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Choline hydroxide promoted sustainable one-pot three-component synthesis of 1H-pyrazolo[1,2-a]pyridazine-2-carbonitriles under solvent-free conditions

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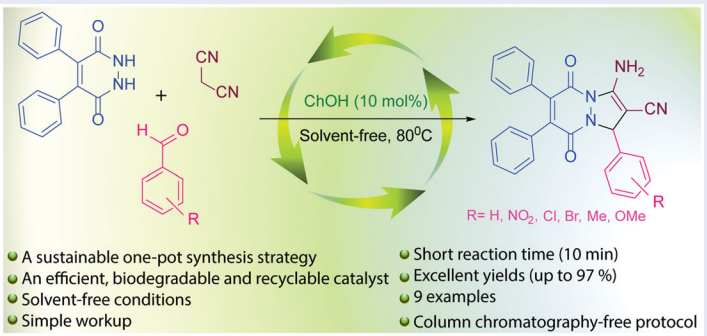
ABSTRACT

A sustainable one-pot three-component synthesis of novel 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile derivatives employing a highly efficient, biodegradable, and recyclable choline hydroxide catalyst under solvent-free conditions is demonstrated. The salient features of this protocol are simple workup, mild reaction conditions, short reaction time (10 min), excellent yields (up to 97%), high atom economy, column chromatography-free protocol, and eco-friendliness. Interestingly, the choline hydroxide was recycled up to five cycles without any considerable loss of efficiency. The structures of the products were deduced by their ^{1}H NMR, ^{13}C NMR, and HRLC-MS spectra.

GRAPHICAL ABSTRACT



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KEYWORDS
Choline hydroxide; 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile; one-pot three-component; solvent-free; sustainable

Introduction

Green chemistry for chemical synthesis addresses the problems pertaining to environmental pollution experienced worldwide. In this context, multi-component reactions (MCRs) under solvent-free conditions have proven to be a valuable asset in organic and medicinal chemistry. This eco-friendly protocol minimizes the number of steps in the synthesis of various biologically important derivatives. Since products are synthesized in

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one-pot, the structural diversity can be achieved directly by varying the reacting components.[1–3]

Nitrogen-containing heterocycles are important skeletons owing to their tremendous application in biologically active pharmaceuticals, agrochemicals, and functional materials.[4–7] 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile derivatives have been reported to have analgesic, anti-hypoxic, anti-inflammatory, and antipyretic activities.[8,9] Hence, the development of new synthetic methods for the efficient synthesis of 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile derivatives is a fascinating challenge in green synthesis.

In recent years, the surge in environmental consciousness in chemical research and industry compelled practicing environmentally benign and sustainable methods involving eco-friendly catalysts and lacking harmful organic solvents. Ionic liquids (ILs) are getting significant worldwide consideration and are being employed comprehensively in chemical transformations as green solvents and/or catalysts owing to their unique properties such as low volatility, tunable solubility, non-flammability, good catalytic activity, and excellent recyclability.[10–13]

Choline chloride (ChCl), belonging to the vitamin B class, is a naturally occurring biocompatible compound. It is used as a chicken feed additive and commercially produced on a large scale.[14,15] Choline chloride-based ionic liquid i.e., ChOH is a non-toxic ionic liquid with a number of benefits such as biodegradability, recyclability, solvation power, ready availability, high water solubility, and good catalytic activity in numerous organic transformations.[16–26]

In continuation of our efforts to develop new green methodologies in organic synthesis,[27–32] we herein present a sustainable one-pot three-component synthesis of novel 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile derivatives employing choline hydroxide catalyst under solvent-free conditions.

Results and discussion

In this protocol, we have used 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione, 4-nitrobenzaldehyde, and malononitrile as model substrates for the optimization of the reaction conditions. We have thoroughly investigated the effect of different organic bases such as DBU, piperidine, triethylamine, pyridine, tetramethylammonium hydroxide and inorganic bases such as KOH, NaOH, Cs_2CO_3, K_2CO_3, and Na_2CO_3, which gave the desired product yields around 47–86% (Table 1, entries 2–11). However, with choline hydroxide as a catalyst, we achieved the desired product in excellent yield (97%) (Table 1, entry 15). To determine the optimum catalyst loading, the model reaction was carried out with different mol % of ChOH. The reaction happened efficiently with 10 mol % of ChOH giving a single product in 97% yield (Table 1, entry 15). Increasing the quantity of ChOH further, displayed no significant enhancement in the yield or reaction rate.

