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Acid-Free Aza Diels–Alder Reaction of Danishefsky's Diene with Imines

Yu Yuan, Xin Li, and Kuiling Ding*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China

kding@pub.sioc.ac.cn

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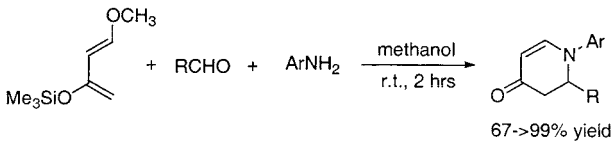
ABSTRACT



A highly efficient aza Diels–Alder reaction of Danishefsky's diene with imines was found to occur in methanol in the absence of any acids at room temperature to give corresponding 2-substituted dihydro-4-pyridone derivatives in high yields. This reaction can be also carried out in a three-component one-pot reaction manner. The reaction was found to proceed through a Mannich-type condensation mechanism.

The aza Diels−Alder reaction of Danishefsky's diene **1** with imine **2** provides a convenient protocol for the synthesis of a type of heterocycles, 2-substituted 2,3-dihydro-4-pyridones **3**, with important synthetic applications in natural or unnatural products.[1] Various Lewis acids such as BF_3•Et_2O,[2] $ZnCl_2$,[3] or lanthanide triflates[4] and Bronsted acids, including HBF_4 or TsOH,[5] have been utilized to promote this reaction.[6] The employment of chiral Lewis acids such as BINOL-Zr[7] or Bis-Oxa-Cu[8] catalyst for this reaction results in the formation of enantioenriched dihydro-4-pyridones with high ee. In our efforts to develop chiral Bronsted acid catalysts for enantioselective addition of imines to Danishefsky's diene, a study on the background reaction in the absence of any acids demonstrated that the reaction proceeded smoothly to give the desired product in good yield. In the present communication, we will report our results on the acid-free aza Diels−Alder reaction of Danishefsky's diene **1** with imines **2**. The correct choice of reaction solvents was found to be critical for affording high conversion of the reaction.

The research was initiated by the work of Akiyama on the catalysis of aza Diels−Alder reaction of Danishefsky's diene **1** with imines **2** by the catalysis of Bronsted acids such as HBF_4, *p*-TsOH, and CF_3CO_2H in methanol or acetonitrile.[5] Accordingly, a chiral carboxylic acid, (*S*)-naproxen, was employed as a chiral Bronsted acid catalyst for developing an asymmetric version of this reaction in methanol. Unfortunately, the isolated adduct **3a** was racemic. To our surprise, an examination on the noncatalyzed background reaction showed that the conversion of **2**a was completed within 2 h in the absence of any acids to give the desired product **3a** in quantitative yield (entry 1 in Table 1). This result allowed us to understand that the reaction system is most probably not catalyzed by a Bronsted acid. To rule out the possibility of the catalysis by adventitious acid in the reaction system, the control experiment was carried out for the reaction of **1** and **2a** in methanol that was freshly distilled over CaH_2 or in the presence of 10 mol % 2,6-di-*tert*-butyl-4-methylpyridine. It was found that the reaction proceeded smoothly

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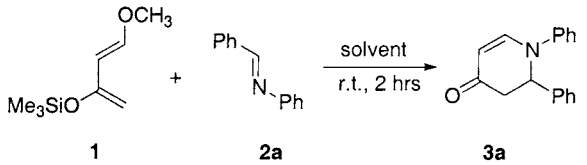
Table 1. Solvent Effect on the Reaction



1 2a 3a

entry	solvent	yield (%)	entry	solvent	yield (%)
1	methanol	>99	7	THF	47
2	methanol[a]	>99	8	toluene	<5
3	methanol[b]	>99	9	ethyl ether	0
4	acetonitrile	>99	10	DCM[c]	<5
5	ethanol	32	11	chloroform	<5
6	DMF	54	12	*d*	0

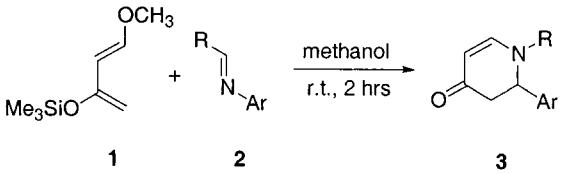
[a] Methanol was distilled over CaH_2. [b] Reaction was carried out in methanol in the presence of 10 mol % 2,6-di-*tert*-butyl-4-methylpyridine. [c] Dichloromethane. [d] (*S*)-(−)-1-phenyl ethanol.

