An Efficient One-Pot Synthesis of Pyrano- and Furoquinolines Employing Two Reusable Solid Acids as Heterogeneous Catalysts[1]

K. V. N. S. Srinivas, Biswanath Das*

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India.
Fax +91(40)27160512; E-mail: biswanathdas@yahoo.com

Received 30 March 2004

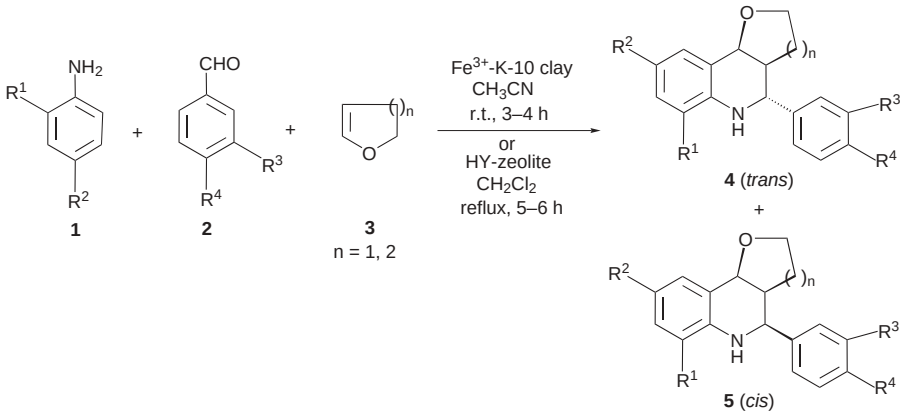
Abstract: Two solid acids, Fe^{3+}-K-10 montmorillonite clay and HY-zeolite have been employed efficiently for single-step synthesis of pyrano- or furoquinolines in high yields and high diastereoselectivities by coupling of three components: anilines, benzaldehydes and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran. Both the heterogeneous catalysts are recoverable and recyclable.

Key words: Pyrano- and furoquinolines, solid acids, multicomponent coupling, diastereoselectivity

Pyranoquinoline derivatives are known to possess various important biological properties such as antiallergic, anti-inflammatory and estrogenic activities.[2] Several bioactive alkaloids contain a pyranoquinoline moiety.[3] Generally the pyranoquinolines are prepared by aza-Diels–Alder reactions of imines (derived from aromatic amines) with 3,4-dihydro-2*H*-pyran. Different Lewis acids are known to catalyze such reactions.[4] However, many of these Lewis acids are not easily available or expensive, non-reusable and afford the mixture of products with unsatisfactory yields. More importantly, several Lewis acids cannot be utilized for single-step coupling of aldehydes, amines and enol ethers because they will be decomposed or deactivated by amines and water formed in the intermediate imine formation step. This may be a reason for the limited number of reported methods for one-pot coupling of these three components, though various methods for multistep coupling are known.[4,5] However, many of the imines are hygroscopic, unstable and difficult to purify and so the process involving the preparation and purification of these imines separately, and subsequent utilization of them for coupling with enol ethers, are not advantageous. The Lewis acid $GdCl_3$, which was used earlier for one-pot preparation of pyranoquinoline derivatives, was also not shown to be reusable.[5] Thus there is a need to develop efficient and economic processes for single step synthesis of pyranoquinolines and related compounds.

In connection with our work on the development of novel synthetic methodologies utilizing the solid acids such as Fe^{3+}-K-10 montmorillonite clay[6a] and HY-zeolite[6b] we have recently observed that these two catalysts can efficiently be employed for one-pot synthesis of pyrano- and furoquinolines by coupling of the three components, anilines (**1**), benzaldehydes (**2**) and 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran (**3**) (Scheme 1).

Different anilines and benzaldehydes were treated with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran to produce a series of pyrano or furoquinolines (Table 1). Fe^{3+}-K-10 clay catalyzed the reaction at room temperature while HY-zeolite under reflux.[7] The times required for the first catalyst to complete the conversion were shorter (3–4 h) than those required for the second catalyst (5–6 h). The products (**4** and **5**) were obtained in high yield and high diastereoselectivities. These were the mixture of *trans*-



Scheme 1

SYNLETT 2004, No. 10, pp 1715–1718
Advanced online publication: 15.07.2004
DOI: 10.1055/s-2004-829576; Art ID: D08104ST

and *cis*-isomers that could be separated by column chromatography over silica gel. The *trans*-isomer (**4**) was the major and *cis*-isomer (**5**) minor in each conversion. The ratio of the isomers produced in a reaction was determined by ^{1}H NMR spectrum of the crude product and the structures of the products were established from the spectral (^{1}H NMR and MS) data of the pure compounds.[7] Previously the cycloaddition of *N*-benzylidiene aniline with vinyl ethers in the presence of Fe^{3+}-K-10 clay was reported[4c] to form two products, one formed by [4+2] addition and the other by [2+2] addition. Here we could not get any product derived by [2+2] addition of 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran with the intermediate imines.

