Journal of Materials and Environmental Sciences
ISSN : 2028-2508
CODEN : JMESCN

J. Mater. Environ. Sci., 2018, Volume 9, Issue 12, Page 3155-3159

http://www.jmaterenvironsci.com

Aqueous solvent as a safe and eco-friendly medium for the clean synthesis of furo[2,3-*d*]pyrimidines

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Received 24 May 2017,
Revised 12 Jan 2018,
Accepted 19 Jan 2018

Keywords
- ✓ Three component reactions,
- ✓ Furo[2,3-*d*]pyrimidines,
- ✓ 1,3-Dimethylbarbituric acid,
- ✓ Isocyanides,
- ✓ Aromatic aldehydes

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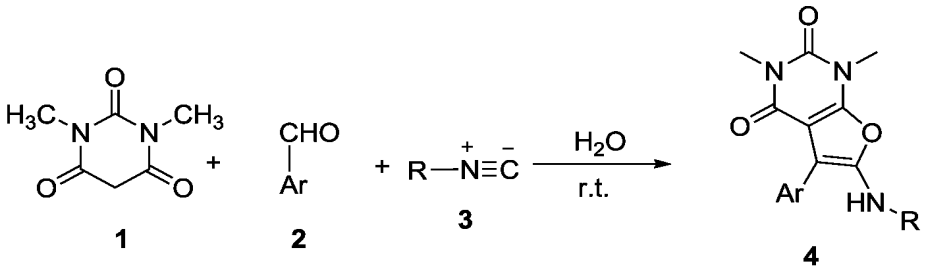
Abstract

An efficient procedure for the one-pot three-component synthesis of various 5-aryl-1,3-dimethyl-6-alkylamino furo[2,3-d]pyrimidines using 1,3-dimethylbarbituric acid and isocyanides in the presence of aromatic aldehydes in water medium is reported. All products were obtained in good yields in simple reaction conditions.

1. Introduction

Deploying of the eco-friendly and safe procedures in synthetic chemistry is one of important goals for an organic chemist [1,2]. Reactions can be influenced by a number of parameters such as solvent [3,4]. Solvent-free methods contain disadvantages when all reactants are in solid phase. Despite the simple dissolving of the chemicals in organic solvents to carry out of a reaction, some negative aspects of these solvents such as safety hazards, eco-toxicity, waste management impels organic chemists to apply a healthy safe and eco-friendly solvent. There is no healthy safe, none toxic and eco-friendly solvent for chemical reactions except water. Because of importance growing of multicomponent reactions in the past decade due to atom economy, development of safe protocols such as utilize of inexpensive and none toxic solvent can be important goal in molecular science [5-9]. In addition to the items listed above, some properties of water such as its viscosity and polarity enables chemists to extract products via a simple workup [10,11].The use of water as a solvent in chemical reactions allows an organic chemist to use various catalysts in the synthesis of organic compounds [12]. Some organic solvents such as benzene, toluene and methanol can be harmful and toxic to human health because of atmosphere pullation [13,14]. In recent years, there are severeal reports on synthesis of heterocyclic systems containing N, O and S atoms [15-20].In continuation of our attempts [21-24] for synthesis of biological active heterocyclic compounds [25-33],we decided to synthesis of furo[2,3-*d*]pyrimidine derivatives by a three-component condensation reaction of 1,3-dimethylbarbituric acid and benzaldehydes in the presence of isocyanides in a safe, efficient and mild condition using water medium [19].



