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Diammonium Hydrogen Phosphate: a Versatile and Inexpensive Reagent for One-Pot Synthesis of Dihydropyrimidinones, Quinazolinones and Azalactones under Solvent-Free Conditions

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Diammonium hydrogen phosphate, $(NH_4)_2HPO_4$, efficiently catalyzes the three-component Biginelli reaction between an aldehyde, a β-dicarbonyl compound and urea or thiourea under solvent-free conditions to afford the corresponding dihydropyrimidinones in high yields. Also, the synthesis of 2,3-disubsitituted-(3*H*)-quinazolin-4-ones is achieved by the one-pot reaction of isatoic anhydride, primary amines and orthoesters in the presence of $(NH_4)_2HPO_4$. The reaction of hippuric acid with aromatic aldehydes and acetic anhydride resulted in the formation of azalactones using catalytic amounts of $(NH_4)_2HPO_4$.

Keywords: Diammonium hydrogen phosphate, Solid phase, Biginelli reaction, Dihydropyrimidinones, Quinazolinones, Azalactones

INTRODUCTION

3,4-Dihydropyrimidin-2(1*H*)-ones and their sulfur analogues (DHPMs) have been reported to possess diverse pharmacological properties such as antiviral, antibacterial, antihypertensive activity [1], as well as efficacy as calcium channel modulators and α_{1a}-antagonists [2]. Also, the biological activity of some alkaloids isolated recently has been attributed to the dihydropyrimidinone moiety [3].

The simple and direct method for the synthesis of DHPMs, reported by Biginelli in 1893, involved the one-pot condensation of an aldehyde, a β-ketoester and urea under strongly acidic conditions [4], and has subsequently been reviewed [5]. Several improved protocols for the preparation of DHPMs have recently been reported [6-15]. However, some of the reported methods suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedures and produce environmental pollutants [6-12]. Moreover, some of the methods are only practicable for aromatic aldehydes [6,10,12]. Therefore, a great need still exists for versatile, simple and environmentally friendly processes whereby DHPMs may be formed under milder and more practical conditions.

Interest in the synthesis of many substituted quinazolinones has been renewed owing to their potential use as physiologically active compounds [16,17] such as antibiotics [18], and potent non-nucleoside reverse transcriptase inhibitors of the human immunodeficiency virus (HIV-1) [19]. A number of synthetic methods for the preparation of substituted (3*H*)-quinazolin-4-ones have been

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described [20-25]. Recently, the synthesis of the mono-substituted quinazolinones in solution and also dry media has been reported [23,26]. Disubstituted 4-(3*H*)-quinazolinones are also synthesized through a multi-step reaction in solution under microwave irradiation [27].

Azalactones are a class of important heterocyclic compounds and exhibit a variety of biological and pharmaceutical properties [28]. They are also useful precursors for the synthesis of amino acids [29], peptides [30], heterocycles [31], biosensors [32], and antitumor or antimicrobial compounds [33]. The Erlenmeyer reaction is the most widely used method for the preparation of these compounds [34], and various reagents are known to effect this condensation [35-41]. Some of these methods, however, suffer from drawbacks, which include the use of hazardous materials [39], commercially non-available [37] or highly corrosive and difficult-to-handle reagents [36], long reaction times [34], low yields [38], drastic reaction conditions and tedious workup procedures [39-41].

Diammonium hydrogen phosphate is a very inexpensive, non-toxic and commercially available compound that can be used in the laboratory without special precautions [42]. To the best of our knowledge, there are no reports regarding the application of diammonium hydrogen phosphate in the preparation of organic compounds. Here we report, for the first time, the use of this reagent in the synthesis of three important classes of heterocyclic compounds, *i.e.*, dihydropyrimidinones, quinazolinones, and azalactones.

EXPERIMENTAL

All of the products are known compounds and were characterized by comparison of their spectroscopic data and melting points with those of authentic samples. Melting points were determined in open capillaries on an Elecrothermal 9200 melting point apparatus and are not corrected. Reaction monitoring was accomplished by thin layer chromatography (TLC) on precoated sheets (Merck, silica gel 60 F_{254}). Diammonium hydrogen phosphate was purchased from Merck Chemical Company [42]. Yields refer to pure isolated products.

General Procedure for the Synthesis of Dihydropyrimidinones

A mixture of aldehyde (2 mmol), the β-dicarbonyl compound (2 mmol), urea or thiourea (3 mmol) and diammounium hydrogen phosphate (0.6 mmol) was heated at 80 ºC under solvent-free conditions. After completion of the reaction, confirmed by TLC (eluent: *n*-hexane:ethyl acetate 3:1), the mixture was washed with water (20 ml) to remove excess of urea or thiourea and then filtered. The remaining solid material was washed with hot ethyl acetate (30 ml). The filtrate was concentrated and the solid product was recrystallized from ethyl acetate/*n*-hexane.

