Published in final edited form as:

Tetrahedron Lett. 2018 October 10; 59(41): 3674–3677. doi:10.1016/j.tetlet.2018.08.056.

Imidazolidin-4-ones via (3+2) cycloadditions of aza-oxyallyl cations onto (*E*)-*N*-arylideneanilines

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Abstract

In the course of our studies on the chemistry of oxyallyl species we uncovered a new (3+2) cycloaddition of aza-oxyallyl systems, generated in situ from *N*-benzyloxy-2-chloroamides in the presence of NEt₃, onto *N*-arylimines yielding imidazolidin-4-ones in moderate to good yields. The cycloadditions are regioselective. Computational modelling using DFT at the M062×/6–311+G** level is in support the observed regioselectivities. Although the path to the *trans* imidazolin-4-one is favored, the *cis* product is preferred by almost 8 kcal/mol and could be formed by base-catalyzed epimerization. All products were isolated by chromatography and characterized by means of their FTIR, NMR and HRMS data.

Graphical Abstract

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Keywords

aza-oxyallyl; aza-cyclopropanone; *N*-arylimine; (3+2) cycloaddition; imidazolidin-4-one

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Supplementary Material

¹H and ¹³C NMR (APT), FTIR and HRMS spectra of compounds **22a–22i**; all computational data associated with this article can be found in the online version, at <https://doi.org/10.1016/j.tetlet.2018.08.056>.

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1. Introduction

The aza-oxyallyl cation has been implicated in the nucleophilic ring opening reactions of α -lactams (nitrogen analogs of cyclopropanones).¹ The valence isomerization of an alkylidene oxazirine (the nitrogen analog of an allene oxide) to an α -lactam was proposed to proceed through an aza-oxyallyl cation which was supported by computation.² An aza-oxyallyl cation was also suggested in the solvolysis of *N*-chloro-*N*-alkoxyphenylacetamides.³ Definitive proof of the intermediacy of aza-oxyallyl cations via trapping with unsaturated systems failed until Jeffrey et al. succeeded in intercepting these elusive species through intermolecular (4+3) cycloaddition reactions with cyclopentadiene and furan.⁴ In a follow-up report on the synthetic applications of aza-oxyallyl cations, Jeffrey and co-workers extended the (4+3) cycloadditions to the diaza-oxyallyl cation and several other cyclic dienes, including 6,6-dimethylfulvene.⁵

They were also able to exploit the aza-oxyallyl-cyclic diene cycloadditions in intramolecular cycloadditions.⁶ Since these ground-breaking studies by Jeffrey et. al., synthetic activity in this area increased, and several intermolecular (3+2) cycloadditions leading to heterocycles have been reported.⁷

In the course of our own studies on the thermal isomerizations of saturated fulvene endoperoxides (e.g., **6**), we disclosed the first method for the generation of the allene oxide-cyclopropanone-oxyallyl triad under neutral conditions⁸.

We also reported *the first examples of intramolecular 1,3-dipolar cycloadditions of oxyallyl cations onto carbonyl groups* (Scheme 1), as well as inter- and intramolecular trapping reactions of oxy-allyl species derived from these reactive intermediates.⁹ Moreover, we unveiled the first aliphatic [3.4] sigmatropic shifts involving an oxy-allyl cation (**13**→**14**).¹⁰ A survey of our results from these efforts are summarized in Schemes 2 and 3.

We have now extended our synthetic effort toward the aza analogs of oxy-allyl cations and discovered that these species are at least as reactive and versatile in terms of their reactivity toward a variety of cycloaddends. Herein, we disclose in a collaborative effort our results from the (3+2) cycloadditions of aza-oxyallyl cations onto imines.

2. Results and Discussion

α -Lactams, valence isomers of aza-oxyallyl cations have first been proposed by Leuchs as reactive intermediates. He observed that α -amino acid *N*-carboxyanhydrides ("Leuchs-anhydrides") lose CO₂ upon heating to give α -lactams that polymerize to form polypeptides.¹¹ We recently developed a method for the synthesis of imidazolidin-4-ones by the condensation of Leuchs anhydrides with imines under loss of CO₂ with DBU in MeOH (Scheme 4).¹²

We then explored the possibility for establishing a more versatile method for imidazolidin-4-ones by employing an azaoxyallyl cation as the key reactant, since our previous method suffered from limited availability of diversely substituted Leuchs anhydrides. We are pleased to report that aza-oxyallyl cations, generated in situ from *N*-benzyloxy-2-chloroamides^{4,5}

and NEt_3 (or Na_2CO_3) as base in trifluoroethanol (TFE) solutions, reacted smoothly with (*E*)-*N*-arylimines¹² to give imidazolidin-4-ones **22** in good yields (Scheme 5). *N*-Arylimines derived from aromatic aldehydes were chosen due to their greater stability and ease of isolation.