Table 1 Preparation of Pyrano- and Furoquinolines Using Solid Acids Fe^{3+}-K-10 Clay and HY-Zeolite[a]

Entry	Aniline (**1**)		Benzaldehyde (**2**)		Olefin (**3**)	Catalyst[b]	Time (h)	Isolated yield (%)	Product ratio[c] (**4**:**5**)
	R^1	R^2	R^3	R^4	n				
a	H	H	H	H	2	i	3.5	86	84:16
						ii	5.0	82	87:13
b	H	H	H	OMe	2	i	4.0	90	91:09
						ii	5.5	85	88:12
c	H	H	H	Cl	2	i	3.0	91	92:08
						ii	5.0	86	89:11
d	H	H	OCH_2O		2	i	4.0	89	85:15
						ii	5.5	83	84:16
e	H	H	Cl	Cl	2	i	3.0	92	90:10
						ii	5.0	88	87:13
f	H	Cl	H	H	2	i	3.5	86	85:15
						ii	5.5	84	86:14
g	H	Me	H	H	2	i	3.5	89	90:10
						ii	5.0	81	87:12
h	H	Me	H	Cl	2	i	4.0	88	83:17
						ii	6.0	83	79:21
i	H	OMe	H	H	2	i	4.0	85	80:20
						ii	5.5	81	78:22
j	Me	H	H	H	2	i	4.0	76	74:26
						ii	6.0	73	77:23
k	H	H	H	H	1	i	3.5	84	82:18
						ii	5.5	79	84:16
l	H	H	H	OMe	1	i	4.0	91	89:11
						ii	5.5	83	83:17
m	H	H	H	Cl	1	i	3.0	85	84:16
						ii	5.0	82	87:13
n	H	H	Cl	Cl	1	i	3.0	88	89:11
						ii	5.5	86	85:15
o	H	Me	H	H	1	i	3.5	87	88:12

Table 1 Preparation of Pyrano- and Furoquinolines Using Solid Acids Fe^{3+}-K-10 Clay and HY-Zeolite[a] (continued)

Entry	Aniline (**1**)		Benzaldehyde (**2**)		Olefin (**3**)	Catalyst[b]	Time (h)	Isolated yield (%)	Product ratio[c] (**4**:**5**)
	R^1	R^2	R^3	R^4	n				
						ii	5.5	82	92:08
p	H	Me	H	Cl	1	i	4.0	84	80:20
						ii	6.0	78	83:17
q	H	OMe	H	H	1	i	4.0	81	78:22
						ii	5.5	77	79:21
r	Me	H	H	H	1	i	4.0	74	76:24
						ii	6.0	71	75:25

[a] All the products were characterized from their spectral (^{1}H NMR and MS) data.
[b] Catalyst: (i) Fe^{3+}-K-10 clay, (ii) HY-zeolite.
[c] Product ratio was determined from the ^{1}H NMR spectrum of the crude product.

In the present protocol the imines generated in situ by condensation of anilines and benzaldehydes act as heterodienes, which undergo aza-Diels–Alder reaction with 3,4-dihydro-2*H*-pyran or 2,3-dihydrofuran in the presence of Fe^{3+}-K-10 clay or HY-zeolite to form the corresponding pyrano- or furoquinolines. The synthesis could not be achieved in absence of any of these catalysts.

The catalysts, Fe^{3+}-K-10 montmorillonite clay and HY-zeolite work under heterogeneous conditions. In recent years, heterogeneous catalysts are gaining more importance due to environmental and economic considerations. The first catalyst can easily be prepared[8] from the readily available and inexpensive $FeCl_3$ and K-10 montmorillonite clay while the second catalyst is commercially available.[7] Both, the catalysts can safely be handled. They can be recovered and reused for at least three times without loosing their activity.

