Chem Sci Trans., 2013, **2(2),** 441-446
DOI:10.7598/cst2013.385

Chemical Science Transactions
ISSN/E-ISSN: 2278-3458/2278-3318

RESEARCH ARTICLE

Facile and Green Syntheses of 5-Arylidene-pyrimidine-2,4, 6-triones and 5-Arylidene-2-thioxo-dihydro-pyrimidine-4, 6-diones Using *L*-Tyrosine as an Efficient and Eco-Friendly Catalyst in Aqueous Medium

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Received 17 September 2012 / Accepted 20 October 2012

Abstract: *L*-Tyrosine has been utilized as an efficient and eco-friendly catalyst for the Knoevenagel condensation of arylaldehydes **1(a-k)** with barbituric acid and 2-thiobarbituric acid containing cyclic active methylene groups in aqueous medium at room temperature to produce 5-arylidene-pyrimidine-2,4,6-triones and 5-arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones **3(a-p).**

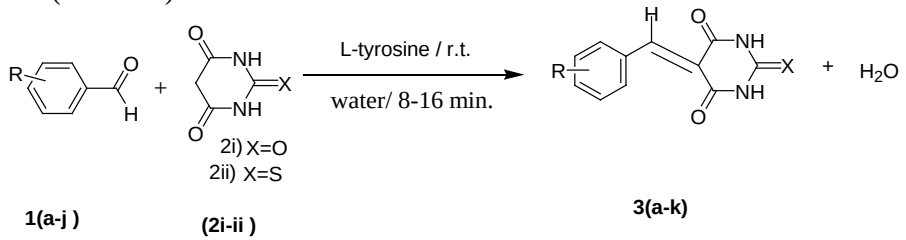
Keywords: Arylaldehydes, Knoevenagel condensation, Barbituric acid, 2-Thiobarbituric acid, *L*-tyrosine

Introduction

Carbon–carbon double bond formation reaction is the most important reaction in organic synthesis[1-3]**.** The Knoevenagel condensation is one such reaction which facilitates C-C double bond formation and has been widely used in synthesis of fine chemicals[4], hetero Diels-Alder reactions[5] and in synthesis of carbocyclic[6] as well as heterocyclic compounds[7] of biological significance. These reactions are usually catalyzed by bases[8-10] such as primary and secondary amines and their corresponding ammonium salts, potassium fluoride in organic solvents. Lewis acids[11-12], alumina[13], Al_2O_3-$AlPO_4$[14], zeolite[15] and ionic liquids[16-20] have also been added to the existing list of substances that assisted Knoevenagel condensation in organic synthesis. The use of water[21-24] as solvent, the most environmentally benign of all solvents, offers a very useful green methodology from both the economical and synthetic points of view. It not only reduces the problem of disposal of organic solvents, but also at times enhances the progress of many organic reactions.

Arylidene-pyrimidine-2,4,6-trione,arylidene-2-thioxodihydropyrimidine-4,6-dione and its derivatives are importance members of pyrimidine family. These compounds have been found to be esteemed variety of pharmacological activities[25–27]. Arylidene-pyrimidine-2,4,6-trione, arylidene-2-thioxo-dihydro-pyrimidine-4,6-dione and its derivatives were found to have hypotensive, transiquilizer and good anti-bacterial agents[28,29]**.**

Thus, the synthesis of arylidene-pyrimidine-2,4,6-trione and arylidene-2-thioxo-dihydro-pyrimidine-4,6-dione are recently of very much importance. There are several methods reported in the literature for the synthesis of arylidene-pyrimidine-2,4,6-triones and arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones such as[30-40] base, acetic acid as catalyst in water under reflux conditions, montmorillonite KSF clay under microwave irradiation, ammonium acetate in acetic acid, montmorillonite K-10, silica gel, basic alumina, NaCl, montmorillonite KFS, KSF/NaCl, $BiCl_3$. Each of these methods have their own advantages but also be affected from disadvantages such as long reaction times, low to moderate yields, tedious work-up procedures, requirement of special apparatus, use of organic solvents, requirement of excess of catalysts and difficulty in recovery and reusability of the catalysts. To the best of our knowledge, *L*-tyrosine has not been used as a catalyst for the synthesis of arylidene-pyrimidine-2,4,6-triones and arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones and attracted our attention to investigate the application of *L*-tyrosine as a catalyst. The aqueous medium reaction has many advantages: reduced pollution, low costs and simplicity in process and handling. Here in, we reported a simple and efficient synthesis of arylidene-pyrimidine-2,4,6-trione and arylidene-2-thioxo-dihydro-pyrimidine-4,6-dione by the Knoevenagel condensation of aromatic aldehydes with barbituric acid and 2-thiobarbituric acid containing cyclic active methylene group in the presence of *L*-tyrosine in aqueous medium (Scheme 1).



