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Montmorillonite clay-catalyzed [4+2] cycloaddition reactions: a facile synthesis of pyrano- and furanoquinolines

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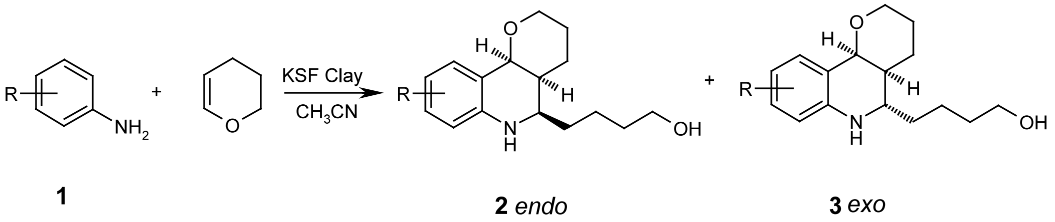
Abstract—Aryl amines react smoothly with cyclic enol ethers such as 3,4-dihydro-2*H*-pyran (DHP) and 2,3-dihydrofuran (DHF) on the surface of montmorillonite KSF under mild reaction conditions to afford the corresponding pyrano- and furano[3,2-*c*]-quinolines in high yields with high diastereoselectivity. © 2002 Published by Elsevier Science Ltd.

The aza-Diels–Alder reaction is one of the most powerful synthetic routes for constructing nitrogen containing six-membered heterocycles.[1] Tetrahydroquinoline derivatives are an important class of compounds in the field of pharmaceuticals and exhibit a wide spectrum of biological activity[2] including psychotropic, antiallergic, anti-inflammatory and estrogenic activity. In addition, pyranoquinoline derivatives are found to possess a vast range of pharmacological activity.[3] The imino-Diels–Alder reaction provides a useful entry to the preparation of pyrano- and furanoquinolines. Imines derived from aromatic amines act as heterodienes and undergo imino-Diels–Alder reactions with various dienophiles. Generally Lewis acids[4–6] are known to catalyze imino-Diels–Alder reactions to produce quinoline derivatives. Recently, metal triflates[7,8] have also been found to be effective Lewis acids in promoting imino-Diels–Alder reactions. However, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants; even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are required because the acids are trapped by nitrogen.[1] Thus, there is still a need to develop a simple and convenient method for the synthesis of quinoline derivatives of biological importance. In recent years, the use of solid acidic catalysts[9] such as clays and zeolites has attracted attention in different areas of organic synthesis because of their environmental compatibility, reusability, high selectivity, non-corrosiveness, low cost and simplicity in operation. In particular, clay catalysts[10] make the reaction processes convenient, more economic, environmentally benign and act as both Bronsted and Lewis acids in their natural and ion-exchanged forms, enabling them to function as efficient catalysts for various organic transformations.[11]

In this report, we describe a simple and highly efficient procedure for the synthesis of pyrano- and furanoquinolines using a heterogeneous catalyst i.e. montmorillonite KSF. Thus, treatment of the aryl amine with 3,4-dihydro-2*H*-pyran (DHP) in the presence of montmorillonite KSF in acetonitrile at ambient temperature afforded the corresponding pyrano[3,2-*c*]-quinoline derivatives **2** and **3** in 87% yield (Scheme 1).



Scheme 1.

Keywords: solid acids; heterogeneous; imino-Diels–Alder reaction; tetrahydroquinolines.

