Published in final edited form as:

Tetrahedron Lett. 2017 October 4; 58(40): 3879–3883. doi:10.1016/j.tetlet.2017.08.070.

Stereochemistry and Reactivity of the HPA-Imine Mannich Intermediate

Daniel Polyak, Ngan Phung, Jian Liu, Robert Barrows, Thomas J. Emge, and Spencer Knapp

Department of Chemistry and Chemical Biology, Rutgers – The State University of New Jersey, 610 Taylor Rd., Piscataway, NJ 08854, USA

Abstract

Homophthalic anhydride (HPA) typically reacts rapidly with benzalimines to afford the formal [4+2] adduct, a 1,2,3,4-tetrahydroisoquinolin-1-one-4-carboxylic acid. The stereochemical outcome of this reaction is consistent with an open transition state comprising an iminium species and enolized HPA, leading to a short-lived amino-anhydride intermediate. In the case of *N*-*tert*-butylbenzalimine, this Mannich-type intermediate, which would normally cyclize at low temperature to a single isomer of the *delta*-lactam, is intercepted by base treatment to afford *beta*-lactam products. A pathway featuring ketene formation followed by ring closure is implicated.

Graphical Abstract

Keywords

carboxylic anhydride; steric hindrance; cycloaddition

1. Introduction

The reaction of imines with cyclic carboxylic anhydrides generally,^{1,2,3} and homophthalic acid (HPA, **1**) in particular,^{4,5} has become an important method for the efficient assembly of lactams with useful biological activity. Such compounds have seen application toward potential anticancer treatments,^{6,8,9} and include a new group of antimalarials from which a clinical candidate has recently emerged.^{10,11,12} Synthetic^{2,3} and computational^{13,14} aspects

Correspondence to: Spencer Knapp.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Supplementary Material

Preparative and spectroscopic details for the *N*-substituent study (Table 1) and β -lactams **35** and **36**, and CIF data for **35** and **36**.

of the HPA-imine reaction, formally a [4+2] cycloaddition of the enolized form of HPA (**2**, Scheme 1), have been investigated extensively. A wide variety of solvents and additives have been shown to accommodate or modify the transformation, which nonetheless occurs rapidly at modest temperatures even in the absence of added acid or base promoters. Under certain conditions, stereoselective, or even enantioselective,^{15,16} formation of the 3,4-*cis*- or 3,4-*trans* 1,2,3,4-tetrahydroisoquinolin-1-one-4-carboxylic acid product (**4**, a “THIQ”) can be achieved, and for most THIQ products treatment of *cis*-**4** with acid, base, or heat promotes complete isomerization to the more stable *trans*-**4**. While examples of non-aromatic imines are known,^{11,17,18,19,20} most investigations have involved N-substituted benzalimines (**3**), and these substrates typically give the highest yields and find the widest application.

Despite earlier considerations of alternative mechanisms,^{2,14,21} more recent analysis of the HPA-imine reaction seems to have settled on a two-step process centered on Mannich-type amino-anhydride intermediate **5**,^{3,13,15,22} the stereochemistry of which translates to the C-3 and C-4 stereocenters of the THIQ product. Under certain conditions, elimination of amine from **5** to afford a Knoevenagel-type alkene product **6** has been observed.²³ By addition of the acyl transfer promoter, 1-methylimidazole, the elimination reaction can be largely avoided, and ring closure to **4** favored.²⁴

In this paper we analyze the effect of the size of the imine substituent **R** for insight into THIQ formation and stereochemistry in the HPA-imine cyclization. An attempt to trap amino-anhydride intermediate **5** by base treatment led to unexpected beta-lactam products.

2. Results and Discussion

2.1. Mechanistic possibilities for the Mannich step

Organization of the reaction components **2** and **3** by an intermolecular hydrogen bond^{13,22} could take place in two different configurations (Scheme 2). The “boat” configuration (**7**) places the aryl group away from the benzo ring, and ought to be favored for small N-substituents **R**. Alternatively, a “chair” configuration (**9**) places the aryl group closer to the benzo ring, and ought to be favored by relatively large **R**. After the Mannich step and subsequent N-cyclization, the “boat” should lead to the *cis* THIQ (**8**), whereas the “chair” should give the *trans* (**10**).

