Iranian Journal of Catalysis 5(2), 2015, 113-117

IRANIAN JOURNAL OF CATALYSIS

Multi-component preparation of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydro pyrimidine-4,5-dicarboxylates using hydrated phosphomolybdic acid as an efficient catalyst

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Received 9 April 2014; received in revised form 10 October 2014; accepted 12 October 2014

ABSTRACT

The synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates can be achieved using one-pot reaction from dialkylacetylene dicarboxylate, amines, and formaldehyde by employing hydrated phosphomolybdic acid ($H_3[P(Mo_3O_{10})_4].xH_2O$) as catalyst at room temperature. The effect of various solvent and catalyst amount was investigated. The salient features of the present method are: simple and straightforward work-up, cost-effective and environmentally benign procedure.

***Keywords**: Tetrahydropyrimidine; Diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates; Dialkylacetylene dicarboxylate; $H_3[P(Mo_3O_{10})_4].xH_2O$.*

1. Introduction

Tetrahydropyrimidine skeletons constitute an important class of drugs and are considered as influential bioactive nitrogen heterocyclic rings. They possess numerous types of interesting pharmacological activities such as antiviral, antimicrobial, anti-inflammatory, anti-mycobacterial, anticancer and muscarinic agonist [1-8]. This wide range of pharmacological activities directed to establish a number of methodologies for the preparation of these skeletons.

The three-component condensation reaction of substituted amines, dialkyl acetylenedicarboxylates and formaldehyde is a deployable reaction for the preparation of tetrahydropyrimidine analogues. This reaction leads to the synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylate analogues. The synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates *via* the three-component condensation reaction of substituted amines, dialkyl acetylenedicarboxylates and formaldehyde involves the use of some acidic catalysts such as $ZrOCl_2$ [5], acetic acid [9], Ag (I) [10], and I_2 [11]. Although some of these methods have good yields, few of revealed literatures for the synthesis of tetrahydropyrimidines are associated with drawbacks like low yields, long reaction time and complicated procedures. Each of the known procedures for the synthesis of corresponding diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates has its merits, however, further studies are still in high demand.

As part of our ongoing projects devoted to the synthesis of heterocycles [11-16], we focused on the preparation of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates *via* one-pot reaction of dialkylacetylene dicarboxylate, amines, and formaldehyde employing hydrated phosphomolybdic acid ($H_3[P(Mo_3O_{10})_4].xH_2O$) as catalyst at room temperature.

2. Experimental

2.1. General

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification.

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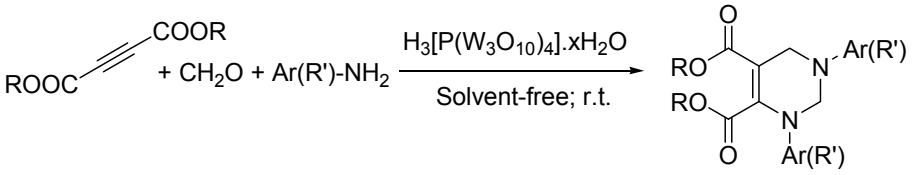


Scheme 1. Preparation of tetrahydropyrimidine derivatives.

The NMR spectra were recorded on a Bruker Avance DPX 400 MHz instrument. The spectra were measured in DMSO-d_6 relative to TMS (0.00 ppm). IR spectra were recorded on a PerkinElmer 781 spectrophotometer. Elemental analysis was performed on a Heraeus CHN-O-Rapid analyzer. Melting points were determined in open capillaries with a Buchi B-510 melting point apparatus. TLC was performed on Polygram SIL G/UV 254 silica gel plates.

2.2. General procedure

A mixture of dialkylacetylene dicarboxylate (1 mmol), aromatic amine (2 mmol), formaldehyde (2 mmol, aqueous solution 37%) and $H_3[P(Mo_3O_{10})_4].xH_2O$ (0.05 g) was stirred for the appropriate time at room temperature (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in ethanol. The catalyst was removed by simple filtration. The organic layer was inserted into ice-water and extracted with $CHCl_3$. Solvent was concentrated and the crude product was purified by plate chromatography (SiO_2) with an eluent of petroleum / ethyl acetate (9/1).

