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Facile and efficient synthesis methods for one pot synthesis of new polycarbonyl compounds

Mitra Saremi*

Department of Chemistry, Ahvaz Branch, Islamic Azad University, Ahvaz, Iran;
t.sanaei@khouzestan.srbiau.ac.ir

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Abstract- An efficient and environmental-friendly synthetic route to 1,8-dioxodecahydroacridines derivatives have been developed via multi-component one-pot Hantzsch reaction of various aldehydes and ammonium acetate with 2 equivalents dimedone in the presence of Phosphorus pentoxide supported on aluminaas catalyst under solvent-free conditions. The present approach offersseveral advantages such as short reaction times, easy isolation and purification of product, and safe, non-toxic, recyclable and economic use of catalyst.

Keywords: synthesis, polycarbonyl, efficient,

Introduction

In recent years, multicomponent reactions, involving three or more reactants in one-pot have been used to synthesize structurally diverse bioactive heterocycliccompounds.1,2 The advantages of multicomponent reactions are high atom-economy, structural diversity, operational simplicity and lack of waste products in a multi-step reaction.[1]

1,8-Dioxohexahydroacridine are comes under a class of Pyridine and its derivatives are an important class of heterocyclic compounds, which acridine derivatives have occupied a unique position in medicinal chemistry.[2] Recently hydro derivatives showed numerous biological activities like antimicrobial activity and potassium channel blockers The products 1,8-dioxooctahydroxanthene derivatives were obtained in satisfactory yields during the reaction of aromatic aldehydes and ammonium acetate with dimedone under solvent-free conditions for 15min and catalysed by the P_2O_5- Al_2O_3.

Despite their importance from a pharmacological, industrial, and synthetic point of view, comparatively fewmethods on their preparation have been reported. In 1822,Arthur Hantzsch reported first synthesis of symmetrically substituted 1,4-dihydropyridine by the one-pot, four-component condensation of two molecules of ethyl acetoacetate, aromatic aldehyde and ammonia.[4] The standard Hantzsch procedure does not need the intervention of any additive or reagent and the reaction was originally conducted either in acetic acid or at reflux in alcohol for rather long periods, resulting in low or modest yields of condensationproducts.[19] Replacement of ammonia by ammoniumacetate allowed the efficient synthesis of Hantzsch compounds in a aqueous medium as well as under solvent-free conditions.[20–21]Very few methods are known in the literature for the synthesis of acridinediones. The most straightforward synthesis of this compounds involve the three-component condensation of an aldehyde, dimedone, and ammonium acetate or appropriate amines in the presence of several catalysts such as p-dodecylbenezenesulfonic acid[9], Amberlyst-15[10], [Hmim]TFA[11], Tris(pentafluorophenyl)borane[12], $FeCl_3$-SiO_2[13], Proline[14] , Acidic Ionic Liquids[15], Brønsted acidic imidazolium salts[16], $Zn(OAC)_2.2H_2O$[17], Silica- Bonded S-Sulfonic Acid[18] and Ceric ammonium nitrate (CAN)[19]. However, these methods suffer from several drawbacks such as long reaction times, use of large quantities of volatile organic solvents, unsatisfactory yields, the use of expensive reagents, difficult workup, catalysts that are harmful to environment and harsh reaction conditions. Therefore, it is of great interest to develop an efficient and heterogeneous method for the synthesis of 1,8-dioxohexahydroacridine derivatives.[5]

In continuation of our investigations on the development of new synthetic methodologies, we herein report a new, convenient, mild and efficient procedure for the synthesis of 1,8-dioxodecahydroacridines from one-pot condensation of various aromatic aldehydes, 1,3-diketones with ammonium acetate using with P_2O_5-Al_2O_3in 120^{o}C temperature(scheme1).

1 2 3 4

Scheme 1

Experimental

All chemicals were purchased from Merck or Fluka Chemical Companies. All compounds are known and their structures were identified by comparing their melting points and ^{1}H and^{13}C NMR data with those reported in the literature. The ^{1}H NMR (500 MHz) was run on a Bruker Avance DPX-250, FT-NMR spectrometer.

General procedure for the synthesis of 1,8-dioxodecahydroacridines using P_2O_5-Al_2O_3 as catalyst.