Alternatively, an “open” transition state²⁵ can be envisioned wherein the enolized form of HPA, or, optionally, its enolate anion, reacts with protonated imine to form the new C-C bond (see **12** and **14**, Scheme 3). At effective reaction *pH* in the range ~6–9, any or all of these species are accessible, given the measured *pK_a* of **1** and the typical *pK_a*’s of protonated imines (Scheme 1). Relatively non-basic imines, however, such as ArN=CH₂CF₃ (estimated *pK_a* ~2) would not be expected to be protonated to any large extent, especially in the presence of added base.²⁴ Nevertheless, these imines also react readily with **1**. In the “open” formulation, the approach of components shown as **11** would be predicted to lead mostly to the *cis* THIQ (**8**), and the alternative **13** should give mostly *trans* (**10**). The former transition state ought to be favored for large **R**, which is oriented away from the benzo ring, and the later transition state favored for relatively small **R**.

A third transition state possibility that has been considered^{14,21} for the HPA-imine reaction resembles an intermolecular iminium Diels-Alder reaction (Scheme 4). The bridged intermediates **16** and **18** could ring-open to provide the respective products **8** and **10** directly, or they could open to the respective Mannich intermediates **12** and **14**, and then re-cyclize to give **8** and **10**. Based on steric considerations alone, transition state **15** ought to be favored for small **R**, and lead to the cis THIQ (**8**), whereas the alternative transition state (**16**) would be favored for large **R** and lead to the trans THIQ (**10**).

A fourth possibility^{2,21} featuring initial N-acylation of the imine by HPA at the conjugated C=O has been dismissed as demanding too high an energy of activation,¹³ and is not considered further here.

2.2 The effect of the size of the imine substituent **R** on the stereochemistry of the THIQ product

For simple N-alkyl-substituted imines of benzaldehyde, successful cyclization to THIQs can be achieved in a variety of solvents at low temperature, even in the absence of additives. We find that chloroform, dichloromethane, ethyl acetate, and acetonitrile all work well as solvents, whereas DMF, *tert*-butyl methyl ether, and 2-butanol give lower yields. A series of benzalimines with differing **R** groups^{21,26} was screened to evaluate the effect of the size of **R** and in some cases, the stereochemistry of the imine (Table 1). Thus, **R** was taken through a series from relatively small Me– (**19**) through *n*-Bu– (**21**), CF₃CH₂– (**23**), and *i*-Bu– (**25**), to relatively bulky *t*-Bu– (**27**). Two 3,4-dihydroisoquinolines, **29** and **31**, were also examined. The imines reacted with HPA (**1**, added last) in dichloromethane solution at –30 °C over a period of 150 minutes, after which time the reaction was quenched at low temperature with aqueous citrate solution. Concentration of the organic solution allowed assessment of the THIQ isomer ratio, as well as the apparent combined yield, by H-1 NMR spectroscopic analysis (2,6-di-*tert*-butyl-4-methylphenol, BHT, was used as an internal integration standard). Each of the reactions was also checked by aliquot after 8 minutes to see whether the cis/trans ratio changed as a function of time, and the ratios were essentially the same at the shorter reaction time. For the products **30** and **32**, the indicators “cis” and “trans” refer to the relative stereochemistry of the ring methines. An early study included reactions of **19**, **25**, and **27** with **1**, but featured different reaction conditions, and reported ratios based on crystallized product.²¹

The imines are assumed to react in the trans configuration, except for **29** and **31**, which are cyclic and forced to be cis. Other investigators have made the same assumption,^{13,15} even though an early report²¹ suggested a possible imine trans-to-cis isomerization as a preliminary step prior to C-C bond formation.

