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Hetero Diels-Alder Reaction of Aldimines Derived from 3-Indoleacetaldehyde and 3-Indolecarboxaldehyde

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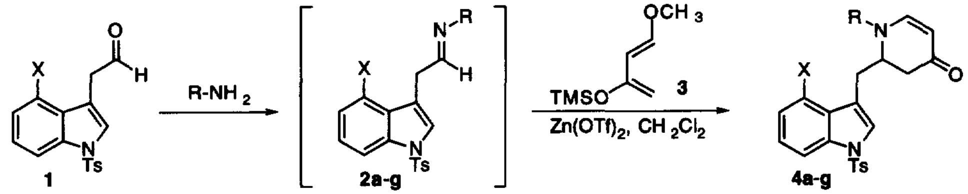
Abstract: Aldimines derived from 3-indoleacetaldehyde and 3-indolecarboxaldehyde undergo Lewis acid catalyzed Diels-Alder reactions. We found that $Zn(OTf)_2$ is an excellent promoter of hetero Diels-Alder reactions of imines with acidic α-hydrogens. Higher yields were obtained with aldimines from 3-indolecarboxaldehyde which does not have the acidic α-hydrogens. © 1997, Published by Elsevier Science Ltd. All rights reserved.

Construction of nitrogen heterocycles through the use of imino-dienophiles in Diels-Alder reactions has received much attention in recent times.[2-7] The use of Lewis acids and activated dienes to counteract the low reactivity has further increased their potential in synthesis.[3] The diastereoselectivity of this reaction has been investigated with α-alkoxy imines[4], imines with carbohydrate templates[5], and imines derived from esters of amino acids.[6] The most recent progress in this area has been made through the use of chiral Lewis acids in asymmetric aza Diels-Alder reactions.[7] In some of these cases, an addition-cyclization pathway was suggested while in others, a cycloaddition pathway was suggested.

Ergot alkaloids comprise an important pharmacologically active alkaloid.[8] They are isolated from dried sclerotium of the filamentous fungus *Claviceps purpurea*. Ergot alkaloids have a wide range of pharmacological activity and their importance is demonstrated by the numerous syntheses of these alkaloids.[9] Hetero Diels-Alder reactions of imino dienophile derived from 3-indoleacetaldehyde followed by a ring closure would give a quick entry into the ergot alkaloid ring system achievable with readily available starting materials. Herein, we describe our investigation of hetero Diels-Alder reaction of aldimines derived from 3-indoleacetaldehyde and 3-indolecarboxaldehyde.

The results of the Diels-Alder reaction of imines derived from 3-indoleacetaldehyde, **2a-g**, and Danishefsky's diene[10] (Scheme 1) are summarized in Table 1. The results of the imines derived from 3-indolecarboxaldehyde, **6h-m**, (Scheme 2) are summarized in Table 2. The imines were generated in situ in the presence of Lewis acid and the diene. We have shown previously that $Zn(OTf)_2$ is an excellent promoter for Diels-Alder reactions of imino-dienophiles.[11] This was verified in this case as well. Substitution of $Zn(OTf)_2$ in entries 2 or 5 in Table 1 with $BF_3{\cdot}Et_2O$, Et_2AlCl, and $ZnCl_2$ gave 0-20% yield of the cycloadduct. TMSOTf was reported to be an excellent promoter with imino-dienophile with acidic α-hydrogens.[12] In the case of imine **2**, low yields were obtained. For example, 27% of the product was obtained with TMSOTf (entry 8) compared with 71% using $Zn(OTf)_2$ (entry 5). It should be pointed out that since the imine was generated in situ one equivalent of water was present. Addition of 4Å molecular sieves to scavenge this moisture did not enhance the yield (entry 6). With the exception of entry 8 and 9, imine **2** gave moderate yields.[13] It is known that aldimines bearing acidic α-hydrogens can be problematic and the aromatic indole group increases the acidity of the

Scheme 1



a, X= H, R= Bn **b**, X= I, R=CH_3
c, X= I, R= n-Bu **d**, X= I, R=Bn
e, X= H, R= n-Bu **f**, X= H, R=i-Pr
g, X= H, R= CH_3O

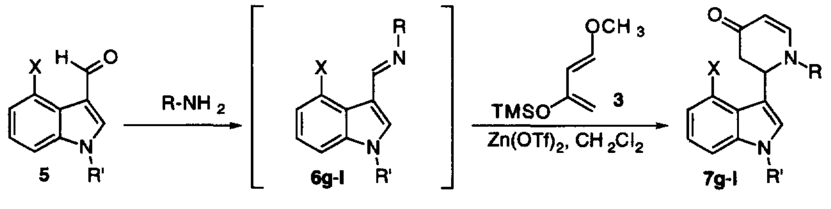
Table 1. Diels-Alder Reactions of Aldimine **2a-g** with Danishefsky's Diene[a]