In order to screen the effect of solvent on the reaction rate as well as yield of the product, the model reaction was carried out using ChOH in different solvents (Table 2). In aprotic solvents such as toluene, tetrahydrofuran, chloroform, dichloromethane, and 1,2-dichloroethane, the reaction was very slow and resulted in a lower yield of the product (Table 2, entries 4–8). Conducting the reaction in protic solvents such as methanol

Table 1. Effect of different bases on the synthesis of 1H-pyrazolo[1,2-a]pyridazine-2-carbonitriles.

Entry	Catalyst	Catalyst loading (mol %)	Reaction time (min)	Yield (%)[a]
1	Without catalyst	–	100	18
2	KOH	10	15	86
3	NaOH	10	15	84
4	$(CH_3)_4N^+OH^-$	10	15	78
5	Cs_2CO_3	10	20	82
6	K_2CO_3	10	20	74
7	Na_2CO_3	10	20	69
8	DBU	10	40	61
9	Piperidine	10	50	59
10	Et_3N	10	55	52
11	Pyridine	10	60	47
12	ChOH	04	40	61
13	ChOH	06	30	70
14	ChOH	08	20	81
15	**ChOH**	**10**	**10**	**97**
16	ChOH	12	10	98

[a]Isolated yields.

Reaction conditions: Reaction of 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione (1 mmol), 4-nitrobenzaldehyde (1 mmol), and malononitrile (1 mmol) under solvent-free conditions at 80 °C.

The bold values indicate the optimized parameters giving the highest yield.

Table 2. Effect of solvent and temperature on model reaction.[a]

Entry	Solvent	Temperature (°C)	Reaction time (min)	Isolated yield (%)
1	Water	100	25	67
2	Methanol	65	20	84
3	Ethanol	79	20	81
4	1,2-Dichloroethane	84	30	72
5	Dichloromethane	40	30	69
6	Chloroform	61	30	63
7	Tetrahydrofuran	66	35	60
8	Toluene	111	45	58
9	Solvent-free	40	60	51
10	Solvent-free	60	40	70
11	Solvent-free	70	20	81
12	**Solvent-free**	**80**	**10**	**97**
13	Solvent-free	100	15	97

[a]*Reaction conditions:* Reaction of 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione (1 mmol), 4-nitrobenzaldehyde (1 mmol), malononitrile (1 mmol), solvent (5 mL), and ChOH catalyst (10 mol %).

The bold values indicate the optimized parameters giving the highest yield.

and ethanol improved both the reaction rates as well as yield of the product (Table 2, entries 2 and 3). Comparatively low reaction rate, as well as yield of the product, is observed in water as a solvent (Table 2, entry 1), it may be owing to less solubility of reactants in water. Moreover, we also conducted this model reaction under a solvent-free condition at 80 °C. As shown in Table 2, entry 12, the reaction time under solvent-free condition was shorter and the yield of the product was also higher than under solvent conditions. The excellent yield of the product formation under solvent-free condition could be explained by uniform dissemination of reactants, which are in close vicinity to react with each other. To optimize the reaction temperature, the same model reaction was studied at different temperatures. An enhanced reaction rate and yield of the product were observed on rising the reaction temperature from 40 °C to 80 °C (Table 2, entries 9–12). The best conversion was achieved with 10 mol % of ChOH at 80 °C and 10 min under solvent-free condition (Table 2, entry 12). However,

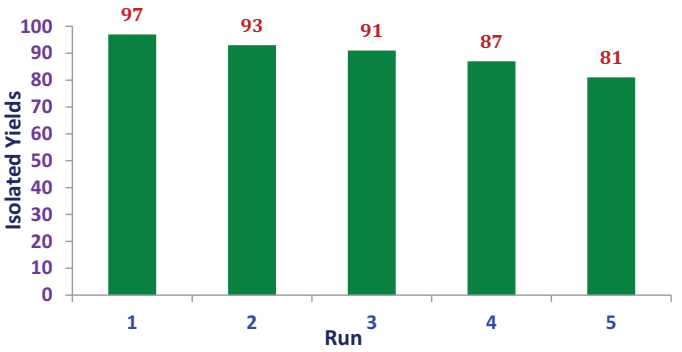


Figure 1. Recyclability study of choline hydroxide.

no more increase was found in the reaction rate and yield of the product when the reaction temperature was raised from 80 °C to 100 °C.