to give the cycloadduct **3a** in the same yields (entries 2−3). With this result in hand, we further examined the solvent effect on the reaction in the absence of acids. Various solvents, including polar and nonpolar ones, were employed for the reaction. Indeed, the solvent effect was found to be evident. As shown in Table 1, the reactions can occur in more polar solvents such as methanol, acetonitrile, ethanol, DMF, and THF (entries 4−7). However, the reaction in a nonpolar solvent such as toluene, diethyl ether, chloroform, or dichloromethane was very sluggish with less than 5% yield (entries 8−11). An attempt to carry out the reaction in a chiral solvent, (*S*)-(−)-1-phenyl ethanol, proved that no reaction occurred at all (entry 12). The significant solvent effect on the reaction suggested that the addition of Danishefsky's diene **1** with imines **2** probably proceeds via a stepwise mechanism rather than a concerted one, which will be further illustrated by ^{1}H NMR spectroscopic evidence.

The aza Diels−Alder reaction of Danishefsky's diene **1** with a variety of imines **2** were then investigated in methanol at room temperature. The reactions of the all of the imines **2** shown in Table 2 with **1** take place smoothly to afford the corresponding adducts **3** in good to excellent yields. The electron-withdrawing group at the para-position of aldimine slightly decreases the yield of the reaction (entry 4). An α,β-unsaturated aldimine furnished the corresponding cycloadduct in excellent yield (entry 5). An aldimine derived from 4-anisidine also worked very well as a substrate (entry 7).

Because imines, particularly those derived from aliphatic aldehydes, are not always stable, it is synthetically useful if aldimines are generated in situ and allowed to react under one-pot reaction conditions. Accordingly, three-component synthesis starting from aldehyde and amine was thus investigated under the experimental conditions mentioned above. The aldehyde was first allowed to react with amine in methanol at room temperature, and Danishefsky's diene **1** was introduced successively. As shown in Table 3, the three components condensation reaction proceeded smoothly to afford the corresponding dihydro-4-pyridone derivatives in good to excellent yields. The yields of the reaction were comparable to those obtained by the reaction of isolated aldimines. The reaction was able to tolerate various aldehydes, including aromatic, olefinic and aliphatic derivatives. Particularly, the reactions of heteroaromatic aldehydes, 2-pyridylaldehyde, and 2-furylaldehyde afforded the corresponding heteroaromatic-substituted dihydro-4-pyridone derivatives in high yields, which may be interesting in the synthesis of some biologically important compounds.

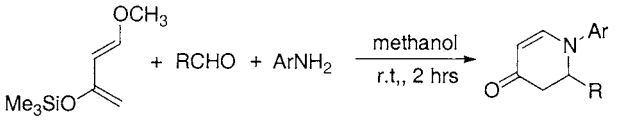
Table 2. Aza Diels−Alder Reaction of Danishefsky's Diene (**1**) with Imines (**2**) in Methanol



1 2 3

entry	R	Ar	yield (%)
1	C_6H_5	C_6H_5	>99
2	4-$MeOC_6H_4$	C_6H_5	95
3	4-ClC_6H_4	C_6H_5	89
4	4-$NO_2C_6H_4$	C_6H_5	63
5	PhCH=CH	C_6H_5	97
6	C_6H_5	4-ClC_6H_4	96
7	C_6H_5	4-$MeOC_6H_4$	95

Table 3. Three-Component Synthesis of Dihydro-4-pyridone Derivatives by One-Pot Aza Diels−Alder Reaction

