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Starch Sulfuric Acid an Effective Catalyst for the Synthesis of Tetrahydroacridinone Derivatives

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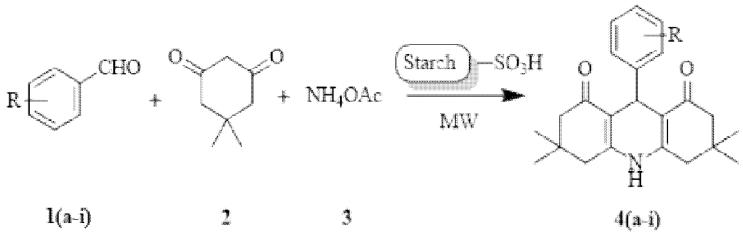
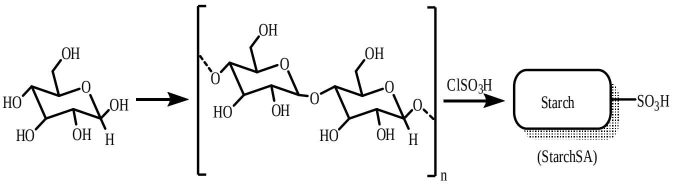
ABSTRACT: Recent developments in 1,4-dihydropyridine chemistry and our continued interest in the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds, prompted us to study the conversion of dimedone into fused 1,4-dihydropyridines in the presence of starch sulfuric acid as heterogeneous catalyst by the reaction of aldehyde (10 mmol), dimedone (10 mmol) and ammonium acetate (10 mmol) in the presence of Starch sulfuric acid (Scheme 1).



Keywords: Starch sulfuric acid; 1,4-dihydropyridines; MW irradiation; Solvent free.

INTRODUCTION: Heterogeneous solid acid catalysts for the synthesis of fine chemicals have attracted considerable attention from both environmental and economical point of view. The solid acids generally have high turnover numbers that can be easily separated from reaction mixtures.1 Replacement of liquid acids with solid acids is desirable in the chemical industry.2,3 Majority of the reports supports for catalytic applications are based on inorganic materials or functional synthetic polymers in which the synthesis of the supports involve high temperature calcinations or polymerization of petrochemical feed stocks.4,5 Recently, the emphasis of science and technology is shifting more towards sustainable resources and processes; in this regard biopolymers are attractive candidates to explore for supported catalysis. Cellulose and starch are the most common biopolymer, their use as supports for catalytic applications were not well explored.4,6.

Carbohydrates are considered as the most abundant molecules of the biomass and have selected two most generous supramolecular carbohydrates: starch molecules, for catalytic activity, because these are very cost-effective, biodegradable, and are obtained from renewable resources. In order to achieve effective catalytic properties, starch was converted to their sulfonic acid derivatives (Fig. 1).

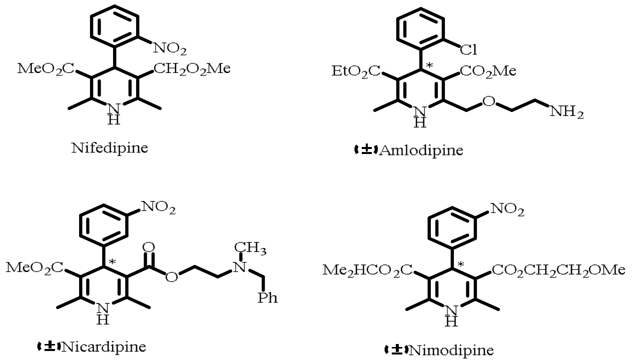


[Figure 1]

4-Aryl-1,4-dihydropyridines (1,4-DHPs) have proved to be valuable as drugs for the treatment of cardiovascular disorders,7 and constitute an important class of calcium channel blockers.8 It is well established that slight structural modification on the DHP ring may result in remarkable change of pharmacological effect.9-12 With a 1,4-DHP parent nucleus, acridine-1,8-diones have been shown to have very high lasing efficiencies13 and used as photoinitiators.14 Many acridinediones have been synthesized by the reactions of aldehydes with two equivalents of 1,3-

cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione and appropriate amines via various methods.15 However, all these compounds belong to symmetrical acridinediones A or B (Figure 1) which contain two identical cyclohexanone rings fused to the DHP rings.

As discussed 4-Aryl-1,4-dihydropyridines derivatives are the most effective of the calcium antagonists or calcium channel blocker they are also widely used in the treatment of hypertension and coronary heart diseases.16 Nifedipine, with symmetrical substituents on its dihydropyridine ring, is achiral; while second-generation derivatives, such as nimodipine, amlodipine, and nicardipine, with unsymmetrical substitution, are chiral, and demonstrate moderate to significant enantioselectivity in their pharmacological effects17-21 (Figure 2).



