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Choline Hydroxide Mediated one-pot Synthesis of 2-amino-4H-Chromene Derivatives in Aqueous Media

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Abstract: A novel, green, and efficient one-pot three-component cyclocondensation protocol has been developed for the synthesis of pyrano[2,3-*d*]pyrimidinone derivatives using choline hydroxide as a biodegradable, cost-effective, and nontoxic basic catalyst. The reaction involves aromatic aldehydes, barbituric acid, and dimedone in an ethanol:water (1:1) solvent system at 80°C, achieving excellent yields (85–96%) within 30 minutes under mild conditions. This environmentally benign approach eliminates the need for hazardous solvents or metal catalysts, features a simple workup procedure with easy product isolation via filtration, and allows catalyst recovery and reuse for up to four cycles with minimal loss in activity. The method highlights the unexplored potential of commercially available choline hydroxide as a sustainable promoter in multicomponent reactions, aligning with green chemistry principles through atom economy, energy efficiency, and reduced waste generation.

Keywords: Choline hydroxide, pyrano[2,3-*d*]pyrimidinone, one-pot synthesis, green chemistry, multicomponent reaction, aqueous medium, barbituric acid, dimedone, aromatic aldehydes

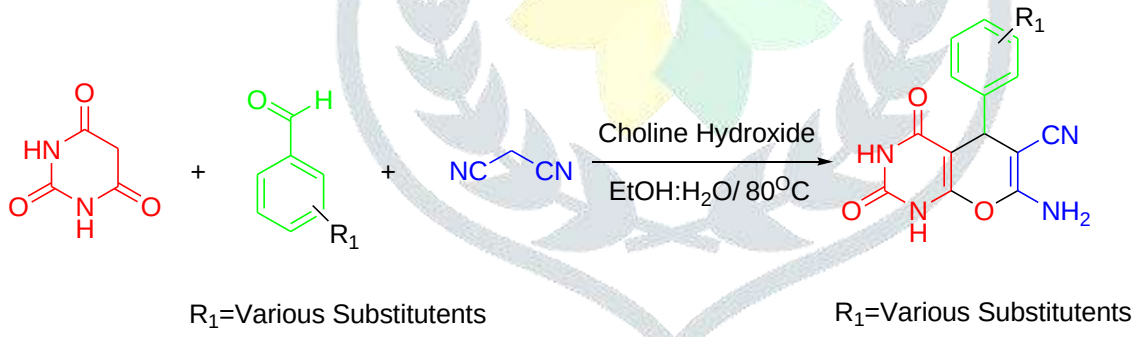
Introduction

Pyrano[2,3-*d*]pyrimidinones and related fused heterocyclic scaffolds have garnered significant attention worldwide due to their broad spectrum of pharmacological activities, including vasodilatory, cardiotonic, antibacterial, antihypertensive, analgesic, bronchodilatory, hepatoprotective, antiallergic, herbicidal, antitumor, antifungal, and antimalarial effects.[1,2] These multifaceted bioactivities have spurred extensive research into developing efficient, scalable, and sustainable synthetic routes for these privileged structures.[3]

Over the past decade, numerous methodologies have been documented employing thermal, ultrasonic, microwave-assisted, and catalytic strategies. [4,5] Common catalysts include L-proline, *N*-methylmorpholine, $H_{14}[NaP_5W_{30}O_{110}]$,

triethylamine, SBA-15-Pr-SO_3H, [BMIm]BF_4, [$KAl(SO_4)_2$], and diammonium hydrogen phosphate (DAHP), often under elevated temperatures or prolonged reaction times. While many of these protocols offer reasonable yields, they frequently suffer from drawbacks such as the use of expensive reagents, toxic solvents, complex catalyst preparation, or poor recoverability-factors that undermine their alignment with green chemistry principles. To address these limitations and establish a truly sustainable pathway, we turned to choline hydroxide-a naturally derived, biodegradable, and commercially inexpensive quaternary ammonium base.[6] Traditionally recognized as a non-caloric sweetener and nutritional supplement in food, pharmaceuticals, cosmetics, and beverages, choline hydroxide has recently emerged as a versatile, eco-friendly organocatalyst in organic synthesis.[7–31] Its nontoxic nature, high water solubility, thermal stability, and mild basicity make it an ideal candidate for promoting condensation reactions under aqueous conditions.