In conclusion, we have developed a very simple and efficient method for one-step synthesis of pyrano- and furoquinolines by coupling of the three components, anilines, benzaldehydes and dihydropyran or furan catalyzed by two recyclable solid acids, Fe^{3+}-K-10 clay and HY-zeolite. The quinoline derivatives were formed in high yields and high diastereoselectivities. The method is associated with the benefits derived from both multicomponent coupling and the utilization of heterocyclic recyclable catalysts. We feel the present protocol will find important applications for the synthesis of pyrano- and furoquinolines.

Acknowledgment

The authors thank CSIR, New Delhi and IICT for financial assistance.

References

(1) Part 41 in the series ‘Studies on Novel Synthetic Methodologies’.
(2) (a) Faber, K.; Stueckler, H.; Kappe, T. *J. Heterocycl. Chem.* **1984**, *21*, 1171. (b) Johnson, J. V.; Rauckman, S.; Beccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942. (c) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umeza, K. *Biochem. Pharmacol.* **1992**, *44*, 1211.
(3) Ramesh, M.; Mohan, P. S.; Shanmugam, P. *Tetrahedron* **1984**, *40*, 4041.
(4) (a) Boger, D. L.; Weinreb, S. M. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, **1987**, Chap. 2 and 9. (b) Boger, D. L.; Weinreb, S. M. *Hetero-Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, **1987**, Chap. 9. (c) Cabral, J.; Laszlo, P.; Montaufier, M. T. *Tetrahedron Lett.* **1988**, *29*, 547. (d) Weinreb, S. M. In *Comprehensive Organic Synthesis*, Vol. 5; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 401–449. (e) Babu, G.; Perumal, P. T. *Tetrahedron Lett.* **1998**, *39*, 3225. (f) Yadav, J. S.; Reddy, B. V. S.; Srinivas, R.; Madhuri, Ch.; Ramalingam, T. *Synlett* **2001**, 240.
(5) Ma, Y.; Qian, C.; Xie, M.; Sun, J. *J. Org. Chem.* **1999**, *64*, 6462.
(6) (a) Srinivas, K. V. N. S.; Das, B. *J. Org. Chem.* **2003**, *68*, 1165. (b) Srinivas, K. V. N. S.; Reddy, E. B.; Das, B. *Synlett* **2002**, 625.
(7) **General Procedure for the Preparation of Pyrano- and Furoquinolines:** To a solution of aniline (1 mmol), benzaldehyde (1 mmol) and 3,4-dihydro-2*H*-Pyran or 2,3-dihydrofuran (0.1 mL) in MeCN or CH_2Cl_2 (10 mL) Fe^{3+}-K-10 clay or HY-zeolite (PQ Corporation, USA; 100 mg) was added. The mixture was stirred at r.t. with the first catalyst but refluxed with the second catalyst under N_2 atmosphere. The reaction was monitored by TLC. After completion of the reaction, the mixture was filtered. The concentrated filtrate was subjected to column chromatography over silica gel and the column was eluted with hexane–EtOAc (20:1) to afford the pyrano- or furoquinolines. Both the catalyst, Fe^{3+}-K-10 clay and HY-zeolite were recovered by washing the residue of filtration with MeCN and CH_2Cl_2, respectively, activated and recycled.
All the prepared compounds are known. The spectral data of some representative pyrano and furoquinolines are given below.

4b: solid, mp 146–147 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 (2 H, d, *J* = 8.0 Hz), 7.18 (1 H, d, *J* = 8.0 Hz), 7.04 (1 H, t, *J* = 8.0 Hz), 6.84 (2 H, d, *J* = 8.0 Hz), 6.64 (1 H, t, *J* = 8.0 Hz), 6.45 (1 H, d, *J* = 8.0 Hz), 4.64 (1 H, d, *J* = 10.0 Hz), 4.36 (1 H, d, *J* = 2.5 Hz), 4.06 (1 H, m), 3.97 (1 H, d, *J* = 3.0 Hz), 3.82 (3 H, s), 3.63 (1 H, t, *J* = 10.0 Hz), 2.02 (1 H, m), 1.82 (1 H, m), 1.64 (1 H, m), 1.44 (1 H, m), 1.28 (1 H, m). MS–FAB: *m/z* = 296 [M^+ + 1].

