Progress towards Tröger's base precursors

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Abstract

Our goal is to synthesize C_2-symmetric flourescent Tröger's base derivitives bearing substituents in the bridged diazocine ring from 4-amino-1,8-naphthalimide dyes. Our attempts at direct synthesis have been unsuccessful. As a result, we have focused our attention on synthesizing a precursor 4-amino-1,8-naphthalimide with a functional group at the 3- position that would allow the dimerization of dye molecules, providing the structural framework of a Tröger's base. To date, we have completed two promising displacements of bromine at the 3- position using Ullmann and Henry type reactions. These reactions show potential for building substituted Tröger's bases. We also report very unique characteristics of the intermediate 3-nitro-4-amino-1,8-naphthalimide

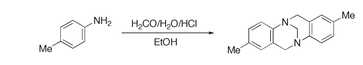
Background

Tröger's bases, first synthesized by Julius Tröger in 1887,[1] have historically been of interest due to the presence of the configurationally stable chiral nitrogens in the dibenzodiazocine nucleus, and have been described as fascinating molecules.[2] Over the past several years, the ease of synthesis of the symmetrical Tröger's bases and the rigidity of the chiral dibenzodiazocine nucleus have made these compounds attractive systems for exploitation in a variety of guest–host molecules, forming the scaffold for the formation of a variety of compounds, including synthetic receptors.[3]

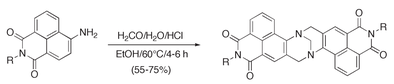
In 1990, Webb and Wilcox described the first unsymmetrical synthesis of Tröger's bases, initiating the potential to use these compounds as nanoscale structural units.[4] Wärnmark began to expand methods of synthesizing unsymmetrical halogenated Tröger's bases via selective lithium-halogen exchange.[5]

We have been interested for a number of years in the synthesis and properties of naphthalimides, particularly with amino-substituents in the 4-position. These compounds find widespread utility, for example, as antiviral agents,[6] fluorescent sensors for metal ions[7] and pH[8] and as elements in the design of molecular logic gates.[9]

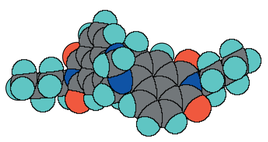
We have previously reported fluorescence properties and synthesis of naphthalimide-containing Tröger's base derivitives.[10] Our current interest is to synthesize similar C_2-symmetric Tröger's bases bearing substituents in the diazocine ring.



Tröger, 1887

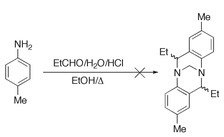


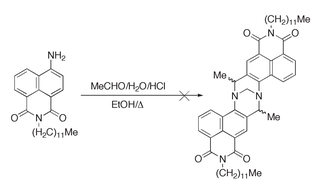
Deprez, *et al.*, 2005

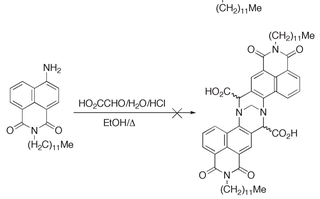


naphthalimide-based Tröger's base
(R = Bu)

Attempts at Direct Synthesis





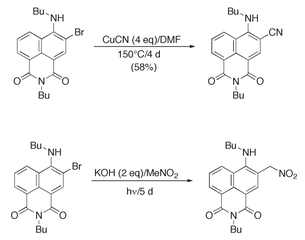


We initially attempted to synthesize a substituted Tröger's base directly by a procedure similar to that of Tröger and our earlier successful syntheses, using acetaldehyde, propionaldehyde, and glyoxylic acid in place of formaldehyde. The choices were predicated on our need to have a substituent in the diazocine ring systrem. Glyoxylic acid has a strongly electron-withdrawing carboxylic acid group directly bonded to the aldehyde, and we reasoned that this may result in a more reactive iminium ion. However, none of these attempts was successful in yielding a Tröger's base derivative.

Incorporation of a Side Chain at C-3

With the failure of the direct synthesis of the required substituted Tröger's bases, we focused our attention on the stepwise synthesis of the target conmpounds. This requires the initial construction of one half of the molecule in a form where there is a side chain at C-3 that is capable of further elaboration to a 1-hydroxyethyl group. The methyl ketone is the obvious choice, but we have been unable to acylate the naphthalimide ring system under either Friedel-Crafts or Vilsmeier-Haack conditions.