Despite its growing utility in various transformations, a thorough literature analysis revealed no prior reports on the application of choline hydroxide for the synthesis of pyrano[2,3-*d*]pyrimidinone derivatives via three-component cyclocondensation in aqueous media. Herein, we disclose a novel, rapid, and operationally simple protocol for the one-pot synthesis of structurally diverse pyrano[2,3-*d*]pyrimidinones through the cyclo-condensation of substituted aromatic aldehydes, barbituric acid, and dimedone using catalytic choline hydroxide (10 mol%) in an ethanol:water (1:1) mixture at 80°C (Scheme 1). The reaction completes within 20–30 minutes, delivering products in excellent yields (87–96%) with high purity upon simple filtration. **(Scheme 1).**



Scheme 1

The catalyst is readily recoverable and reusable for at least five consecutive cycles with negligible decline in efficiency, further enhancing the sustainability of the process. This methodology not only fills a critical gap in the synthetic repertoire but also exemplifies the untapped potential of choline hydroxide as a green, multifunctional catalyst for constructing biologically relevant heterocyclic frameworks under environmentally responsible conditions.

Results and discussion

To standardize and set the reaction conditions we carried out various optimization protocols in terms of the amount of Choline Hydroxide (10 % mole), time, solvent and temperature. To set the conditions we carried out a model reaction of between benzaldehyde (1 mmol), malononitrile (1.0 mmol) and barbituric acid (1.0 mmol). The product

was formed in a trace amount of yield when the reaction was carried out without the aid of any catalyst and solvent which indicated the need for the solvent to proceed with the reaction. We have studied various solvent system and after studying various reactions on different solvent system, Dichloromethane, Chloroform, water, ethanol, and ethanol: water system, but we are happy to know that we ended the reaction giving the product in 10%, 13%, 42%, 62%, and 85 % yield respectively, proving that ethanol: water (1:1) system will be more efficient to yield the product in 8 hrs. Further, we have checked and examined the effect of mole % Choline Hydroxide catalyst in aforesaid reaction protocol and as expected we ended the reaction yielding trace, 52 %, 88 %, 85 % of the product when 0%, 5 %, 10 % and 20 % of catalyst was utilized. Further, we have carried out standardization of reaction on the temperature of the reaction and as per expectation at room temperature, 30 ^{O}C, 50 ^{O}C 80 ^{O}C, and 100 ^{O}C it yielded 15%, 36% 88% and 90% of the product within 8 hrs. Thus from the above observation, it is clear that a 10% mole of the catalyst was sufficient to carry out the reaction at 80^{O}C utilizing ethanol: water solvent system.

Table 2. % Mole of Catalyst

Entry	Catalyst	Time	Yield
1	No Catalyst	8 Hrs	Trace
2	5 %	8 Hrs	52%
3	10%	8 Hrs	88 %
4	20%	8 Hrs	85 %

Finally, to set reaction time, we have performed the reaction under the set reaction conditions for 30 min, 120 min, 180 min, and 240 min. To our surprise, the reaction was good enough to give the expected product in 30 min of reaction time in 88% yield. Extended reaction time doesn't yield a major amount of product which indicated that to obtain the maximum amount of product yield only 30 minutes of reaction time was sufficient.

Table 3. Screening of Temperature in Solvent System

Entry	Solvent	Time	Yield
1	Ethanol: Water	8 Hrs, RT	66%
2	Ethanol: Water	30 min/ 80^{O}C	88%
3	Ethanol:Water	60 min/80^{O}C	90%
4	Ethanol: Water	120 Min/ 80^{O}C	91%

Experimental

Chemicals were purchased from commercial suppliers and used without further purification. Yields refer to isolated products. Melting points were determined by an Electrothermal 9100 apparatus and are uncorrected. The IR spectra were obtained on an FT-IR Hartman- Bomen spectrophotometer as KBr disks, or neat. The ^{1}H NMR (400 MHz) spectra were recorded on a Bruker Avance NMR spectrometer in $CDCl_3$ solution. The progress of the reaction was monitored by TLC using silica-gel SILG/UV 254 plates. All products are known and were characterized by comparing their physical and spectral data with those of the authentic samples. **General procedure:** A mixture of aldehyde (1 mmol), barbituric acid (1 mmol), and malononitrile (1 mmol), was taken in a round bottom flask which was dissolved in ethanol: water (10 ml), to which 10 mole % of Choline Hydroxide was added at room temperature which was vigorously stirred at room temperature for 10 min. Further, the reaction was subjected to heating in ethanol: water system at 80 °C for 20 minutes. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on crushed ice. Further, it was filtered off and washed with cold H_2O (3×10 mL). Finally, the crude product was recrystallized from hot ethanol to give the pure product in 88 % yield

