



## TRIETHANOLAMINE AS AN EFFICIENT CATALYST FOR ONE-POT SYNTHESIS OF 2-AMINO-3-CYANO-4*H*-PYRAN DERIVATIVES

Amol U. Khandebharad, Swapnil R. Sarda, Mahesh G. Soni, Bhushan J. Joshi,

Siddhartha M. Runwal, Brijmohan R. Agrawal\*

<sup>a</sup>Department of Chemistry, J. E. S. College, Jalna, (MS) India.

Email: brijmohandevandan@gmail.com

### Abstract

An efficient and green synthesis of 2-Amino-3-cyano-4*H*-pyran Derivatives using triethanolamine as a catalyst for the three-component one pot reaction of aromatic aldehydes, ethylacetoacetate and malononitrile under ultrasound irradiation is described. This protocol offers several advantages such as atom efficiency, short reaction time, simple work-up and simple reaction condition.

### Introduction:

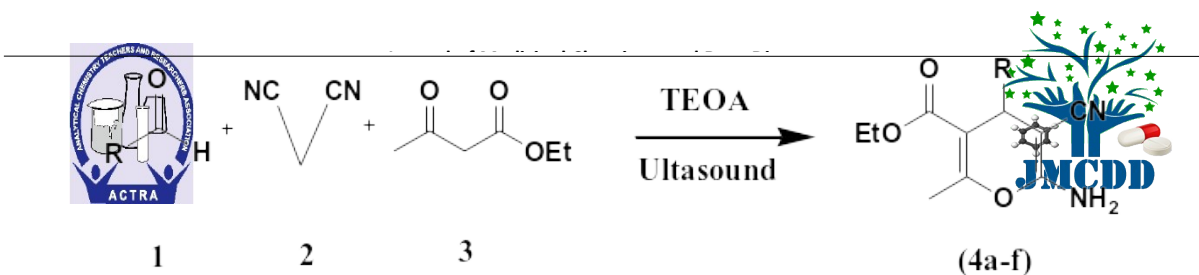
2-Amino-3-cyano-4*H*-pyran are an important class of pharmacologically active organic compounds. Considerable interest has been focused on the synthesis of 2-Amino-3-cyano-4*H*-pyran because of their wide range of biological activities and therapeutics. 4*H*-pyran derivatives are well distributed in naturally occurring compounds<sup>1</sup>. Organic compounds containing 4*H*-pyran ring shown biological activities such as antimicrobial<sup>2</sup>, anti-inflammatory<sup>3</sup>, anticancer<sup>4</sup>, cytotoxic<sup>5</sup>, anti-HIV<sup>6</sup>, antimalarial<sup>7</sup>, antihyperglycemic, and antidyslipidemic<sup>8</sup>, along with antineurodegenerative disorders like Alzheimer's, Parkinson disease, Huntington's disease etc. 4*H*-pyran moiety form the basis for a number of drugs are in used in the treatment of various ailments, such as hypertension, asthma, ischemia, and urinary incontinence<sup>9</sup>. These types of heterocyclic compounds have of pharmaceutical potentials. 4*H*-pyran moiety derivatives used in the field of medicinal<sup>10</sup>, agrochemical<sup>11</sup>, cosmetics, and pigment industries etc.



Due to a wide range of applicability in medicinal, industrial and in the fields of synthetic organic chemistry, there is increasing interest in the development of efficient methodologies for the synthesis of 2-Amino-3-cyano-4*H*-pyran moiety. Generally pyran derivatives synthesis carried out in a two-step reaction between a Michael acceptor malononitriles and  $\beta$ -dicarbonyl compounds in the presence of a base as the catalyst like piperidine, morpholine or metal alkoxides etc. A number of synthetic strategies have been developed for the preparation of 2-Amino-3-cyano-4*H*-pyran derivatives using catalysts such as  $\text{KF}/\text{Al}_2\text{O}_3$ <sup>12</sup>, Baker's yeast<sup>13</sup>, hexadecyldimethylbenzyl ammonium bromide (HDMBAB)<sup>14</sup>,  $\text{InBr}_3$ <sup>15</sup>, and  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62} \cdot 18\text{H}_2\text{O}$ <sup>16</sup>, ionic liquid<sup>17</sup> etc.