In order to demonstrate the industrial applicability of this protocol, the reaction of 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione, 4-nitrobenzaldehyde, and malononitrile catalyzed by ChOH was carried out on a larger scale (25 mmol). To our delight, the outcomes were reproducible with 97% yield of the product as obtained in smaller scale (1 mmol). On the same scale, the recyclability study of the catalyst was investigated using the above model reaction. Upon the completion of the reaction (monitored using TLC), water was added to the reaction mass; the product was isolated by filtration. ChOH being soluble in water was recovered by evaporation of water under vacuum from the filtrate. Recovered choline hydroxide was reused without further purification. As depicted in Figure 1, ChOH could be reused for at least five times without any substantial loss in its activity.

FT-IR analysis

FT-IR is a powerful tool for ascertaining types of chemical bonds in a molecule by generating an infrared absorption spectrum that is like a molecular "fingerprint." The wavelength of light absorbed is characteristic of the chemical bond as can be seen in Figure 2. The Fresh and recycled (after 5th run) choline hydroxide have been characterized by FT-IR spectroscopy. The comparative study of the fresh and recycled ChOH proves that there is no significant change observed in the IR spectra of ChOH. The broad absorption peak around 3297 cm^{-1} is a characteristic of O–H stretching vibration. The aliphatic C–H stretching vibration observed around 2959 cm^{-1}. The methyl bending vibration was observed at 1472 cm^{-1}. The band near 1357 cm^{-1} corresponds to the stretching vibration of the C–N bond. The band at 1081 cm^{-1} corresponds to C–O stretch in a primary alcoholic group. The C–H bending vibrations of $–CH_2–$ group was observed near 947 and 877 cm^{-1}.

Based on the current investigational observations and literature reports,[22,23] the proposed reaction mechanism for the synthesis of 1H-pyrazolo[1,2-a]pyridazine-2-carbonitriles is showed in Figure 3. The initial step involves the Knoevenagel condensation of an aromatic aldehyde with malononitrile catalyzed by ChOH to produce an intermediate arylidenemalononitrile (vi). ChOH catalyst deprotonates the malononitrile to

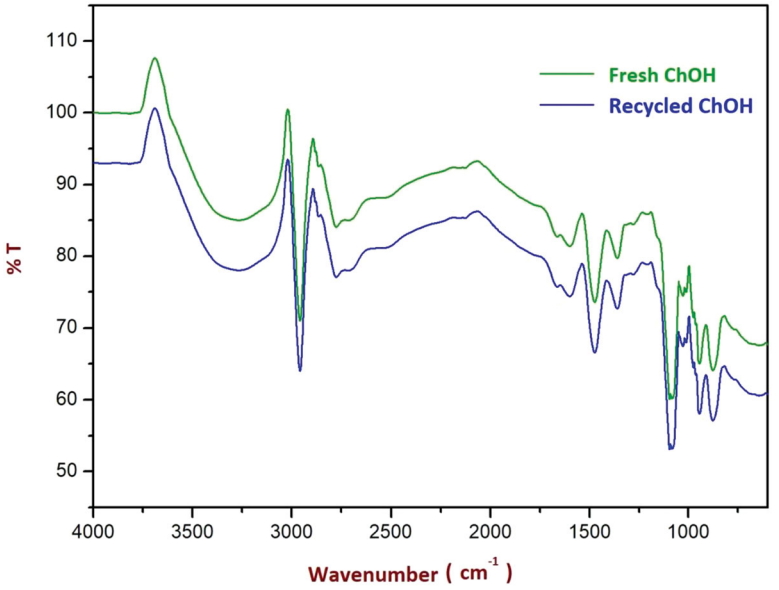


Figure 2. FT-IR spectra of fresh and recycled ChOH.