Shceme 1. Synthesis offuro[2,3-*d*]pyrimidines

2. Experimental

2.1. Material and Methods

Melting points and IR spectra of all compounds were measured on an Electrothermal 9100 apparatus and a Shimadzu Prestige 21 FT-IR spectrometer, respectively. Also, the ^{1}H and ^{13}C NMR spectra were obtained with a BRUKER DRX-400 AVANCE instruments using $CDCl_3$ as a solvent and TMS as internal standard at (400.1, 100.1) MHz, respectively. Elemental analyses for C, H and N were performed using a Heraeus CHN-O-Rapid analyzer. In addition, the mass spectra were recorded on a Shimadzu GCMS-QP5050A mass spectrometer operating at an ionization potential of 70 eV. Isocyanides, 1,3-dimethylbarbituric acid and aromatic carbaldehyde derivatives were purchased from Fluka, Merck and Acros companies and used without further purification.

2.2. Synthesis

General procedure for preparation of furo[2,3-*d*]pyrimidine derivatives (Exemplified by **4e**).

To a magnetically stirred solution of 2-fluorobenzaldehyde (1 mmol) and 1,3-dimethylbarbituric acid (1 mmol) in H_2O(5 mL) was added, dropwise, a mixture of cyclohexylisocyanide (1.1 mmol) in H_2O (3 mL) over 10 min at room temperature. After appropriate time stirring for reaction moieties at room temperature and completion of the reaction (monitored by TLC), the residue was filtered off and crude product washed by diethyl ether (2×3 mL), then the residual was recrystalized in a mixture of ethyl acetate/n-hexane (2:1) to afford final product **4e**.

- 6-(Cyclohexylamino)-1,3-dimethyl-5-(2-fluorophenyl)furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4e**)

Pale white Powder, yield: (78%, 0.29 g), mp 192-195°C; ^{1}H NMR ($CDCl_3$)δ_H: 1.19-2.00 (10H, m, 5×CH_2 of cyclohexyl); 3.25 and 3.37 (6H, 2s, 2×NCH_3); 3.67 (1H, m, NC*H*); 6.46 (1H, d, *J* = 8.2 Hz, N*H*); 7.07 (1H, t, *J* = 9.3 Hz, Ar*H*); 7.18 (1H, t, *J* = 7.4 Hz, Ar*H*); 7.35-7.44 (2H, m, Ar*H*). ^{13}C NMR ($CDCl_3$)δ_C: 23.76, 23.80 and 24.40 (3s, 3×*C*H_2 of cyclohexyl); 28.40 and 28.61 (2s, 2×N*C*H_3); 31.60 and 31.65 (2s, 2×*C*H_2 of cyclohexyl); 47.85 (s, N*C*H of cyclohexyl); 93.11 (s, C_{4a}); 96.73 (s, C-5); 114.77 (d, *J* = 20.1 Hz, *C*H); 116.83 (d, *J* = 7.0 Hz, *C*); 123.43 (d, ^{2}J = 12.5 Hz, *C*H); 130.53 (d, ^{3}J = 8.2 Hz, *C*H); 134.11 (d, *J* = 4.5 Hz, *C*H); 150.03 (s, C-6); 154.00 (s, C-2); 158.11(s, C_{7a}); 160.60 (d, ^{1}J = 136.8 Hz, *C*); 161.07 (s, C-4). Anal.Calcd for $C_{20}H_{22}FN_3O_3$ (371.41): C, 64.68; H, 5.97; N, 5.12%. Found: C, 64.61; H, 5.88; N, 5.19 %. MS: *m/z* (%) =371 ([M]$^+$, 1), 351 (5), 312 (46), 285 (52), 165 (36), 84 (100), 43 (28).IRν_{max}, cm^{-1}: 3314 (NH), 1679 (C=O).

