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Imino *Diels-Alder* Reactions: Efficient Synthesis of Pyrano- and Furanoquinolines Catalyzed by 4-Nitrophthalic Acid

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Summary. 4-Nitrophthalic acid was found to be an effective catalyst for the imino *Diels-Alder* reaction of *N*-benzylideneanilines with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran to afford pyrano- and furanoquinolines in good yields. It was also found that aryl amines react smoothly with 3,4-dihydro-2*H*-pyran and 2,3-dihydrofuran under the same condition to afford the corresponding pyrano- and furanoquinolines in high yields. This catalyst is inexpensive, easily available, water soluble, and stable to aqueous reaction conditions.

Keywords. 4-Nitrophthalic acid; Imino *Diels-Alder* reactions; 3,4-Dihydro-2*H*-pyran; 2,3-Dihydrofuran; Tetrahydroquinolines.

Introduction

The products containing pyrano- and furanoquinoline moieties are widely distributed in Nature and found to associate with a wide range of biological activities. Pyranotetrahydroquinolines are found in several alkaloids [1] such as veprisine, flinderesine, and oricine. These alkaloids possess important biological activities such as anti-allergic [2], psychotropic [3], anti-inflammatory [4], and estrogenic activities [5]. The alkaloids skimimianine and balflouridine which contain furanoquinoline moieties also show biological activity, which has led to the synthesis of pyrano- and furanoquinolines derivatives over the years [6]. Therefore, it is not surprising that many synthesis methods have been developed for these types of compounds. Among them, the *Lewis* acid catalyzed imino *Diels-Alder* reaction between *N*-benzylideneanilines and nucleophilic olefins is one of the powerful synthesis tools for constructing nitrogen containing six membered hetrocyclic compounds.

Since the pioneering work of *Povarov* [7], this reaction has been extensively studied with use of different *Lewis* acids, such as $BF_3 \cdot OEt_2$ [8], $GbCl_3$ [9], $InCl_3$ [10], $LiClO_4$ [11], $ZrCl_4$ [12], $BiCl_3$ [13], $SbCl_3$ [14], and protic acids such as *TFA* [15], *Ts*OH [16], $(COOH)_2$ [17]. Although the imino *Diels-Alder* reaction promoted by *Lewis* acid is known, more then stoichiometric amounts of the *Lewis* acid are required due to co-ordination of the *Lewis* acid to the imine nitrogen and generally, these *Lewis* acid catalysts are moisture sensitive and get easily decomposed or deactivated in the presence of even trace amounts of water and are thus difficult to handle. Further disposal of these acids leads to environmental pollution. The imino *Diels-Alder* reaction has also been successfully carried out using K-10 clay [18], urea nitrate [19], lanthanide triflates [20], *CAN* [21], $KHSO_4$ [22], and I_2 [23]. In the quest for developing a less toxic, potential green catalyst, we thought of using 4-nitrophthalic acid (4-*npa*) as a catalyst for this reaction. The 4-*npa* is inexpensive,

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stable solid, water soluble, and easily available. 4-*npa* is easier to handle than metal halides such as $ZrCl_4$, $BiCl_3$, $SbCl_3$, and protic acids such as *TFA* or *TsOH*. In this paper we report on the synthesis of substituted pyrano- and furanoquinolines *via* an imino *Diels-Alder* reaction using 4-*npa* as a catalyst. To the best of our knowledge there is no report of the use of 4-*npa* as a mild and inexpensive catalyst for this type of reactions.

Results and Discussion

Preliminary studies were carried out to study the effect of solvents, catalytic concentration, and temperature on the model reaction of *N*-benzylidene **1a** and 3,4-dihydropyran (*DHP*) in the presence of 4-*npa*, and the results are summarized in Table 1.

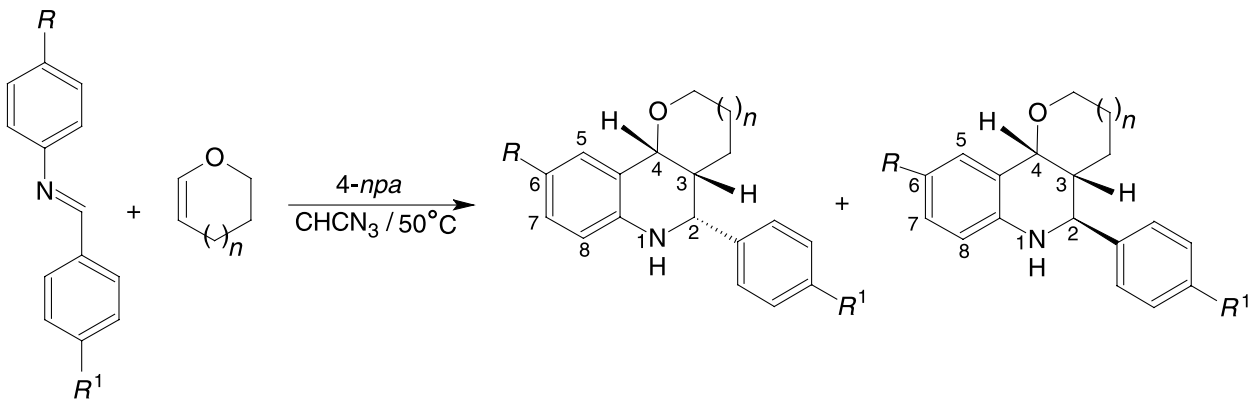
Table 1. Screening catalytic activity of 4-*npa* for the synthesis of tetrahydroquinolines