The observed trend towards more cis product for increasing size of the N-substituents (Me < *n*-Bu < *i*-Bu < *t*-Bu) is consistent with an open transition state (Scheme 3), but less so for the hydrogen-bonded transition state (Scheme 2) or the iminium Diels-Alder transition state (Scheme 4), both of which predict the opposite order. For the electron-withdrawing trifluoroethyl N-substituent (**23** → **24**), prior N-protonation of the imine would not be favored, but the hydrogen-bonded pathway could still be operative without showing a clear

stereochemical preference.²² The cis, cyclic imines **29** and **31** could proceed through the open transition state of Scheme 3 without showing a strong stereochemical preference, since steric hindrance is reduced for both possibilities. Addition of a sub-stoichiometric amount of trifluoroacetic acid increased the amount of trans isomer **30** slightly. It should be noted that this reaction generates an acidic product (**4**, Scheme 1) as it proceeds, which complicates the analysis of the presence and reactivity of the resulting iminium species **3**.

2.3 Trapping of the Mannich intermediate with methanolic hydroxide and formation of beta-lactam products

The reaction of the bulky N-*tert*-butylbenzalimine **27** with HPA (**1**) is expected to be slower than that of the other imine substrates, and competition studies²¹ show that this is indeed the case. In particular, the reaction pathway might be intercepted at the stage of the Mannich intermediate (**5**), since the bulky N-substituent might slow the N-cyclization step even more than the Mannich step. An attempt was made to trap the amino-anhydride intermediate **5** in the reaction of **27** with **1** (acetonitrile solution, –30 °C, 10 min) by adding the nucleophilic combination hydrogen peroxide / pyridine.²⁷ However, the amino diacid hydrolysis product **34** was not observed; only the familiar cis delta-lactam **28** was isolated.

Quenching the same reaction instead with a more nucleophilic trapping reagent, namely 5% methanolic sodium hydroxide, led unexpectedly to a pair of new lactams eventually determined to be **35** and **36** (4:1, 39% combined yield, Scheme 5). The usual cyclization product, cis delta-lactam **28**, was not formed at all, according to H-1 NMR analysis of the crude reaction product. The structure of cis beta-lactam **36** was secured by X-ray crystallographic analysis (Figure 1) following selective crystallization from a solution of the crude product in methanol and then slow evaporation from acetonitrile/toluene. Crystals of the trans isomer **35** suitable for X-ray studies (Figure 1) were obtained by crystallization of its N-ethylammonium salt from methanol solution. The solution structures assigned to **35** and **36** are consistent with their H-1 and C-13 NMR spectra, and mass spectroscopic analysis. Full experimental details of the reaction of **27** and **1**, the trapping procedure, and the isolation and characterization of beta-lactams **35** and **36** are given in the Supplementary Materials section.

Formation of the beta-lactams **35** and **36** from the Mannich intermediate **33** can be understood by postulating ketene formation under the influence of basic hydroxide (Scheme 5). Intramolecular trapping of this ketene (**38**) by the nearby amino group would lead to the beta-lactam enolate (**39**), protonation of which from either face would then provide the two beta-lactams, **35** and **36**. While beta-lactams have been prepared by Staudinger reaction of ketenes with imines, the intermolecular reaction of aryl ketenes with benzalimines requires prolonged heating.^{28,29} In contrast, formation of **35** and **36** occurs rapidly at –30 °C. This observation would seem to rule out simple intermolecular reaction of the ketene derived from the enolate of **1** with **27** under the influence of base. Direct cyclization of amino anhydride **33** to the kinetically less favored beta-lactam products rather than the delta-lactam alternative (**28**) would be surprising without the intervention of a high energy intermediate such as ketene **38**, and indeed the latter process (delta-N-cyclization) proceeds at –30 °C in the absence of hydroxide.

3. Conclusion

An open transition state (Scheme 3) best accommodates the influence of steric bulk of the N-substituent **R** on the reaction of HPA (**1**) with simple N-substituted benzalimines (**3**). For less basic imines like **23**, or for reaction conditions in which iminium formation is less favored, the cyclic hydrogen-bonded transition states (**7** and **9**, Scheme 2) may make important contributions. An unprotonated and non-hydrogen-bonded imine is probably relatively unreactive in this cycloaddition.

