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Brønsted acid-catalyzed aza Diels–Alder reaction of Danishefsky's diene with aldimine generated in situ from aldehyde and amine in aqueous media

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Abstract

Three-component aza Diels–Alder reaction, starting from aldehyde, aniline, and Danishefsky's diene, took place smoothly under the influence of HBF_4 in aqueous media to afford dihydro-4-pyridone derivatives in high yields.

Keywords: aza Diels–Alder reaction; Danishefsky's diene; Brønsted acid; imines; aqueous media.

The development of novel organic reactions in aqueous media has attracted much attention[1] because organic solvents, in particular halogenated solvents, are harmful to the environment. It is important to develop environmentally benign synthetic reactions. We have recently reported that Brønsted acid effectively activates imines in aqueous media.[2] Thus, on treatment of aldimine and silyl enolate in the presence of a catalytic amount of HBF_4, Mannich-type reaction took place smoothly in aqueous media to afford β-amino carbonyl compounds in high yields. Three-component syntheses of β-amino carbonyl compounds starting from aldehyde and aniline have also been successfully achieved. It turned out that imine could be generated smoothly in the presence of aqueous Brønsted acid. Furthermore, the Brønsted acid-catalyzed Mannich-type reaction proceeded smoothly in water without an organic solvent in the co-existence of a surfactant such as SDS (sodium dodecyl sulfate).[3,4]

The aza Diels–Alder reaction of Danishefsky's diene with imine is an important reaction for the preparation of dihydro-4-pyridones.[5] Numerous kinds of Lewis acids,[6,7] including chiral catalysts,[8] have been developed as activators. The aza Diels–Alder reaction of Danishefsky's diene in aqueous media has not been reported yet except for Waldmann's report, wherein $LiClO_4$ was employed as a promoter.[7c] In this article, we wish to report that Brønsted acid-catalyzed aza Diels–Alder reaction of aldimine and Danishefsky's diene proceeded smoothly to afford dihydro-4-pyridones in high yields in aqueous media. Furthermore, three-component synthesis of dihydro-4-pyridones from aldehyde, amine, and

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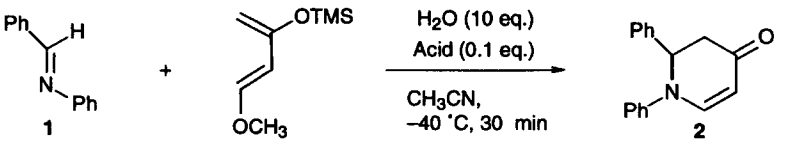
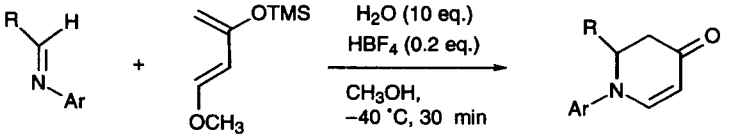
Danishefsky's diene also proceeded smoothly.[9] Although Grieco extensively studied the aza Diels–Alder reaction of diene with imine in aqueous media,[10] this is the first example of the aza Diels–Alder reaction of Danishefsky's diene with imine, generated in situ from aldehyde and amine in aqueous media.

At the outset, an aldimine (**1**) and Danishefsky's diene (1.5 equiv.) were treated with 0.1 equivalent of Brønsted acid in aqueous media and the results are shown in Scheme 1. The aza Diels–Alder reaction took place smoothly in CH_3CN at −40°C to afford an adduct (**2**) in high yield. Although *p*-TsOH and CF_3CO_2H also worked equally well, HBF_4 gave the best results.



Scheme 1. HBF_4; 91%, *p*-TsOH; 76%, CF_3CO_2H; 89%

After screening solvents, we found that the best results were achieved with methanol. The Brønsted acid-catalyzed aza Diels–Alder reaction with several kinds of aldimine in methanol took place fairly quickly to afford the corresponding adducts in excellent yields and the results are shown in Scheme 2, Table 1. An α,β-unsaturated aldimine also furnished the corresponding cycloadduct in high yield (entry 4). An aldimine derived from *p*-anisidine also worked well.



Scheme 2.

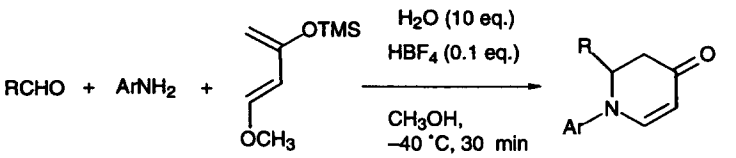
Table 1
Results of the aza Diels–Alder reaction[a]

Entry	R	Ar	Yield/%
1	Ph	Ph	98
2	*p*-$NO_2C_6H_4$	Ph	87
3	*p*-$CH_3C_6H_4$	Ph	95
4	PhCH=CH	Ph	89
5	Ph	*p*-$MeOC_6H_4$	90

a) 1.5 equiv of diene was employed.

Because imines, in particular those derived from aliphatic aldehyde, are not always stable, it is synthetically useful if aldimines were generated in situ and were allowed to react under one-pot reaction conditions. Next, three-component synthesis starting from aldehyde and amine was thus investigated. The results of the three-component synthesis are shown in Scheme 3, Table 2. Interestingly, even in the presence of water, aldimines were generated in situ spontaneously and the aza Diels–Alder reaction took place smoothly to afford the adducts in good to high yields. Aldimines derived from aliphatic aldehyde worked well. This is the first example of the three-component aza Diels–Alder reaction using Danishefsky's diene in aqueous media.[11]

Finally, we studied the aza Diels–Alder reaction in water.[12] Three-component synthesis starting from aldehyde, *p*-methoxyaniline, and Danishefsky's diene was successfully achieved in the co-existence of



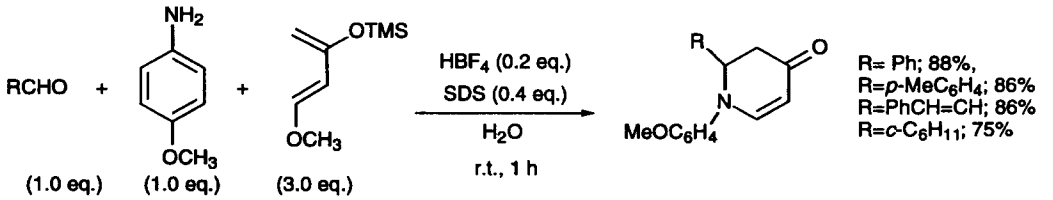
Scheme 3.

Table 2
Results of the three-component synthesis[a]

Entry	R	Ar	Yield/%
1	Ph	Ph	95
2	Ph	*p*-$MeOC_6H_4$	88
3	*p*-$CH_3C_6H_4$	Ph	79
4	*p*-$NO_2C_6H_4$	Ph	65
5	*c*-C_6H_{11}	Ph	80
6	$PhCH_2CH_2$	Ph	75
7	$(CH_3)_2CH$	Ph	77
8	2-furyl	Ph	58

a) 1.0 equiv of amine and 1.5 equiv of dilene were employed.

HBF_4 and a surfactant such as SDS (sodium dodecyl sulfate) in water without an organic solvent to afford the adduct in good yield (Scheme 4).



Scheme 4.

In summary, we have found that Brønsted acid catalyzed the aza Diels–Alder reaction of Danishefsky's diene in aqueous media for the first time.

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