In recent years, some new alternative methods such as solid state heating, microwave irradiation, combined microwave and ultrasound irradiation<sup>18</sup>, and electro-oxidation<sup>19</sup>, have been reported for the synthesis of 2-Amino-3-cyano-4*H*-pyran derivatives. However these methods are valuable, they suffered from harsh reaction condition, toxic reagents, strong acidic or basic conditions, prolonged reaction time, poor yields and low selectivity. Although, several modifications have been made to counter these problems, there is a need to develop better strategies for the synthesis of 2-Amino-3-cyano-4*H*-pyran derivatives. In continuation of our work, herein a green approach for the one pot synthesis of 2-Amino-3-cyano-4*H*-pyran derivatives using aromatic aldehydes, ethylacetoacetate, malononitrile and triethanolamine as a catalyst under ultrasound irradiation has been reported.

As per green chemistry concerned number of method developed in organic chemistry such as solvent free synthesis, use of ionic liquids<sup>20</sup>, microwave irradiation<sup>21</sup> and ultrasound irradiation etc. Recently large number of organic reactions can be carried out in higher yields, shorter reaction times and milder conditions under ultrasonic irradiation<sup>22,23</sup>. The chemical applications of "Sonochemistry" has been increasingly used in organic synthesis in recent years.



## Experimental:

### i) Materials and Methods



Melting points were measured in open glass capillaries on a Perfit Electrothermal melting-point apparatus and were uncorrected.  $^1\text{H}$  NMR was recorded at room temperature on a 200 MHz Varian Inova Spectrometer in  $\text{CDCl}_3$  and using TMS as internal standard. IR spectra (using KBr pellets) were obtained with a Varian 640FT-IR instrument. The reactions were monitored on TLC using pre-coated plates (silica gel on aluminum, Merck). Column chromatography was performed using Acme silica gel (100-200 mesh). All reagents were obtained from commercial sources and used without further purification. Solvents for chromatography were distilled before use. The products were also characterized by comparison of their melting point with literature values.

### ii) Synthesis of 2-Amino-3-cyano-4H-pyran:

A mixture of ethyl acetoacetate (1 mmol), aromatic aldehydes, (1 mmol), malononitrile (1 mmol) were added to triethanolamine (10 mol%) as a catalyst and reaction vessel was irradiated in ultrasonic bath at  $60^\circ\text{C}$  for appropriate time (Table-1). After completion of reaction as monitored by TLC, the mixture was poured in cold water (50 mL), solid was filtered and washed with 1 M sodium bicarbonate solution, brine and finally with water and then recrystallized from ethanol. The so-obtained products were identified by comparison with authentic samples,  $^1\text{H}$  NMR, IR and their melting points (Table-1).

#### Ethyl 6-amino-5-cyano-2-methyl-4-phenyl-4H-pyran-3-carboxylate (4a):

FT-IR (KBr)  $\nu_{\text{max}}$  3404, 2190, 1688  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.03 (t,  $J = 7.0$  Hz, 3H,  $\text{OCH}_2\text{CH}_3$ ), 2.31 (s, 3H,  $\text{CH}_3$ ), 3.87 (qd,  $J = 7.0, 1.4$  Hz, 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.29 (s, 1H, H-4),



6.78 (b, s, 2H, NH<sub>2</sub>), 7.12-7.31 (m, 5H, H-Ar); <sup>13</sup>C (50MHz, DMSO-*d*<sub>6</sub>) δ 13.6 (OCH<sub>2</sub>CH<sub>3</sub>), 18.1 (CH<sub>3</sub>), 38.2 (C-4), 57.3 (C-3), 60.0 (OCH<sub>2</sub>CH<sub>3</sub>), 107.2 (C-5), 119.6 (C≡N), 126.6 (C-4'), 127.1 (C-2' and C-6'), 128.2 (C-3' and C-5'), 144.8 (C-1'), 156.5 (C-6), 158.3 (C-2), 165.3 (C=O).

## Results and Discussion:

Recently there is a growing demand for the development of organic reactions in ecofriendly media. Synthetic manipulations have to be made to minimize the use of hazardous chemicals by replacing the traditional organic solvents in reactions and their subsequent workup with other non-toxic solvents. There is need to replace toxic solvents by greener solvents because in industrial processes huge amount of solvent get wasted. The ultrasound (20–100 kHz) uses the energy to create cavitations, which involve the formation, growth, and collapse of microscopic bubbles in a liquid. These bubbles are generated when the “negative” pressure during the rarefaction phase of the sound wave is sufficiently large to disrupt the liquid. Ultrasonication can also accelerate many multi-component reactions (MCRs).

