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Der Pharma Chemica, 2012, 4(5):1897-1901
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

L-tyrosine catalyzed Knoevenagel condensation: Facile synthesis of cyanoacrylonitriles cyanoacrylates and cyanoacrylamides in solvent free condition under grindstone method.

G. Thirupathi*, M. Venkatanarayana, P. K. Dubey and Y. Bharathi Kumari

Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad College of Engineering, Kukatpally, Hyderabad (A.P), India-500 085

ABSTRACT

L-tyrosine has been utilized as an efficient catalyst for the Knoevenagel condensation of arylaldehydes with active methylene compounds such as malononitrile, ethylcyanoacetate and cyanoacetamide in solvent free condition under grindstone method at room temperature to afford cyanoacrylonitriles, cyanoacrylates and cyanoacrylamides.

Keywords: Activemethylene compounds, arylaldehydes, Knoevenagel condensation, physical grinding, L-tyrosine

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INTRODUCTION

Toda introduced a method called the grindstone method [1-3]. In this method, solids are ground together using a pestle and mortar to get the products**.**These reactions is more efficient and selective than those carry out in the corresponding solutions.

Carbon–carbon bond formation reaction is the most important reaction in organic synthesis [4-8]. The Knoevenagel condensation is one such reaction which facilitates C-C double bond formation and has been widely used in synthesis of olefins, cosmetic, perfume and pharmaceutical industry. These reactions are usually catalyzed by bases [8-16] such as primary and secondary amines and their corresponding ammonium salts, piperidine, pyridine, ethylene diamine and sodium ethoxide in organic solvents. Lewis acids, [17-22] zeolite, [23] heterogeneous catalysts, [24] microwave irradiation, [25] ionic liquids,[26] and grinding techniques have also been added to the existing list of substances that assisted Knoevenagel condensation in organic synthesis. The grinding techniques are 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.

Tyrosine is an known to be an efficient, bi-functional, zwitterionic and eco-friendly catalyst. It is available in both the enantiomeric, (S)-Tyrosine and (R)-Tyrosine, forms**.** The two functional groups of Tyrosine enable it to act both as an acid as well as a base catalyst in chemical condensation reactions.

In this report, we highlight our findings on the L-tyrosine catalyzed condensation of arylaldehydes with active methylene compounds such as malononitrile, ethylcyanoacetate, and cyanoacetamide in solvent free condition under

grind stone method at room temperature to afford cyanoacrylonitriles, cyanoacrylates and cyanoacrylamides in solvent free condition under grindstone method at room temperature.

MATERIALS AND METHODS

Experimental Section:
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 on a gemini-200 and av-400 operating at 200 and 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-e) from 1 (a-e) and malononitrile.
A mixture of **1** (10 mmol), malononitrile **2** (10 mmol) and L-tyrosine (2 mmol) was physical grinded in solvent free condition under grindstone method at room temperature for a specified period of time **(Table 1).** After completion of reaction (as shown by TLC checking), 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-e).** The latter were then recrystallised from methanol to afford pure **3(a-e).** Compounds are known, and products were identified by spectral and melting-point comparison with the authentic samples.

General Procedure for the preparation of 3(f- j) from 1(a-e) and ethylcyanoacetate.
A mixture of **1** (10 mmol), ethylcyanoacetate **2** (10 mmol) and L-tyrosine (2 mmol) was physical grinded in solvent free condition under grindstone method at room temperature for a specified period of time **(Table 1).** After completion of reaction (as shown by TLC checking), 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.** The latter were then recrystallised from methanol to afford pure**3 (f-j).** Compounds are known, and products were identified by spectral and melting-point comparison with the authentic samples.

General Procedure for the preparation of 3(k-o) from 1(a-e) and cyanoacetamide.
A mixture of **1** (10 mmol), cyanoacetamide **2 (**10 mmol) and L-tyrosine (2 mmol) was physical grinded at room temperature for a specified period of time **(Table 1).** After completion of reaction (as shown by TLC checking), 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.** The latter were then recrystallised from methanol to afford pure **3(k-o).** Compounds are known, and products were identified by spectral and melting-point comparison with the authentic samples.