Entry	Solvent	Mol% 4-*npa*	Temperature/ °C	Time/ h	Yield/ %[a]
1	CH_3CN	25	25	8.00	72
2	CH_3CN	10	50	5.00	74
3	CH_3CN	25	50	3.00	90
4	CH_3CN	25	reflux	2.10	78
5	Toluene	25	50	5.00	55
6	*Me*OH	25	50	4.00	76
7	*Et*OH	25	50	4.00	72
8	*THF*	25	50	3.45	56
9	CH_2Cl_2	25	reflux	3.30	65
10	CH_3CN	40	50	2.45	88
11	CH_3CN/H_2O (3/1, *v*/*v*)	25	50	3.00	80

[a] Isolated yields

Though the reaction proceeds at room temperature, the isolated yields are low and the reaction is sluggish. At reflux temperature, the formation of impurities was observed. At 50°C, the reaction proceeds smoothly and gave desired products in good yields. Among the various solvents, acetonitrile was found to be the best solvent for this transformation. Also, we examined the reaction in the acetonitrile/water system. Remarkably, the reaction proceeded smoothly in CH_3CN/H_2O (3/1, *v*/*v*) system and afforded the desired product in good yield. At 10 mol% of catalyst, the reaction was sluggish and at 25 mol%, the optimal results were obtained. Increasing the concentration of the catalyst beyond 25 mol% did not show an appreciable advantage.

Thus, in the presence of 25 mol% of 4-*npa*, *N*-benzylidene derivative **1a** was treated with *DHP* in acetonitrile at 50°C. After 3 h the pyranoquinolines **3a** and **4a** were obtained in a ratio of 39:61 in overall yields of 90% (Scheme 1). The structures of the compounds were established by IR, ^{1}H NMR, and mass spectral analysis. It was observed that the pyran ring was *cis*-fused in the tetrahydroquinoline moiety and the stereochemistry of the products was established based on the coupling constant of C_2–H ($J_{3,2} = 4.4$–5.7 Hz) in **3** indicating the *cis* relationship between C_3–H and C_2–H, whereas in **4** ($J_{3,2} = 10.08$–11.12 Hz) the coupling indicated *trans*. In all cases, $J_{3,4}$ was found to be 2.6–3.0 Hz indicating a *cis* ring junction between the quinoline and pyran rings which is in accordance with literature values [12]. The results obtained with substituted *N*-benzylideneanilines and dihydrofuran/3,4-dihydro-2*H*-pyran are summarized in Table 2.