Selected spectral data

*Diethyl 1,3- bis (4-chlorophenyl)- 1,2,3,6- tetrahydro pyrimidine-4,5-dicarboxylate (**Table 2, Entry 4**):*

^{1}HNMR (400 MHz, $CDCl_3$): δ= 0.98 (t, *J* = 7.3 Hz, 3H), 1.18 (t, *J* = 7.3 Hz, 3H), 3.78-3.85 (q, *J* = 7.3 Hz, 2H), 3.97-4.05 (q, *J* = 7.3 Hz, 2H), 4.17 (s, 2H), 4.88 (s, 2H), 6.79 (d, *J* = 8.1 Hz, 2H), 6.90 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 13.3, 14.2, 47.3, 52.9, 54.2, 68.5, 99.7, 117.1, 118.2, 125.5, 129.5, 132.3, 141.9, 145.9, 146.1, 146.4, 163.8, 165.1 ppm. Found: C, 58.87; H, 4.99; N, 6.27 $C_{22}H_{22}Cl_2N_2O_4$; requires: C, 58.81; H, 4.94; N, 6.23%].

*Dimethyl 1,2,3,6- tetrahydro-1,3- dip-tolylpyrimidine-4,5-dicarboxylate (**Table 2, Entry 7**):*

^{1}HNMR (400 MHz, $CDCl_3$): δ=2.21 (s, 3H), 2.28 (s, 3H), 3.91 (s, 3H), 4.12 (s, 3H), 4.19 (s, 2H), 4.91 (s, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 6.93 (d, *J* = 8.3 Hz, 2H), 7.02 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 20.0, 20.5, 47.1, 59.5, 60.8, 68.1, 78.9, 98.7, 117.1, 117.2, 124.5, 129.4, 135.3, 140.8, 145.7, 146.2, 163.1, 164.8 ppm. Found: C, 69.61; H, 6.45; N, 7.47 $C_{22}H_{24}N_2O_4$; requires: C, 69.46; H, 6.36; N, 7.36%].

*Diethyl 1,2,3,6-tetrahydro-1,3-dip-tolylpyrimidine-4,5-dicarboxylate (**Table 2, Entry 8**):*

^{1}HNMR (400 MHz, $CDCl_3$): δ= 1.00 (t, *J* = 7.2 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H), 2.20 (s, 3H), 2.26 (s, 3H), 3.92-3.98 (q, *J* = 7.2 Hz, 2H), 4.08-4.14 (q, *J* = 7.2 Hz, 2H), 4.19 (s, 2H), 4.90 (s, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 13.1, 13.9, 19.9, 20.3, 47.0, 59.3, 60.7, 67.9, 78.9, 98.6, 117.0, 117.2, 124.4, 129.3, 135.3, 140.7, 145.7, 146.1, 163.0, 164.7 ppm. Found: C, 70.66; H, 6.99; N, 6.95 $C_{24}H_{28}N_2O_4$; requires: C, 70.57; H, 6.91; N, 6.86%].

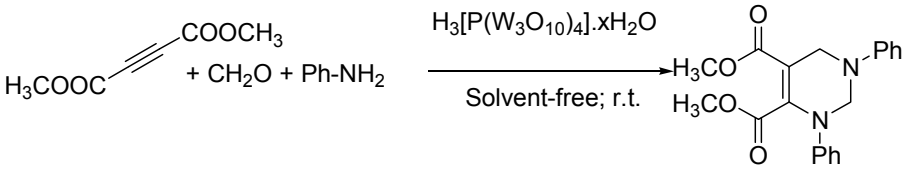
*Diethyl 1,2,3,6- tetrahydro-1,3- dimethylpyrimidine-4,5-dicarboxylate (**Table 2, Entry 14**):*

^{1}HNMR (400 MHz, $CDCl_3$): δ= 0.97 (t, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.1 Hz, 3H), 2.47 (s, 3H), 2.87 (s, 3H), 3.49 (s, 2H), 3.90 (s, 2H), 3.90-3.95 (q, *J* = 7.1 Hz, 2H), 4.01-4.10 (q, *J* = 7.1 Hz, 2H) ppm. ^{13}CNMR (100 MHz, $CDCl_3$): δ= 13.3, 14.2, 47.0, 50.3, 59.8, 61.1, 68.2, 90.9, 159.5, 164.1, 164.8 ppm. Found: C, 56.29; H, 7.93; N, 10.98 $C_{12}H_{20}N_2O_4$; requires: C, 56.23; H, 7.87; N, 10.93%].