Table-1. Synthesis of alkenes with Knoevenagel condensation in solvent free condition under grindstone method at room temperature

				Time	Yield	mp	mp.(Lit. r.f)
S.NO.	R	X	Condition	(min)	(%)	(°C)	(°C)
a	C_6H_5	CN	r.t.	5	97	84-85	83-84[27,34]
b	C_6H_5	COOEt	r.t.	6	94	47-49	49[32,33]
c	C_6H_5	$CONH_2$	r.t.	8	91	197-199	197-199[12]
d	p-(Me_2N)-C_6H_4	CN	r.t.	7	95	188-189	200-201[34]
e	p-(Me_2N)-C_6H_4	COOEt	r.t.	8	92	125-127	140-141[30]
f	p-(Me_2N)-C_6H_4	$CONH_2$	r.t.	10	90	197-198	198-199[13]
g	p-(OH)-C_6H_4	CN	r.t.	7	95	187-188	183[9,37]
h	p-(OH)-C_6H_4	COOEt	r.t.	8	92	171-172	219[31,32,33]
i	p-(OH)-C_6H_4	$CONH_2$	r.t.	10	90	244-245	245-246[16]
j	p-(NO_2)-C_6H_4	CN	r.t.	4	97	161-162	159[29]
k	p-(NO_2)-C_6H_4	COOEt	r.t.	6	95	170-172	168 [32,33]
l	p-(NO_2)-C_6H_4	$CONH_2$	r.t.	7	93	231-232	233-234[12,35,36]
m	p-(Cl)-C_6H_4	CN	r.t.	5	96	161-163	162[28]
n	p-(Cl)-C_6H_4	COOEt	r.t.	6	93	92-94	92-94 [32,33]
o	p-(Cl)-C_6H_4	$CONH_2$	r.t.	8	92	208-210	210[20,12]

RESULTS AND DISCUSSION

Treatment of aromatic aldehydes **1(a-o)** with Active methylene compounds **2(a-c)** i.e. malononitriles, ethyl cyanoacetate and ethyl cyanoacetamide in the presence L-tyrosine in solvent free condition under grind stone

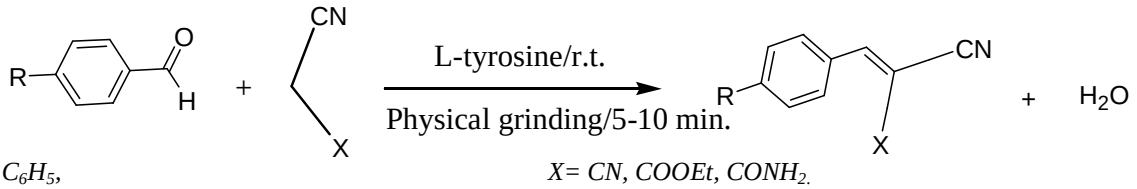
method at room temperature for 5-10 min. resulted in the formation of cyanoacrylonitriles, cyanoacrylates and cyanoacrylamides. **3(a-o)** in **90–97%** yields **(table-1) (scheme-1).** This method is very facile and convenient for the preparation of large amount of Knoevenagel products with high yields in less time. L-tyrosine acts as a base to induce the reaction.

In the absence of L-tyrosine, the reaction does not proceed the reactants in the solvent free condition under grind stone method at room temperature for 1 h. The use of L-tyrosine as a catalyst helps to avoid the use of environmentally unfavourable organic solvents as reaction medium. It is inexpensive, readily available and found to retain its activity even in the presence of water and other active functional groups such as CHO, −CO, NO_2, and CN present in the substrates. In all cases, the reaction proceeded smoothly with catalytic amount of L-tyrosine to give products of good purity. In the above reaction, the product has been assigned E-configuration on the basis of the assumption that the groups with maximum stereo chemical bulk would be more stable in a trans configuration.

The above reactions of arylaldehydes **1(a-o)** with active methylene compounds **2(a-c).**i.e., Malononitriles, ethyl cyanoacetate and ethyl cyanoacetamide were 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-o)** with active methylene compounds **2(a-c)** i.e. malononitriles, ethyl cyanoacetate and ethyl cyanoacetamide in the solvent free condition under the grind stone method 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 Active methylene compounds **2(a-c)** i.e. malononitriles, ethyl cyanoacetate and ethyl cyanoacetamide 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 the solvent free condition under the grind stone method at room temperature.