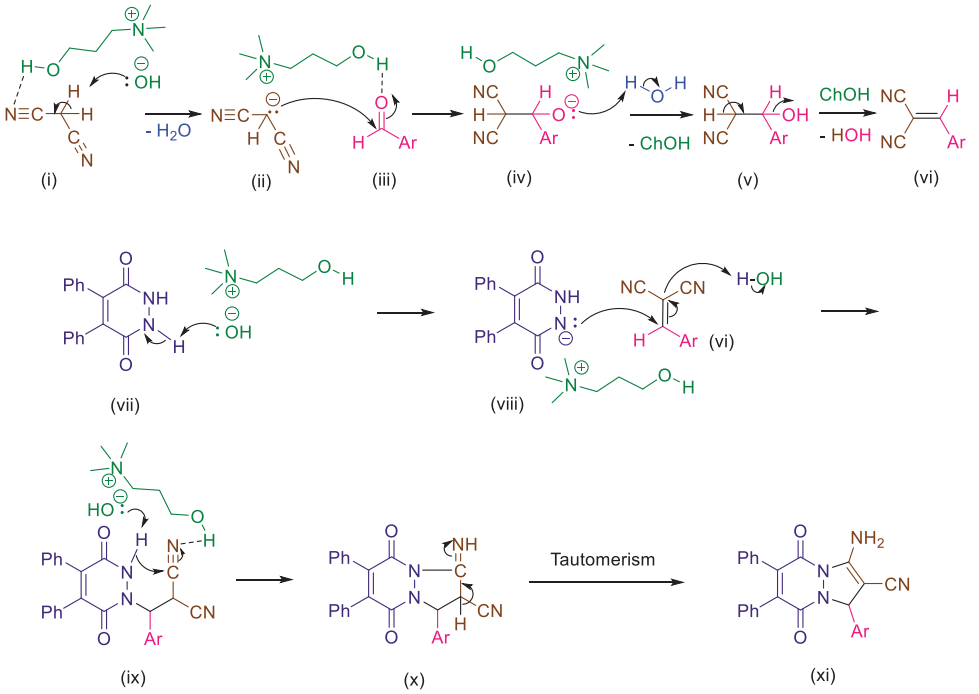


Figure 3. Proposed mechanism for 1H-pyrazolo[1,2-a]pyridazine-2-carbonitriles formation catalyzed by choline hydroxide.

generate a resonance stabilized carbanion (ii). This carbanion attacks the electrophilic carbonyl group which is already activated via hydrogen bonding with ChOH. Subsequently, phthalhydrazide (vii) gets deprotonated by ChOH to generate an anion (viii), which undergoes the Michael-type addition to arylidenemalononitrile (vi),

followed by intramolecular cyclization and tautomerism to afford the final product 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile (xi). The hydrogen bonding interaction of ChOH with the nitrogen of nitrile group in (ix) is responsible for increasing electrophilicity of nitrile group thereby facilitating the intramolecular cyclization.

Experimental

Materials and methods

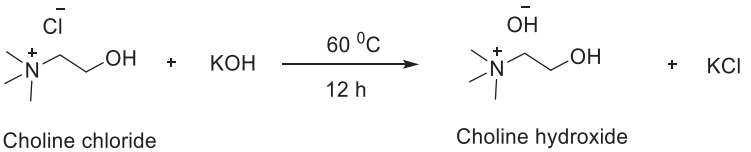
All the solvents and reagents were purchased from S D Fine-Chem Limited and used without further purification. The progress of all reactions was monitored using aluminum TLC plate, silica gel coated with fluorescent indicator F254 (Merck) detecting the spots by means of UV light as a visualizing agent. ^{1}H NMR and ^{13}C NMR spectra were obtained with 500 MHz instrument (Agilent NMR spectrometer) in $(CD_3)_2SO$ at ambient temperature. The chemical shifts values are stated as δ value (ppm) relative to an internal standard tetramethylsilane ($Si(CH_3)_4 = 0.00$ ppm). Mass spectra (HRLC-MS) were recorded on Model: 1290 Infinity UHPLC System, 1260 infinity Nano HPLC with Chipcube, 6550 iFunnel Q-TOFs (Make: Agilent Technologies, USA). All synthesized compounds were analyzed using HRLC-MS, ^{1}H NMR, and ^{13}C NMR spectra. Infrared spectra were recorded on a JASCO-FT/IR 4100 LE ATR PRO450-S spectrometer. Melting points were found out by standard melting point device procured from Sunder Industrial Product, Mumbai and are uncorrected.

