An Efficient One-Pot Synthesis of Polyhydroquinolines at Room Temperature Using HY-Zeolite[1]

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An efficient one-pot synthesis of polyhydroquinolines by four-component coupling reactions of aldehydes, ethyl acetoacetate, dimedone and ammonium acetate in the presence of HY-zeolite at ambient temperature has been achieved. The conversions took shorter times to form the products in excellent yields. HY-zeolite can be recovered and reused.

Key words polyhydroquinoline; four-component coupling; one-pot conversion; HY-zeolite; heterogeneous catalyst

In recent years heterogeneous catalysts have attracted a great attention due to efficiency, economic and environmental considerations. HY-zeolite is an important heterogeneous catalyst used in various chemical transformations, such as liquid phase acylation of amines,[2] direct conversion of aldehydes into nitriles and ketones into amides,[3] selective removal of N-Boc protecting group from aromatic amines[4] and one-pot synthesis of 2,3-dihydro-2,2-dimethylbenzofurans.[5] Thus the remarkable catalytic activity together with easy availability, operational simplicity and recoverability of HY-zeolite encouraged us to utilize this catalyst for the synthesis of polyhydroquinolines having 1,4-dihydropyridine moiety.

1,4-Dihydropyridines exhibit a variety of biological properties. They can cure the disordered heart ratio as a chain-cutting agent of factor IV channel and also possess the calcium channel agonist-antagonist modulation activities.[6—8] These compounds also behave as neuroprotectants, cerebral antiischaemic agents and chemosensitizers.[9,10]

1,4-Dihydropyridines were synthesized more than a century ago by Hantzsch by heating a mixture of an aldehyde, a β-ketoester and ammonia in ethanol under reflux for several hours.[11] Different other heating approaches for the syntheses of polyhydroquinoline derivatives have subsequently been reported.[12—16] However, these methods require drastic reaction conditions and long reaction times. Recently microwave irradiation has also been applied for the preparation of polyhydroquinolines.[17] Yb(OTf)$_3$[18] or iodine[19] have been found to catalyze the Hantzsch reaction at ambient temperature but using the first catalyst the times required for the conversions were 2—8 h while using the second catalyst at room temperature the time of conversions was 1.5—6 h. The second catalyst should also properly be removed from the reaction mixture during work-up.

In continuation of our work[20—24] on the applications of heterogeneous catalysts on organic transformations we report here a convenient and efficient method for the synthesis of polyhydroquinolines (containing 1,4-dihydropyridine moiety) using HY-zeolite as a catalyst. Four-component coupling reactions of aldehydes, ethyl acetoacetate, dimedone and ammonium acetate were carried out using this catalyst at room temperature (Chart 1).

A series of polyhydroquinoline derivatives were prepared following the above method using various aldehydes (Table 1). Both aromatic and aliphatic aldehydes underwent the conversion smoothly. Aromatic aldehydes containing electron donating as well as electron withdrawing groups worked well. The aryl moiety having different groups or the same group at different positions did not show much differences in the yields of the products. Heterocyclic aldehyde like furfural also underwent the facile transformation. The polyhydroquinoline derivatives were formed within 2.0—2.5 h at room temperature in excellent yields (87—93%). In absence of the catalyst no product could be detected within 3 h at room temperature under the present experimental conditions. The present catalyst can conveniently be handled and removed from the reaction mixture. Moreover, it can be recovered and reused for at least three times without loss of its activity.

In conclusion, we have developed a convenient and efficient protocol for one-pot synthesis of polyhydroquinolines by four-component coupling reactions of aldehydes, ethyl acetoacetate, dimedone and ammonium acetate in the presence of HY-zeolite as a catalyst. The method is associated with several advantages such as simple experimental procedure (column chromatography), utilization of a heterogeneous catalyst, milder conditions, short reaction times, excellent yields and reusability of the catalyst. We feel the method will find important applications for the synthesis of polyhydroquinolines.

Experimental

To a mixture of an aldehyde (1 mmol), ethyl acetoacetate (1 mmol), dimedone (1 mmol) and NH_4OAc (1.5 mmol) in CH_3CN (10 ml) was added HY-zeolite (100 mg) (PQ Corporation, U.S.A.). The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the mixture was filtered and the catalyst was recovered from the residue by washing with EtOAc (3×10 ml) and was subsequently activated by heating at 80 °C for 12 h for recyclization. CH_3CN was removed from the above filtrate and water (10 ml) was added. The mixture was extracted with EtOAc (3×10 ml) and the extract was concentrated. The solid mass was subjected to column chromatography over silica gel using 30% EtOAc in hexane as eluent to obtain pure polyhydroquinone derivative. The structures of all the products (which are known compounds)[12,16,18,25] were established from their spectral (IR, ^{1}H-NMR and MS) data.

The recovered HY-zeolite was utilized consecutively three times for the reaction of benzaldehyde, ethyl acetoacetate, dimedone and ammonium acetate (Table 1, entry 1) following the above procedure to produce the corresponding polyhydroquinoline with the yields of 90, 89 and 87%.

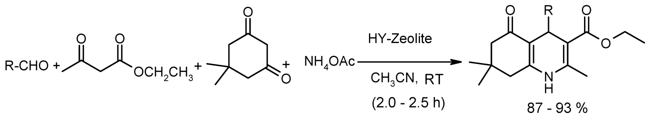

Chart 1

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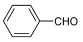
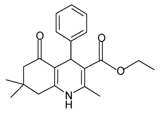
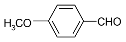
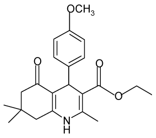
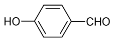
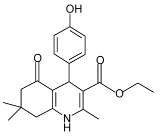
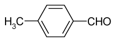
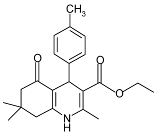
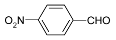
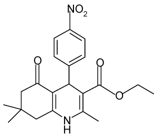
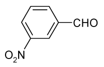
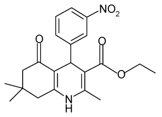
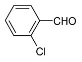
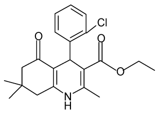
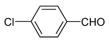
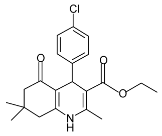
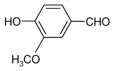
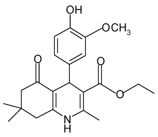
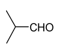
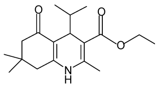
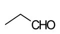
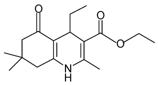
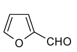
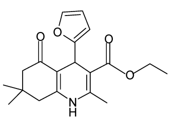
Table 1. Synthesis of Polyhydroquinolines at Room Temperature Using HY-Zeolite[a]

Entry	Aldehyde	Product	Time (h)	Yield (%)[b]	Ref.
1			2.0	93	16
2			2.0	90	16
3			2.25	92	18
4			2.25	90	16
5			2.5	88	16
6			2.5	87	12
7			2.25	90	16
8			2.5	92	16
9			2.0	90	16
10			2.5	88	25
11			2.5	90	18
12			2.25	90	18

[a] The structures of the products were established from their spectral (IR, ^{1}H-NMR and MS) data. [b] Yields are given for isolated products.

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References and Notes

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