SCHEME-1



R= C_6H_5,
P-(Me_2N)-C_6H_4,
P-(OH)-C_6H_4,
P-(NO_2)-C_6H_4,
P-(Cl)-C_6H_4

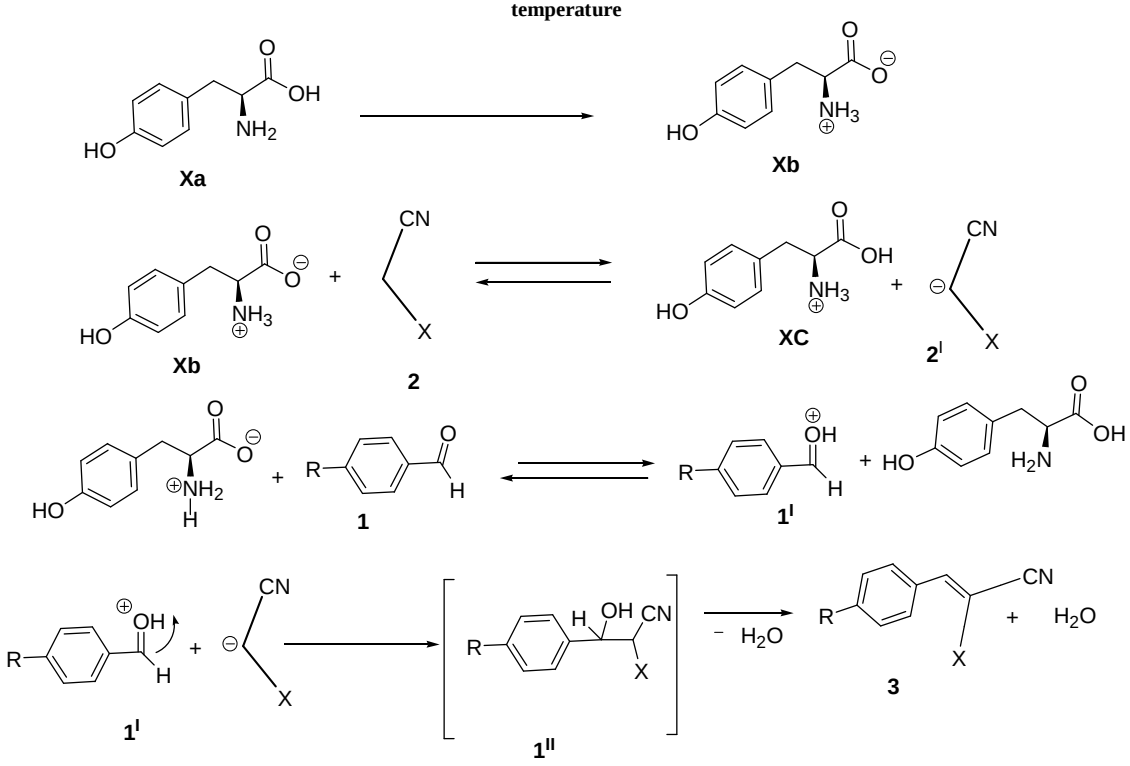
X= CN, COOEt, $CONH_2$.

A plausible mechanism for the formation of **3** from **1** and **2** 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 Activemethylene compounds **2** i.e. malononitriles, ethyl cyanoacetate and ethyl cyanoacetamide forming the carbanion of Activemethylene compounds .i.e.**(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: possible mechanism for the formation of 3 from 1 and 2 in the presence of L-tyrosine under solvent free condition at room temperature



CONCLUSION

In summary, L-tyrosine has been employed as an efficient catalyst for the preparation of aryl olefinic compounds by a Knoevenagel reaction in the solvent free condition under the grind stone method at room temperature. This method is applicable to a wide range of arylaldehydes **1(a-e)** and active methylene compounds **2(a-c).** to afford cyanoacrylonitriles, cyanoacrylates and cyanoacrylamides in solvent free condition under grindstone method 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 cyanoacrylonitriles, cyanoacrylates and cyanoacrylamides in solvent free condition under grindstone method at room temperature.

Acknowledgements
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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