Scheme 1

Table 2. The synthesis of 2-aryltetrahydroquinolines using 4-*npa* at 50°C

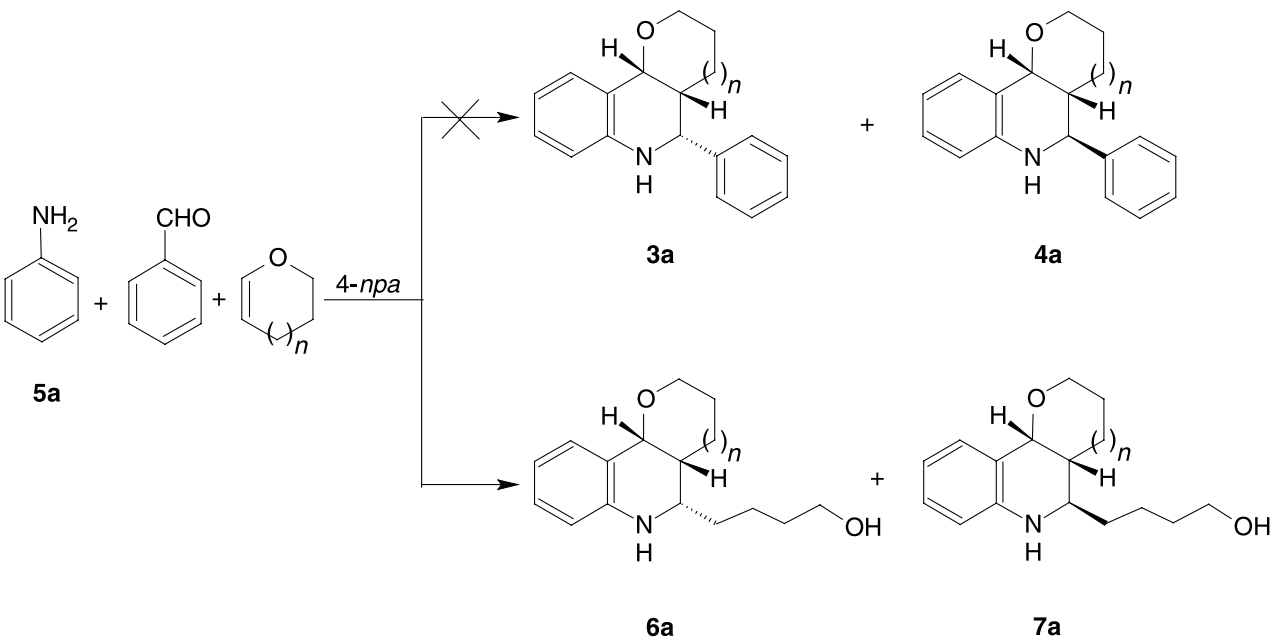
Products	*R*	R^1	*n*	Time/ h	Product ratio[a] 3:4	Yield/ %[b]
a	H	H	1	3.00	39:61	90
b	*Me*	H	1	3.00	42:58	92
c	O*Me*	H	1	3.00	35:65	93
d	F	H	1	4.00	30:70	78
e	Cl	H	1	4.00	45:55	81
f	H	H	0	4.00	49:51	80
g	O*Me*	H	0	4.00	56:44	82
h	Cl	H	0	5.00	43:53	77
i	*Me*	H	0	4.00	52:48	82

[a] Product ratio was based on isolation by column chromatography
[b] Isolated yields

There are reports in literature on the three component one pot synthesis of pyrano- and furanoquinolines using aryl amines, aryl aldehydes, and *DHP* [9, 14]. Hence anticipating similar results, we tried one pot synthesis by using benzaldehyde, aniline, and *DHP* catalyzed by 4-*npa*. However, the reaction did not give the expected pyranoquinolines **3a** or **4a**, instead we got pyranoquinolines of type **6a** and **7a** in the ratio of 48:52. The results indicate that in the presence of 4-*npa*, the masked aldehyde *DHP* reacts faster than benzaldehyde with aniline to form the *N*-benzylideneaniline which undergoes imino *Diels-Alder* reaction to yield pyranoquinolines of the type **6a** and **7a**. In this 4-*npa* catalyzed domino reaction, benzaldehyde remained unreacted. Encouraged by these interesting results, we carried out the reaction of various aryl amines with dihydropyran and dihydrofuran (Scheme 2) and results are summarized in Table 3. A similar domino reaction of aromatic amines with cyclic enol ethers catalyzed by $InCl_3$ has been reported [10b]. These results indicate that 4-*npa* can be used has an efficient catalyst in the imino *Diels-Alder* reaction of *N*-benzylideneanilines with cyclic enol ethers and also in the domino reaction of anilines with cyclic enol ethers leading to the formation of pyrano- and furanoquinolines.

From these results, we propose the following possible mechanism to account for the reaction. An aromatic amine first reacts with cyclic enol ether to form 2-azadiene and the second step proceeds *via* the imino *Diels-Alder* reaction between this 2-azadiene and another molecule of cyclic enol ether (Scheme 3).

In conclusion, a very interesting and a facile synthesis of substituted pyrano- and furanoquinolines using cheaper, water stable, and water soluble 4-nitrophthalic acid catalyzed imino *Diels-Alder* reaction of *N*-benzylideneanilines with cyclic enol ethers



Scheme 2

Table 3. The synthesis of 2-alkoxytetrahydroquinolines using 4-*npa* at 50°C

Products	R^2	*n*	Time/h	Product ratio[a] 6:7	Yield/%[b]
a	H	1	4.00	48:52	82
b	*Me*	1	3.30	42:58	85
c	O*Me*	1	3.30	45:55	86
d	Cl	1	4.00	51:49	75
e	F	1	4.00	58:42	75
f	Br	1	4.00	49:51	76
g	H	0	4.00	60:40	80
h	*Me*	0	5.00	74:26	75
i	O*Me*	0	4.00	70:30	78
j	C*l*	0	4.00	72:38	78
k	F	0	5.00	80:20	76
l	Br	0	5.00	78:22	76

[a] Product ratio was based on isolation by column chromatography
[b] Isolated yields