Table 1 shows that in some cases only *trans* isomers are formed, and in a few cases mixtures of *cis/trans* isomers are isolated. The transition state leading to the products may favor one or the other isomer; the presence of base during the cycloadditions may also affect the *cis/trans* ratios by way of base-catalyzed epimerization, especially at higher temperatures. These issues are addressed below in computational work. Also the reaction conditions in several cases needs some comment. The method for generating the aza-oxyallyl cation in each case (either with NEt_3 as base at 0 °C in TFE or Na_2CO_3 at 80 °C in the same solvent) was chosen based on which method furnished the best yields.

To gain greater insight, the reaction was computationally modeled using DFT at the M062x/6-311+G** level. As a model, the reaction of *N*-phenylbenzylimine with an *N*-methoxyphenyl aza-oxyallyl intermediate was used. The computed enthalpic barrier is 6.7 kcal/mol on the path (Figure 1) to the *trans* imidazolin-4-one (8.3 kcal/mol to the *cis* stereoisomer). The structure suggested asynchronicity in the cycloaddition and shows advanced bond formation with the imine nitrogen relative to the imine carbon. This transition state is over 25 kcal/mol lower than the alternatives paths to imidazolidin-4-one regioisomers (Table S1 in supplementary material). Although the path to the *trans* imidazolin-4-one is favored, the *cis* product is preferred by almost 8 kcal/mol and could be formed by basecatalyzed epimerization.

3. Conclusions

Aza-oxyallyl species are reactive intermediates that may serve as important building blocks for various heterocycles, providing that the right cycloaddends are found that exhibit considerable reactivity in a (3+2) cycloaddition process. We uncovered a new regioselective cycloaddition of the aza-oxyallyl species onto *N*-arylimines giving rise to imidazolidin-4-ones. The present method is superior to our method via the Leuchs anhydrides because the latter are difficult to obtain in diverse substitution patterns, thus rendering the method of limited value. Moreover, the reductive removal of *N*- OCH_2Ph groups to give the 3-hydroxyimidazolidin-4-one derivatives, which, to the best of our knowledge, are not accessible by other methods. Computational modeling correctly predicts the observed regioselectivities with an asynchronous pathway, favoring *trans* stereoselectivity, though the *cis* product in the model system should be favored by 8 kcal/mol and is indeed the dominant product in several cases due to base-catalyzed epimerization. Further studies are under way exploring cycloadditions of other C=N containing cycloaddends and will be reported in due course.

General procedure for the cycloadditions.

To a solution of imine (0.25 mmol) in TFE (2 mL), α -haloamide (0.5 mmol) and Na_2CO_3 or Et_3N (1 mmol) was added. The reaction was stirred at 0 °C or refluxed at 80 °C. Once the reaction was complete, as judged by TLC analysis, the reaction mixture was diluted with

ethyl acetate, filtered through Celite, the filtered cake washed with ethyl acetate. The filtrate was then concentrated under rotary evaporation. The resulting residue was purified by silica gel chromatography (ethyl acetate/*n*-hexane) to afford the cycloadducts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

During the preparation of this manuscript, our dear colleague and friend, Prof. Nuket Ocal, tragically passed away. We are deeply grateful to Dr. Ocal's tireless efforts, dedication, her –and her students'– invaluable contributions to this project. N. Ocal acknowledges financial support of this work by the Scientific and Technological Research Council of Turkey (TUBITAK, project no. 112T880). I. Erden acknowledges financial support of this work by funds from the National Institutes of Health (Grant No. SC1GM082340). S. Gronert acknowledges support from the National Science Foundation (CHE-1565852).