5b: solid, mp 154–155 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 (1 H, d, *J* = 8.0 Hz), 7.30 (2 H, d, *J* = 8.0 Hz), 7.00 (1 H, m), 6.82 (2 H, d, *J* = 8.0 Hz), 6.77 (1 H, t, *J* = 8.0 Hz), 6.50 (1 H, d, *J* = 8.0 Hz), 5.26 (1 H, d, *J* = 3.0 Hz), 4.60 (1 H, d, *J* = 3.0 Hz), 3.84 (1 H, m), 3.82 (3 H, s), 3.58 (1 H, m), 3.22 (1 H, m), 2.04 (1 H, m), 1.58–1.30 (4 H, m). MS–FAB: *m/z* = 296 [M^+ + 1].

4c: semi-solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32 (4 H, s), 7.16 (1 H, d, *J* = 8.0 Hz), 7.04 (1 H, t, *J* = 8.0 Hz), 6.68 (1 H, t, *J* = 8.0 Hz), 6.48 (1 H, d, *J* = 8.0 Hz), 4.67 (1 H, d, *J* = 10.0 Hz), 4.92 (1 H, d, *J* = 2.5 Hz), 4.05 (1 H, m), 3.95 (1 H, br s), 3.68 (1 H, t, *J* = 10.0 Hz), 2.01 (1 H, m), 1.80 (1 H, m), 1.63 (1 H, m), 1.44 (1 H, m), 1.22 (1 H, m). MS–FAB: *m/z* = 300 [M^+ + 1].

5c: viscous. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 (1 H, d, *J* = 8.0 Hz), 7.35 (4 H, s), 7.02 (1 H, t, *J* = 8.0 Hz), 6.74 (1 H, d, *J* = 8.0 Hz), 6.53 (1 H, d, *J* = 8.0 Hz), 5.24 (1 H, d, *J* = 8.0 Hz), 4.65 (1 H, d, *J* = 2.5 Hz), 3.72 (1 H, m), 3.55 (1 H, m), 3.40 (1 H, m), 2.08 (1 H, m), 1.57–1.32 (4 H, m). MS–FAB: *m/z* = 300 [M^+ + 1].

4d: solid, mp 152–153 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18 (1 H, d, *J* = 8.0 Hz), 7.04 (1 H, t, *J* = 8.0 Hz), 6.92 (1 H, d, *J* = 2.5 Hz), 6.84–6.62 (3 H, m), 6.46 (1 H, d, *J* = 8.0 Hz), 5.96 (2 H, s), 4.62 (1 H, d, *J* = 10.0 Hz), 4.36 (1 H, d, *J* = 3.5 Hz), 4.10 (1 H, m), 3.98 (1 H, br s), 3.70 (1 H, m), 2.02 (1 H, m), 1.85–1.22 (4 H, m). MS–FAB: *m/z* = 310 [M^+ + 1].

5d: solid, mp 160–161 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 (1 H, d, *J* = 8.0 Hz), 7.04 (1 H, t, *J* = 8.0 Hz), 6.92–6.76 (4 H, m), 6.56 (1 H, d, *J* = 8.0 Hz), 5.96 (2 H, s), 5.24 (1 H, d, *J* = 6.0 Hz), 4.60 (1 H, d, *J* = 3.0 Hz), 3.78 (1 H, br s), 3.60–3.38 (2 H, m), 2.05 (1 H, m), 1.60–1.38 (4 H, m). MS–FAB: *m/z* = 310 [M^+ + 1].

4m: solid, mp 147–148 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35 (4 H, s), 7.14 (1 H, d, *J* = 8.0 Hz), 7.05 (1 H, t, *J* = 8.0 Hz), 6.64 (1 H, d, *J* = 8.0 Hz), 6.42 (1 H, d, *J* = 8.0 Hz), 4.58 (1 H, d, *J* = 5.0 Hz), 4.08 (1 H, m), 3.85–3.42 (3 H, m), 2.45 (1 H, m), 2.00 (1 H, m), 1.72 (1 H, m). MS–FAB: *m/z* = 286 [M^+ + 1].

5m: solid, mp 152–153 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (1 H, d, *J* = 8.0 Hz), 7.36 (4 H, s), 7.05 (1 H, t, *J* = 8.0 Hz), 6.68 (1 H, t, *J* = 8.0 Hz), 5.25 (1 H, d, *J* = 8.0 Hz), 4.65 (1 H, d, *J* = 3.0 Hz), 3.78 (1 H, br s), 3.62–3.40 (2 H, m), 2.18 (1 H, m), 1.62–1.50 (2 H, m). MS–FAB: *m/z* = 286 [M^+ + 1].

(8) Laszlo, P.; Mathy, A. *Helv. Chim. Acta* **1987**, *70*, 557.