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RESEARCH ARTICLE

Hexamethylenetetramine as an Efficient Catalyst for One-Pot, Three Component Synthesis of 2-Amino-4*H*-Pyran Derivatives

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Abstract: Hexamethylenetetramine has been found to be an efficient catalyst for the preparation of 2-amino-4*H*-pyran derivatives in ethanol. The products were obtained with very good yields.

Keywords: Hexamethylenetetramine, 2-Amino-4*H*-pyran, Dimedone, Multicomponent reaction

Introduction

Tetrahydrobenzo [*b*] pyrans have shown a broad spectrum of biological and pharmacological activities[1], such as anticancer, antianaphylactin, anticoagulant and diuretic characteristics[2-4]. These compounds have been of interest to the medicinal chemist for many years. They have been used as cognitive enhancers for the treatment of neurodegenerative diseases, including Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, AIDS-associated dementia, and Down's syndrome, as well as for the treatment of schizophrenia and myoclonus[5], additionally; these compounds are used as photoactive materials[6] and occur in a variety of natural products[7]. Because of their applications, the syntheses of heterocyclic derivatives of these compounds have attracted a great deal of attention in medicinal chemistry. One-pot multi-component condensations represent as possible instrument to perform a near ideal synthesis because they possess one of the aforementioned qualities, namely the possibility of building-up complex molecules with maximum simplicity and brevity[8].

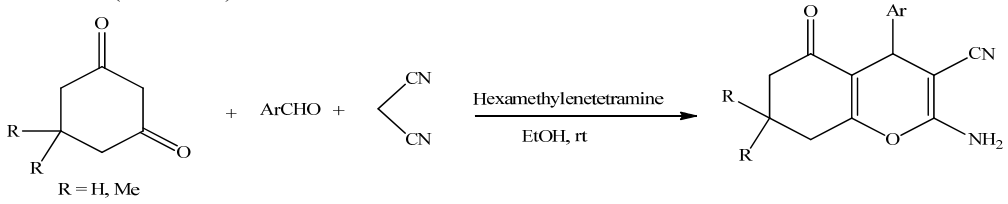
2-Amino-4*H*-pyrans are generally prepared by the condensation of dimedone with aromatic aldehydes and malononitrile under refluxing in DMF or acetic acid[9,10] or the bicomponent condensation of dimedone with α-cyanocinnamonitriles in the presence of ethanolic piperidine[11].

In recent years, hexadecyldimethyl benzyl ammonium bromide[12], triethylbenzyl-ammonium chloride[13], rare earth perfluorooctanoate[14], (*S*)-proline[15], the use of microwave irradiation[16], KF-basic alumina under ultrasound irradiation[17] and amino- functionalized ionic

liquid[18], Caro's acid-silica gel[19], 1,4-Diazabicyclo[2.2.2]octane (DABCO)[20], $Ce(SO_4)_2 \cdot 4H_2O$[21], cerium(III) chloride[22] and ZnO-beta Zeolite[23] have been reported to catalyze these reactions. However, in these methods are very useful but many of these methods are associated with several drawbacks such as applications of expensive reagents, low yields, drastic reaction conditions, the use of harmful organic solvents, high temperatures, extended reaction times, occurrence of side products, unsatisfactory yields and complicated experimental procedure. Hence, there is a need to develop a convenient, efficient and practically useful process for the synthesis of 2-amino-4*H*-pyrans.

Hexamethylenetetramine is a heterocyclic organic compound with the formula $(CH_2)_6N_4$. This white crystalline compound is highly soluble in water and polar organic solvents. It has a cage-like structure similar to adamantane. Hexamethylenetetramine has received significant attention as a powerful catalyst for effecting various organic transformations[24-27].

In our continued interest in the development of highly expedient methods for the synthesis of heterocyclic compounds[28-31], we wish to introduce hexamethylenetetramine as a mild and highly efficient catalyst for the preparation of 2-amino-4*H*-pyrans under room temperature condition (Scheme 1).



Scheme 1

Expermental

Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus. ^{1}H NMR spectra were recorded on a Bruker AQS AVANCE-500 MHz spectrometer using TMS as an internal standard ($CDCl_3$ solution). IR spectra were recorded from KBr disk on the FT-IR Bruker Tensor 27. GC/Mass analysis was performed using Agilent 6890 GC system Hp-5 capillary 30 m×530 μm×1.5 μm nominal. All products were characterized by spectra and physical data.

Preparation of 2-amino-4H-pyrans: General procedure

A mixture of benzaldehyde (1 mmol), malononitrile (1 mmol) and an *α*-methylencarbonyl compound (1 mmol) in the presence of hexamethylenetetramine (0.03 g) was taken in a round-bottomed flask in ethanol (5 mL) and stirred at room temperature for appropriate time as indicated in Table 4. After completion of the reaction which was monitored by TLC, the mixture was obtained was filtered off and washed with H_2O. The crude products were purified by recrystallization from EtOH.

