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Indium chloride catalyzed intramolecular cyclization of *N*-aryl imines: synthesis of pyrrolo[2,3-*d*]pyrimidine annulated tetrahydroquinoline derivatives

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Abstract

The intramolecular aza Diels–Alder cyclization reaction of aldimines derived from aromatic amines and *N*-prenyl/cinnamyl derivatives of pyrrolo[2,3-*d*]pyrimidine were efficiently catalyzed by $InCl_3$ to afford the corresponding tetrahydroquinoline derivatives in good yields.

Keywords: Imines; Tetrahydroquinoline; Pyrrolo[2,3-*d*]pyrimidine; Indium chloride

1. Introduction

The intramolecular aza Diels–Alder reaction is a useful synthetic tool for constructing N-containing six-membered heterocycles such as tetrahydroquinolines, octahydroacridines, tetrahydrochromanoquinolones and dihydro-4-pyridones.[1–5] Of these, the tetrahydroquinoline skeleton is found in a number of alkaloids and derivatives thereof and is found to exhibit a wide range of biological activities,[5–7] for example, indersine, oricine and veprisine and their derivatives exhibit psychotropic, anti-allergic, anti-inflammatory and estrogenic activities.[8–11]

Pyrrolo[2,3-*d*]pyrimidine derivatives are reported to possess various biological activities such as anti-HCV, anti-HIV type 1, anti-HSV, adenosine kinase inhibition, Aurora-A kinase inhibition and cAMP phosphodiesterase inhibition.[12–15] Many naturally occurring compounds such as mycalisine A, cadeguomycin and 2-deoxycadeguomycin are found to possess a pyrrolo[2,3-*d*]pyrimidine moiety.[16,17] Hence, new and efficient syntheses of such compounds are still important.

In continuation of our research[18–20] on the development of highly expedient methods for the synthesis of heterocyclic compounds of biological importance, we disclose here our preliminary investigations on the indium chloride promoted synthesis of novel pyrrolo[2,3-*d*]pyrimidine annulated tetrahydroquinoline derivatives through intramolecular aza Diels–Alder reaction of the *N*-alkenylimines of 1,3-dimethyl-1-pyrrolo[2,3-*d*]pyrimidine-2,4-dione-6-carbaldehyde **1**.

The substrate *N*-alkenyl 1,3-dimethyl-1-pyrrolo[2,3-*d*]-pyrimidine-2,4-dione-6-carbaldehydes **3a**–**b** were prepared in good yields (70–80%) from 1,3-dimethyl-1-pyrrolo[2,3-*d*]-pyrimidine-2,4-dione-6-carbaldehyde **1** by treatment with 1-bromo-3-methyl-but-2-ene **2a** or cinnamyl bromide **2b** in dry DMF in the presence of K_2CO_3 (Scheme 1).[21] The same reaction when carried out in 10% aqueous sodium hydroxide in the presence of a catalytic amount of PTC resulted in a lower yield of the products (40–58%).

Reaction of *N*-prenyl aldehyde **3a** with aromatic amines **4a**–**f** in the presence of indium trichloride generated the corresponding imine in situ which then underwent intramolecular aza Diels–Alder cycloaddition in one-pot

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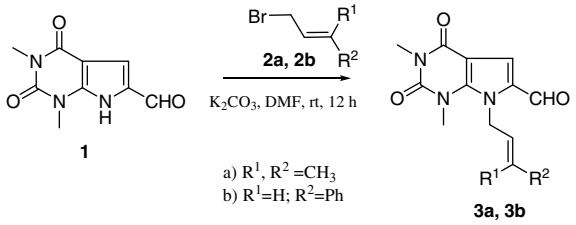


Scheme 1.

reaction to yield a mixture of *cis*- and *trans*-tetrahydroquinoline derivatives in moderate yield (55–65%) (route a).

However, in the absence of the catalyst reaction of aldehyde **3a** with aniline derivatives **4a–f** in refluxing ethanol yielded an isolable imine which could be cyclized in the presence of $InCl_3$ to give better yields of the products in short reaction times (85–93%) (route b) (Scheme 2).

The intermediate imines were characterized on the basis of ^1H NMR, ^{13}C NMR and elemental analysis. The structure of imine **5e** was further confirmed by X-ray crystal analysis[22] (Fig. 1).

In an effort to demonstrate the utility of the $InCl_3$ catalyzed aza Diels–Alder cyclization, the reaction was carried out with anilines with varied substituents and the results are summarized in Table 1.

In all cases the products were obtained as a mixture of cis- and trans-isomers, which were separated by column chromatography using silica gel. The ratios of the products were determined from the ^1H NMR spectra of the crude products.

