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o-Benzenedisulfonimide as a Reusable Brønsted Acid Catalyst for an Efficient and Facile Synthesis of Quinolines *via* Friedländer annulation.

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Abstract

The synthesis of quinolines via Friedländer annulation was carried out in the presence of catalytic amount of *o*-benzenedisulfonimide as Brønsted acid organocatalyst; the reaction conditions were mild and the yields of the target products were good. The organocatalyst was easily recovered and purified, ready to be used in further reactions

Keywords: homogeneous catalysis; quinoline; Brønsted acid; 2-aminoarylketone; α-methyleneketone.

Quinolines and their derivatives are very important compounds[1] that show a broad range of biological activities such as anti-malarial,[2] anti-inflammatory,[3] anti-bacterial,[4] anti-asthmatic,[5] and anti-hypertensive[6]. In addition, quinolines are advantageously employed in the fields of bioorganic[7] and industrial organic chemistries.[8]

Probably, quinolines represent a major class of heterocycles and a significant number of preparations have been known since the late 1800s;[1] quinolines have generally been synthesized by well-known classical syntheses such as Skraup, Doebner-von Miller, Friedländer, Pfitzinger, Conrad-Limpach, and Combes.[1]

Among them, the Friedländer annulation[9] appears to be still one of the simplest and direct approaches for the synthesis of quinolines. The Friedländer protocol consists typically of the reactions between aromatic *o*-aminoketones or aldehydes and another carbonylic compound with an activated α-methylene group. The reaction can be promoted by acid or base catalysis or by heating; however, under basic or thermal conditions sometimes the reaction between 2-aminobenzophenone and simple ketones or β-keto esters fails. [9] In general, better yields of quinolines were achieved under acid catalysis. [9] Several acid catalysts such as Brønsted acids [9] (recent examples are hydrochloric acid in water, [10] sulfamic acid, [11] sulfuric acid, [12] dodecylphosphonic acid, [13] PEG-supported sulfonic acid, [14] propylsulfonic silica, [15] sulfonic acid-functionalized ionic liquids, [16] and oxalic acid [17]), and Lewis acids [9] (recent examples are $Zr(NO_3)_4$ or

$Zr(HSO_4)_4$, [18] Lewis acid ionic liquid, [19] LASC, [20] ceric ammonium nitrate, [21] $GdCl_3 \cdot 6H_2O$, [22] and $BiCl_3$ [23]) were widely used; however, some of these procedures are complicated by harsh reaction conditions, use of harmful organic solvents, low yields, and difficulties in the work-up procedures.

We have recently reported the use of *o*-benzenedisulfonimide (**1**, Fig. 1) in catalytic amounts as a safe, nonvolatile, and noncorrosive Brønsted acid in some acid-catalyzed organic reactions such as etherification, [24 and 25] esterification, [24, 25 and 26] acetalization, [24 and 25] Ritter reaction, [27] Nazarov electrocyclization, [28] disproportionation of dialkyl diarylmethyl ethers, [29] and Hosomi–Sakurai reaction [30] under very mild and selective conditions. This organocatalyst, highly soluble in both organic solvents and water, is easily recovered and purified from the reaction mixture, owing to its complete solubility in water, and it is ready to be used in further reactions with economic and ecological advantages.

Figure 1

Scheme 1

The synthesis of **1** has been described for the first time in 1920s and recently modified.[24] The key intermediate is *o*-benzenedisulfonyl chloride, which can be prepared starting from *o*-benzenedisulfonic acid dipotassium salt, anthranilic acid, 2-aminobenzenesulfonic acid, and 1,2-bis(methylsulfanyl)benzene. Nowadays, both *o*-benzenedisulfonyl chloride and **1** are commercially available from Sigma–Aldrich and Qventas, respectively.

In the light of these shortcomings, in this Letter we wish to propose a simple and efficient quinoline synthesis via Friedländer annulation in the presence of **1** as reusable Brønsted acid catalyst.