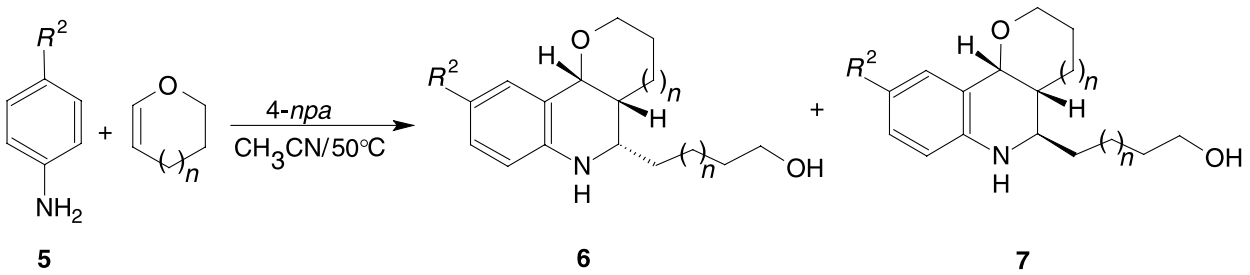
and the domino reaction of anilines with cyclic enol ethers are described.

Experimental

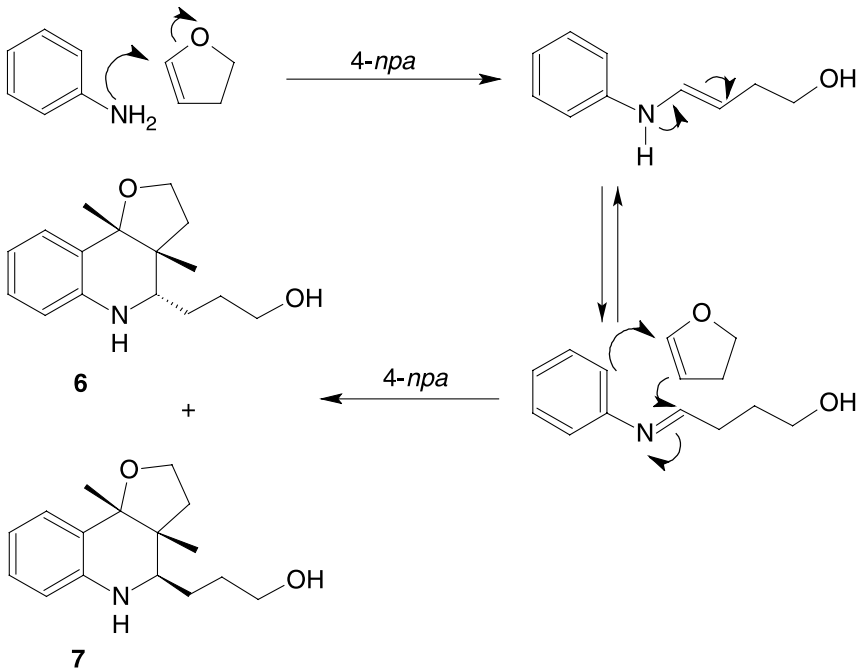
All melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel and they were purified by column chromatography. ^{1}H NMR spectra were recorded on a Bruker-300 MHz spectrometer using *TMS* as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer. The compounds **3a–3h** [12], **4a–4h** [9], **6a–6l** [10b], and **7a–7l** [10b] are known, their identities were proven by means of IR, NMR, and mass spectra.

*General Procedure for the Synthesis of Tetrahydroquinolines **3** and **4***

4-*npa* (0.25 mmol) was added to a mixture of 1.0 mmol *N*-benzylidene **1** and 1.2 mmol 3,4-dihydro-2*H*-pyran or 2,3-



Scheme 3



Scheme 4

dihydrofuran **2** in 5 cm^3 acetonitrile. The reaction mixture was stirred at 50°C for the appropriate time. After completion, the reaction mixture was quenched with 25 cm^3 saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate ($3 \times 10\,cm^3$). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography on SiO_2 with an ethyl acetate and petroleum ether mixture as elutent to afford the corresponding tetrahydroquinolines **3** and **4**.

*General Procedure for the Synthesis of Tetrahydroquinolines **6** and **7***

4-*npa* (0.25 mmol) was added to a mixture of 1.0 mmol aryl amine **1** and 2.5 mmol 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran **2** in 5 cm^3 acetonitrile. The reaction mixture was stirred at 50°C for the appropriate time. After completion, the reaction mixture was quenched with 25 cm^3 saturated $NaHCO_3$ aqueous solution and extracted with ethyl acetate ($3 \times 10\,cm^3$). The combined organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography on SiO_2 with an ethyl acetate and petroleum ether mixture as elutent to afford the corresponding tetrahydroquinolines **6** and **7**.

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