(a) R= C_6H_5, (b)R = CH_3-C_6H_4, (c) R = OCH_3-C_6H_4, (d) P-(Me_2N)-C_6H_4, (e) P-(OH)-C_6H_4, (f) *P*-(NO_2)-C_6H_4, (g) *P*-(Cl)-C_6H_4, (h) *P*-(F)-C_6H_4, (i) *m*-(NO_2)-C_6H_4, (j) *m*-(OCH_3)-C_6H_4, (k) *o*-(OH)-C_6H_4

Scheme 1. Knoevenagel condensation of arylaldehydes with barbituric acid and 2-thiobarbituric acid in presence of *L*-tyrosine as an Eco-Friendly catalyst in aqueous medium at temperature

Experimental

Melting points were measured in open capillary tubes and are uncorrected. TLC was done on plates coated with silica gel-G and spotting was done using iodine or UV lamp. IR-spectra were recorded using FT-IR in KBr phase. ^{1}H-NMR spectra were recorded at 400 MHz, respectively. Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples.

*General Procedure for the preparation of **3(a-k)** from **1(a-k)** and barbituric acid (**2i**)*

A mixture of **1** (10 mmol), barbituric acid **2** (10 mmol) and *L*-tyrosine (2 mmol) was stirred in aqueous medium at room temperature for a specified period of time (Table 1). After completion of reaction, the mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (100 mL) and dried to obtain crude **3(a-k).** The latter were then recrystallised from ethanol to afford pure **3(a-k).** Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples.

*General procedure for the preparation of **3(l-p)** from **1(l-p)** and 2-thiobarbituric acid **(2ii)***

A mixture of **1** (10 mmol), 2-thiobarbituric acid **2** (10 mmol) and *L*-tyrosine (2 mmol) was stirred in aqueous medium at room temperature for a specified period of time (Table 1). After completion of reaction, the mixture was poured into ice-cold water (50 mL). The separated solid was filtered, washed with water (100 mL) and dried to obtain crude **3(l-p).** The latter were then recrystallised from ethanol to afford pure **3(l-p).** Compounds are known and products were identified by spectral and melting-point comparison with the authentic samples**.**

Results and Discussion

Treatment of aromatic aldehydes **1(a-k)** with barbituric acid and 2-thiobarbituric acid **(2i-ii)** containing cyclic active methylene groups in the presence *L*-tyrosine in aqueous medium at room temperature for 8-16 min. resulted in the formation of arylidene-pyrimidine-2,4,6-triones and arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones **3(a-p)** in 92-96% yields (Table 1) (Scheme 1). This method is very facile and convenient for the preparation of large amount of Knoevenagel products with high yields in less time**.** *L*-tyrosine acts as a base to induce the reaction**.**

Table 1. Synthesis of arylidene-pyrimidine-2,4,6-triones and arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones with Knoevenagel condensation in aqueous medium at room temperature

S.No	R	X	Time, min	Yield %	mp, °C	mp. °C Ref [41-45]
a	C_6H_5	O	8	93	257-259	256-258
b	4-CH_3-C_6H_4	O	14	92	274-276	276-277
c	4-OCH_3-C_6H_4	O	14	93	295-297	296-298
d	*p*-(Me_2N)-C_6H_4	O	15	92	261-262	262-263
e	*p*-(OH)-C_6H_4	O	16	92	299–301	297-299
f	*p*-(NO_2)-C_6H_4	O	10	96	172-173	272-274
g	*p*-(Cl)-C_6H_4	O	9	95	298-300	297-298
h	*p*-(F)-C_6H_4	O	8	95	296-298	295-297
i	*m*-(NO_2)-C_6H_4	O	8	96	231-234	231-233
j	*m*-(OCH_3)-C_6H_4	O	14	93	186-188	187-190
k	*o*-(OH)-C_6H_4	O	16	92	248-249	249-251
l	C_6H_4	S	8	95	298-301	>300
m	4-$CH_3C_6H_4$	S	8	96	>300	>300
n	4-$CH_3OC_6H_4$	S	14	93	299-302	>300
o	4-FC_6H_4	S	16	92	218-219	217-218
p	4-ClC_6H_4	S	8	95	291-293	291-292

