rev. 1961, 61, 179–211.
[26] The spin-correction procedure was applied to eliminate the spin contamination error (see SI for more details).
[27] For an example of cationic TMP-rearrangement, see: X. Tao, G. Kehr, X. Wang, C. G. Danillic, J. Grimmer, G. Erker, Chem. Eur. J. 2016, 22, 9504–9507.