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Eco-friendly Synthesis of benzopyran Derivatives by Using Greener Catalysts

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ABSTRACT

A protocol has been developed for the efficient synthesis of structurally diverse terahydrobenzo[b]pyran via three-componentreactions of dimedone, malanonitrile with various aldehydes and in the presence of gel entrapped NaOH as a catalyst.

Keywords : Gel Entrapped Base Catalyst, terahydrobenzo[b] pyran, recyclability

I. INTRODUCTION

Multicomponent reactions (MCRs) have attracted considerable attention owing to high synthetic efficiency, and, in many cases, the facile construction of novel molecular libraries. These methodologies are of particularly great utility when they lead to the formation of privileged medicinal scaffolds.Tetrahydrobenzo[*b*]pyransare an important class of heterocyclic scaffolds in the field of drugs and pharmaceuticals. These compounds are widely used anti-coagulant, anti-cancer and anti-ancaphylactiaspasmolytic agents.[1-4] In addition, they have been shown to act as cognitive enhancers, for the treatment of neurodegenerative disease, including Huntington's disease, amyotrophic lateral Sclerosis, Alzheimer's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of Schizophrenia and myoclonus.[5, 6] The polyfunctionalizedbenzopyrans are used as cosmetics, pigments and biodegradable agrochemicals.[7] Other than their biological importance, some tetrahydrobenzo[*b*]pyrans have been widely used as photoactive materials.[8]Looking at their importance from pharmacological and industrial point of view, several methods for the multi-component synthesis of tetrahydrobenzo[*b*]pyrans have been reported. These include both homogeneous as well as heterogeneous conditions, catalyzed by Na_2SeO_4, hexadecyldimethylbenzyl ammonium bromide,[9] NaBr,[10] tetra-methyl ammonium hydroxide $(CH_3)_4\ N^+OH^-$,[11] TEBA,[12] KF-montmorillonite,[13] KF-alumina,[14]organocatalysts,[15] acetic acid,[16] diammonium hydrogen phosphate[17]and hexadecyltrimethylammonium bromide.[18]Microwaves[19]and ultrasonic irradiation[20]have also been used to promote the reaction. Although the literature on synthesis of tetrahydrobenzo[*b*]pyrans enjoys a rich array of versatile methodologies, new efficient approaches can be valuable additions to the contemporary arsenal of synthetic strategies.

The concept of gel entrapped base catalysts(GEBCs) combines the advantages of alkali and organic bases with those of heterogeneous supports.[21]These catalysts are prepared by immobilization of alkali or organic bases by entrapping them in an aqueous gel matrix of agar-agar which is a polymer composed of repeating agarobiose units alternating between 3-linked β-D-galactopyranosyl (G) and 4-linked 3, 6-anhydro-α-L-galactopyranosyl (LA) units.The use of GEBCs in organic transformationsabates the amount of bases used and affords easy and efficient separation of products from the catalyst simply by filtration. Often, bases like alkalis absorb moisture when exposed to airand get spoiled. On the contrary, the GEBCs do not absorb moisture on exposure to air and remain intact. They also provide excellent opportunity of recyclability and reusability which is rarely possible using bases alone as catalyst.Further advantages of GEBCs include their ease of handling and being less corrosive.However, despite of their well recognized advantages, there have been only limited and sporadic reports dealing with the use of GEBCs in organic synthesis.[22]

In continuation to our research work devoted to the development of green methodologies for MCRs.[23] we report herein an efficient synthesis oftetrahydrobenzo[*b*]pyransfrom dimedone, malanonitrileand aryl aldehydes in the presence of Gel entrapped NaOH as a catalyst.

Results and Discussion

We focused our initial studies on synthesis of Gel entrapped NaOH (acronymed as GENaOH). A series of experiments were under taken in which different concentrations of NaOH (5-25 %) were dissolved in a varying amount of agar-agar in water. After a considerable experimentation, we found that 20 % *w/w* of agar-agar aqua gel containing 10 % NaOH resulted in the formation of soft gel that served as GEBC in the present work. The GENaOH was light yellow jelly like substance that could be cut into pieces .The changes in physical nature of GENaOH were studied in different solvents. The GENaOH swelled in water and become soft. The nature of gel remained intactin organic solvents like ethanol, acetone, dichloromethane, toluene and isopropanol.

The TGA analysis of agar-agar and GENaOHare displayed in fig. The TGA profiles shows three different weight losses at different temperatures. The forth weight loss which occure below 150 ^{0}C for GENaOH as well as agar could be due to removal of physisorbed or occluded water. The second step of decomposition which is initial above 240 ^{0}C in both agar-agar as well as GENaOH differed in their amount of respective weight losses (GENaOH ~8%, agar- agar 63.5% could be assigned to thermal decomposition of agar polymer was agar-agar. The decomposition of remaining polymer matrix is accompanied with ~21 % weight loss. Third step in the temperature range of 440-480^{0}C. On the other hand the additional exothermic weight loss centered at 710 ^{0}C is observed and could be assigned the decomposition of carbonates frame if any. The entrappment of NaOH in gel matrix is evidenced by the comparatively large residual weight observed in the TGA profile of GENaOH than that of agar-agar.