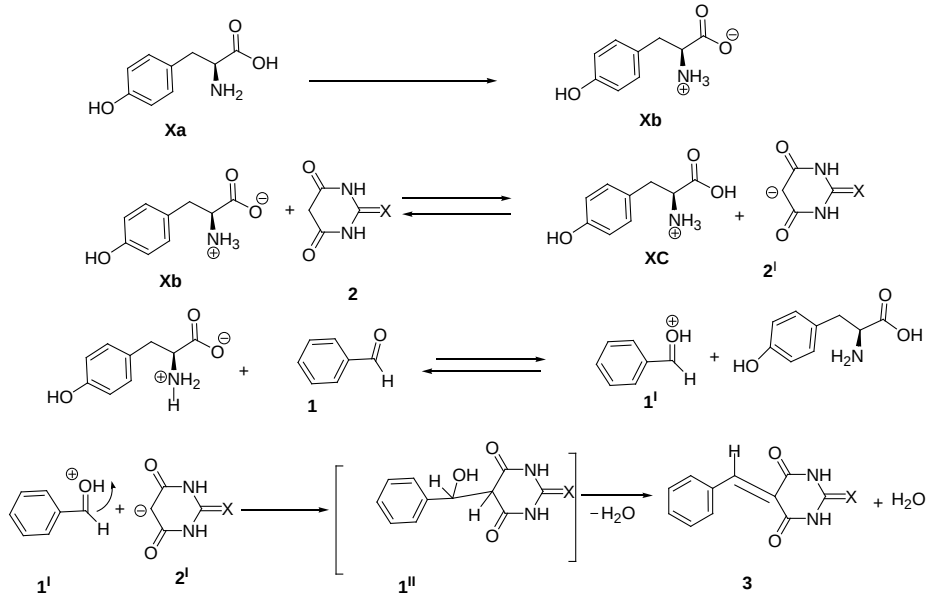
In the absence of *L*-tyrosine, the reaction does not proceed the reactants in aqueous medium at room temperature for 18 h**.** The use of *L*-tyrosine as a catalyst helps to avoid the use of environmentally unfavourable organic solvents as reaction medium**.** In all cases, the reaction proceeded smoothly with catalytic amount of *L*-tyrosine to give products of very good purity**.**

The above reactions of arylaldehydes **1(a-k)** with barbituric acid and 2-thiobarbituric acid **(2i-ii)** containing cyclic active methylene group was attempted in the presence of various

bases like NaOH, KOH were too strong bases to result in more by-products**.** Low yield was obtained and long reaction time is needed using K_2CO_3, ammonium acetate, piperidine and triethylamine as catalyst for condensation of arylaldehydes **1(a-k)** with barbituric acid and 2-thiobarbituric acid **(2i-ii)** containing cyclic active methylene group in aqueous medium at room temperature**.**

From Table 1, it was shown that the condensation of arylaldehydes with electron withdrawing group such as $–NO_2$ and -Cl at para position with barbituric acid and 2-thiobarbituric acid **(2i-ii)** containing cyclic active methylene group can be carried out in relatively shorter time and higher yield than with electron donating group such as –OH and *N*, *N*-dimethyl arylaldehydes in aqueous medium at room temperature.

A plausible mechanism for the formation of **3** from **1** and **2(i-ii)** in the presence of *L*-tyrosine as catalyst is shown in the Scheme 2**.** In the mechanism shown in Scheme-2, *L*-tyrosine, in its zwitterionic form **(Xb),** abstracts a proton from barbituric acid and 2-thiobarbituric acid**(2i-ii)** containing cyclic activemethylene group forming the carbanion of barbituric acid and 2-thiobarbituric acid **(2^{I})**. Which then attacks the protonated arylaldehydes **(1^{I})** forming the corresponding intermediate **(1^{II})** that loses water to form the end product **3.**



Scheme 2. Plausible mechanism for the formation of **3** from **1** and **2(i-ii)** in the presence of *L*-tyrosine as an Eco- Friendly catalyst in aqueous medium at room temperature

Conclusion

In summary, *L*-tyrosine as an efficient and Eco-Friendly catalyst for the preparation of arylidene-pyrimidine-2,4,6-trione and arylidene-2-thioxo-dihydro-pyrimidine-4,6-dione by Knoevenagel reaction in aqueous medium at room temperature. This method is applicable to a wide range of arylaldehydes **1(a-p)** and barbituric acid and 2-thiobarbituric acid containing cyclic active methylene group to produce arylidene-pyrimidine-2, 4,6-trione and arylidene-2-thioxo-dihydro-pyrimidine-4,6-dione **3(a-p)** in aqueous medium at room temperature.

The attractive features of this procedure are the mild reaction conditions, high conversions, operational simplicity and inexpensive and ready availability of the catalyst, all of which make it a useful and attractive strategy for the preparation of arylidene-pyrimidine-2,4,6-triones and arylidene-2-thioxo-dihydro-pyrimidine-4,6-diones in aqueous medium at room temperature.

Acknowledgement

The authors are thankful to the Jawaharlal Nehru Technological University Hyderabad, India for providing financial support and to the principal of Jawaharlal Nehru Technological University Hyderabad college of Engineering, Kukatpally, Hyderabad for providing laboratory facilities.

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