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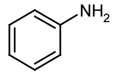
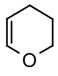
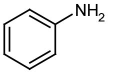
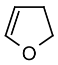
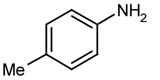
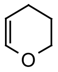
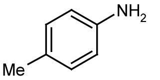
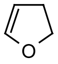
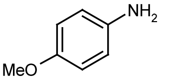
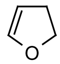
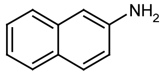
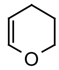
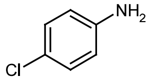
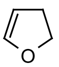
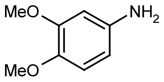
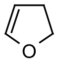
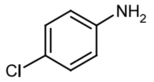
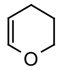
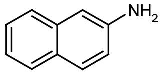
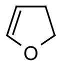
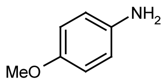
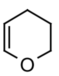
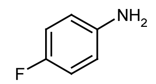
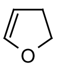
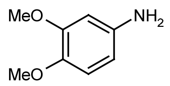
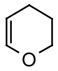
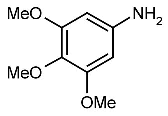
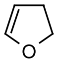
Similarly, several aryl amines reacted smoothly with 3,4-dihydro-2*H*-pyran to give the corresponding pyranoquinolines in 82–90% yield (Table 1). The reactions proceeded efficiently at ambient temperature under mild conditions to give the products in high yields. In most of the cases, the products were obtained as a mixture of *endo*- and *exo*-isomers, favoring the *endo*-diastereomer. The product ratios were determined from the ^{1}H NMR spectra of the crude products. The stereochemistry of the product **2a** was assigned on the basis of coupling constants and NOE studies. The two six-membered quinoline and tetrahydropyran rings are *cis*-fused as indicated by the small coupling constant value $J_{\mathrm{H4–H5}} = 5.6$ Hz for H5 (5.0 ppm) proton as well as the observation of an NOE cross peak between them in the NOESY spectrum. The middle six-membered quinoline ring conformation was confirmed as a twist conformation, which is consistent with the small coupling constant value $J_{\mathrm{H6–H7}} = 6.9$ Hz, for H7 (δ 3.34 ppm) and the presence of NOE cross peaks between H5–H6 and H5–H7 in the NOESY spectrum. The six-membered tetrahydropyran ring adopts a chair conformation as confirmed by the large coupling constant values $J_{\mathrm{H14ax–H13ax}} = 11.9$ Hz for H14ax (δ 3.39 ppm) and

Table 1. Montmorillonite KSF clay-promoted synthesis of pyrano- and furanoquinolines

Entry	Aryl amine	Olefin	Reaction time (h)	Yield (%)[a]	*Endo:Exo*[b]
a			4.0	87	95: 5
b			3.0	85	92: 8
c			3.5	89	98: 2
d			3.0	90	99: 1
e			3.5	88	99: 1
f			4.0	82	85:15
g			3.0	91	97: 3
h			3.5	89	98: 2
i			4.0	90	97: 3
j			4.5	85	85:15
k			3.5	88	95: 5
l			3.0	89	92: 8
m			4.0	90	98: 2
n			4.5	87	90:10

[a] Isolated and unoptimized yields after column chromatography.

[b] Product ratios were determined from the ^{1}H NMR spectra of the crude products.

$J_{H6-H12ax}=12.1$ Hz for H6 (δ 2.00 ppm) as well as by the presence of an NOE cross peak between H_4–H_{14ax} (as shown in Fig. 1) and the absence of an NOE cross peak between H5–H14 in the NOESY spectrum.

Furthermore, the reactions of anilines with 2,3-dihydrofuran in the presence of montmorillonite KSF in acetonitrile resulted in the formation of furano[3,2-*c*]quinoline derivatives **4** and **5** in 85–91% yield (Scheme 2).

In all the cases the products were obtained as a mixture of *endo*- and *exo*-isomers, which could not be separated by column chromatography. The ratio of diastereomers was determined by ^{1}H NMR spectroscopy of the crude products. In all cases, the reactions were clean and highly diastereoselective, affording the corresponding *endo*-diastereomer **4** with only a minor amount of the *exo*-diastereomer **5**. All the products were characterized by ^{1}H, ^{13}C NMR, IR and mass spectroscopy. This methodology is equally effective with electron rich and electron deficient anilines. There are several advantages in the use of montmorillonite clay for this transformation, which include mild reaction conditions, improved yields, enhanced selectivity, simplicity in operation and simple experimental and work-up conditions. This method does not require anhydrous solvents or stringent reaction conditions whilst no precautions need to be taken to exclude moisture from the reaction medium. The solvent acetonitrile appears to be superior giving the best results. The reaction may proceed via an imino-Diels–Alder process between a 2-azadiene (formed in situ from the cyclic enol ether and aniline) and another equivalent of enol ether resulting in the formation of fused quinoline derivatives (Scheme 3).