The structures assigned to cycloadducts **6a–f** and **7a–f** were confirmed by the examination of their respective ^1H NMR spectra. The Ha proton of **6a** appeared as a doublet at δ 4.77 ($J = 6.3$ Hz). This small coupling constant is consistent with a cis-diaxial relationship for these two protons. Furthermore, the stereochemistry of H_a was confirmed by the observation of a strong NOE enhancement of H_a upon the irradiation of H_b (8.1%).

In a similar way, the Ha proton of **7a** exhibited a doublet at δ 4.63 ($J = 10.6$ Hz) indicating the trans stereochemistry of H_a with respect to H_b (Scheme 2).

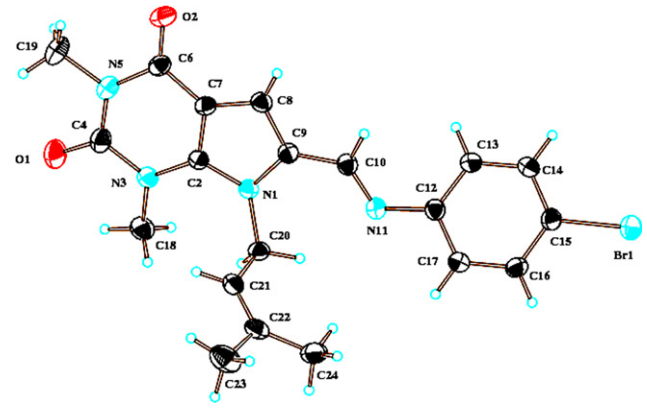


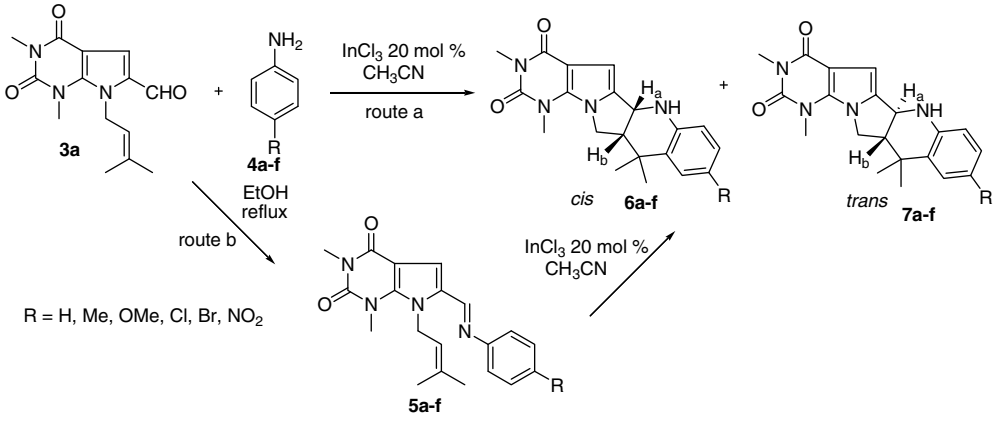
Fig. 1. Ortep diagram of compound **5e**.

Further, to examine the effect of substitution on the dienophile on the cycloaddition process, we prepared *N*-cinnamyl-pyrrolo[2,3-*d*]pyrimidine-6-carbaldehyde **3b** as previously described (Scheme 1). Aldehyde **3b** underwent intramolecular cycloaddition with **4a–f** in the presence of indium trichloride to afford the corresponding cis- and trans-cycloadducts **9a–f** and **10a–f** in good yields (87–90%).

The structures of cycloadducts **9a** and **10a** were established by the examination of their ^1H NMR spectra and NOE experiments. The enhanced yields and short reaction times for the formation of products **9a–f** and **10a–f** relative to the cycloaddition of **3a** with **4a–f** in acetonitrile, clearly showed the greater reactivity of the phenyl-substituted dienophile in **3b** (Scheme 3).

From the above results, it can be seen that the cyclization proceeds by a stepwise mechanism as shown in Scheme 4.[23–25] However, under thermal conditions without any Lewis acid, cyclization of the *N*-arylimines was not observed. This further confirms the stepwise mechanism.

To study the scope and limitations of the cycloaddition reaction, the same reactions were carried out with the Lewis acid catalysts, namely, $BF_3{\cdot}OEt_2$, $Yb(OTf)_3$, $Sc(OTf)_3$ and $InCl_3$. Indium trichloride proved to be very efficient as we found the overall yield of the products was high (90%) when compared to the other Lewis acid catalysts. The results obtained for the cycloaddition of **3a**



Scheme 2.