In a typical reaction, A mixture of ethyl acetoacetate (1 mmol), aromatic aldehydes, (1 mmol), malononitrile (1 mmol) were added to triethanolamine (10 mol%) as a catalyst and reaction vessel was irradiated in ultrasonic bath at 60 °C for appropriate time (Table-1). The reaction as monitored by TLC and after completion of reaction the mixture was poured in cold water (50 mL), solid was filtered and washed with 1 M sodium bicarbonate solution, brine and finally with water. The obtained crude product of 2-Amino-3-cyano-4*H*-pyran recrystallized from hot ethanol. The obtained 2-Amino-3-cyano-4*H*-pyran products were identified by comparison with authentic samples, <sup>1</sup>HNMR, IR and their melting points (Table-1).

Furthermore, the effect of reaction temperature was examined and the reaction proceeded smoothly at 60 °C (Table-1). The model reaction was conducted in a range of different temperatures, including room temperature, Room temperature, 30, 40, 50 and 60 °C, in the presence of 10 mol % triethanolamine catalysts (Table-2). As can be concluded from Table 1, the

reaction proceeded slowly at 60 °C. At room temperature reaction is very slow and gives poor yield of product. With increasing temperature to 60 °C, reaction yield was increased and time of reaction was decreased, when the reaction was heated above 60 °C, so high temperatures did not further improved yield and decrease time of reaction. The greatest yield in the shortest reaction time 30 to 45 min. was obtained at 60 °C.

2-Amino-3-cyano-4*H*-pyran have been synthesized in the presence of a catalytic amount of triethanolamine, which is itself a relatively benign compound used as an emulsifier and

surfactant in many industrial products such as liquid laundry detergents, dishwashing liquids, general cleaners, hand cleaners, printing inks etc. The advantages of this procedure are green reaction conditions, availability of the catalyst, good yields and short reaction times.

**Table-1:** Synthesis of 2-Amino-3-cyano-4*H*-pyran (4a-f)

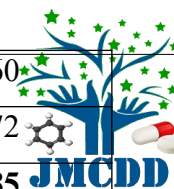
Entry (4a-f)	Aldehyde (1)	Time(min)	Yield (%)	m.p	m.p (lit)
4a	Benzaldehyde	45	75	178	178-179
4b	4-chloro- benzaldehyde	30	80	166	171-172
4c	4-methoxy- benzaldehyde	45	85	130	132-133
4d	4-F- Benzaldehyde	25	72	150	154-157
4e	4-NO <sub>2</sub> - Benzaldehyde	30	68	180	182-183
4f	4-Me- Benzaldehyde	40	82	176	175-176
7.	2-Cl- Benzaldehyde	30	80	190	191-192

**Table-2:** Effect of temperature on Synthesis of 2-Amino-3-cyano-4*H*-pyran<sup>a</sup>

Sr. No.	Temperature	Reaction times	Yield(%) <sup>b</sup>
1	RT	180 min	35
2	30 °C	120 min	54



3	40 °C	80 min	60*
4	50 °C	60 min	72
5	60 °C	45 min	85



<sup>a</sup>**Reaction conditions:** Ethyl acetoacetate (1 mmol), benzaldehyde (1 mmol), malononitril (1 mmol) and triethanolamine catalyst (10 mol%) ultrasound irradiation.

<sup>b</sup>**Isolated yield**

### Conclusion:



In summary, we reported a simple, eco-friendly, three-component one pot reaction for the synthesis of green an efficient synthesis of availability of the catalyst using triethanolamine as a catalyst. This protocol offers several advantages such as short reaction time, simple work-up and simple reaction condition. Use of triethanolamine as a catalyst is cheap easily availability makes this method superior as compare to other reported methods.

### Acknowledgements:

We are thankful to Dr. R. S. Agrawal, Principal J.E.S.College Jalna, for providing laboratory facilities and kind support.