Various 2-aminobenzophenones **2a**, **c**–**e** and 2-aminoacetophenone (**2b**) were reacted at 80 °C with a number of carbonyl compounds **3a**–**c** or **5a**–**c** bearing one activated α-methylene group, usually in the presence of 5 mol % of **1** in order to synthesize quinolines **4a**–**f** or **6a**–**i** (Scheme 1); the results are listed in Table 1.[31]

Table 1

The target products **4a**–**f** and **6a**–**i** were obtained in good to excellent yields (15 examples: average yield 90%) reacting either cyclic or acyclic ketones, diketones, β-ketoester under mild, easy, and solvent-free conditions. Interestingly, the reaction between **2a** and **5b**, carried out at reflux in an organic solvent (MeCN, THF, or EtOH) and in the presence of 5 mol % of **1**, did not complete even after long time (48 h). Performing the same reaction in H2O, the yield of **6b** was only 72% after 24 h. Note that the reactions between **2b** and **3a**–**c** or **5a**–**c** took place usually slower (Table 1;

entries 4–6, 10–12). Moreover, by using the less reactive **3a**, the products **4a** and **4d** were obtained in lower yields and longer times; it was also necessary to use 10 mol % of **1** (Table 1; entries 1 and 4). It must be stressed that the presence of a strong electron-withdrawing group influenced the progress of the reaction: reacting **2d** with **5b**, it was necessary to use 10 mol % of **1** for the completion of the reaction (Table 1; entry 14).

Furthermore, **1** was recovered in excellent yields (about 90%), simply by evaporating under reduced pressure aqueous layer and washings. The recovered **1** was reused as catalyst in other two consecutive reactions between **2a** and **5b**. The results are listed in Table 2: the reaction time increased, but the yields of **6b** and the recovery of **1** were always good.

Table 2

In conclusion, we have proposed a mild, easy, and efficient method for the synthesis of quinolines through Friedländer annulation in the presence of *o*-benzenedisulfonimide (**1**) as a reusable homogeneous catalyst. The advantages of performing the Friedländer reaction in the presence of **1** as catalyst can be summarized as follows: (1) use of a safe, nonvolatile, noncorrosive Brønsted acid; (2) high yields of recovering of **1** at the end of the reactions simply evaporating aqueous washings; (3) the target products **4** and **6** are obtained generally in excellent yields under easy and mild reaction conditions; and (4) the reactions are carried out under solvent free conditions with economic benefits.

Acknowledgments

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stirred at 80°C. The reaction was monitored by GC and GC–MS until the complete disappearance of 2a (6 h). The reaction mixture was poured into ethyl acetate–H_2O (100 ml, 1:1). The aqueous layer was separated and extracted with ethyl acetate (2 _ 50 ml). The combined organic extracts were washed with H_2O (2_ 50 ml) and dried over Na2SO4. After solvent removal under reduced pressure, the crude residue was the virtually pure (GC, GC–MS, ^{1}H NMR, ^{13}C NMR) title compound 6b, pale brown solid; yield: 100% (1.46 g). The aqueous layer and the aqueous washings were collected and evaporated under reduced pressure. After removal of the water, virtually pure (^{1}H NMR) *o*-benzenedisulfonimide (1) was recovered (101 mg, 92% yield).
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36. 7-Nitro-9-phenyl-1,2,3,4-tetrahydroacridine (6h) is known in the literature;37 however, no physical and spectral data are reported. EI–MS, m/z (%) = 304 [M^+,100]. ^{1}H NMR (200 MHz, CDCl3): d 8.28–8.21 (m, 2H), 8.01 (d, J = 9.05 Hz), 7.58–7.47 (m, 3H), 7.18–7.01 (m, 2H), 3.18–3.11 (m, 2H), 2.60–2.25 (m, 2H), 1.89–1.86 (m, 2H), 1.79–1.77 (m, 2H); 13C NMR (50 MHz, $CDCl_3$): d 163.4, 148.2, 148.0, 144.7, 135.1, 130.6, 129.9, 128.8, 128.7, 128.4, 125.5, 122.7, 121.7, 34.3, 27.9.4, 22.5, 22.3.
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Table 1