The intermediate Mannich adduct (**33**, Scheme 5) was effectively intercepted by base treatment, leading to beta-lactams **35** and **36**. A mechanism that proceeds through the intermediacy of ketene **38** best accounts for their formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the NIH (AI090662) and Medicines for Malaria Venture for financial support, and to Rutgers University for undergraduate research support for D. P. and N. P.

References

1. Castagnoli N Jr. *J. Org. Chem.* 1969; 34:3187–3189. [PubMed: 5811404]
2. González-López M, Shaw JT. *Chem. Rev.* 2009; 109:164–189. [PubMed: 19140773]
3. Krasavin M, Dar'ın D. *Tetrahedron Lett.* 2016; 57:1635–1640.
4. Haimova MA, Mollov NM, Ivanova SC, Dimitrova AI, Ognyanov VI. *Tetrahedron.* 1977; 33:331–336.
5. Cushman M, Gentry J, Dekow FW. *J. Org. Chem.* 1977; 42:1111–1116. [PubMed: 845705]
6. Ng PY, Tang Y, Knosp WM, Stadler HS, Shaw JT. *Angew. Chem. Int. Ed.* 2007; 46:5352–5355.
7. Nguyen TX, Abdelmalak M, Marchand C, Agama K, Pommier Y, Cushman M. *J. Med. Chem.* 2015; 58:3188–3208. [PubMed: 25811317]
8. Cinelli MA, Reddy PVN, Lv P-C, Liang J-H, Chen L, Agama K, Pommier Y, van Breemen RB, Cushman M. *J. Med. Chem.* 2012; 55:10844–10862. [PubMed: 23215354]
9. Chatterjee, M., Hartung, A., Holzgrabe, U., Mueller, E., Peinz, U., Sotriffer, C., Zilian, D. WO2015185114A1. p. 38
10. Jiménez-Díaz M-B, Ebert D, Salinas Y, Pradhan A, Lehane AM, Myrand-Lapierre M-E, O'Loughlin KG, Shackelford DM, Lage de Almeida MJ, Clark J, Dennis ASM, Diep J, Deng X, Endsley AN, Fedewa G, Guiguemde A, Gomez-Lorenzo MG, Holbrook G, Horst J, Kim K, Liu J, Lee MCS, Matheny A, Martínez MS, Miller G, Rodriguez-Alejandre A, Sanz L, Sigal M, Spillman NJ, Stein PD, Wang Z, Zhu F, Waterson D, Knapp S, Shelat AA, Fidock DA, Gamo FJ, Charman SA, Mirsalis JC, Ma H, Ferrer S, Kirk K, Angulo-Barturen I, Kyle DE, DeRisi JL, Floyd DM, Guy RK. *Proc. Nat. Acad. Sci.* 2014; 111:E5455–E5462. [PubMed: 25453091]
11. Floyd DM, Stein P, Wang Z, Liu J, Castro S, Clark JA, Connelly M, Zhu F, Holbrook G, Matheny A, Sigal MS, Min J, Dhinakaran R, Krishnan S, Bashyum S, Knapp S, Guy RK. *J. Med. Chem.* 2016; 59:7950–7962. [PubMed: 27505686]
12. <https://clinicaltrials.gov/ct2/show/NCT02867059>. Website viewed July 11, 2017.
13. Pattawong O, Tan DQ, Fettinger JC, Shaw JT, Cheong PH-Y. *Org. Lett.* 2013; 15:5130–5133. [PubMed: 24070216]
14. Kaneti J, Bakalova SM, Pojarlieff IG. *J. Org. Chem.* 2003; 68:6824–6827. [PubMed: 12919059]

