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A facile and efficient protocol for the synthesis of 2-amino-3-cyano-4H-pyran derivatives at ambient temperature

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An efficient and simple synthesis of some 2-amino-3-cyano-4H-pyran derivatives was developed by the one-pot and three-component reaction of aldehydes, ethyl acetoacetate, and malononitrile in the presence of ammonia as catalyst at room temperature. The reaction is rapid and clean, and gives the products in high yields.

1. Introduction

Polyfunctionalized 4H-pyrans are an important class of organic compounds due to their useful biological and pharmacological activities,[1] such as antiallergic,[2] antitumor[3] and antibacterial activity[4-8]. A number of 2-amino-4H-pyrans are used in cosmetic and pigments, and utilized as potentially biodegradable agrochemicals[9,10]. Polysubstituted 4H-pyrans also constitute a structural unit of many natural products[11,12]. 4H-Pyran derivatives are also potential calcium channel antagonists,[13] which are structurally similar to biologically active 1,4-dihydropyridines (1,4-DHPs).

Generally, 2-amino-4-aryl-3-cyano-4H-pyrans were synthesized by the cyclization of arylidenemalononitriles and active methylene compounds in the presence of organic bases such as piperidine,[14] pyridine,[15] triethylamine[16,17]. Most of these methods involve use of volatile solvents and require longer reaction time (~ 12 h) and difficult to recover catalyst. Recently, one-pot synthesis of these compounds has been reported using Mg/La mixed oxide[18] and MgO[19,20] as basic catalyst. More

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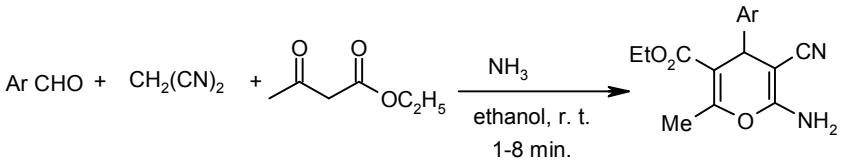
recently, we reported the multicomponent synthesis of 2-amino-4H-pyran derivatives in aqueous medium[21,22].

Thus, in view of importance of this class of compounds, the development of a simple, efficient and versatile method for the preparation of 2-amino substituted 4H-pyrans is an active area of research and there is a scope for further improvement towards milder reaction conditions and higher product yields. Herein, we report a rapid and clean method for the synthesis of 2-amino-4H-pyran frame-works via a multi-component reaction of aromatic aldehydes, ethyl acetoacetate, and malononitrile in the presence of ammonia as catalyst at ambient temperature.

2. Results and discussion

In this procedure, a mixture of benzaldehyde derivatives **1** (0.5 mmol), ethyl acetoacetate (0.5 mmol), malononitrile (0.5 mmol) and 25% ammonia (0.2 mL) in ethanol (5 mL) is stirred at ambient temperature for 1-8 min until solid precipitates. The precipitated solid was filtered and purified by recrystallization from ethanol. The 2-amino substituted 4H-pyran derivatives **2a-i** were obtained in good to excellent yields (Table 1). The synthesized compounds **2a-i** are previously known and the structure of them were confirmed by comparison of physical characteristics and spectral data with those of known compounds[21]. Both electron-poor and electron-rich aldehydes were well tolerated. Despite using so much ammonia, no 1,4-dihydropyridine product was detected.

Table 1. Three-component synthesis of 2-amino-4-aryl-3-cyano-4H-pyran derivatives [a]



Entry	Ar	Time (min)	Product	Yield (%) [b]	Mp (˚C)
1	C_6H_5	4	**2a**	90	190-192
2	2-$NO_2C_6H_4$	5	**2b**	79	177.5-178.5
3	3-$NO_2C_6H_4$	1	**2c**	97	187-188
4	4-$NO_2C_6H_4$	5	**2d**	78	175-176
5	2-$OMeC_6H_4$	5	**2e**	78	196-197
6	2-ClC_6H_4	3	**2f**	98	191-192
7	2-BrC_6H_4	4	**2g**	98	183-184
8	4-BrC_6H_4	8	**2h**	70	180-181
9	2-furyl	3	**2i**	90	203-204

[a]All reactions were conducted with aldehyde (0.5 mmol), ethyl acetoacetate (0.5 mmol), malononitrile (0.5 mmol), and ammonia 25% (0.2 mL) at room temperature in ethanol. [b]Isolated yields after recrystallization.

3. Conclusions

In summary, the one-pot three-component reaction protocol developed in the present study offers a fast and an efficient method for the synthesis of 2-amino substituted 4H-pyrans at room temperature. The experimental procedure is very simple and represents an attractive alternative to existing methods. This reaction protocol has the potential for developing combinatorial libraries.

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4. Experimental

Typical procedure for the synthesis of 2-amino-3-cyano-4H-pyrans **2a-i**: To a stirred mixture of benzaldehyde (0.05 ml, 0.5 mmol), malononitrile (0.033 g, 0.5 mmol) in ethanol (5 ml) was added ethyl acetoacetate (0.06 ml, 0.5 mmol) and ammonia 25% (0.20 ml, 2.1 mmol). The mixture was stirred at room temperature under an open atmosphere for the appropriate time (Table 1). The precipitated solid was filtered, washed with water and then recrystallized from ethanol.

The structures of compounds **2a-i** were confirmed by the comparison of melting points and spectral data with those reported in the literature[21].

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