Synthesis of quinolines **4** or **6.**

Entry	Reactants		Products and Yields [a,b] (%)	**1** %	Time (h)	Quinolines **4** or **6** mp[c] (°C)	lit. mp (°C)
1	**2a**	**3a**	**4a,** 90[d]	10	28	147–148	144[32]
2	**2a**	**3b**	**4b,** 93	5	3	100–101	97[33]
3	**2a**	**3c**	**4c,** 95	5	4	110–111	113[33]
4	**2b**	**3a**	**4d,** 55[d]	10	48	109–110	110[34]
5	**2b**	**3b**	**4e,** 85	5	16	waxy solid	oil[34]
6	**2b**	**3c**	**4f,** 92	5	16	viscous oil	oil[34]
7	**2a**	**5a**	**6a,** 90	5	4	130–131	128–130[35]
8	**2a**	**5b**	**6b,**100[e]	5	6	136–137	137[34]
9	**2a**	**5c**	**6c,**100	5	4	155–156	151–153[20]
10	**2b**	**5a**	**6d,** 83	5	48	60–61	60[34]
11	**2b**	**5b**	**6e,** 100	5	24	78–79	78[20]
12	**2b**	**5c**	**6f,** 100	5	16	68–69	78[23]
13	**2c**	**5b**	**6g,** 95	5	4	162–164	163[34]
14	**2d**	**5b**	**6h,** 80[d]	10	8	143–144	-[36]
15	**2e**	**5b**	**6i,** 92	5	4	151–152	153[33]

[a] Yields refer to the pure and isolated products.

[b] Structures and purity of all the products were confirmed by comparison of their physical (mp) and spectral data with those reported in the literature

[c] Crystallization solvent: MeOH.

[d] The reaction carried out with 5 mol % of **1,** after 48 hours was not complete.

[e] The reactions carried out at reflux in MeCN, THF or EtOH, after 48 hours were not complete.

Table 2

Consecutive reactions with **1**.

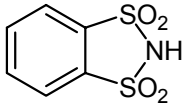
Entry	Time (h)	Yield (%)of **6a** [a,b]	Recover(%)of **1**
1	6	100	92,[c] 101 mg
2	6	92	88,[d] 89 mg
3	8	90	90, 80 mg

[a] The reactions were performed at 80°C.

[b] Yields refer to the pure and isolate product.

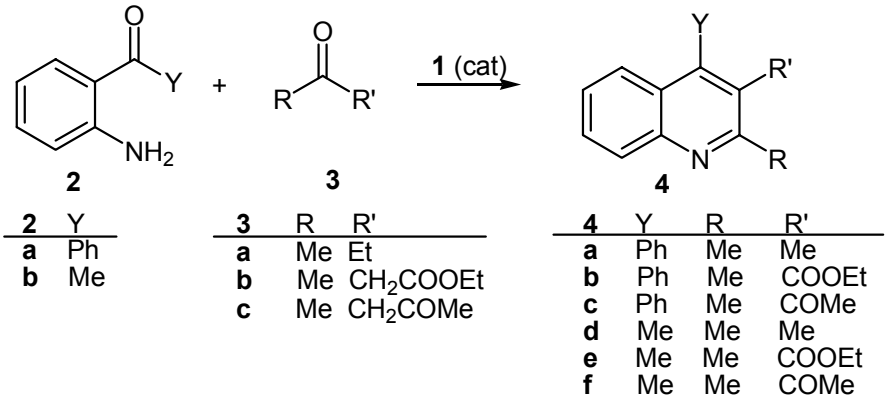
[c] The recovered **1** was used as catalyst in entry 2.