3. Results and Discussion

Initially, the catalytic cyclo-condensation reaction of dimethylacetylene dicarboxylate, aniline and formaldehyde was studied (Scheme 2).

Using $H_3[P(Mo_3O_{10})_4].xH_2O$ as the catalyst, the reaction was followed in different solvents and under solvent-free conditions which the results were summarized in Table 1. No Significant effect of the reaction solvent on the yield was observed. Lower yield and longer reaction time was obtained in toluene (Table 1, Entry 1). Protic solvents such as methanol provided better yield and lower reaction time (Table 2, Entry 5). In terms of yields and reaction time, we achieved the best conditions using 3 mol% of catalyst under solvent-free condition (Table 1, Entry 6). Next, the effect of catalyst concentration was studied. The complete conversion of starting material was achieved using different concentration of the catalyst.



Scheme 2. Preparation of dimethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate.

Table 1. Optimization of the reaction conditions in the synthesis of dimethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate (Scheme 2).

Entry	Catalyst (g)	Temp. (°C)	Solvent (5 mL)	Time (min)	Yield (%)[a]
1	0.05	r.t.	Toluene	48	55
2	0.05	r.t.	$CHCl_3$	26	89
3	0.05	r.t.	CH_3CN	22	88
4	0.05	r.t.	EtOAc	28	88
5	0.05	r.t.	MeOH	17	89
6	0.05	r.t.	-	10	90
7	0.02	r.t.	-	17	85
8	0.035	r.t.	-	13	88
9	0.075	r.t.	-	10	90

[a]Isolated Yields.

Table 2. Preparation of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates using $H_3[P(Mo_3O_{10})_4].xH_2O$ as catalyst (Scheme 1).

Entry	Amine	R	Time (min)	Yield (%)[a]	m.p. (°C)		Ref.
					Found	Reported	
1	Aniline	Me	10	90	Oil	Yellow oil	[9]
2	Aniline	Et	13	89	86-88	85-86	[9]
3	4-Chloro aniline	Me	15	89	Oil	Viscous	[11]
4	4-Chloro aniline	Et	17	88	Oil	Oil	-
5	4-Bromo aniline	Me	12	90	153-155	152-153	[11]
6	4-Bromo aniline	Et	15	88	149-151	143-145	[10]
7	4-Methyl aniline	Me	8	92	Oil	Oil	-
8	4-Methyl aniline	Et	10	90	Oil	Yellow oil	[9]
9	4-Methoxy aniline	Et	10	87	117-119	114–116	[10]
10	Butyl amine	Et	10	75	Oil	Yellow oil	[9]
11	Benzyl amine	Me	12	89	Oil	Yellow oil	[9]
12	Benzyl amine	Et	15	88	Oil	Yellow oil	[9]
13	Methyl amine	Me	8	90	Oil	Viscous	[11]
14	Methyl amine	Et	10	89	Oil	Oil	-

[a]Isolated yields; all known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples [5-11].

However increasing the catalyst concentration to 3 mol% led to a significant improvement in the product yield after 10 min. Increasing the amount of catalyst did not improve the yield significantly. Finally, we achieved an optimized condition using 3 mol% of catalyst and solvent-free condition at ambient temperature.

Having established the optimized reaction conditions, we then successfully synthesized a variety of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydro pyrimidine-4,5-dicarboxylates, and the results were summarized in Table 2.