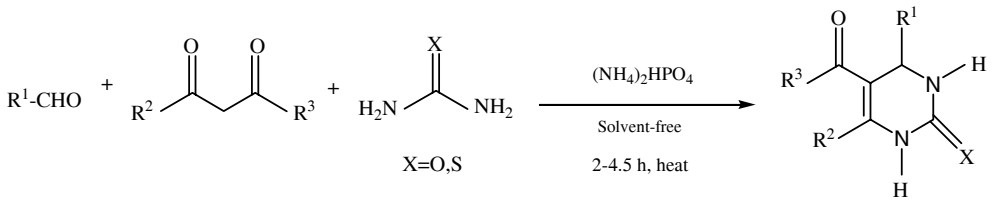
General Procedure for the Synthesis of Quinazolinones

A mixture of isatoic anhydride (1 mmol), amine (1.25 mmol), orthoester (1.5 mmol) and $(NH_4)_2HPO_4$ (0.5 mmol) was heated to 80 ºC under solvent-free conditions. The progress of the reaction was followed by performing TLC (eluent: *n*-hexane:ethyl acetate 3:2) on a sample dissolved in ethyl acetate. The mixture was cooled to room temperature and poured into cold water (50 ml). The precipitates were filtered and washed with water. Recrystallization from 96% ethanol gave the corresponding 2,3-disubstituted-4(3*H*)-quinazolinone.

General Procedure for the Synthesis of Azalactones

The catalyst (0.1 mmol) was added to a solution of aldehyde (1 mmol) and hippuric acid (1.1 mmol) in acetic anhydride (3.3 mmol). The reaction mixture was heated to 80 ºC and stirred under reflux conditions for the appropriate time (Table 3). Progress of the reaction was followed by TLC (eluent: *n*-hexane:ethyl acetate 3:1). The reaction mixture was cooled to room temperature and ethanol (10 ml) was added. The mixture was stirred for 10 min until a yellow solid precipitated. The mixture was allowed to stand overnight, and then it was cooled in an ice bath. The crude azalactones were obtained after filtration and washing with hot water. Recrystallization from acetone/water afforded the pure products.

Diammonium Hydrogen Phosphate



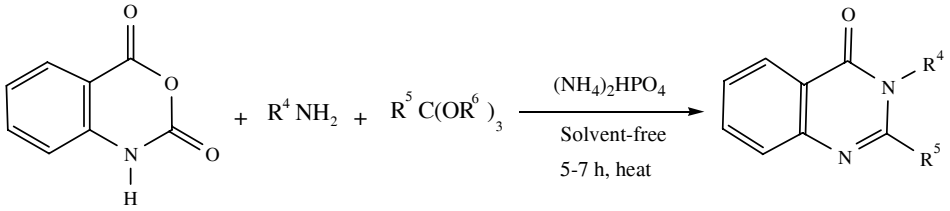
Scheme 1

Table 1. Synthesis of DHPMs Using $(NH_4)_2HPO_4$

Entry	R^1	R^2	R^3		Time (h)	Yield (%)	M.p. (^oC)	
							Found	Reported[13a]
1	C_6H_5	Me	OEt	O	2.5	94	203-204	206
2	2-NO_2-C_6H_4	Me	OEt	O	3.45	90	204-206	208-210
3	2-MeO-C_6H_4	Me	OEt	O	4	93	260-262	259-260
4	3-O_2N-C_6H_4	Me	OEt	O	4.3	91	225-227	227-229
5	3-HO-C_6H_4	Me	OEt	O	5	90	165-166	167-170
6	4-O_2N-C_6H_4	Me	OEt	O	3.5	92	209-210	209-212
7	4-Cl-C_6H_4	Me	OEt	O	4.10	95	211-213	209-212
8	4-F-C_6H_4	Me	OEt	O	3.45	93	185-187	182-184
9	3,4-$(MeO)_2$-C_6H_3	Me	OEt	O	4	93	176-177	175-177
10	C_6H_5-CH=CH	Me	OEt	O	4	90	232-233	230-232
11	*n*-C_3H_7	Me	OEt	O	3	84	154-155	154
12	*n*-C_6H_{13}	Me	OEt	O	3.5	88	150-153	152-154
13	C_6H_5	C_6H_5	OEt	O	4	91	156-157	155-157
14	C_6H_5	Me	OMe	O	2	97	208-210	210-212
15	4-Cl-C_6H_4	Me	OMe	O	3	96	203-205	203-205
16	4-O_2N-C_6H_4	Me	OMe	O	4	95	233-236	233-235
17	2,4-$(Cl)_2$-C_6H_3	Me	OMe	O	3	97	255-256	252-253
18	C_6H_5	Me	Me	O	3	90	233-234	229-231
19	4-O_2N-C_6H_4	Me	Me	O	3.5	92	228(dec)	229(dec)
20	C_6H_5	Me	OEt	S	5	94	208-211	209-211
21	3-O_2N-C_6H_4	Me	OEt	S	4	95	204-206	203-205
22	3-HO-C_6H_4	Me	OEt	S	4.5	93	185-187	183-184
23	C_6H_5	Me	Me	S	3	92	186(dec)	185(dec)