- 6-(Cyclohexylamino)-1,3-dimethyl-5-(2,4-dinitrophenyl)furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4i**)

Yellow Powder, yield: (86%, 0.4 g), mp 126-128°C; ^{1}H NMR ($CDCl_3$)δ_H: 1.25-2.04 (10H, m, 5×CH_2 of cyclohexyl); 3.28 and 3.32 (6H, 2s, 2×NCH_3); 3.70 (1H, m, NC*H*); 6.61 (1H, brs, N*H*); 7.83 (1H, t, *J* = 9.6 Hz, Ar*H*); 8.26 (1H, dd, *J* = 2.0 and *J* = 9.6 Hz, Ar*H*); 9.07 (1H, d, *J* = 2.0 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$)δ_C: 23.62, 23.84 and 24.51 (3s, 3×*C*H_2 of cyclohexyl); 28.33 and 28.65 (2s, 2×N*C*H_3); 31.57 and 31.61 (2s, 2×*C*H_2 of cyclohexyl); 47.82 (s, N*C*H of cyclohexyl); 94.07 (s, C_{4a}); 95.91 (s, C-5); 125.35 (s, *C*H); 131.05 (s, *C*); 132.54 (s, *C*H); 137.14 (s, *C*H); 146.22 (s, *C*); 149.06 (s, *C*); 149.11 (s, C-6); 153.15 (s, C-2); 159.03 (s, C_{7a}); 162.10 (s, C-4). Anal.Calcd for $C_{20}H_{21}N_5O_7$ (443.41): C, 54.17; H, 4.77; N, 15.79%. Found: C, 54.22; H, 4.81; N, 15.85%. MS: *m/z* (%) =443 ([M]$^+$, 7), 360 (22), 344 (36), 275 (52), 176 (100), 84 (74), 43 (11).IRν_{max}, cm^{-1}: 3310 (NH), 1646 (C=O), 1321 (NO_2).

- 6-(Cyclohexylamino)-1,3-dimethyl-5-(3-fluorophenyl)furo[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**4k**)

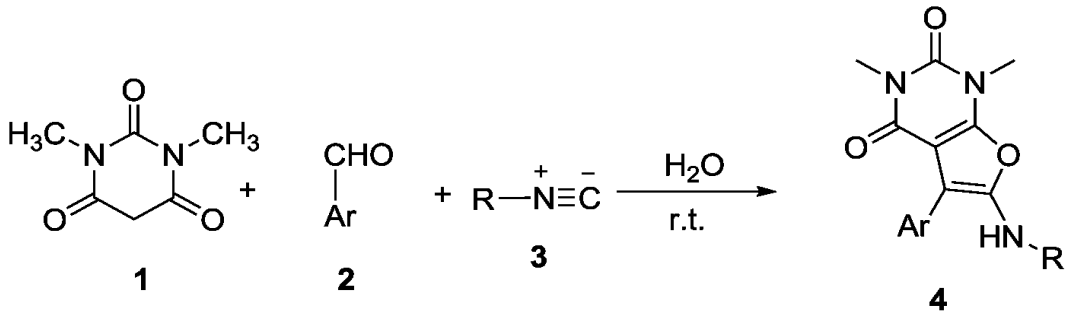
Yellow Powder, yield: (81%, 0.3 g). mp 165-168°C; ^{1}H NMR ($CDCl_3$)δ_H: 1.12-1.19 (10H, m, 5×CH_2 of cyclohexyl); 3.14 and 3.36 (6H, 2s, 2×NCH_3); 3.65 (1H, m, NC*H*); 6.22 (1H, d, *J* = 8.0Hz, N*H*); 7.08 (1H, m, Ar*H*); 7.34 (1H, q, *J* = 8.0 Hz, Ar*H*); 7.41 (1H, d, *J* = 9.0 Hz, Ar*H*); 7.47 (1H, d, *J* = 7.6 Hz, Ar*H*). ^{13}C NMR ($CDCl_3$)δ_C: 23.51, 23.77 and 24.36 (3s, 3×*C*H_2 of cyclohexyl); 28.32 and 28.56 (2s, 2×N*C*H_3); 31.61 and 31.66 (2s, 2×*C*H_2 of cyclohexyl); 47.93 (s, N*C*H of cyclohexyl); 93.43 (s, C_{4a}); 97.05 (s, C-5); 114.11 (d, *J* = 23.9 Hz, *C*H); 115.97 (d, *J* = 6.0 Hz, *C*H); 122.44 (s, *C*H); 124.68 (d, *J* = 8.5 Hz, *C*H); 126.08 (s, *C*); 150.07 (s, C-6); 155.00 (s, C-2); 160.11(s, C_{7a}); 161.41 (d, *J* = 133.6 Hz, *C*); 162.03 (s, C-4). Anal.Calcd for $C_{20}H_{22}FN_3O_3$ (371.41): C, 64.68; H, 5.97; N, 5.12%. Found: C, 64.57; H, 5.82; N, 5.23%. MS: *m/z* (%) =371 ([M]$^+$, 2), 353 (9), 285 (8), 138 (100), 84 (12), 41 (20).IRν_{max}, cm^{-1}: 3324 (NH), 1684 (C=O).