Results and Discussion

At first, the synthesis of 2-amino-4*H*-pyran was investigated through condensation dimedone, benzaldehyde and malononitrile in the presence of catalytic amount of hexamethylenetetramine, for optimization of the reaction conditions. The reaction of dimedone (1 mmol), benzaldehyde (1 mmol) with malononitrile (1 mmol) in different solvents and the absence of solvent under room temperature in the presence of a catalytic amount of hexamethylenetetramine was studied (Scheme 1). The results are summarized in Table 1. Ethanol was found to be a good solvent for this reaction.

Table 1. Synthesis of 2-amino-4*H*-pyran in different conditions in the presence of hexamethylenetetramine

Entry	Temperature	Time, min	Yield, %[a]
1	Room temperature	35	92
2	Reflux	25	65

[a] *Yields refer to isolated products*

Next, we studied the effect of different amounts of catalyst in the condensation of dimedone (1 mmol), benzaldehyde (1 mmol) with malononitrile (1 mmol). The results are summarized in Table 2.

We investigated above reaction in different temperatures in order to define the best condition. The results are summarized in Table 3.

Table 2. Synthesis of 2-amino-4*H*-pyran in different solvents in the presence of hexamethylenetetramine

Entry	Solvent	Time min	Yield, %[a]
1	No solvent	60	45
2	Water	150	80
3	Ethanol	35	92
4	Acetonitrile	120	55

[a] *Yields refer to isolated products*

Table 3. Synthesis of 2-amino-4*H*-pyran in the presence of different amounts of hexamethylenetetramine

Entry	Catalyst	Time, min	Yield, %[a]
1	0.01	60	86
2	0.02	90	89
3	0.03	35	92

[a] *Yields refer to isolated products*

The optimized methodology was applied to the synthesis of a variety of 2-amino-4*H*-pyran derivatives. Hexamethylenetetramine as an efficient medium for this reaction affords the product in excellent yield. Using this optimized condition, we examined three-component condensation of various aldehydes with active *α*-methylencarbonyl compounds and malononitrile. The results are summarized in Table 4. The results clearly indicate the scope of the reaction with respect to different substrates. It is noteworthy to mention that, the effect of the nature of the substituents on the aromatic ring showed no obvious effect on this conversion, because they were obtained in high yields in relatively short reaction times. All compounds were known and their physical data were compared with those of authentic compounds and found to be identical.

Table 4. Hexamethylenetetramine catalyzed synthesis of 2-amino-4*H*-pyran derivatives.

Entry	Active methylene compound	Ar	Time, min	Yield, %[a]	mp, °C	
					Found	Reported
1	dimedone	C_6H_5	90	91	230	228-230[32]
2	dimedone	4-NO_2-C_6H_4	35	92	179	179-180[32]
3	dimedone	3-NO_2-C_6H_4	60	90	212	208-211[32]

Contd….

4	dimedone	4-Cl-C_6H_4	30	88	216	215-216[32]
5	dimedone	4-MeO-C_6H_4	100	81	204	201-202[32]
6	dimedone	4-Me-C_6H_4	105	87	224	223-225[32]
7	dimedone	3-MeO-C_6H_4	60	70	188	186-187[21]
8	dimedone	2-MeO-C_6H_4	20	90	198	195-197[20]
9	dimedone	3-Br-C_6H_4	30	75	292	293-294[21]
10	1,3-cyclohexanedione	C_6H_5	30	93	240	239-241[32]
11	1,3-cyclohexanedione	4-NO_2-C_6H_4	30	95	237	234-236[32]
12	1,3-cyclohexanedione	3-NO_2-C_6H_4	60	93	201	198-200[32]
13	1,3-cyclohexanedione	4-Cl-C_6H_4	90	91	229	226-229[32]
14	1,3-cyclohexanedione	4-MeO-C_6H_4	60	81	198	195-197[32]
15	1,3-cyclohexanedione	4-Me-C_6H_4	90	94	226	223-225[32]

[a]*Yields refer to isolated products*

Conclusion

In conclusion, we have demonstrated a highly efficient procedure for the preparation of 2-amino-4*H*-pyrans through the multi-component reaction of aldehydes, *α*-methylencarbonyl compounds and malononitrile in the presence of hexamethylenetetramine. This simple procedure is an efficient methodology that has advantages such as short reaction times, easy work up, high yields of products, mild condition as well as simple experiment and isolation procedures which makes it very useful and attractive process for the synthesis of these biology active compounds.

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