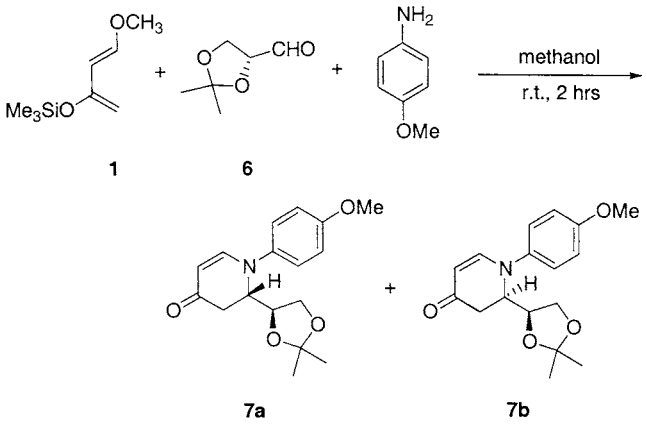


1 4 5 3

entry	R	Ar	yield (%)
1	C_6H_5	C_6H_5	>99
2	4-$MeOC_6H_4$	C_6H_5	91
3	4-ClC_6H_4	C_6H_5	80
4	4-$NO_2C_6H_4$	C_6H_5	67
5	C_6H_5	4-$MeOC_6H_4$	91
6	PhCH=CH	C_6H_5	93
7	$PhCH_2CH_2$	C_6H_5	89
8	$(CH_3)_2CH$	C_6H_5	76
9	2-furyl	C_6H_5	74
10	2-pyridyl	C_6H_5	91

The development of methods to effect the hetero Diels−Alder asymmetrically in this field has been the subject of intense activity during the past decade. The diastereoselectivity of this reaction has been investigated with chiral C-acylimine,[9] chiral alkoxy imines,[10] chiral aliphatic,[11] imines derived from chiral amino sugars,[12] chiral amino esters,[13] or chiral amino alcohols.[14] Enantioselective methods employing chiral Lewis acids have also emerged.[7,8,15] We chose to utilize (*R*)-2,3-di-*O*-isopropylideneglyceraldehyde **6** as the chiral auxiliary due to its low cost and easy availability in organic

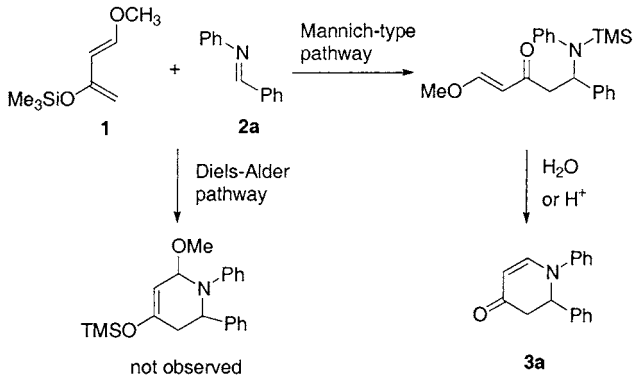
Scheme 1



synthesis.[16] An attempt to form the imine of 4-anisidine in situ in the presence of Danishefsky's diene in methanol at room temperature afforded the expected cycloproduct with two diastereomers **7a** and **7b** in moderate yield (66%) and good stereoselectivity (80/20) (Scheme 1).

An important question arises regarding the mechanism of the condensation of Danishefsky's diene with aldimine in methanol. A concerted [4 + 2] cycloaddition mechanism has been suggested in the Lewis acid-catalyzed reaction reported by Danishefsky[3], whereas a Mannich-type condensation mechanism was identified in the present reaction system (Scheme 2). In methanol-d_4, the ^{1}H NMR spectrum of the crude product from the reaction of Danishefsky's diene with aldimine revealed the exclusive presence of a Mannich-type condensation adduct.[17]

Scheme 2



In conclusion, the aza Diels−Alder reaction of Danishefsky's diene with imines has been found to proceed efficiently in methanol in the absence of any acids at room temperature to give corresponding 2-substituted dihydro-4-pyridone derivatives in high yields. The further evolution of this reaction to a three-component one-pot procedure and an asymmetric version using a chiral auxiliary was also achieved. The determination of the primary product formed in the reaction system combined with the observed solvent effect demonstrated that the reaction proceeded through a stepwise Mannich-type condensation mechanism.

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Supporting Information Available: Experimental details and spectral data for the cycloadducts, ^{1}H NMR spectra of the crude condensation adduct of the reaction between **1** and **2a** in methanol and diastereomers of **7**, ^{1}H−^{1}H COSY spectrum of **7a**, and ^{1}H NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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