Tetrahedron Letters 54 (2013) 6114–6117

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

The syntheses and structures of bis(alkylimino)isoindolines

Ingrid-Suzy Tamgho, James T. Engle, Christopher J. Ziegler *

Department of Chemistry, University of Akron, Akron, OH 44326-3601, United States

ARTICLE INFO

Article history:
Received 15 July 2013
Revised 28 August 2013
Accepted 30 August 2013
Available online 10 September 2013

Keywords:
Bis(alkylimino)isoindolines
X-ray structures
Heterocyclic compounds
Schiff bases

ABSTRACT

In this Letter, we present a synthetic and structural study into bis-imino substituted diiminoisoindolines, which can be synthesized either via $CaCl_2$ mediated reaction of phthalonitrile with primary amines, or via direct reaction of these amines with unsubstituted diiminoisoindoline. The preferred synthesis does depend on the methodology, and in two cases singly substituted adducts were formed. The single crystal X-ray structures show that, with the exception of the bis-naphthyl compound, the anti conformation is preferred, and that the ionizable hydrogen atom resides on an exocyclic nitrogen rather than the central isoindoline nitrogen atom.

Introduction

The chemistry of isoindolines has been the key for the development of phthalocyanines as well as related macrocycles and chelating ligands.[1–3] The synthesis of the parent isoindoline, 1,3-diiminoisoindoline (DII, **2**) was first reported in the early 1950s.[1] Compounds derived from DII exhibit rich metal binding properties. The metal complexes of the phthalocyanines, for example, show excellent optical properties and are used as synthetic dyes in industry or as potential photosensitizers in medicine.[5,6] Additionally, the DII derived hemiporphyrazine family of macrocycles can also bind metal ions and have been used as components for material applications.[7,8] DII can also be used as a precursor of isoindoline-based chelating ligands, in particular the bis(iminopyridyl)diiminoisoindoline.[7,9,10]

The first examples of the products were reported following the discovery of DII by Linstead and coworkers.[11,12] These ligands are the product of the condensation of DII and primary alkyl and arylamines. Later in the 1970s, to avoid the formation of phthalocyanine (self-condensation of DII), $CaCl_2$-catalyzed condensation of phthalonitrile (precursor of DII) with primary arylamines was employed.[10] It was then found that the bis(arylimino)isoindolines (where the aryl group is a coordinating base such as pyridine,[4,10,13] imidazole,[14] or thiazole[15]) can form N/S tridentate and pincer-like isoindoline ligands that can coordinate to an extensive range of transition metal cations. However studies into the reactivity of bis(alkylimino)isoindoline were not extended. Since early work in the 1950s only synthesis,[16–20] studies on the amino/imino tautomerization,[21,22] and metal complexes with lanthanides[23,24] of these ligands have been reported.

In this Letter, we are revisiting the synthesis and characterization of several bis(alkylimino)isoindolines, several of which structures were successfully elucidated. We have examined methods for the preparation of these compounds: the direct reaction of DII with primary amines (method A), and the reaction of primary amines with phthalonitrile using Siegl's conditions (method B).[10] We observed that the condensation of DII with bulky amines and cyclic amines did not lead to high yields of products, and often afforded only the monosubstituted adducts, regardless of reaction time or solvent conditions. Siegl's method, however, was shown to produce improved yields for bulky and cyclic amines. For non-sterically hindered amines, Siegl's method did not show increased yields. Structural elucidation of several of the reaction products revealed that the ionizable hydrogen atoms are located at the exocyclic amine position rather than on the isoindoline nitrogen. This is in contrast with the ^{1}H NMR spectra for these compounds, which reveal symmetric structures in solution. In the solid state, extensive hydrogen bonding was observed.