3. Results and discussion

It was observed that three component condensation reaction of 1,3-dimethylbarbituric acid **1** and benzaldehydes**2** in the presence of isocyanides **3** proceeds smoothly to generate furo[2,3-*d*]pyrimidine derivatives **4** in high yields in water medium under neutral conditions (Scheme 1).

To explore the scope and limitations of the reaction, the procedure was extended to various aromatic aldehydes **2a-k** (Table I). The spectral data and physical properties of the furo[2,3-*d*]pyrimidine **4a-k** are in a good agreement with those of literature reported. Results from Table I showed that reaction time for synthesized compounds have short reaction time in comparison to previous reported compounds in literature. To prove the efficiency of presented methodology spectroscopic characterization of new compounds has been done for **4e, 4i** and **4k**.

Table I: Three component condensation reaction of 1,3-dimethylbarbituric acid and benzaldehydes in the presence of isocyanides.



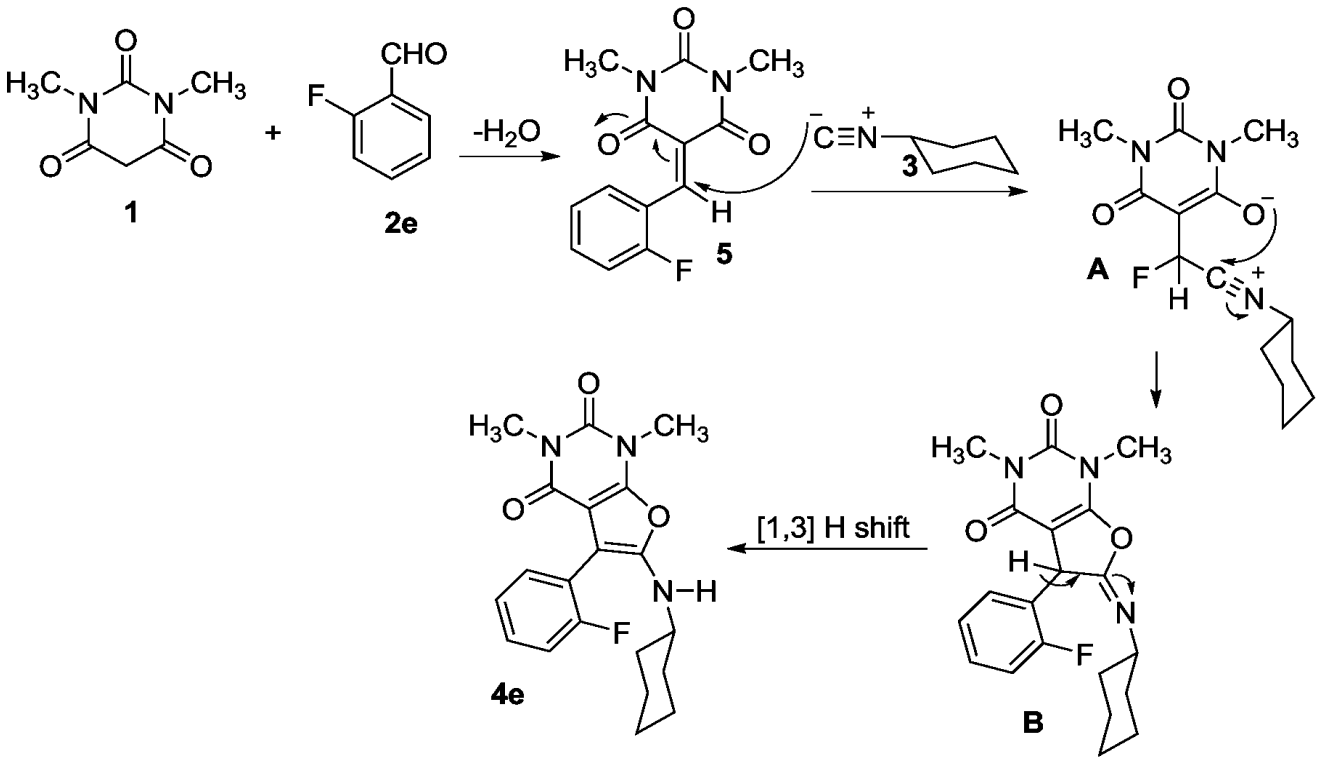
Entry	R	Ar	Time (min)	Yield (%)	m.p.[a]	m.p.[b]	ref.
4a	cyclohexyl	4-methoxyphenyl	160	86	124-127	122-124	20
4b	*t*-butyl	2-pyridyl	95	91	175-178	178-181	11
4c	*t*-butyl	3-pyridyl	115	82	178-181	137-140	11
4d	cyclohexyl	4-pyridyl	70	88	157-159	151-154	11
4e	cyclohexyl	2-flourophenyl	85	78	192-195	--------	
4f	cyclohexyl	phenyl	90	84	125-128	124-126	20
4g	cyclohexyl	2-pyridyl	70	86	131-134	131.5-133.5	11
4h	*t*-butyl	3-chlorophenyl	50	92	149-152	149-152	21
4i	cyclohexyl	2,4-dinitrophenyl	120	86	126-128	--------	
4j	2,6-dimethyphenyl	3-nitrophenyl	45	82	214-216	214-217	22
