



The syntheses and structures of bis(alkylimino)isoindolines



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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.

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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 hemiporphyrane 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 thiazole¹⁵) 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 tauto-

merization,^{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 ^1H 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 diiminoisoindolines 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

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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 ₂ H ₅	C ₂ H ₅	A	75
5	1-cyclopropylimino-3-iminoisoindoline	C ₃ H ₅	H	A	45
6	1,3-biscyclopropyliminoisoindoline	C ₃ H ₅	C ₃ H ₅	B	69
7	1,3-bisallyliminoisoindoline	C ₃ H ₅	C ₃ H ₅	A	51
8	1,3-bis-n-propyliminoisoindoline	C ₃ H ₇	C ₃ H ₇	A	68
9	1,3-bis-n-butyliminoisoindoline	C ₄ H ₉	C ₄ H ₉	A	72
10	1,3-bis-t-butyliminoisoindoline	C ₄ H ₉	C ₄ H ₉	B	77
11	1,3-biscyclopentyliminoisoindoline	C ₅ H ₉	C ₅ H ₉	B	75
12	1,3-bis-(3-pentylimino)isoindoline	C ₅ H ₁₁	C ₅ H ₁₁	B	68
13	1,3-bispentyliminoisoindoline	C ₅ H ₁₁	C ₅ H ₁₁	A	74
14	1,3-biscyclohexyliminoisoindoline	C ₆ H ₁₁	C ₆ H 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 CaCl₂.¹⁰ 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 bulkier 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

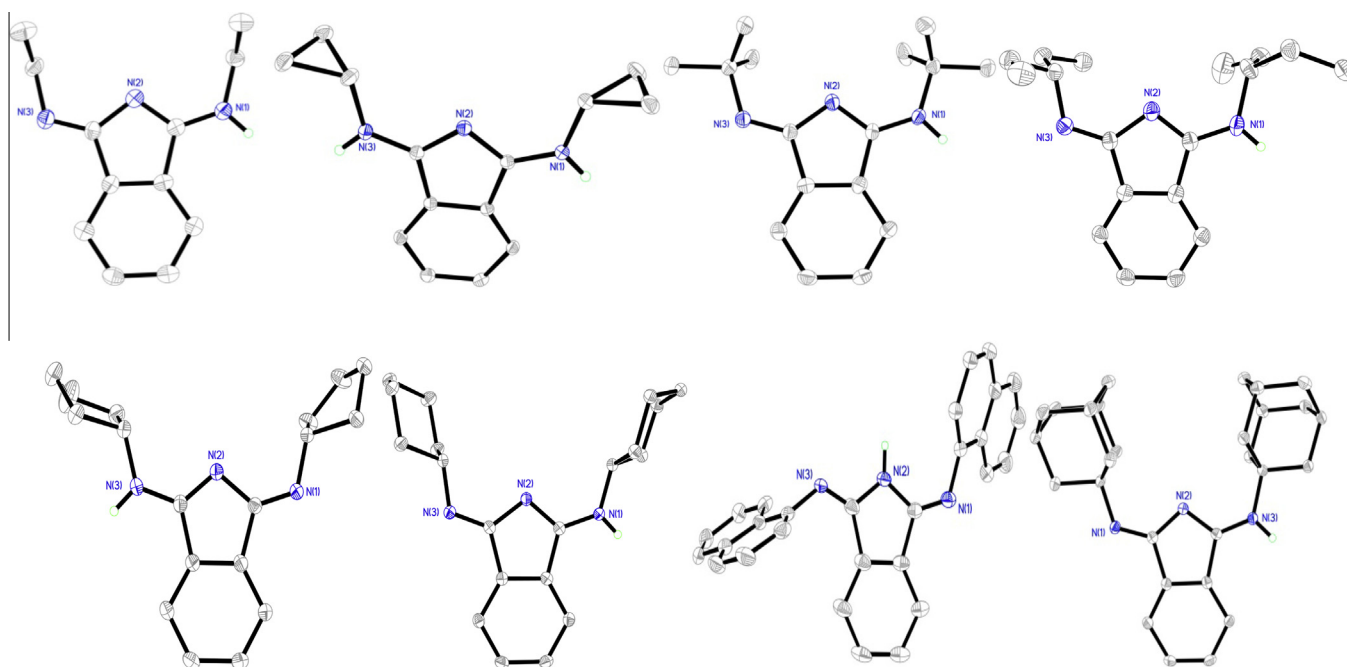


Figure 1. Structures of bis-substituted diiminoisoindolines with 35% thermal ellipsoids. Top, left to right: **4**, **6**, **10**, **12**; Bottom, left to right **13**, **14**, **15**, **17**. Non-ionizable hydrogen atoms have been omitted for clarity. The chloride anion for compound **6** was also omitted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

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