Results and discussion

A series of fifteen substituted diiminoindolines have been synthesized in this study. Several of them have been previously reported (R = methyl,[11,16–18,21] ethyl,[12] propyl,[18] butyl,[11,17,18] and cyclohexyl[16,17]) but have not been fully characterized. Two methods were employed for the synthesis of the substituted isoindolines. The first one was the procedure used by Linstead and coworkers; refluxing diiminoisoindoline **2** with two equivalents of an alkyl amine in ethanol for 24 h.[4] The second method was

* Corresponding author. Tel.: +1 330 972 2531; fax: +1 330 972 6085.
E-mail address: ziegler@uakron.edu (C.J. Ziegler).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.08.134

Table 1
The syntheses and yields of substituted isoindolines 3–17

Compound	Name	R_1	R_2	Method	Yield
3	1,3-bismethyliminoisoindoline	CH_3	CH_3	A	78
4	1,3-bisethyliminoisoindoline	C_2H_5	C_2H_5	A	75
5	1-cyclopropylimino-3-iminoisoindoline	C_3H_5	H	A	45
6	1,3-biscyclopropyliminoisoindoline	C_3H_5	C_3H_5	B	69
7	1,3-bisallyliminoisoindoline	C_3H_5	C_3H_5	A	51
8	1,3-bis-n-propyliminoisoindoline	C_3H_7	C_3H_7	A	68
9	1,3-bis-n-butyliminoisoindoline	C_4H_9	C_4H_9	A	72
10	1,3-bis-t-butyliminoisoindoline	C_4H_9	C_4H_9	B	77
11	1,3-biscyclopentyliminoisoindoline	C_5H_9	C_5H_9	B	75
12	1,3-bis-(3-pentylimino)isoindoline	C_5H_{11}	C_5H_{11}	B	68
13	1,3-bispentyliminoisoindoline	C_5H_{11}	C_5H_{11}	A	74
14	1,3-biscyclohexyliminoisoindoline	C_6H_{11}	C_6H_{11}	B	75
15	1,3-bis-α-naphthyliminoisoindoline	$C_{10}H_7$	$C_{10}H_7$	B	59
16	1-α-naphthylimino-3-iminoisoindoline	$C_{10}H_7$	H	B	45
17	1,3-bisadamantyliminoisoindoline	$C_{10}H_{15}$	$C_{10}H_{15}$	B	80

Siegl's procedure; phthalonitrile **1** was reacted with two equivalents of alkyl amine refluxing in *n*-butanol for 48 h, catalyzed by $CaCl_2$.[10] In both cases, evolution of ammonia was observed. Compound **1** also reacted with ammonia in a sodium methylate solution to form compound **2**. The bis(imino)isoindoline yields ranged between 45% and 80% after purification either by flash chromatography or recrystallization from various solvents. The compounds produced in this study listed by method of preparation and yields are shown in Table 1.

The optimal method for the syntheses of these compounds varied based on the identity of the primary amine. For the non-sterically hindered amines, such as methyl, ethyl, propyl, butyl, and pentyl amines, direct reaction with DII afforded the desired bis-substituted product in good yield. However, for the bulker amines and cycloalkyl amines, Siegl's alternative method more efficiently produced the desired bis-substituted amines. One exception is seen with the naphthylamine reaction, where both the bis substituted isoindoline and the monofunctionalized 1-amino-3-amino-isoindoline are produced. Additionally, when DII is used as a starting material for cyclopropylamine, only the monofunctional adduct, 1-cyclopropylimino-3-iminoisoindoline, is produced. In contrast, for the less bulky amines, Siegl's method from phthalonitrile provided no advantages in yield versus direct reaction with DII. All of the resultant compounds were fully characterized, including by NMR spectroscopy and mass spectrometry.

We were able to structurally elucidate several of the bis-substituted isoindolines as well as two examples of the monosubstituted compounds. The data collection and structure parameters for the crystal structures presented in this Letter are provided in the Supplementary Information. Figure 1 shows the structures of several of the bis-substituted compounds (**4**, **6**, **10**, **12**–**15,** and **17**) and Figure 2 shows the structures for two of the monofunctionalized compounds (**5** and **16**). All of the compounds were isolated and structurally characterized as neutral species with the exception of **6**, which was elucidated as the HCl salt see (Scheme 1).