Similarly, the multi-component reaction of substituted dialkylacetylene dicarboxylate, aniline and formaldehyde proceeded effectively over $H_3[P(Mo_3O_{10})_4].xH_2O$ and the yield of products was in the range of 75-92%. In general, aromatic amines were well tolerated in this reaction system (Table 2, Entries 1-14). Based on the obtained results, the steric effects of the substituents in dialkylacetylene dicarboxylates played significant role in the rate of the reaction. When diethylacetylene dicarboxylate were used in this process, the corresponding product was obtained in good yields but in longer reaction time (Table 2). Electron donating group on the amine was able to facilitate the transformation by giving evidently shorter reaction times (Table 2).

In order to estimate the efficiency and generality of this methodology, the obtained result in the synthesis of dimethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine -4,5-dicarboxylate by this method has been compared with those of the previously reported methods. The results are summarized in Table 3. It was found that the present method is convincingly superior to the reported methods with respect to reaction time and the yield of the product.

Our attention was then turned to the possibility of recycling the catalyst from the reaction media since the recovery and reuse of the catalyst are highly preferable for a greener process. At the completion of the reaction, the reaction mixture was poured into $CHCl_3$ and stirred for 5 min. The solid catalyst separated was filtered via simple filtration, dried and reused for subsequent reactions. The reusability of the catalyst was investigated by using aniline/ diethyl acetylene dicarboxylate/ formaldehyde as model substrates. After 5 recycles, the catalyst still had a high activity and gave the corresponding product in good yield (Fig. 1).

4. Conclusions

In summary, a simple and efficient method for the one-pot three-component synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine-4,5-dicarboxylates was described from the three-component reaction of dialkylacetylene dicarboxylates, amines and formaldehyde in the presence of 3 mol % $H_3[P(Mo_3O_{10})_4].xH_2O$ as catalyst. This procedure is a green and useful procedure for the synthesis of diethyl/methyl 1,3-diaryl-1,2,3,6-tetrahydropyrimidine -4,5-dicarboxylate derivatives.

Acknowledgment

We are thankful to the Kerman University of Medical Sciences research council for partial support of this research.

Table 3. Comparison results of $H_3[P(Mo_3O_{10})_4].xH_2O$ with other catalysts reported in the literature.

Entry	Catalyst	Condition	Yield (%)[a]	Ref.
1	$AgBF_4$/L-proline	DMF, r.t.; 5 h	80	[10]
2	I_2	MeOH; r.t.; 35 min	82	[11]
3	HCl	Water; reflux; 140 min	57	[5]
4	H_2SO_4	Water; reflux; 125 min	62	[5]
5	HNO_3	Water; reflux; 90 min	65	[5]
6	Acetic acid	Water; reflux; 75 min	72	[5]
7	$ZrOCl_2$	Water; reflux; 20min	90	[5]
8	$H_3[P(Mo_3O_{10})_4].xH_2O$	Solvent-free; r.t.; 10 min	90	This work

[a]Isolated Yield; based on the preparation of dimethyl 1,2,3,6-tetrahydro-1,3-diphenylpyrimidine-4,5-dicarboxylate.

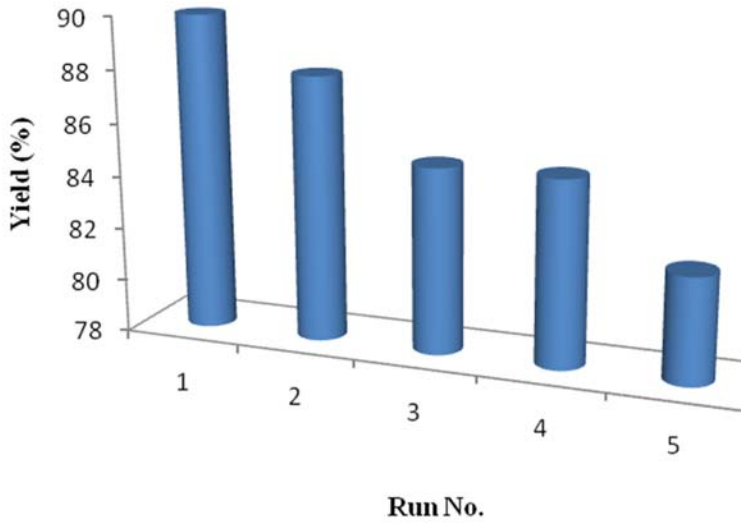


Fig. 1. Reusability of the catalyst.

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