A mixture of dimedone (2 mmol), substituted aromatic aldehyde (1 mmol), ammonium acetate (1 mmol)) and P_2O_5-Al_2O_3(0.002 g) was heated on the oil bath at 120 ° for the appropriate time(see Table 3). The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was cooled to room temperature and hot ethanol was added. The solid residue was dissolved in hot ethanol and filtered off. The crude product was collected from the filtrate after cooling to room temperature and recrystallized from ethanol-H_2O to give product in high yields. All of the 1,8-dioxodecahydroacridine derivatives are known and were identified by comparison of their physical and spectroscopic data (IR, NMR).

Results and discussion

The P_2O_5-Al_2O_3catalyzed Hantzsch reaction was carried out using benzaldehyde, dimedone and ammonium acetate as a model reaction to investigate different parameters, such as effect of solvent and concentration of the catalyst. Furthermore, we have screened several solvents for this reaction (Table 1).

Table1. Optimization of solvent for the Hantzsch reaction.

ENTRY	SOLVENT	TIME(MIN)	YEILD(%)
1	ETHANOL	300	70
2	CH$_3$CN	300	65
3	CHCL$_3$	300	60
4	THF	300	-
5	WATER	300	75
6	SOLVENT	15	92

the quantity of the catalyst can improve the reaction yield and shorten reaction time (Table 2). First, Hantzsch reaction was carried out in absence of catalyst at ambient temperature; it was found just10 % product formed after 24 h. Even though amount of the catalyst decreased from 0.005 to 0.003g, no change in the yields, whereas using 0.02g P_2O_5-Al_2O_3, in model reaction generated 93% product.

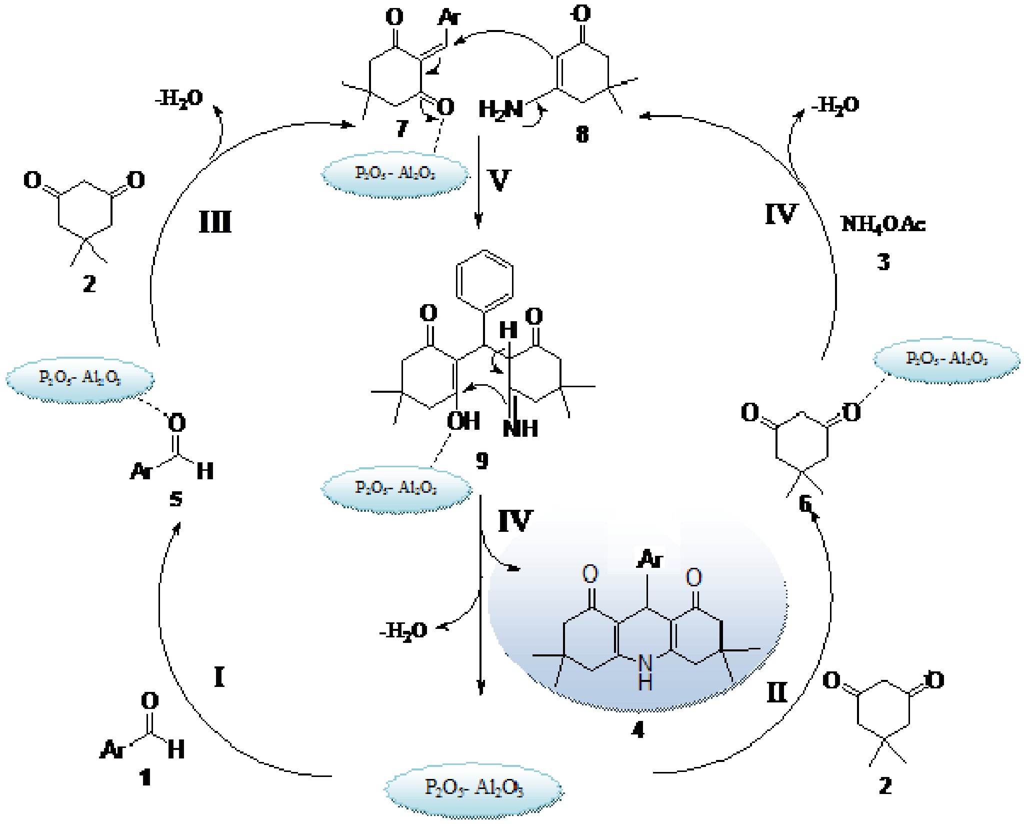
TABLE 2. COMPARISON OF THE EFFICIENCIES OF DIFFERENT CATALYSTS FOR THE SYNTHESIS OF 1,8-DIOXODECAHYDROACRIDINES