For the bis-substituted isoindolines, we were able to make two important structural observations from the single crystal data. First, the group on the imines in these compounds can be oriented

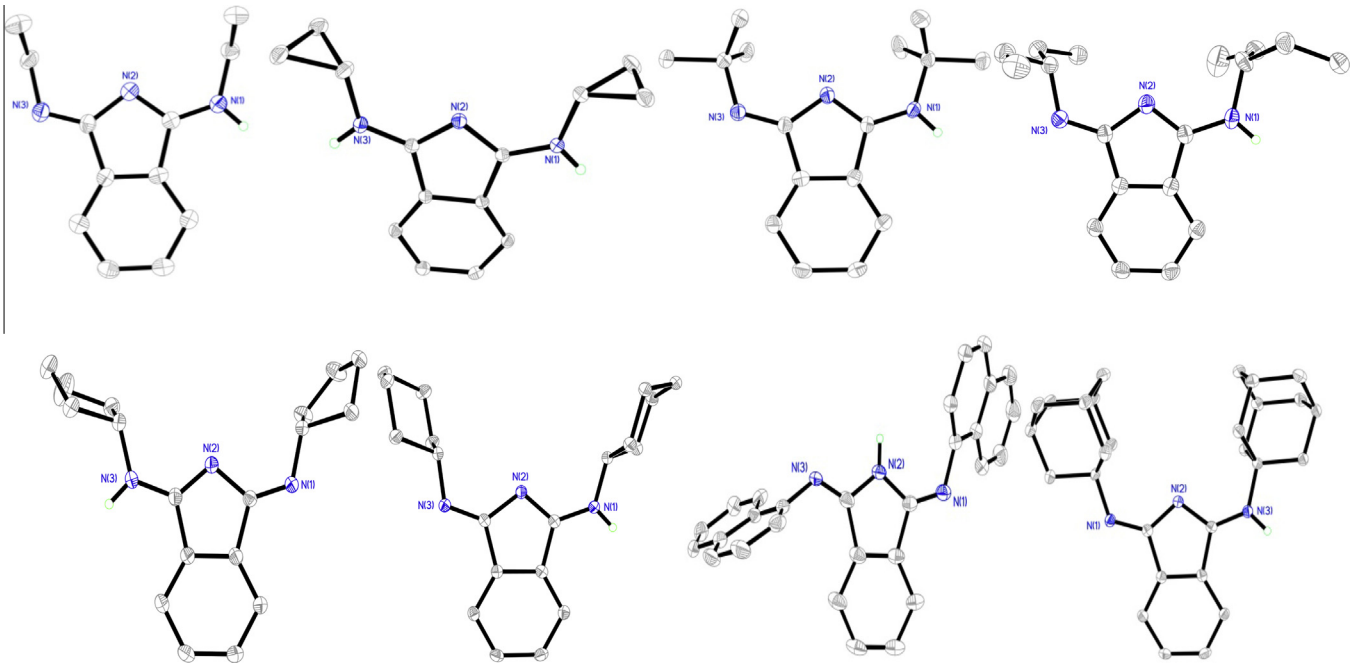


Figure 1. Structures of bis-substituted diiminoisoindolines with 35% thermal ellipsoids. Top, left to right: **4**, **6**, **10**, **12**; Bottom, left to right **13**, **14**, **15**, **17**. Non-ionizable hydrogen atoms have been omitted for clarity. The chloride anion for compound **6** was also omitted for clarity.

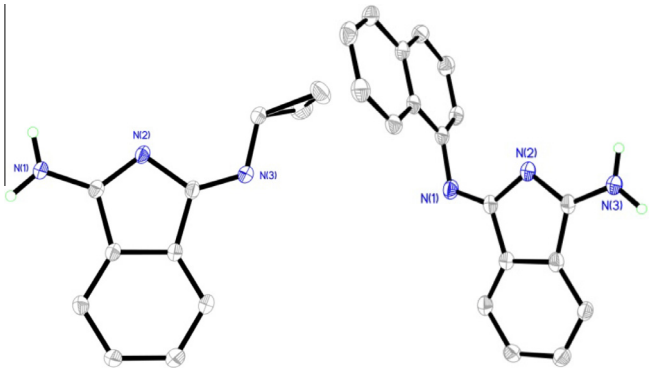
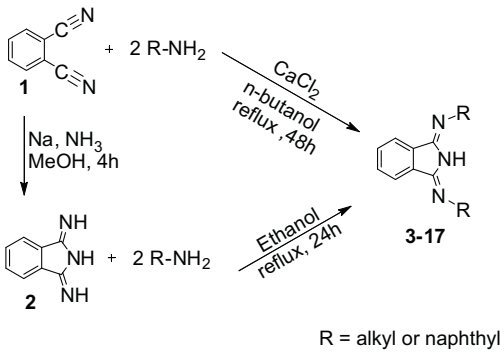


Figure 2. Structures of mono-substituted diiminoisoindolines **5** (left) and **16** (right) with 35% thermal ellipsoids. Non-ionizable hydrogen atoms have been omitted for clarity.