General procedure for the synthesis of choline hydroxide (ChOH)

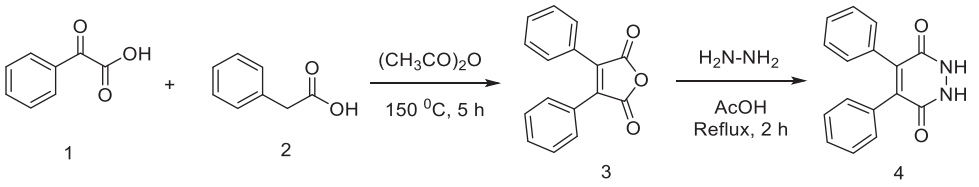
The ChOH was prepared according to the literature.[2,4,23,33] Choline chloride (10 mmol) and KOH (10 mmol) in methanol (15 mL) were heated at 60 °C for 12 h with constant stirring. After cooling to room temperature, the reaction mixture was filtered to remove solid KCl and the obtained solution was concentrated under vacuum to remove methanol. The residue was used without further purification (Scheme 1).

Synthesis of 2,3-diphenyl maleic anhydride (3)

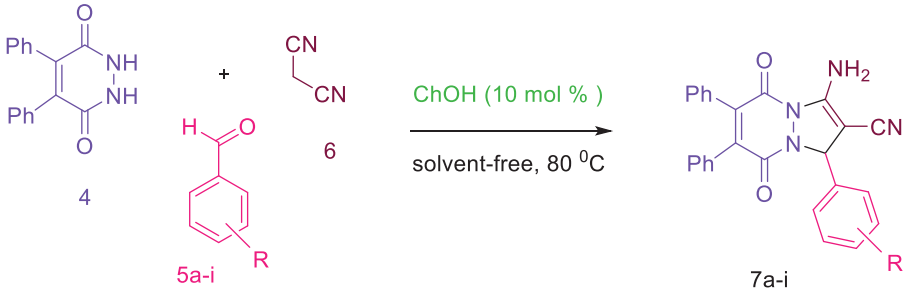
A mixture of benzoyl formic acid **1** (5.0 g, 33 mmol), phenylacetic acid **2** (4.53 g, 33 mmol) and acetic anhydride (50 mL) was reflux at 150 °C for 5 h. Later the reaction mixture was allowed to cool and poured over ice-cubes. Subsequently the solid was filtered off, washed with water, and dried. On crystallization from ethanol, 2,3-diphenyl-maleic anhydride was obtained as pale yellow needles (6.024 g, 72.36%, mp 151–152 °C, lit.[29] mp 148 °C) (Scheme 2).[30,31]



Scheme 1. Synthesis of Choline hydroxide (ChOH).



Scheme 2. Preparation of 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione.



Scheme 3. One-pot three-component synthesis of 1H-pyrazolo[1,2-a]pyridazine-2-carbonitriles.

Synthesis of 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione (4)

2:1 Mixture (5.0 g) of hydrazine hydrate and water was added drop-wise to a mixture of 2,3-diphenylmaleic anhydride (2.40 g, 10 mmol) in acetic acid (10 mL). Sodium acetate anhydrous (0.88 g, 10 mmol) was added and the reaction mixture was heated to reflux for 2 h. After cooling, the suspension was poured into water (20 mL), and the precipitate was filtered, delivering 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione (2.164 g, 81.97%, mp 218 °C, lit.[29] mp 216–217 °C) (Scheme 2).[17,24]

General procedure for the synthesis of 1H-pyrazolo[1,2-a]pyridazine-2-carbonitriles