References and notes

1. Lengyel JC Sheenan, *Angew. Chem. Int. Ed.* 1968, 725–36.
2. Cohen AD, Showalter BM, Toscano JP, *Org. Lett.* 2004, 6, 401–403. [PubMed: 14748603]
3. Kikugawa Y, Shimada M, Kato M, Sakamoto T, *Chem. Pharm. Bull.* 1993, 41, 2192–2194.
4. Jeffrey CS, Barnes KL, Eickhoff JA, Carson CR, *J. Am. Chem. Soc.* 2011, 13, 7688–7691.
5. Barnes KL, Koster AK, Jeffrey CS, *Tetrahedron Lett.* 2014, 55, 4690–4696.
6. Acharya A, Eickhoff JA, Jeffrey CS, *Synthesis*, 2013, 45, 1825–1836.
7. (a)Zhao H-W, Zhao Y-D, Liu Y-Y, Zhao L-J, Feng N-N, Pang H-L, Chen X-Q, Song X-Q, J. Du, *RSC Adv.* 2017, 7, 12916–12922(b)Wang G, Chen R, Wu M, Sun S, Luo X, Chen Z, Guo H, Chong C, Xing Y, *Tetrahedron Lett.* 2017, 58, 847–850(c)Jiang S, Li K, Yan J, Shi K, Zhao C, Yang L, Zhong G, *J. Org. Chem.* 2017, 82, 9779–9785 [PubMed: 28829132] (d)Zhao H-W, Zhao YD, Liu Y-Y, Du J, Pang H-L, Chen X-Q, Song X-Q, Feng N-N, E. J. Org. Chem 2017, 24, 3466–3472(e)DiPoto MC, Hughes RP, Wu J, *J. Am. Chem. Soc.* 2015, 137, 14861–14864. [PubMed: 26562355]
8. Erden I, Amputch M, *Tetrahedron Lett.* 1987, 28, 3779–3782.
9. (a)Erden I, Drummond J, Alstad R, Xu F, *Tetrahedron Lett.* 1993, 34, 1255–1258(b)Erden I, Drummond J, Alstad R, Xu F, *J. Org. Chem.* 1993, 58, 3611–3612(c)Erden I, Ma J, Gärtner C, Azimi S, Gronert S, *Tetrahedron*, 2013, 69, 5044–5047 [PubMed: 23956469] (d)Erden I, Gärtner C, *Tetrahedron Lett.* 2009, 50, 2381–2383. [PubMed: 20161263]
10. Erden I, Xu F, Cao W, *Angew. Chem. Int. Ed.* 1997, 36, 15161518.
11. Leuchs H, Geiger W, *Chem. Ber.* 1908, 1721–1726.
12. Sucu BO, Ocal N, Erden I, *Tetrahedron Lett.*, 2015,56, 2590–2592Ling R; Yoshida M; Mariano PS *J. Org. Chem.* 1996, 61, 4439–4449. [PubMed: 11667350]

Figure 1. Transition state for trans imidazolin-4-one formation modeled at the M062×/6–311+G** level (carbon: grey, hydrogen: white, nitrogen: blue, and oxygen: red).

Scheme 1.

Aza-oxyallyl interconversions and trapping with dienes.

Scheme 2.

Oxy-allyl cation generation from saturated fulvene peroxides and first example of intramolecular 1,3-dipolar cycloaddition with a carbonyl group.

Scheme 3.

Inter- and intramolecular trapping, as well as sigmatropic shifts of oxy-allyl cations derived from saturated fulvene endoperoxides

Scheme 4.

Synthesis of imidazolidin-4-ones from Leuchs anhydride and imines.

Scheme 5.

(3+2) Cycloadditions of aza-oxyallyl cations with imines.

Table 1.

Imidazolin-4-ones via (3+2) cycloadditions of aza-oxyallyl cations with imines

2-Chloroa mide	Imine	Conditions	Product(s)	Yiel d %
19a ^[a]	 21a	TFE, 0 °C NEt ₃	 22a	61
19a	 21b	TFE, 0 °C NEt ₃	 22b <i>cis/trans</i> =4	43
19a	 21c	TFE, 80 °C Na ₂ CO ₃	 22c	64
19a	 21d	TFE, 80 °C Na ₂ CO ₃	 22d	55
19b ^[b]	21a	TFE, 0 °C NEt ₃	 22e <i>cis/trans</i> =1.5	66
19b	21b	TFE, 0 °C NEt ₃	 22f	54
19b	 21e	TFE, 0 °C NEt ₃	 22g <i>cis/trans</i> =1.5	66

2-Chloroa mide	Imine	Conditions	Product(s)	Yiel d %
19b	 21f	TFE, 80 °C Na ₂ CO ₃	 22h	71
19b	 21g	TFE, 80 °C Na ₂ CO ₃	 22i <i>cis/trans=2.3</i>	68

[a] **a**:R=Ph

[b] **b**: R=Me