Scheme 1.

either toward the isoindoline ring (a syn conformation) or away from the ring (an anti conformation).[25,26] In all of the cases with the exception of the bis-napthyl compound **15**, the alkyl groups adopt an anti conformation. The prevalence of this structure results from two factors: the steric bulk of the imine substituents, and the presence of stabilizing hydrogen bonds. A second structural aspect that can be observed in the bis substituted isoindolines is the tautomerization of the ionizable hydrogen atom. These compounds can tautomerize between protonation at the central nitrogen atom position and protonation at one of the two imine positions. Inspection of the difference map, the length of the imine C–N bonds, and the presence of hydrogen bonding all indicate that the protons typically reside on the external imine bond positions rather than the central isoindoline nitrogen atom. Once again, the only exception is observed in the bis naphthyl species, which has the ionizable hydrogen atom on the central isoindoline nitrogen atom position.

Previously, Negrebetiskii and coworkers published a study on the E–Z isomerization of the imine bonds on the bis-methyl substituted diiminoisoindoline.[21] These experiments were carried out in 3:1 chloroform/acetone using a 90 MHz NMR instrument. We investigated the temperature dependent ^{1}H NMR of compound **9** in two solvent systems: DMSO and 3:1 chloroform/acetone. Although we did observe sharpening of peaks from the butyl group, some coalescence of the phenyl AA'BB' spin system, and downfield shifts for the ionizable protons (see Supplementary Information), we were not able to freeze out a proton localized form of **9**. However, our observations were consistent with the room temperature fast exchange of H^{+} between the nitrogen atoms in **9**.

In two reactions, we observed the formation of a monofunctionalized adduct. For cyclopropylamine, the identity of the product depended on the method of synthesis. Method A, reaction of DII with the amine, only resulted in the monofunctionalized product, 1-cyclopropylimino-3-iminoisoindoline. In the case of the monofunctionalized naphthalene product, the route to the product was slightly more complex. Initially, the bis-substituted product was produced via Siegl's method, however we observed the presence of an additional equivalent of naphthylamine in the product, which was confirmed by X-ray crystallography. When we attempted to remove this equivalent of naphthylamine via chromatography, we isolated 1-α-naphthylimino-3-iminoisoindoline instead.

The structures of both compounds are shown in Figure 2. Both compounds show similar structural features. In particular, we observe a longer bond distance to the unsubstituted exocyclic nitrogen than in the modified one; there is some multiple bond delocalization between the C–NH_2 and C–$N_{central}$ atoms. Additionally, we located both N-bound hydrogen atoms at the terminal unsubstituted imine nitrogen atom rather than at the central isoindoline nitrogen atom. This is readily confirmed via inspection of the hydrogen bonding in the solid. Both substances form hydrogen bonded dimers, where one of the terminal imine hydrogen atoms forms a complimentary hydrogen bond with the central nitrogen atom from a neighboring equivalent. 1-Cyclopropylimino-3-iminoisoindoline forms an additional hydrogen bond between the second unsubstituted imino hydrogen atom and a substituted imine nitrogen atom on a neighboring equivalent, forming one dimensional hydrogen bonded chain in the solid state. This same interaction is not present in the 1-α-naphthylimino-3-iminoisoindoline compound as the steric bulk of the naphthyl group prevents the formation of a 1D hydrogen bonded network.

Conclusions

In conclusion, we have revisited the synthesis of bis-substituted diiminoisoindolines. Both the original method developed by Linstead and the more recent procedure presented by Siegl can be used to generate these compounds, but for cyclic and bulky amines, Siegl's method provides more complete reactions and higher yields of product. The structures of these compounds presented herein reveal the conformational and protonation states of these substituted isoindolines. We are continuing our work on the fundamental chemistry of diiminoisoindoline and related compounds.

Acknowledgments

We would like to thank the University of Akron for support of this research and the National Science Foundation (CHE-9977144) for funds used to purchase the diffractometer used in this work.

Supplementary data

CCDC numbers 949736-949745 contain the structural data for compounds. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via: www.ccdc.cam.ac.uk/data_request/cif. Supplementary data (experimental procedures, characterization of the previously described compounds 3-17, and additional X-ray crystallographic data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.134.