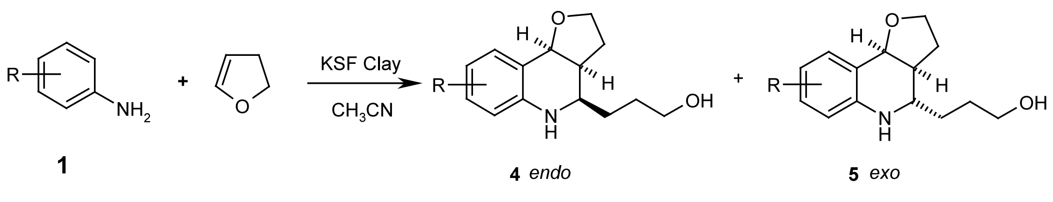
Several examples illustrating this simple and convenient method for the synthesis of tetrahydroquinolines are summarized in Table 1. Finally, the clay was recovered by filtration, washed with methanol and recycled for use in subsequent reactions (after activation at 120°C for 4–5 h) with gradual decrease in activity; for example, the reaction of aniline and dihydropyran under the present reaction conditions afforded 87, 83 and 78% yields over three cycles. These results clearly show the advantage of our method over protic and Lewis acid-catalyzed procedures.

In summary, the paper describes a simple and efficient method for the synthesis of tetrahydroquinoline derivatives from aryl amines and 2 equiv. of cyclic enol ethers using montmorillonite KSF clay as a heterogeneous catalyst. The notable features of this procedure are mild reaction conditions, greater selectivity, high yields of products, cleaner reaction profiles, ready availability of the reagents at low cost and enhanced rates making it a useful and attractive process for the synthesis of fused pyrano- and furano[3,2-*c*]quinolines of biological importance.

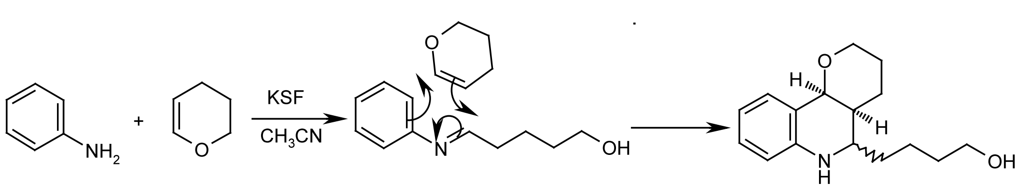
Acknowledgements

B.V.S. and P.S.R.R. thank CSIR New Delhi for the award of fellowships.

Figure 1. Chemical structure and important NOE's of compound **2a**.



Scheme 2.



Scheme 3.

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    Experimental procedure: A mixture of the aryl amine (5 mmol), dihydrofuran or dihydropyran (12 mmol) and montmorillonite KSF clay (1.5 g) in acetonitrile (5 mL) was stirred at ambient temperature for the appropriate time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate (10 mL). The combined organic layers were concentrated in vacuo and the resulting product was purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 2:8) to afford pure product. **2c**: ^{1}H NMR ($CDCl_3$) δ: 1.45–1.55 (m, 6H), 1.58–1.67 (m, 4H), 2.05 (dddd, 1H, $J=2.4$, 5.7, 4.0, 12.4 Hz), 2.25 (s, 3H), 2.55 (m, 1H, NH), 3.28–3.35 (m, 1H), 3.40 (m, 1H), 3.57 (t, 1H, $J=4.0$ Hz), 3.65 (t, 2H, $J=6.2$ Hz), 5.0 (d, 1H, $J=5.7$ Hz), 6.35 (d, 1H, $J=8.4$ Hz), 6.80 (dd, 1H, $J=2.1$, 8.4 Hz), 7.20 (d, 1H, $J=2.1$ Hz). IR (KBr) ν: 3396, 2940, 1609, 2862, 1575, 1521, 1469, 1345, 1212, 1079, 807, 759. EIMS: m/z: 275 M^+, 202, 158, 144, 105, 91, 57.

    4d: ^{1}H NMR ($CDCl_3$) δ: 1.60–1.75 (m, 4H), 1.80–1.90 (m, 1H), 1.98–2.15 (m, 1H), 2.25 (s, 3H), 2.55–2.65 (m, 1H), 3.38–3.45 (m, 1H), 3.70 (t, 2H, $J=5.3$ Hz), 3.80 (dd, 2H, $J=3.0$, 8.1 Hz), 5.08 (d, 1H, $J=8.1$ Hz), 6.40 (d, 1H, $J=8.3$ Hz), 6.80 (dd, 1H, $J=2.1$, 8.3 Hz), 7.20 (d, 1H, $J=2.1$ Hz). IR (KBr) ν: 3365, 2934, 2861, 1619, 1506, 1461, 1304, 1069, 812, 755. EIMS: m/z: 247 M^+, 194, 150, 136, 91.