[Figure 2]

Features of DHPs molecules came in sight in 1970, and in forthcoming years several new molecules having dihydropyridine scaffold are in clinical use as DHPs have a broad range of pharmacological actions as agents in vasodilation, bronchodilation, hepatoprotection and geroprotection and as antiatherosclerosis, antidiabetes, antitumor, antimutagenic, antioxidant, anticonvulsant and antiradical agents. 22

EXPERIMENTAL SECTION:

Preparation of starch sulfuric acid: To a magnetically stirred mixture of starch (5.00 g) in CHCl3 (20 ml), chlorosulfonic acid (1.00 g, 9 mmol) was added dropwise at 0 °C during 2 h. After complete addition, the mixture was stirred for 2 h until HCl was removed from reaction vessel. Then, the mixture was filtered and washed with methanol (30 ml) and dried at room temperature to obtain starch sulfuric acid as cream powder (5.06 g).

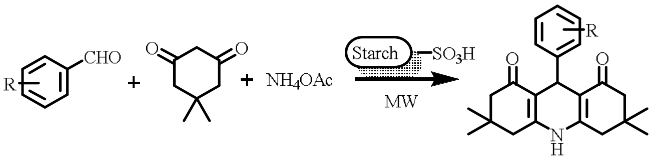
General procedure: ***Synthesis of 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones:*** A mixture of aldehyde (10 mmol), dimedone (10 mmol), ammonium acetate (10 mmol) and starch sulfuric acid (0.4 g) was taken in 25 ml of beaker and mixed well. The mixture was then irradiated at 540 watt for appropriate of time. The progress of the reaction was monitored by TLC. After completion of reaction the reaction was extracted with ethyl acetate and filtered. The fitrate was evaporated under reduced pressure to afford final product which was recrystallized with ethanol to get pure product. Final product obtained was in full agreement with the spectral data.

Reusabilty of catalyst: After completion of reaction the obtained product was extracted with ethyl acetate and insoluble starch sulfuric acid (SSA) as easily separated by simple filtration and directly reused for the same reaction model.

Spectral analysis: 9-phenyl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones (4a):
IR cm-1: 3553, 1622, 752.
1H NMR (DMSO-d6) δ ppm = 0.836 (s, 6H, 2×CH3), 0.991 (s, 6H, 2×CH3), 1.929 (s, 2H, -CH2), 2.119 (s, 2H, -CH2), 2.336 (s, 2H, -CH2), 2.456 (s, 2H, -CH2), 5.353 (s, 1H, -CH), 7.250 (t, 1H, Ar-H), 7.353 (d, 2H, Ar-H), 7.550 (d, 2H, Ar-H), 9.907 (s, 1H, -NH).
MASS: 350 [M+1].

RESULTS AND DISCUSSION: Numerous synthetic methods have been reported for the preparation of 1,4-dihydropyridine derivatives under classical or modified conditions.23-31 However, some of these methods suffer from long reaction times, low yields, use of large quantities of volatile organic solvents, harsh reaction conditions and tedious workups, therefore, development of an efficient and versatile method is still required.

Recent developments in 1,4-dihydropyridine chemistry and our continued interest in the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds, prompted us to study the conversion of dimedone into fused 1,4-dihydropyridines in the presence of starch sulfuric acid as heterogeneous catalyst by the reaction of aldehyde (10 mmol), dimedone (10 mmol) and ammonium acetate (10 mmol) in the presence of Starch sulfuric acid (Scheme 2).



1(a-i) **2** **3** **4(a-i)**

[Figure 3]

To carry out the reaction with a catalyst, the appropriate amount of catalyst required was to be investigated. So, we first optimized the appropriate quantity of catalyst required with different power of microwave irradiation (Table 1). Synthesis of 9-(4-chlorophenyl)-3,3,6,6-tetramethyl-3,4,6,7-tetrahydroacridine-1,8(2H,5H,9H,10H)-dione (Table 2, Entry 3c) was chosen as a model reaction by the reaction of 4-chlorobenzaldehyde, dimedone and ammonium acetate. At first, reaction was carried out using 0.2, 0.4 and 0.6 g of SSA with 180 watt power of microwave irradiation but the obtained result was not satisfactory (Table 1, Entry 1). Therefore, we again increased the power of microwave irradiation with similar quantities of catalyst until we afforded the higher amount of yield (Table 1, Entry 2-5).