References and notes

1. McKeown, N. B. *Phthalocyanine Materials: Synthesis, Structure, and Function*; Cambridge University Press: Cambridge, 1998.
2. Bekaroglu, O. *J. Porphyrins Phthalocyanines* **2000**, *4*, 465–473.

3. Torres, T. *J. Porphyrins Phthalocyanines* **2000**, *4*, 325–330.
4. Elvidge, J. A.; Linstead, R. P. *J. Chem. Soc.* **1952**, 5000–5007.
5. Ishii, K. *Coord. Chem. Rev.* **2012**, *256*, 1556–1568.
6. Ali, H.; van Lier, J. E. Porphyrins and Phthalocyanines as Photosensitizers and Radiosensitizers. In *Handbook of Porphyrin Science*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; ; World Scientific Publishing: Singapore, 2010; Vol. 4, pp 1–99.
7. Ziegler, C. J. The Hemiporphyrazines and Related Systems. In *Handbook of Porphyrin Science*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; ; World Scientific Publishing: Singapore, 2012; Vol. 17, pp 114–226.
8. Fernández-Lázaro, F.; Torres, T.; Hauschel, B.; Hanack, M. *Chem. Rev.* **1998**, *98*, 563–576.
9. Siegl, W. O. *Inorg. Chim. Acta* **1977**, *25*, L65–L66.
10. Siegl, W. O. *J. Org. Chem.* **1977**, *42*, 1872–1878.
11. Clark, P. F.; Elvidge, J. A.; Linstead, R. P. *J. Chem. Soc.* **1953**, 3593–3601.
12. Clark, P. F.; Elvidge, J. A.; Golden, J. H. *J. Chem. Soc.* **1956**, 4135–4143.
13. Gagne, R. R.; Marritt, W. A.; Marks, D. N.; Siegl, W. O. *Inorg. Chem.* **1981**, *20*, 3260–3267.
14. Kaiser, J.; Kripli, B.; Speier, G.; Parkanyi, L. *Polyhedron* **2009**, *28*, 933–936.
15. Martic, G.; Engle, J. T.; Ziegler, C. J. *Inor. Chem. Comm.* **2009**, *14*, 1749–1752.
16. Luts, H. A. *J. Pharm. Sci.* **1969**, *58*, 496–497.
17. Sato, R.; Senzaki, T.; Shikazaki, Y.; Goto, T.; Saito, M. *Chem. Lett.* **1984**, 1423–1426.
18. Sato, R.; Nakayama, M.; Yuzawa, Y.; Goto, T.; Saito, M. *Chem. Lett.* **1985**, 1887–1890.
19. Gordienko, O. V.; Negrebetskii, V. V.; Ivanchenko, V. I.; Kornilov, M. Yu. *Zh. Obshch. Khim.* **1989**, *59*, 2771–2779.
20. Tamgho, I.-S.; Engle, J. T.; Ziegler, C. J. *J. Org. Chem.* **2012**, *77*, 11372–11376.
21. Negrebetskii, V. V.; Balitskaya, O. V.; Kornilov, M. Y. *J. Gen. Chem. USSR (Engl. Transl.)* **1983**, *53*, 2320–2324.
22. Armand, J.; Deswarte, S.; Pinson, J.; Zamarlik, H. *Bull. Soc. Chim. Fr.* **1971**, 671–673.
23. Bochkarev, M. N.; Balashova, T. V.; Maleev, A. A.; Pestova, I. I.; Fukin, G. K.; Baranov, E. V.; Kurskii, Y. A. *Russ. Chem. Bull., Int. Ed.* **2008**, *57*, 2162–2167.
24. Maleev, A. A.; Balashova, T. V.; Fukin, G. K.; Katkova, M. A.; Lopatin, M. A.; Bochkarev, M. N. *Polyhedron* **2010**, *29*, 10–15.
25. Zhang, Z.-Q.; Njus, J. M.; Sandman, D. J.; Guo, C.; Foxman, B. M.; Erk, P.; van Gelder, R. *Chem. Commun.* **2004**, 886–887.
26. Engle, J. T.; Allison, A. N.; Standard, J. M.; Tamgho, I.-S.; Ziegler, C. J. *J. Porphyrins Phthalocyanines* **2013**, *17*, 1–10.