### References:

1. Goel, A.; Ram, V. J. *Tetrahedron*, **2009**, 65, 7865–7913.
2. Morgan, L. R.; Jursic, B. S.; Hooper, C. L.; Neumann, D. M.; Thangaraj, K.; Leblance, B. *Bioorg. Med. Chem. Lett.* **2002**, 12, 3407–3411.
3. Moon, D. O.; Kim, K. C.; Jin, C. Y.; Han, M. H; Park, C.; Lee, K. J.; Park, Y. M.; Choi, Y. H.; Kim, G. Y. *Int. Immunopharmacol.* **2007**, 7, 222–229.
4. Wu, J. Y. C.; Fong, W. F.; Zhang, J. X.; Leung, C. H.; Kwong, H. L.; Yang, M. S.; Li, D.; Cheung, H. Y. *Eur. J.Pharmacol.* **2003**, 473, 9-17.

- 
- 
5. Raj, T.; Bhatia, R. K.; Kapur, A.; Sharma, M.; Saxena, A. K.; Ishar, M. P. S. *Eur. J. Med. Chem.* **2010**, 45, 790–794.
  6. Flavin, M. T.; Rizzo, J. D.; Khilevich, A.; Kucherenko, A.; Sheinkman, A. K.; Milaychack, V.; Lin, L.; Chen, W.; Greenwood, E. M.; Pengsuparp, T.; Pezzuto, J. M.; Hughes, S. H.; Flavin, T. M.; Cibulski, M.; Boulanger, W. A.; Shone, R. L.; Xu, Z. Q. *J. Med. Chem.* 1996, 39, 1303-1313.
  7. De Andrade-Neto, V. F.; Goulart, M. O.; Da Silva Filho, J. F.; Da Silva, M. J.; Pinto, M. D. C.; Pinto, A. V.; Zalis, M. G.; Carvalho, L. H.; Krettli, A. U. *Bioorg. Med. Chem. Lett.* **2004**, 14, 1145-1149.
  8. Kumar, A.; Maurya, R. A.; Sharma, S. A.; Ahmad, P.; Singh, A. B.; Bhatia, G.; Srivastava, A. K. *Bioorg. Med. Chem. Lett.* **2009**, 19, 6447-6451.
  9. Shia, D.; Moua, J.; Zhuanga, Q.; Wang, X. J. *Chem. Res.* 2004, 821-823.
  10. Shaabani, A.; Ghadari, R.; Sarvary, A.; Rezayan, A. H. *J. Org. Chem.* 2009, 74, 4372-4374.
  11. Hafez, E. A. A.; Elnagdi, M. H.; Elagamey, A. G. A.; Eltaweel, F. M. A. A. *Heterocycles* 1987, 26, 903–907.
  12. Wang, X. S.; Zhou, J. X. Zeng, Z. S.; Li, Y. L.; Shi, D. Q.; Tu, S. J. *Arkivoc* **2006**, (xi), 107-113.
  13. Pratap, U. R.; Jawale, D. V.; Netankar, P. D.; Mane, R. A. *Tetrahedron Lett.* **2011**, 52, 5817-5819.
  14. Jin, T. S.; Wang, A. Q.; Shi, F.; Han, L. S.; Liu, L. B.; Li, T. S. *Arkivoc* **2006**, (xiv), 78-86.
  15. Yadav, J. S.; Sunitha, V.; Subba-Reddy, B. V.; Das, P. P.; Gyanchander, E. *Tetrahedron Lett.* **2008**, 49, 855-857.
  16. Heravi, M. M.; Jani, B. A.; Derikvand, F.; Bamoharram, F.; Oskooie, H. A. *Catal. Commun.* **2008**, 10, 272-275.
  17. Peng, Y.; Song, G. *Catal. Commun.* **2007**, 8, 111-114.
  18. Peng, Y.; Song, G.; Dou, R. *Green Chem.* **2006**, 8, 573-575.
  19. Fotouhi, L.; Fatehi, A.; Heravi, M. M. *Int. J. Electrochem. Sci.* **2008**, 3, 721-726.

20. Sarda SR, Kale J D, Wasmatkar S K, Kadam VS, Ingole PG, Jadhav WN, Pawar RP (2009) *Molecular Diversity*, 13, 545-549.
21. Kappe CO, Dallinger D, *Molecular Diversity*, **2009**, 13(2), 71-193.
22. J. T. Li, Y. J. Bian, H. J. Zang and T. S. Li, *Synth. Commun.*, 2002, 32, 547–551.
23. M. R. Nabid, S. J. T. Rezaei, R. Ghahremanzadeh and A. Bazgir, *Ultrason. Sonochem.*, 2010, 17, 159–161.

