800 **RESEARCH PAPER** DECEMBER, 800–801 JOURNAL OF CHEMICAL RESEARCH 2005

Synthesis of enamines using easily prepared silica gel supported sulfuric acid catalyst

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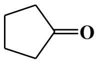
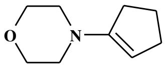
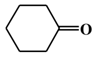
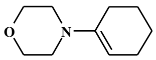
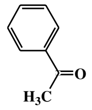
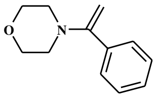
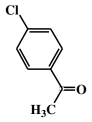
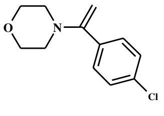
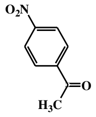
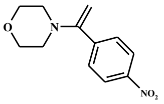
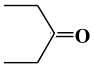
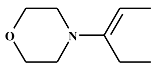
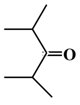
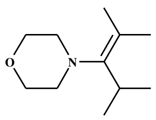
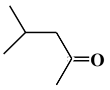
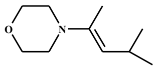
A variety of enamines are easily and efficiently synthesised in short reaction times and moderate to high yields from corresponding acyclic and cyclic ketones using sulfuric acid–silica catalyst.

Keywords: enamines, morpholine, sulfuric acid–silica gel catalyst, supported reagents

There are several methods for the preparation of enamines,[1-10] all of them have merits and drawbacks. Disadvantages include that they are conducted in benzene as a solvent, an acidic catalyst such as *para*-toluene sulfonic acid,[1] Dowex-50,[2] montmorinollite K10 clay,[3] $BF_3.OEt_2$[4] or acetic acid[5] and a water adsorbing agent in the category of calcium carbide,[6] magnesium sulfate,[7] calcium hydride[8] or/and molecular sieves.[9] Also there are: difficulties for the removal of produced water in the reaction media, long reaction times, good yields only for cyclopentanone and cyclohexanone enamines, low to moderate yields for acyclic and large size ring systems, and using water adsorbing agents in azeotropic solvent system. Heterogeneous organic reactions have proven useful both in the laboratory and in industry. In these reactions, the reagents are supported on porous solids. The advantages of such procedures over conventional solution phase reactions result from good dispersion of active reagent sites, associated selectivity, and easier work-up. The recyclability of some of the solid supports renders the processes truly eco-friendly. In view of the current trust on synthesis using silica gel[11] and the emphasis on green chemistry,[12] there is merit in developing an easy and eco-friendly method for the preparation of

Table 1 Comparison of the reaction times and yields in the presence and absence of sulfuric acid/silica gel catalyst

Entry	Ketone	Enamine	R.T/Cata./min[a]	Yield/Cata./%[b]	R.T/hours[c]	Yield/%[d]
1			25	87	5	80–90
2			50	76	8	85
3			75	53	No reaction	0
4			55	61	–	–
5			50	69	–	–
6			90	45	175	22
7			120	37	250	65
8			150	33	–	–

[a]R.T/Cata.(min): reaction times in the presence of sulfuric acid/silica gel catalyst;
[b]Yield/Cata.(%): reaction yields in the presence of sulfuric acid/silica gel catalyst;
[c]R.T(h.): reaction times in the absence of sulfuric acid/silica gel catalyst (ref.10b);
[d]Yield (%): reaction yields in the absence of sulfuric acid/silica gel catalyst(ref.10b).

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enamines using inexpensive, commercially available starting materials and non-polluting catalysts. Condensation of secondary amines with ketones is the most common method employed for the synthesis of enamines. Usually, it is executed in benzene and requiring warming or even reflux in most cases. In continuation of our experiments for the developing of organic reactions in easy and eco-friendly routes,[13] we re-examined this procedure using sulfuric acid–silica gel catalyst for the preparation of enamines.

Results and discussion

The ability of sulfuric acid–silica gel catalyst to facilitate the reaction of various cyclic and acyclic ketones with morpholine was demonstrated, and the resulting data summarised in Table 1. From Table 1, it is understood that the excellent yields referred to cyclic and low yields referred to acyclic ketones respectively. In order to evaluate the influence of catalyst, the reaction of selected ketones and morpholine were re-examined without catalyst. However, the reaction times are long and acetophenone remained unchanged after long reaction times. (Table 1).

To examine the effects of various acid/silica gel ratio in the reaction times and yields, we used different ratio of acid/silica gel catalyst for the synthesis of enamine derived from the reaction of cyclohexanone and morpholine (Table 2). As indicated, the best ratio of acid/silica gel catalyst found to be 25/100 part by weight respectively. Use of excess reagent affected neither the reaction yields nor the reaction times.

The other important observation is the best ratio of substrate/catalyst that was found to be 1/1 weight by weight respectively. Use of excess catalyst affected neither the yields nor the reaction times (Table 3).

Therefore, this methodology can be used for the preparation of enamines derived from a wide variety of cyclic, acyclic ketones and secondary amines. To the best of our knowledge this is the first example of sulfuric acid/silica gel catalysis of this reaction.

Experimental

All ketones, morpholine, Merck No. 10757, 60F254 silica gel, sulfuric acid and solvents were purchased from Merck Company.

Table 2 Effects of various acid/silica gel ratio in the yields and reaction times of 4-(cyclohex-1-en-1-yl)morpholine formation

Acid/silica gel ratio(g/g)[a]	Yields (%) of 4-(cyclohex-1-en-1-yl)morpholine	Reaction times/min
1/20	43	85
3/20	59	65
5/20	76	50
10/20	75	50

[a]Calculated catalyst percents are: 1/20(5%),3/20(15%),5/20(25%), 10/20(50%).

Table 3 Effects of various substrate / 25% catalyst ratio in the yields and reaction times of 4-(cyclohex-1-en-1-yl)morpholine formation

Weight ratio of catalyst/5g cyclohexanone	Yields (%) of 4-(cyclohex-1-en-1-yl)morpholine	Reaction times/min
1	51	75
3	68	60
5	76	50
7	77	50

All products are known and were characterised by comparison of their physical and spectroscopic data with those of authentic samples. ^1H NMR and ^{13}C NMR structure confirmation was obtained using a Bruker-spectrospin 300 MHz, FT–IR spectra was obtained using a Bomem MB-100 instrument and found to be comparable with those reported. The reaction was followed by TLC and examination *i.e.* disappearance of C=O signals of ketones.

Sulfuric acid/silica gel catalyst preparation

Merck No. 10757, $60F_{254}$ silica gel was dried in an oven at 110°C for 48 h. The dewatered silica gel (20 g) was poured into CH_3OH (50 ml) and agitated using a stirrer at room temperature for 30 min and 98% sulfuric acid (5 g in 20 ml CH_3OH) was added to the reaction mixture. After 30 min the removing of CH_3OH by distillation yields sulfuric acid–silica gel catalyst (25% w/w acid/silica gel respectively).

Preparation of cyclopentyl-1-morpholine: general procedure

An appropriate amount of cyclopentanone (4.2 g, 50 mmol), morpholine (8.6 g, 100 mmol), sulfuric acid-silica gel catalyst (25% w/w acid/silica gel respectively) and toluene (25 ml) were stirred at reflux temperature. After 25 min the reaction was stopped, the mixture was filtered to remove the catalyst, the water and toluene were distilled and appropriate brown liquid enamine (6.65 g, 43 mmol, 87% yield, b.p. 107–110 °C at 12 mmHg) was obtained after distillation from the mixture.

Received 11 June 2005; accepted 8 July 2005
Paper 05/3293

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