[d] The recovered **1** was used as catalyst in entry 3.



1

Figure 1

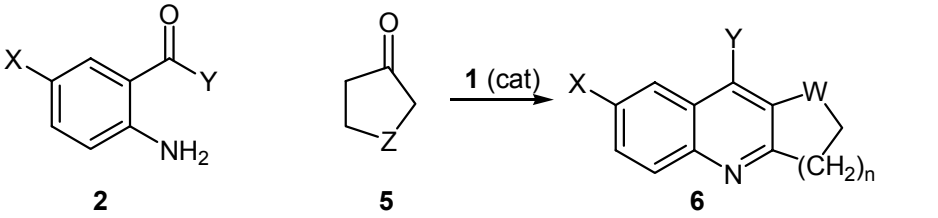


2 **3** **4**

2	Y
a	Ph
b	Me

3	R	R'
a	Me	Et
b	Me	CH_2COOEt
c	Me	CH_2COMe

4	Y	R	R'
a	Ph	Me	Me
b	Ph	Me	COOEt
c	Ph	Me	COMe
d	Me	Me	Me
e	Me	Me	COOEt
f	Me	Me	COMe



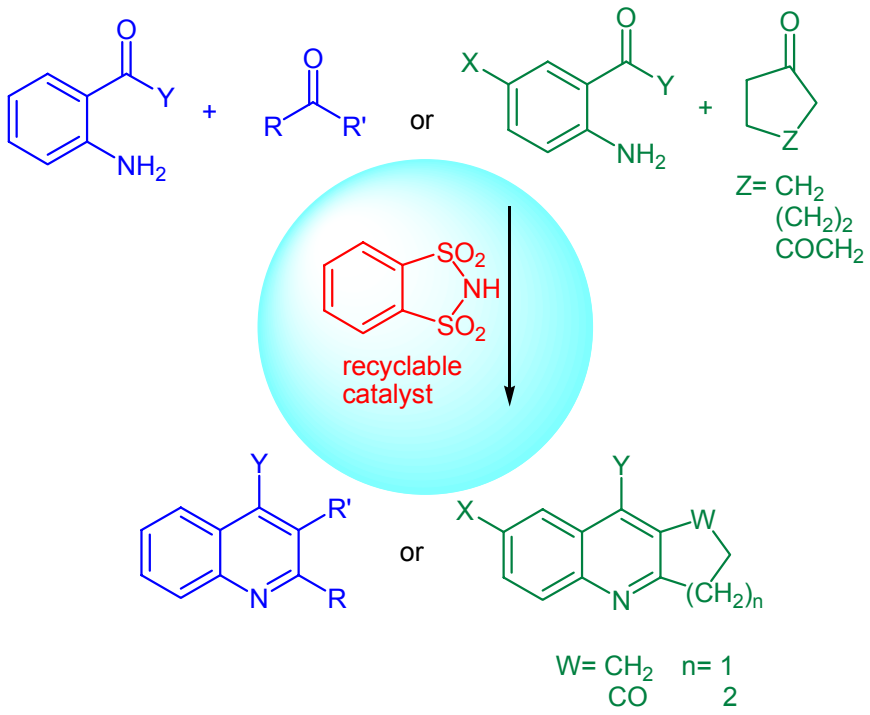
2 **5** **6**

2	X	Y
a	H	Ph
b	H	Me
c	Cl	Ph
d	NO_2	Ph
e	Cl	2-ClC_6H_4

5	Z
a	CH_2
b	CH_2-CH_2
c	CH_2-CO

6	X	Y	n	W
a	H	Ph	1	CH_2
b	H	Ph	2	CH_2
c	H	Ph	2	CO
d	H	Me	1	CH_2
e	H	Me	2	CH 2
f	H	Me	2	CO
g	Cl	Ph	2	CH_2
h	NO_2	Ph	2	CH_2
i	Cl	2-ClC_6H_4	2	CH_2

Scheme 1



Graphical abstract