Table 3. Synthesis of various pyrano [2, 3-*d*] pyrimidine derivatives

[a]Melting points in line with values in reported literature [4-5]

Entry	Compound	Ar	Time (Min)	Yield (%)	M.P. (°C)
1.	a	Ph	**30**	**88**	204-206[a]
2.	b	4-Me-Ph	**30**	**88**	162-164[a]
3.	c	4-Me_2N-Ph	**20**	**82**	180-182[a]
4.	d	4-NO_2-Ph	**20**	**70**	230-232[a]
5.	e	3-NO_2-Ph	**20**	**72**	258-260[a]
6.	f	2-Cl-Ph	**30**	**70**	207-209[a]
7.	g	3-Cl-Ph	**30**	**76**	210-212[a]
8.	h	4-Cl-Ph	**25**	**84**	230-232[a]
9.	i	4-MeO-Ph	**30**	**85**	277-279[a]

Analytical data of selected compounds:

7-amino-2, 4-dioxo-5-phenyl-2, 3, 4, 5-tetrahydro-1H-pyrano [2, 3-d] pyrimidine-6-carbonitrile **(1a): M. P.** 204-206^{O}C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (s, 1H) 7.51-7.66 (m, 5H), 7.78 (s, 2H), 7.89 (s, 1H), 7.92 (s, 1H). IR (KBr, cm^{-1}): *v* 3392, 3064, 2223, 1718, 1677, 1565, 676.

7-Amino-6-cyano-5-(4-chlorophenyl)-4-oxo-2- thioxo-5H-pyrano[2,3-d]pyrimidinone (8h): M. P. 230-232 ^{O}C, ^{1}H NMR (400 MHz, DMSO–d_6) δ: 4.27 (1H, s, H-5), 7.05 (2H, br s, NH_2), 7.22 (2H, d, J = 47.11; H, 2.63; N, 8.2 Hz, H–Ar), 7.28 (2H, d, J = 8.2 Hz, H–Ar) 11.05 (1H, br s, NH), 12.05 (1H, br s, NH) ppm; IR (KBr) 3389, 3305, 3187, 3073, 2196, 1718, 1674, 1600, 1410, 1280 cm^{-1}.

Conclusion:

In conclusion, we have developed an efficient and environmentally benign protocol for the one-pot, three-component synthesis of diverse pyrano[2,3-d]pyrimidinone derivatives using choline hydroxide as a mild, cost-effective, and nontoxic catalyst. The reaction proceeds via cyclo-condensation of aromatic aldehydes, barbituric acid, and dimedone in an ethanol:water solvent system at 80°C, affording high yields within 30 minutes. This method aligns with the principles of green chemistry by employing a biodegradable catalyst, aqueous medium, mild conditions, and a simple workup procedure, thereby demonstrating the untapped potential of choline hydroxide as a versatile and sustainable basic catalyst in multicomponent organic synthesis.

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Graphical Abstract

Choline Hydroxide mediated One-Pot Synthesis of Pyrano [2, 3-d] pyrimidinone Derivatives in Aqeous Media

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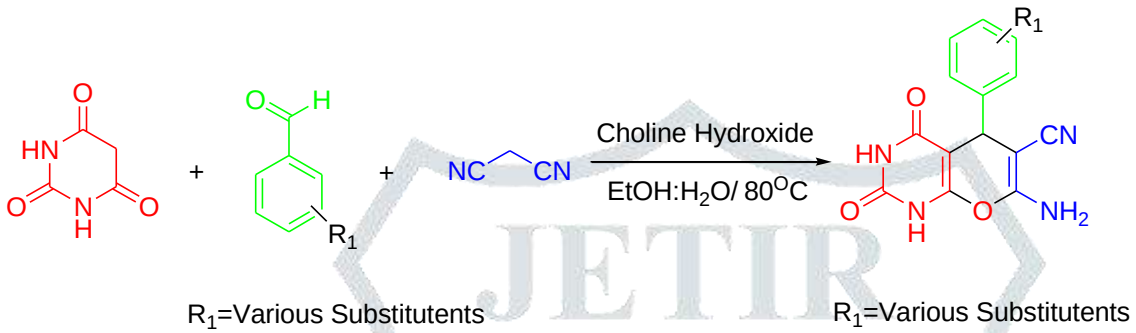

