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Alkaline salt-catalyzed aza Diels–Alder reactions of Danishefsky's diene with imines in water under neutral conditions

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Two- or three-component aza Diels–Alder reactions of Danishefsky's diene with imines or aldehydes and amines in water took place smoothly under neutral conditions in the presence of a catalytic amount of an alkaline salt such as sodium triflate to afford dihydro-4-pyridones in high yields.

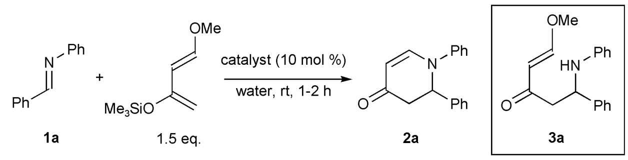
Aza Diels–Alder reactions are among the most powerful methodologies for the construction of nitrogen-containing six-membered ring compounds.[1] Recent advances in these reactions have been made by a number of Lewis acid-catalyzed versions in organic solvents.[2–4] On the other hand, development of more environmentally friendly synthetic processes is a rising interest in the chemical community. In addition to its abundance and for economical and safety reasons, water has naturally become an alternative as an environmentally benign solvent, and thus, successful examples of aqueous reactions have been already reported in the literature.[5] In water, aza Diels–Alder reactions have been mostly realized by acid catalysis *via* iminium salts[6] or by Brønsted acids.[7] In the course of our efforts to develop organic reactions in aqueous media using Lewis acid catalysis,[8] we have recently reported that aza Diels–Alder reactions proceeded smoothly in water with a silver catalyst.[9] In further investigations in this area, we have surprisingly discovered that aza Diels–Alder reactions with Danishesky's diene[10] were achieved under neutral conditions in the presence of an alkaline salt such as sodium triflate.

This unexpected finding has emerged, when a background reaction was examined in water with aldimine **1a** in the absence of a catalyst. Only a trace amount of the desired product **2a** was detected by ^{1}H NMR analysis, although most of Danishefsky's diene still remained after 2–3 h at room temperature (Table 1, entry 1). To our surprise, however, the presence of 10 mol% of sodium dodecyl sulfate (SDS) provided 68% yield of the dihydropyridone (entry 2). Intrigued by this finding, the effect of several water-soluble salts was then examined. The aza Diels–Alder reaction with sodium alkanesulfonates also gave the cycloadduct in high yields as the hydrophobicity of the catalysts increased (entries 3–6). In these cases, the Mannich-type intermediate **3a**, which could be easily converted to **2a** by acid treatment (1 M aq. HCl), was detected by ^{1}H NMR analysis of the crude mixture.[11] These results suggested a stepwise mechanism for the aza Diels–Alder reaction. Furthermore, remarkable results were observed with alkaline triflate, perchlorate,[12] or iodide (entries 7–11), while traces to moderate yields were obtained with carboxylate catalysts (entries 18–21). To our best knowledge, alkaline triflates or iodides have not hitherto been reported as efficient catalysts for reactions involving silyl enol ethers in water. Besides, it is noteworthy that, contrary to the previous examples of acid-catalyzed aza Diels–Alder reactions, the reaction proceeded smoothly under neutral conditions.

To gain mechanistic insight into the reaction, Bu_4NI was used instead of an alkaline salt (entry 12). Although a certain amount of **3a** was observed in the crude mixture, the yield of **2a** after acid treatment was similar to that with NaI. High yield was also obtained with a hydrophobic and non-nucleophilic catalyst such as $NaBPh_4$ (entry 13). On the other hand, only a trace amount of the desired product was observed with other sodium halides as well as hydrophobic ammonium bromide (entries 14–16, 17). These results suggested that the efficiency of the reaction may be related to the hydrophobicity and/or the nature of the anions.

The aza Diels–Alder reactions of Danishefsky's diene were then investigated in water in the presence of 10 mol% of NaOTf with a range of imines (two-component reactions). As shown in

Table 1 Aza Diels–Alder reactions of Danishesky′s diene with imine **1a** in water



Entry	Catalyst	% Ratio[a] **2a/3a**	% Yield[b] **2a**	Entry	Catalyst	% Ratio[a] **2a/3a**	% Yield[b] **2a**
1	None	—	<5	12	n-Bu_4NI	64:36	89
2	n-$C_{12}H_{25}OSO_3Na$	>99:1	68	13	$NaBPh_4$	>99:1	90
3	n-$C_{12}H_{25}SO_3Na$	96:4	83	14	NaBr	—	<5
4	n-$C_8H_{17}SO_3Na$	88:12	80	15	NaCl	—	<5
5	$PhSO_3Na$	48:52	65	16	NaF	—	<5
6	$EtSO_3Na$	—	<5	17	n-$C_{16}H_{33}Me_3NBr$	—	<5
7	LiOTf	>99:1	89	18	PhCOONa	—	<5
8	NaOTf	>99:1	87	19	CF_3COONa	44:56	44
9	KOTf	>99:1	80	20	CH_3COONa	—	<5
10	$LiClO_4$	>99:1	90	21	n-$C_{11}H_{23}COONa$	—	<5
11	NaI	94:6	87				

[a] Determined by ^{1}H NMR analysis of the crude mixture. [b] Isolated yield of **2a**. Acid treatment (1 M aq. HCl) was carried out only when **3a** was detected in the crude mixture.

