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Antimony chloride doped on hydroxyapetite catalyzed stereoselective one-pot synthesis of pyrano[3,2-*c*]quinolines

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Abstract—Antimony chloride doped on hydroxyapetite ($SbCl_3$–HAP) has been shown to be an efficient catalyst for the one-pot stereoselective synthesis of *trans*-pyrano[3,2-*c*]quinolines from anilines, benzaldehydes and 3,4-dihydro-2*H*-pyran (DHP). The catalyst was recoverable and reusable.

Substituted tetrahydroquinolines constitute an important class of natural products possessing biological activities such as psychotropic,[1] antiallergenic,[2] anti-inflammatory,[3] anti-arrhythmic,[4] immunosupressive[5] and anticancer properties.[6] An easy way to construct nitrogen-containing six-membered heterocyclic compounds is via the aza-Diels–Alder reaction between *N*-aryl imines and nucleophilic olefins. Various Lewis acid catalysts such as BF_3OEt_2,[7] $InCl_3$,[8] $GdCl_3$[9] and $ZrCl_4$,[10] and transition metal complexes such as $Co_2(CO)_8$ and $Ni(CO)_4$[11] have been used for this purpose.

Antimony(III) chloride has been used catalytically in various organic reactions as an efficient Lewis acid.[12] Hydroxyapatite [HAP, $Ca_{10}(PO_4)_6(OH)_2$], the main component of bones and teeth, has ion-exchange ability, adsorption capacity, acid–base properties, and provides a support due to its capability of accommodating various kinds of metal cations into its framework.[13] HAP is recyclable and inert and so any side reactions which might be induced by the support itself are minimal. Metal ions impregnated on solid supports offer several advantages in preparative procedures, such as simple work-up, easy handling, mild reaction conditions, cleaner products, enhanced selectivity, reduction in by-products and the waste produced and much improved reaction rates. In our ongoing pursuits[14] to explore the uses of $SbCl_3$ as a Lewis acid catalyst in organic synthesis, we wished to employ $SbCl_3$–HAP to effect the reaction between anilines, benzaldehydes and 3,4-dihydro-2*H*-pyran (DHP) in one-pot to construct tetrahydroquinolines.

A mixture of benzylideneaniline (10 mmol) and DHP (14 mmol) was refluxed in acetonitrile in the presence of $SbCl_3$–HAP (1.6 mol %)[15] with stirring under N_2. The formation of a new product was noticed in 2 h which was isolated in 85% yield by column chromatography over silica gel. This compound was found to be *trans*-5-phenyl-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano-[3,2-*c*]quinoline as revealed by the comparison of its spectral and physical data with that of an authentic sample.[10] The product displayed the most diagnostic ^1H NMR feature for structural assignment, that is a coupling constant $J\,(4a,5) = 10.8$ Hz, indicative of a trans disposition of protons H-4a and H-5. The most significant and notable feature of the present reaction is the formation of a single trans isomer in contrast to the earlier observations[8–10] where the formation of a mixture of cis and trans (H-4a and H-5) products was noticed. Benzylideneaniline is available commercially so its direct usage is feasible. For other imines which are not available commercially, two step reactions would be required for the formation of tetrahydroquinolines. First, the synthesis of imines from anilines and benzaldehydes and second, the imino-Diels–Alder reaction. Since most

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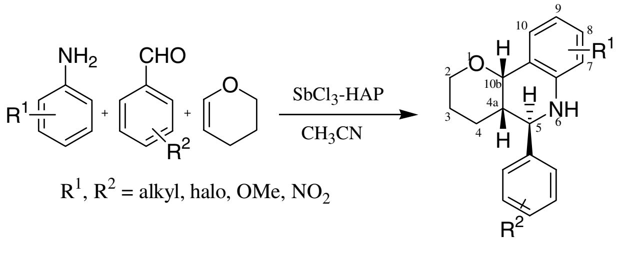
of the imines are hygroscopic in nature and decompose at high temperature, they are difficult to purify by distillation or column chromatography and therefore we contemplated performing both imine formation and Diels–Alder reaction with DHP in the presence of $SbCl_3$–HAP in one-pot. Benzaldehyde (10 mmol), aniline (10 mmol) and $SbCl_3$–HAP (1.6 mol %, 3.1 g) were refluxed in dry acetonitrile in the presence of 4 Å molecular sieves with stirring under N_2. Complete formation of benzylideneaniline was observed in 30 min and at this point DHP (14 mmol) was added and the reaction mixture was heated at reflux. To our delight, the imino-Diels–Alder reaction was completed in 2 h resulting in the formation of trans product as described in Scheme 1.

In another set of experiments, the reaction was carried out with $SbCl_3$ alone and with $SbCl_3$–Al_2O_3,[14] when the formation of both cis and trans stereoisomers was observed (Table 1). The reaction did not occur with HAP alone in refluxing acetonitrile, even after 10 h. However since the use of $SbCl_3$–HAP resulted in the formation of only the trans isomer, it follows that HAP probably plays some role in the stereochemical outcome of the reaction. The mechanism of the reaction seems to be $SbCl_3$–HAP catalyzed formation of imine followed by imino-Diels–Alder reaction.

A notable feature of the $SbCl_3$–HAP catalyst is its reusability. The catalyst was recovered and used ten times for the reaction between *p*-tolualdehyde, *o*-toluidine and DHP without any significant decrease in its efficiency as shown in Figure 1. Substituted anilines and benzaldehydes have also been used and the results are shown in Table 2.