In order to assess the catalytic activity of GENaOH inthesynthesis of tetrahydrobenzo[*b*]pyrans**(Scheme 1),** an equimolar mixture of dimedone, malanonitrile and benzaldehyde (5 mmol each) was stirred in the presence of 1 gm of GENaOH in ethanol at ambient temperature till the completion of reaction as monitored by thin layer chromatography. The reaction proceeded efficiently yielding the corresponding tetrahydrobenzo[*b*]pyran in 91% yield in just 5-15minutes. In order to check the generality of this methodology, a series of tetrahydrobenzo[*b*]pyrans were prepared by reaction of dimedone, malanonitrile with various aryl aldehydes.We were gratified to find that with both electron-poor and electron-rich benzaldehydes, the corresponding products were obtained in excellent yields. The reaction of the sterically hindered *o*-nitrobenzaldehydeeven gave higher yields high lightening the general applicability of the protocol. The striking feature of all the reactions was the isolation of products. During the course of the reaction the product precipitates out and can be isolated simply by filtration.The product obtained after sufficient washing with water was found to be practically pure.The identity of all the compounds was ascertained on the basis of IR, ^{1}H NMR,

^{13}C NMR and mass spectroscopy data. The physical and spectroscopic data are in consistent with the proposed structures.

It has been well established that in case of the GEBCs, the reagent trapped in the gel may leach into the solvent. To study the leaching of NaOH in solvent, 1 gmGENaOH was stirred in 5 mL of ethanol at room temperature. The GENaOH was filtered and water (3 mL) was added to the filtrate. The NaOH leached out was determined by titration with 0.1 N succinic acid solution using phenolphthalein as an indicator. The study revealed that only 3.91 % NaOH leached out from gel into ethanol. Using the amount of NaOH same as that leached out, the reaction between dimedone, malanonitrile and benzaldehyde did not gave quantitative yield of the corresponding product. This clearly demonstrated that catalysis was solely due to intact GENaOH rather than leached NaOH.

A proposed mechanism for the formation oftetrahydrobenzo[*b*]pyrans using GENaOH. The mechanism suggests that in step-1 Knoevenagel condensation takes place to form the α-cynocinnamonitrile derivative. In step-2 the active methylene of dimedone react with the electrophilic C=C double ofα-cynocinnamonitrile giving the intermediate 6, which tautomerizes into 7. The latter is then cyclized by nucleophilic attack of the OH group on the cyano (CN) moiety, giving intermediate 8. Finally, the expected product 4 is afforded by tautomerizeation (8-4).

The use of catalyst is especially interesting when it can be used several times. To investigate the possibility of catalyst recycling, the reaction of dimedone, malanonitrile with benzaldehyde using GENaOH in ethanol was carried out. After completion of the reaction, the GENaOH was recovered by simple filtration, washed with ethanol and reused in another reaction with identical substrates. The catalyst could be reused for five runs without noticeable drop in the yield of product.

Experimental

Infrared spectra were recorded on a Perkin-Elmer FTIR spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avon 300 MHz spectrometer using DMSO/$CDCl_3$ as solvent and TMS as internal reference. Mass spectra were recorded on a Shimadzu QP2010 GCMS with an ion source temperature of 280 ^{0}C. The thermal gravimetric analysis (TGA) curves were obtained by using the instrument STA 1500 in the presence of static air at a linear heating rate of 10 °C/min from 25 ° to 1000 °C.Melting points were determined in an open capillary and are uncorrected. All chemicals were obtained from local suppliers and used without further purification.

Preparation of gel entrapped NaOH

To a boiling mixture of agar-agar (20 Mg) in water (60 mL) wasadded a solution of NaOH (10 gm) in water (100 mL). The resultant solution was boiled with stirring for five minutes and cooled in ice bath to yield the desired GENaOH.

General procedure for the multi-component synthesis of tetrahydrobenzo[*b*]pyrans

A mixture of dimedone (5 mmol), malanonirile (5 mmol) and aryl aldehyde (5 mmol) was stirred in the presence of GENaOH (1 gm) in 5 mL of ethanol at ambient temperature till the completion of the reaction as monitored by TLC. The resulting crude product was filtered off, washed with water and recrystallized from ethanol to afford the desired product.

Spectral data of representative compounds

2-Amino-3-cyano-5,6,7,8-tetrahydro-7,7-dimethyl-5-oxo-4-phenyl-4H-benzopyra: IR (KBr): υ 3396, 3323, 3213, 2961, 2199, 1976, 1660, 1371 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05 (s, 3H), 1.12 (s, 3H), 2.21 (d, 1H), 2.22

(d, 1H), 2.44 (s, 2H), 4.39 (s, 1H), 4.50 (s, 2H), 7.17-7.31 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): 27.39, 28.92, 32.13, 35.88, 50.52, 59.03, 113.36, 120.03, 126.92, 127.50, 128.57, 144.78, 158.91, 162.73, 196.05; MS (EI): m/z = 294 (M^+).

Conclusion

We have described a general and highly efficient procedure for the preparation of multi-component synthesis of tetrahydrobenzo[*b*]pyransfromdimedone, malanonitrileand aryl aldehydes in the presence of gel entrappedNaOH. The method offers several significant advantages, such as high conversions, easy handling, clean reaction profile,no energy consumption, high conversions, cost effective short reaction timeandgreen methodology which make it a useful and an attractive addition to the existing methodologies.

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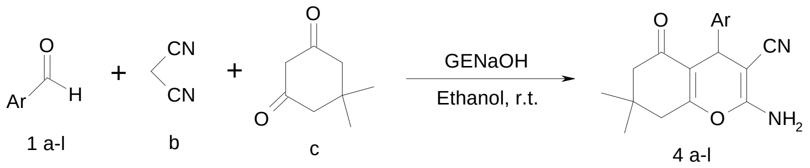

Scheme 1: GENaOH catalyzed multicomponent synthesis of tetrahydrobenzo[b]pyrans

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