After complete optimization we found that 540 watt power with 0.4 g of the catalyst was found to give the appropriate reaction condition which completes the reaction with higher amount of yield (Table 1, Entry 3). All the reactions were irradiated for 40 sec during these optimizations. Further increase in the power of microwave did not improve the yield to higher extent. Hence, 540 watt power of mw with 0.4 g of the catalyst was kept as optimum reaction condition for synthesizing further derivatives.

With the help of optimized reaction conditions various substituted aromatic aldehydes were investigated by reacting with dimedone and ammonium acetate in presence of Starch SA under microwave irradiation furnishing the corresponding fused 1,4-dihydropyridines in good to excellent yields as shown in Table 2, Entry 4(a-i). All the products were smoothly synthesized within 35-50 sec giving 85-95% of the yield.

Various electron-withdrawing and electron-donating groups on aromatic aldehydes were investigated and we did not observe any obvious effect with respect to electronic effect of the substituent on aromatic ring to afford the product. The obtained products were easily isolated with good to excellent yields.

The reaction can be postulated as the Knoevenagel condensation of aldehyde and dimedone followed by the Michael addition of the formed arylidene dimedone intermediate with ammonium acetate and subsequent ring closure to afford the corresponding tetrahydroacridinone derivatives in which the DHP ring is enclosed. One of the advantages of solid acid catalysts is their recyclability. We were able to separate starch sulfuric acid from the reaction medium smoothly. Reaction of 4F-benzaldehyde, dimedone and ammonium acetate was chosen as model reaction to examine the reusability of catalyst and the results were shown in Figure 3.

Table 1: Optimization of amount of catalyst with respect to different power of microwave irradiation.

Sr. No.	Power (Watt)	Amount of catalyst (g)	Yield (%)^{a,b}
1	180	0.2	85
		0.4	87
		0.6	89
2	360	0.2	87
		0.4	91
		0.6	93
3	***540***	0.2	94
		0.4	***95***
		0.6	95
4	720	0.2	94
		0.4	95
		0.6	93
5	Hi	0.2	93
		0.4	94
		0.6	92

^{a}Isolated Yield. ^{b}Reaction irradiated for 40 sec.

Table 2: Synthesis of fused 1,4-dihydropyridines using starch sulfuric acid as catalyst.

Entry	R_1	Time (sec)	Yield (%)^a	M.P. (^{0}C)^b
4a	C_6H_5	38	93	277-278
4b	$4\text{-}ClC_6H_4$	40	95	294-296
4c	$2\text{-}ClC_6H_4$	42	92	217-219
4d	$4\text{-}FC_6H_4$	35	94	215-218
4e	$4\text{-}NO_2C_6H_4$	48	85	282-283
4f	$4\text{-}OHC_6H_4$	50	88	>300
4g	$4\text{-}CH_3OC_6H_4$	45	91	272-273
4h	$4\text{-}CH_3C_6H_4$	46	90	>300
4i	$4\text{-}Me_2NC_6H_4$	52	89	265-267

^{a}Yields were isolated, ^{b}Recorded melting points were compared with literature data.[32,33]

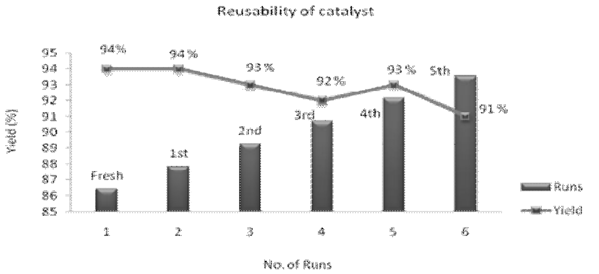


Figure 4: Reusability of Catalyst

The Figure 3 shows the successful reuse of the catalyst. For all runs 0.4 g of the catalyst with 540 watt power of mw was used and irradiated for 35 sec. In Figure 1, the graph was plotted against number of runs vs. yield of product obtained. The bars in the graph indicate the increasing number of runs and the line shows the obtained yield. For screening the catalytical activity of the catalyst 5-6 runs were performed and the yield obtained from 94-91%. From results it was noticed that there was no any significant decrease observed in the catalytical activity and in the product yield (Figure 3). Thus, this process could also be interesting for large-scale synthesis.

CONCLUSION: The current work presents a benign and proficient approach towards the synthesis of 9-aryl-3,3,6,6-tetramethyl-hexahydroacridine-1,8-diones. This procedure offers several advantages including solvent-free reaction condition, wide scope of substrates, use of very cheap and reusable starch sulfuric acid as a catalyst, high yield and facile separation of products. All of these points make this process as a very useful and practical alternative in the synthesis of these compounds, even in large-scale preparation.

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