ENTRY	TEMPERATURE(°C)	AMOUNT OF CATALYST(G)	TIME(MIN)	YEILD(%)
1	**AMBIENT**	**-**	**24 H**	**10**
2	**60**	**0.002**	**180**	**50**
3	**80**	**0.002**	**60**	**65**
4	**100**	**0.002**	**30**	**85**
5	**120**	**0.002**	**15**	**95**
6	**120**	**0.003**	**45**	**90**
7	**120**	**0.004**	**45**	**90**
8	**120**	**0.001**	**30**	**85**

In order to test the substrate generality of P_2O_5-Al_2O_3 catalyzed Hantzsch reaction, the condensation of various aldehyde with ethyl acetoacetate and urea were studied under the optimized conditions. The results are summarized in Table3. It can be noticed that a wide range of aldehyde can efficiently contribute in the Hantzsch reaction. However, the benzaldehyde bearing electron-withdrawing substituents furnished Hantzsch reaction with excellent yields (99%) 45 min. On the other hand, for aldehyde containing an electron-donating group to give yields (9%). This can be explained that electron-withdrawing groups improve the electrophilicity of carbonyl carbons aldehyde, which facilitates the reaction, while electron donating groups reduce the electrophilicity.

Table 3. Preparation of 1,8-dioxodecahydroacridines 4a-f using P_2O_5-Al_2O_3(0.02 g) as catalyst

ENTRY	AR	PRODUCT	TIME(MIN)	YEILD(%)	M.P(^{O}C)	REF M.P(^{O}C)
1	C_6H_5	4A	15	95	192-195	(190-192)[19]
2	4-$NO_2C_6H_4$	4B	5	94	286-289	(286-288)[21]
3	4-CLC_6H_4	4C	10	93	300-302	(299-301)[21]
4	4-$CH_3C_6H_4$	4D	20	90	269-271	(190-192)[8]
5	4-CNC_6H_4	4E	10	96	239-242	(241-243)[21]
6	4-$OCH_3C_6H_4$	4F	15	93	270-272	(270-272)[20]



Scheme 2. The possible mechanism of synthesis of 1, 8-dioxo-decahydroacridines

A tentative mechanism to rationalize the product formation is shown in scheme2. 1,8-dioxodecahydroacridines **4** may be formed either through steps **(I—III)** or through steps **(IV—V)**. The role of Phosphorus pentoxide supported on alumina (Lewis Acid) comes in steps **(I)** and **(IV)**, where it catalyzes the Knoevenagel type coupling of aldehydes with active methylene compounds and in steps **(III)** and **(VI)**, where it catalyzes the Michael type addition of intermediates **5**, **6** and **7**, **8** to give product**4**.

Selected physical and ^{1}HNMR data of the products

3,3,6,6-Tetramethyl-9-(4-nitrophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4b)

m.p. 299 – 301 °C ; ^{1}H NMR ($CDCl_3$, 500 MHz): δ: 0.85 (s, 6H, 2Me), 1.01 (s, 6H, 2Me), 1.96 (d, J=16.5 Hz, 2H, H-2a,7b),2.23 (d, J=16.5 Hz, 2H, H-2a',7b'), 2.33 (d, J=16.5 Hz,2H, H-4c,5d), 2.52 (d, J=16.5 Hz, 2H, H-4c',5d'), 4.90(s, 1H, H-9), 7.5 (d, J=8.5 Hz, 2H, ArH), 8.1 (d, J=8.5 Hz, 2H, ArH), 6.1 (brs, 1H, NH).

3,3,6,6-Tetramethyl-9-(4-chlorophenyl)-1,2,3,4,5,6,7,8-octahydroacridine-1,8-dione (4c)

m.p. 299 – 301 °C ; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.96 (s, 6H, $2CH_3$), 1.09 (s, 6H, $2CH_3$);2.16 (d, J ＝16 Hz, 2H, H-2a,7b), 2.27 (d, J ＝16 Hz, 2H,H-2a',7b'), 2.28 (d, J ＝16.5 Hz,H-4c,5d), 2.35 (d, J ＝16.5 Hz, H-4c',5d'), 5.06 (s, 1H, H-9), 7.07 (brs, 1H, NH), 7.17 (d, J＝8.3 Hz, 2H, ArH), 7.29 (d, J ＝8.3 Hz, 2H, ArH).

Conclusion

In conclusion, we have reported a simple new catalytic method for the synthesis of 1,8-dioxodecahydroacridines by one-pot three-component reaction of dimedone, aromatic aldehydes, and ammonium acetate using P_2O_5-Al_2O_3as an efficient, reusable, and green heterogeneous catalyst. High yields, short reaction times and easy work-up are just a few of the advantages of this procedure.

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