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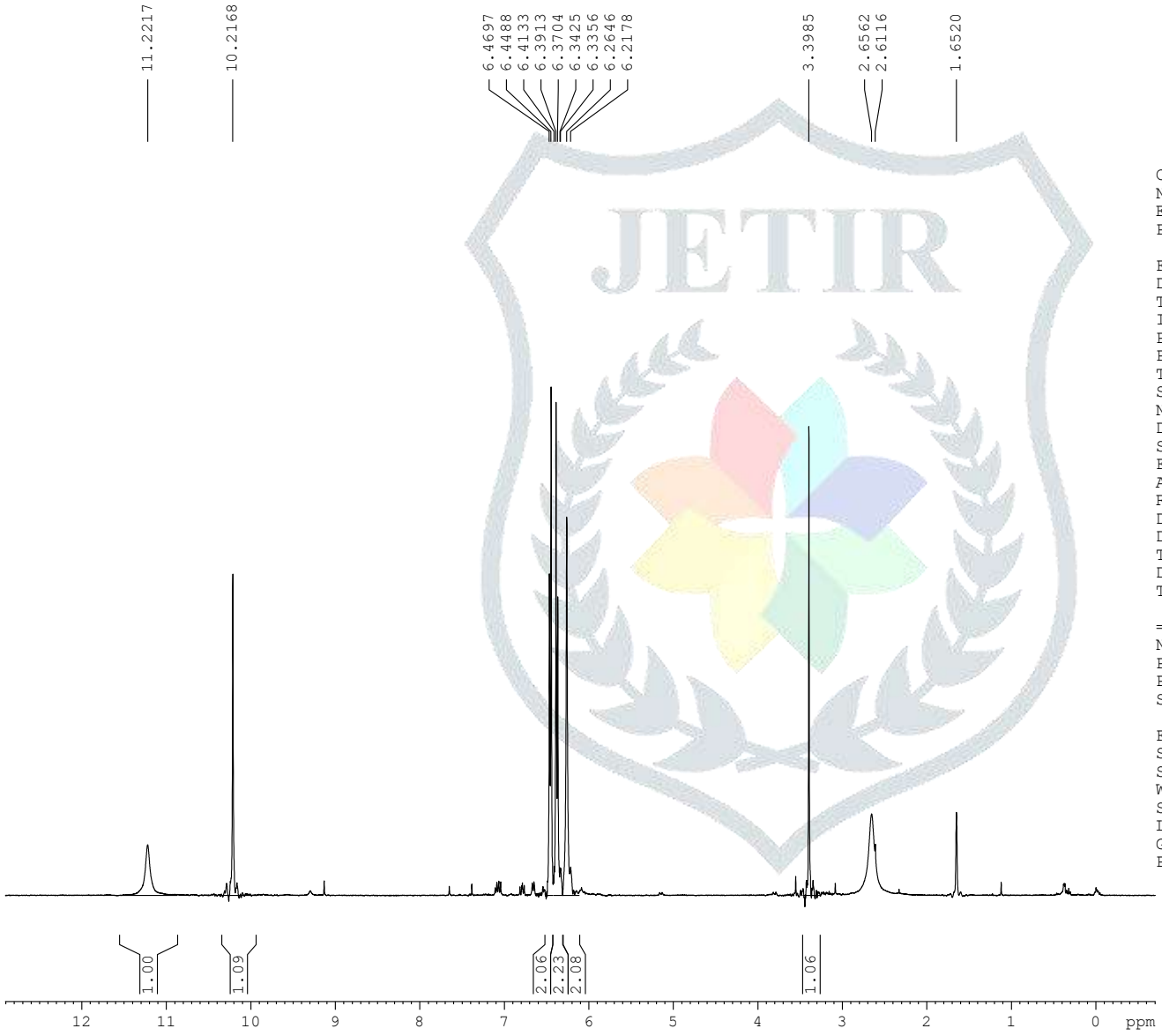

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AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

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DW                41.600 usec
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TE                293.3 K
D1           1.00000000 sec
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PL1                -3.00 dB
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SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
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^{1}H NMR Spectrum of 8h