15. Jarvis CL, Hirschi JS, Vetticatt MJ, Seidel D. *Angew. Chem. Int. Ed.* 2017; 56:2670–2674.
16. Cronin SA, Collar AG, Gundala S, Cornaggia C, Torrente E, Manoni F, Botte A, Twamley B, Cannon SJ. *Org. Biomol. Chem.* 2016; 14:6955–6959. [PubMed: 27381361]
17. Yu N, Poulain R, Gesquiere J-C. *Synlett.* 2000:355–356.
18. Wang L, Liu J, Tian H, Qian C, Sun J. *Adv. Synth. Cat.* 2005; 347:689–694.
19. Vara Y, Bello T, Aldaba E, Arrieta A, Pizarro JL, Arriortua MI, Lopez X, Cossio FP. *Org. Lett.* 2008; 10:4759–4762. [PubMed: 18816130]
20. Bonnaud B, Carlessi A, Bigg DCH. *J. Heterocycl. Chem.* 1993; 30:257–265.
21. Cushman M, Madaj EJJ. *Org. Chem.* 1987; 52:907–915.
22. Hong J, Wang Z, Levin A, Emge TJ, Floyd DM, Knapp S. *Tetrahedron Lett.* 2015; 56:3001–3004. [PubMed: 26124537]
23. Kandinska MI, Kozekov ID, Palamareva MD. *Molecules.* 2006; 11:403–414. [PubMed: 17962773]
24. Liu J, Wang Z, Levin A, Emge TJ, Rablen PR, Floyd DM, Knapp S. *J. Org. Chem.* 2014; 79:7593–7599. [PubMed: 25036978]
25. Mahrwald R. *Chem. Rev.* 1999; 99:1095–1120. [PubMed: 11749441]
26. Di Maso MJ, Snyder KM, De Souza Fernandes F, Pattawong O, Tan DQ, Fettinger JC, Cheong PH-Y, Shaw JT. *Chem. Eur. J.* 2016; 22:4794–4801. [PubMed: 26929008]
27. Rynard CM, Thankachan C, Tidwell TT. *J. Am. Chem. Soc.* 1979; 101:1196–1201.
28. Coulthard G, Unsworth WP, Taylor RJK. *Tetrahedron Lett.* 2015; 56:3113–3116.
29. Wang Y, Liang Y, Jiao L, Du D-M, Xu J. *J. Org. Chem.* 2008; 71:6983–6990.

Highlights

- Steric-based evidence indicates that the HPA-imine formal cycloaddition may prefer an open transition state (Scheme 3)
- This reaction has recently become important for the preparation of anti-cancer and anti-malarial drug candidates (refs. 6–12).
- The Mannich-type intermediate (**33**) was trapped by base treatment, leading to a pair of beta-lactams, **35** and **36**.
- Their formation implies a ketene intermediate (**38**), the low temperature N-cyclization of which provides products (Scheme 5).

Figure 1.
ORTEP representations of the trans (**35**, left) and cis (**36**, right) beta-lactams.

Scheme 1.

The formal cycloaddition of HPA (**1**) with benzalimines to afford 1,2,3,4-tetrahydroisoquinolin-1-one-4-carboxylic acids.

Scheme 2.

Intramolecularly hydrogen bonded transition state possibilities for the HPA-imine reaction.

Scheme 3.

“Open” transition state possibilities for the HPA-imine reaction.

Scheme 4.

Iminium Diels-Alder transition state possibilities for the HPA-imine reaction.

Scheme 5.

Trapping the Mannich intermediate **33** with base, and formation of beta-lactam products **35** and **36**.

Table 1

THIQ products from the reaction of benzalimines with HPA. Each reaction was run at $-30\text{ }^{\circ}\text{C}$ in dichloromethane solution for 150 min.

Imine	Product	Cis/trans	NMR yield
19	20	1:7 (mostly trans)	72%
21	22	1:2.8 (trans preferred)	85%
23	24	1:1.1 (no preference)	89%
25	26	6:4:1 (mostly cis)	89%
27	28	all <i>cis</i>	84%
29	30	1:1.6 (trans preferred) with 0.2 equiv TFA 1:1.9 (trans preferred)	81% 79%
31	32	1:1.4 (trans preferred)	66%