4k	cyclohexyl	3-flourophenyl	75	81	165-168	--------	

a: Previously reported melting points.
b: Found melting points.

All synthesized compounds **4a-k** displayed distinct absorption bands at the carbonyl and amine regions resulting from the carbonyl and NH groups, respectively.

The ^{1}H NMR spectrum of **4e** exhibited multiplet signals for five (-C*H*$_2$-) of cyclohexyl group at δ=1.19-2.00 ppm and also a multiplet signals arising from NC*H* proton at δ= 3.67 ppm, respectively. Two *N*-methyl protons of barbituric acid moiety resonate δ=3.25 and 3.37 ppm. The N*H* proton and all arylic protons of **4e** appear at δ=6.46 ppm and aromatic region δ= 7.07-7.44 ppm, respectively.

The ^{1}H decoupled ^{13}C NMR spectrum of **4e** showed eight signals readily recognized as arising from aliphatic carbons of cyclohexyl ring at δ= 23.76-47.85 ppm and also two N*C*H$_3$ group at (δ= 28.40 and 28.61 ppm), respectively. The characteristic signals for the carbonyl groups of C-2 and C-4 were observed at δ= 154.00 and 161.07 ppm, respectively.An illustrative mechanism for this reaction is shown in Scheme 2.



Scheme 2. Proposed mechanism for the synthesis of furo[2,3-*d*]pyrimidines

Conclusion

In conclusion we have developed an efficient route for the synthesis of furo[2,3-*d*]pyrimidine derivatives via a one-pot condensation reaction using water media as a green solvent without any catalyst and hazard effects.

Acknowledgments-The author is grateful to the Research Council of Urmia University for the financial support.

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