RESULTS AND DISCUSSION

The one-pot synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones And -thiones was achieved by the three-component condensation of aldehydes, β-dicarbonyl compounds and urea (or thiourea) in the presence of diammonium hydrogen phosphate. All of the reactions were performed under solvent-free conditions at 80 ^oC and the products were isolated in high



Scheme 2

Table 2. Synthesis of 2,3-Disubstituted-(3*H*)-quinazolin-4-ones Using $(NH_4)_2HPO_4$

Entry	R^4	R^5	R^6	Time (h)	Yield (%)	M.p. (°C)	
						Found	Reported[25a]
1	4-ClC_6H_4	Me	Et	6.2	91	159-160	159-160
2	4-MeC_6H_4	Me	Et	5.5	88	149-150	150-152
3	C_6H_5	Me	Et	6	87	145-147	144-145
4	C_6H_5	C_6H_5	Me	6.5	85	154-156	155-156
5	4-MeC_6H_4	C_6H_5	Me	5.8	89	180-182	179-181
6	4-BrC_6H_4	Et	Et	6.8	80	171-172	171-172
7	4-MeC_6H_4	Et	Et	5.5	91	162-163	162-164
8	Et	Et	Et	5.9	87	93-94	93-94
9	Et	Me	Et	6.8	84	64-66	63-65
10	$C_6H_5CH_2$	Me	Et	5.2	90	230-233	231-232
11	$C_6H_5CH_2CH_2$	Me	Et	6.3	89	100-102	100-101
12	$C_6H_5CH_2CH_2$	Et	Et	6.4	92	102-104	103-104
13	$C_6H_5CH_2CH_2$	*n*-Pr	Me	6.8	90	104-106	105-106
14	$C_6H_5CH_2CH_2$	C_6H_5	Me	6	85	174-176	175-176

yields (Scheme 1, Table 1).

Several aromatic aldehydes carrying either electron-releasing or electron-withdrawing substituents in *ortho*, *meta* and *para* positions also afforded high yields. An important advantage of this method is its efficient synthesis of corresponding DHPMs from aliphatic aldehydes.

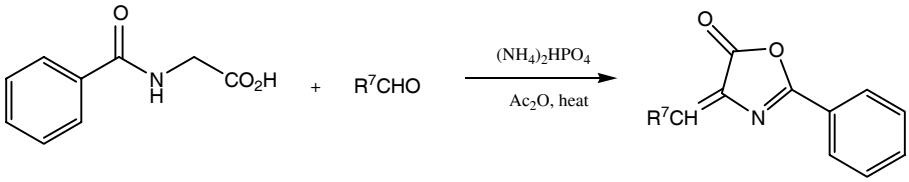
Thiourea was successfully used instead of urea to provide the corresponding 3,4-dihydropyrimidin-2(1*H*)-thiones, which also attract much interest due to their biological activity. For example, monastrol, known as a mitotic kinesin Eg5 motor protein inhibitor and a potential new lead for the development of anticancer drugs, was obtained in 93% yield using the present method (Table 1, entry 22) [43].

We also investigated the ability of diammonium hydrogen phosphate to promote the synthesis of 2,3-disubstituted-(3*H*)-quinazolin-4-ones by the reaction of isatoic anhydride, primary amines and orthoesters in the absence of solvent (Scheme 2).

Different kinds of substituted aromatic amines were reacted with isatoic anhydride and a variety of orthoesters in the presence of catalytic amounts of $(NH_4)_2HPO_4$ under solvent-free conditions with good yields (Table 2, entries 1-7). 2-Phenylethylamine, benzylamine and ethylamine, aliphatic model compounds, were used with an efficiency similar to that of aromatic amines (Table 2, entries 8-14).

The smooth cyclocondensation of a wide variety of aromatic aldehydes with hippuric acid and acetic anhydride was performed in the presence of diammonium hydrogen

Diammonium Hydrogen Phosphate



Scheme 3

Table 3. Synthesis of Azalactones Using $(NH_4)_2HPO_4$

Entry	R^7	Time	Yield	M.p. (^oC)	
		(h)	(%)	Found	Reported[35a]
1	C_6H_5	2.6	81	166-167	168
2	4-Me-C_6H_4	2.4	91	140-142	143
3	4-MeO-C_6H_4	1.8	90	152-154	156
4	2,4-$(MeO)_2$-C_6H_3	1.7	89	168-170	167
5	4-O_2N-C_6H_4	2.5	87	238-239	241
6	4-Cl-C_6H_4	2.5	89	184-186	185
7	4-Me_2N-C_6H_4	1.3	90	214-215	213
8	3-O_2N-C_6H_4	2.3	82	163-165	165
9	C_6H_5-CH=CH	2.5	92	131-133	132
10	5-Me-2-Furyl	2	87	139-141	141

phosphate to afford the corresponding azalactones in high yields (Scheme 3, Table 3).

In conclusion, diammonium hydrogen phosphate is an inexpensive, non-hygroscopic and commercially available reagent that can be used for the multi-component, one-pot synthesis of dihydropyrimidinones, quinazolinones, and azalactones in high yields. This reagent is non-toxic and easy to handle and the workup procedure is very simple.

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