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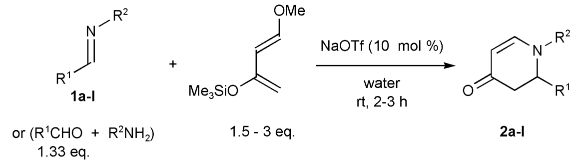
Table 2, the reactions with all imines **1a–g** afforded the corresponding cycloadducts in good to excellent yields. In some cases, the use of 3 equivalents of Danishefsky's diene improved the yields.

The three-component reaction starting from an aldehyde and an amine is synthetically useful not only because it enables the formation of unstable imines *in situ*, particularly those derived from aliphatic aldehydes, but also because it simplifies the procedure. Interestingly, aldimines **1a–c**, **h-l** were spontaneously generated in water to provide the desired adducts in good to high yields (Table 2). A possible catalysis by a trace amount of benzoic acid, which might be generated from benzaldehyde by adventitious oxidation, was ruled out since only hydrolysis of the Danishefsky's diene occurred when the reaction was performed in the presence of 2 mol% of PhCOOH for the substrates shown in entry 1. The neutrality of the reaction mixture in the presence of NaOTf also allowed the aza Diels–Alder reaction to proceed with equimolar amounts of benzaldehyde and aniline (entry 2). Furthermore, the hydrolysis rate of Danishefsky's diene was determined in water or a solution of 10 mol % of NaOTf. Approximately 10% of the diene was hydrolyzed after 1 h in both cases, which confirmed the neutrality of the reaction mixture in the presence of NaOTf.

In conclusion, two- or three-component aza Diels–Alder reactions of Danishesky's diene with imines, or aldehydes and amines, in water under neutral conditions have been found to proceed smoothly at room temperature in the presence of an alkaline salt such as sodium triflate to give the corresponding dihydro-4-pyridinone derivatives in high yields. In spite of several efforts, it is not clear at this stage whether the metallic cation, the anion, or both play an important role in the reaction. In addition, due to the heterogeneous reaction conditions, other possibilities could not be ruled out. Further investigations to elucidate the mechanistic aspects of these unprecedented and interesting aza Diels–Alder reactions in water are now in progress.[13]

Table 2 NaOTf-catalyzed two- and three-component aza Diels–Alder reactions in water with Danishesky's diene[a]



				% Yield	
Entry	R^1	R^2	Product	2-comp.[b]	3-comp.[c]
1[d]	Ph	Ph	**2a**	87	80
2[e]	Ph	Ph	**2a**	—	80
3[f]		Ph	**2b**	72	81
4	Ph	p-BrC_6H_4	**2c**	96[f]	83[d]
5[d]	Ph	p-$MeOC_6H_4$	**2d**	83	—
6[d]	p-BrC_6H_4	Ph	**2e**	92	—
7[f]	p-$NO_2C_6H_4$	Ph	**2f**	94	—
8[f]	p-$NMe_2C_6H_4$	Ph	**2g**	87	—
9[d]	Ph	o-$MeOC_6H_4$	**2h**	—	74
10[d,g]	3-py	Ph	**2i**	—	68
11[d]	c-C_6H_{11}	Ph	**2j**	—	74
12[d]	$Ph(CH_2)_2$	Ph	**2k**	—	70
13[d]	$(CH_3)_2CHCH_2$	Ph	**2l**	—	76

[a] Unless specified, the Danishefsky′s diene was added slowly over 30–45 min. [b] Two-component reaction. [c] Three-component reaction. [d] 1.5 eq. diene. [e] With 1 : 1 : 1.5 ratio of PhCHO:$PhNH_2$:diene. The diene was added at once. [f] 3 eq. diene. [g] 26% of **3i** was detected by ^1H NMR analysis.

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11 General procedure: in a 5 mL round-bottom flask was placed *N*-benzylideneaniline **1a** (54.4 mg, 0.30 mmol). A stock solution of a catalyst (0.6 mL, 0.05 M) and Danishefsky's diene (90 μL, 0.45 mmol) were then added successively. After stirring for 1–2 h, the reaction mixture was diluted with CH_2Cl_2, and the organic materials were extracted. The organic phases were combined and dried over Na_2SO_4. If the presence of the intermediate **3a** was detected on the ^1H NMR spectrum of the crude mixture, the sample was diluted in CH_2Cl_2, treated with 1 M aq. HCl (except for poor yield, the Danishefsky's diene completely disappeared before the acidic treatment), extracted, and dried over Na_2SO_4. The crude mixture was purified by preparative TLC (silica gel) affording the cycloadduct **2a**.

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