In summary, we have shown that $SbCl_3$–HAP is an efficient catalyst for both the imino-Diels–Alder reaction between imines and DHP and the three component one-pot reaction of araldehydes, anilines and DHP to afford only the *trans*-pyrano[3,2-*c*]quinolines in good yields. The catalyst has also been shown to be recoverable and reusable.



Scheme 1. Three-component reaction sequence.

Table 1. Comparison of results with $SbCl_3$ and $SbCl_3$–Al_2O_3

Entry	Substituents		Catalyst	Time (h)	**4a,5** *trans/cis*	Overall yield (%)
	R^1	R^2				
1	2-CH_3	4-CH_3	$SbCl_3$	5.0	53:47	62
2	2-CH_3	4-CH_3	$SbCl_3$–Al_2O_3	4.5	65:35	70
3	2-CH_3	4-CH_3	$SbCl_3$–HAP	3.5	100:0	83

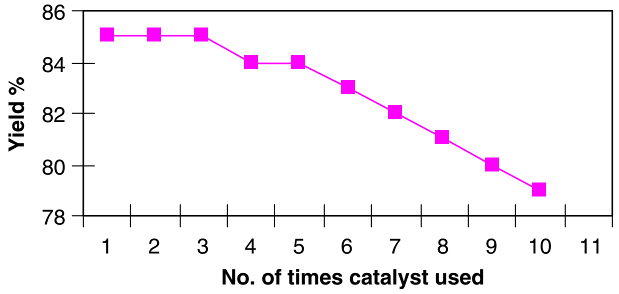


Figure 1. Results of recycling the catalyst.

Table 2. $SbCl_3$–HAP catalyzed one pot stereoselective aza-Diels–Alder reaction

Entry	Substituents		Products **3**	Time (h)	Yield[a] (%)	Melting point[b] (°C)
	R^1	R^2				
1	H	H	**a**	2.5	85	Oil
2	H	4-Cl	**b**	2.5	83	122
3	2-CH_3	4-CH_3	**c**	3.5	83	125
4	4-F	H	**d**	3.0	82	Oil
5	4-Br	H	**e**	3.5	80	Oil
6	4-OCH_3	H	**f**	2.0	82	98–100
7	4-CH_3	H	**g**	3.0	82	Oil
8	H	4-NO_2	**h**	2.5	82	169–170
9	2-CH_3	H	**i**	3.0	81	130–132

[a] Isolated yields.

[b] Melting points are uncorrected.

General procedure: A mixture of the appropriate benzaldehyde (10 mmol), aniline (10 mmol) and $SbCl_3$–HAP (1.6 mol %, 3.1 g) was refluxed in acetonitrile (20 mL) under nitrogen for about 30–60 min till the formation of imine was complete (TLC). The reaction mixture was cooled, DHP (14 mmol) was added to it and then refluxed for another 1.5–3.0 h till the completion of the reaction (TLC). Acetonitrile was distilled off under reduced pressure, the reaction mixture was diluted with ethyl acetate (70 mL) and filtered. The filtrate was washed with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue was added to a small silica gel (60–120 mesh) column and eluted with 8:2 mixtures of petroleum ether and ethyl acetate to afford pure *trans*-pyrano[3,2-*c*]quinolines (81–85%). The spectral data of all the known compounds were found to be identical with those of the authentic samples.[10,11]

The product **3c** *trans*-7-methyl-5-(*p*-tolyl)-3,4,4a,5,6,10b-hexahydro-2*H*-pyrano[3,2-*c*]quinoline has the following physical and spectral data.

White crystalline; mp: 125 °C. IR, ν_{max}/cm^{-1} (KBr): 3396, 2950, 1610, 1515, 1475. ^1H NMR: ($CDCl_3$, 400 MHz) δ 1.33 (1H, m), 1.48 (1H, m), 1.65 (1H, m), 1.86 (1H, m), 2.04 (3H, s), 2.08 (1H, m), 2.38 (3H, s), 3.73 (1H, dt, $J = 11.6$, 2.4 Hz), 3.86 (1H, br s), 4.10 (1H, td, $J = 11.2$, 2.2 Hz), 4.40 (1H, d, $J = 2.4$ Hz), 4.74 (1H, d, $J = 10.8$ Hz), 6.65 (1H, t, $J = 7.2$ Hz), 7.00 (1H, d, $J = 7.2$ Hz), 7.12 (1H, d, $J = 7.2$ Hz), 7.20 (2H, d, $J = 8.0$ Hz), 7.35 (2H, d, $J = 8.0$ Hz). ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 17.2, 21.2, 22.0, 24.1, 38.8, 54.5, 68.8, 75.0, 116.8, 120.0, 121.1, 127.8, 128.8, 129.3, 130.2, 137.6, 139.6, 142.8 HRMS (EI): m/z at 293.4026 (M^+) (calcd for $C_{20}H_{23}NO$, 293.4028).

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15. *Preparation of the catalyst*: To an antimony(III) chloride (2.28 g, 10 mmol) solution in 100 mL of distilled water was added 60 g of hydroxyapatite powder. The mixture was stirred at room temperature for 5 h followed by the removal of water under reduced pressure. The resultant free flowing powder was then activated at 110 °C in an oven for 2 h and was used throughout the experimentation. Ganai, B. A. Ph.D. Thesis December **2005**, University of Jammu, Jammu 180 006, India.