Entry	X	R-NH2	Temp., Time	Yield(%)
1	H	Bn-NH_2	0°C, 10 h	44
2	I	CH_3-NH_2	rt, 2 h	85
3	I	n-Bu-NH_2	0°C, 8 h	57-62
4	I	Bn-NH_2	0°C, 8 h -> rt	68
5	H	n-Bu-NH_2	0°C, 13 h	71
6	H	n-Bu-NH_2	0°C, 5h/4ÅMS	39
7	H	i-Pr-NH_2	0°C, 13 h	49-54
8	H	n-Bu-NH_2[b]	0°C, 9h/TMSOTf	27
9	H	CH_3O-NH_2[c]	0°C, 2.5h ->rt, 3h	0

[a] One equivalent of $Zn(OTf)_2$ was used to promote the reaction. In all but entry 8, the imine was generated in situ. [b] TMSOTf was used to promote the reaction. [c] Isolated imine was used.

α-hydrogens of imine **2**. Our efforts to isolate a variety of alkyl and aryl imines **2** were not successful. Neither was stabilized aryl imine **2** (e.g. X=H, R=m-$PhNO_2$). On the other hand, methoxyamine gave imine **2g** (X=H, R=OCH_3) in 87% yield; however, this compound was not reactive under our reaction conditions (entry 9). Imine **6** without the acidic α-hydrogens can be easily isolated in stable form, and good yields were obtained in the the Diels-Alder reactions (Scheme 2, Table 2).

Scheme 2



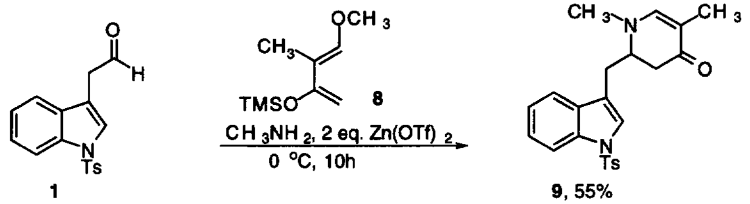
h, X=H, R=CH_3, R'=SO_2Ph **k**, X=H, R=n-Bu, R'=SO_2Ph
i, X=H, R=CH_3, R'=SO_2tol **l**, X=H, R=n-Bu, R'=SO_2tol
j, X=I, R=CH_3, R'=SO_2tol **m**, X=H, R=i-Pr, R'=SO_2tol

Table 2. Diels-Alder Reactions of Aldimine **6h-m** with Danishefsky's Diene[a]

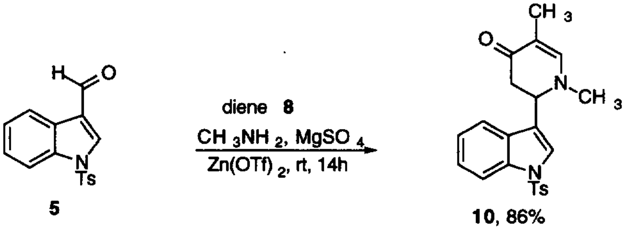
Entry	X	R-NH2	R'	Temp., Time	Yield(%)
1	H	CH_3-NH_2	SO_2Ph	rt, 30 h	75
2	H	CH_3-NH_2	SO_2tol	rt, 29 h	92
3	I	CH_3-NH_2	SO_2tol	rt, 29 h	94
4	H	*n*-Bu-NH_2	SO_2Ph	rt, 31.5	81
5	H	*n*-Bu-NH_2	SO_2tol	0°C, 13 h	71
6	H	*i*-Pr-NH_2	SO_2tol	0°C, 13 h	49

[a] 1 equivalent of $Zn(OTf)_2$ was used to promote the reaction.

A number of ergot alkaloids contain a methyl substitution at carbon-8. The versatility of this approach is demonstrated by the use of diene **8** which incorporates the methyl substituent in the desired position. The cycloaddition under standard conditions gave cycloadduct **9** in 50% yield (Equation 1). As expected, the aldimine derived from **5** without the α-acidic hydrogen gave the cycloadduct **10** in higher yield (Equation 2).



(1)



(2)

In summary, we have shown that $Zn(OTf)_2$ is an excellent promotor of imino Diels-Alder reactions with acidic α-hydrogens. The lower yields with aldimines derived from 3-indoleacetaldehyde seem to be due to the acidic α-hydrogens. Aldimines from 3-indolecarboxaldehyde, without the acidic hydrogens, gave higher yields of the adduct.

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13. New Compounds showed IR, ^{1}H NMR, and ^{13}C NMR spectra in accord with their assigned structures.

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