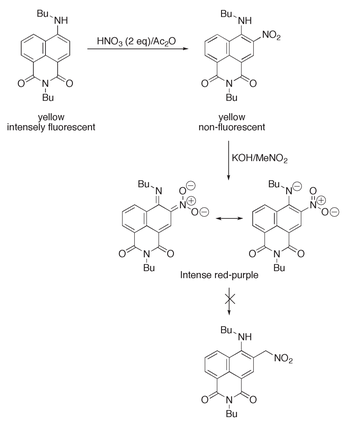
Accordingly, we have turned our attention to incorporating a one-carbon group capable of further elaboration into this position by the Ullmann approach, to incorporate a nitrile group that could be elaborated to the 3-acetyl group by Grignard addition, or the Henry reaction, to incorporate a nitromethyl side chain that can be alkylated with methyl iodide and transformed into the 3-acetyl group by a Nef reaction. We have now succeeded in accomplishing both reactions to give over 50% isolated yield of the required products.



Can we use a Henry reaction with a 3-nitro-1,8-naphthalimide derivative?

Given the success of the Henry reaction with the brominated naphthalimide derivative, the possibility existed that we might also be able to displace an aromatic nitro group with the nitromethane anion under free radical conditions of the Henry reaction. Nitration of the parent naphthalimide could be effected highly selectively by the reaction between the highly fluorescent naphthalimide and concentrated nitric acid in acetic anhydride. The reaction conditions have not yet been optimized, but the mononitro product is obtained in modest yield after 5 days at room temperature. Interestingly, the product, which is a non-fluorescent yellow solid, shows some water solubility, which results in lower yields than we expected.

When we attempted to displace the nitro group under Henry reaction conditions, however, we obtained a deep red-purple solution from which only starting material was recovered. It appears that the nitronaphthalimide is a strong enough acid to be deprotonated completely under the reaction conditions, and therefore not amenable to displacement by a nucleophile or free radical.



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Acknowledgments

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Similar compounds, distinct spectra

The ^{1}H NMR spectra of the 3-bromo- and 3-nitro- compounds are comparable in the aromatic and alkyl regions, but very distinct in the methylene protons neighboring the 4-amino and amide nitrogens. In the spectrum of the 3-bromo compound, both of these methylene groups produce triplets. In the spectrum of the 3-nitro compound, however, the methylene group bonded directly to the imide nitrogen produces a triplet at 4.14 (2 H, t J = 7.5 Hz), while each proton on the methylene group directly bonded to the nitrogen of the 4-amino group produces a distinct doublet of doublets of doublets, one at 3.76 (1 H, ddd J = 5.3, 10.9, 14.2 Hz) and one at 4.37 (1 H, ddd J = 5.3, 10.9, 14.2 Hz). This pattern shows that there is no free rotation around the C—N bond due to hydrogen bonding between the 4-amino hydrogen and the nitro group. It is interesting to note that although the bromine is bigger, it allows free rotation of this bond where the nitro does not. Furthermore, the conformation of the 4-amino alkyl chain may be locked into one of two conformations by the hydrogen bonding, forming configurationally stable atropisomers.

The single crystal X-ray structure analysis of 3-bromo-*N*-butyl-4-butylamino-1,8-naphthalimide has been determined, and it is known that the molecule is planar, except for the *N*-butyl group attached to the imide nitrogen, which occupies a plane approximately perpendicular to the ring system.[11] This geometry is reproduced well by AM1calculations. Such a conformation places the two methylene groups attached to nitrogen in a geometry where the two hydrogens of the methylene group are essentially equivalent, thus leading to the observed triplet resonances. The observation that the hydrogens of the butylamino methylene group are not equivalent in the nitro compound is most reasonably accounted for by the assumption that there is restricted rotation around the C—N bond, and that this butyl group, also, is perpendicular to the plane of the ring. That this may be the case, and, more importantly, that the two atropisomers may be configurationally stable at room temperature, is supported by the observation that this product, which gives a single spot on TLC on silica gel, gives two bands when subjected to flash chromatography on cornstarch. We have not yet characterized the two bands completely, so we do not yet unequivocally assert that this is the case. However, should it be, this will be the first case of configurationally stable atropisomers where a biaryl ring system is not part of the atropisomeric moiety. The origin of this we attribute to an unusually strong intramolecular hydrogen bond between the oxygen of the nitro group and the hydrogen of the butylamino group, which prevents rotation about the C—N bond, and maintains the sp^2 hybridization of the amino nitrogen.

The AM1 calculated minimum energy structures for the two compounds are shown next to the spectra as space-filling models. As can be seen, the hydrogen bond between the amino hydrogen and the nitro group leads to very different chemical shifts for the methylene hydrogens bonded to the amino nitrogen. the coupling constants are consistent with the *anti* conformation of the butyl group, as shown.