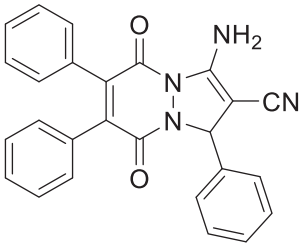
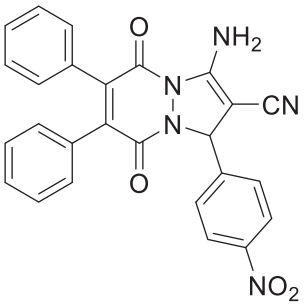
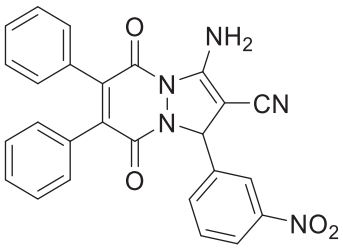
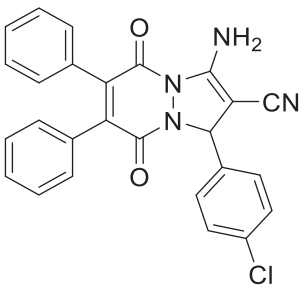
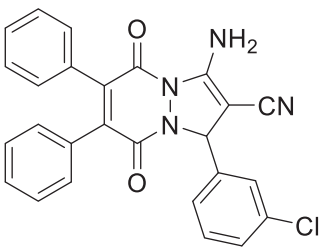
In a general procedure, a mixture of 4,5-diphenyl-1,2-dihydropyridazine-3,6-dione **4** (1.0 mmol), aromatic aldehyde **5** (1.0 mmol), malononitrile **6** (1.0 mmol) and choline hydroxide (10 mol %) was stirred at 80 °C for 10 min. After completion of the reaction (monitored using TLC), water (5 mL) was added, and the 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile was filtered off and washed with water. It is then recrystallized from hexane:ethyl acetate (3:1) solvent system to afford the corresponding 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile derivative (Scheme 3; Table 3).

Characterization data for selected 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile

7a: 3-amino-5,8-dioxo-1,6,7-triphenyl-5,8-dihydro-1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile

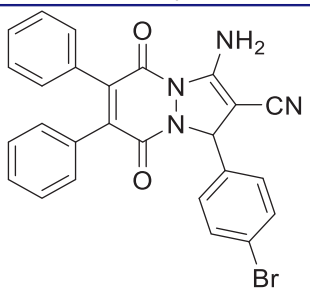
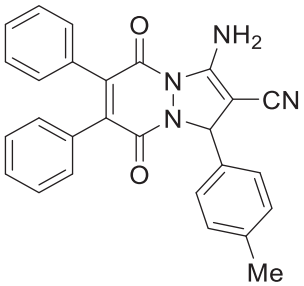
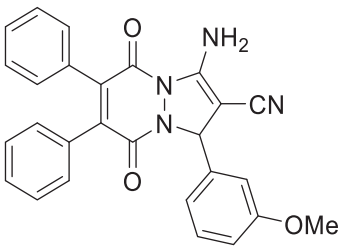
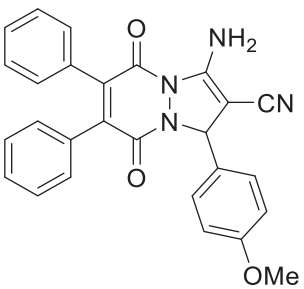
Yield: 81% (0.339 g, 0.8 mmol); Yellow powder; m.p. 280–282 °C.

Table 3. Yields of the synthesized novel 1 H-pyrazolo1,2-apyridazine-2-carbonitriles.

Entry	Notation	Structure of product	Time (min)	Isolated yield (%)
1	7a		15	81
2	**7b**		**10**	**97**
3	7c		10	93
4	7d		10	91
5	7e		10	89

(*continued*)

Table 3. Continued.

Entry	Notation	Structure of product	Time (min)	Isolated yield (%)
6	7f		10	87
7	7g		20	79
8	7h		20	76
9	7i		20	74

The bold values indicate the optimized parameters giving the highest yield.

^{1}H NMR (500 MHz, DMSO-d_6) δ 8.236 (2 H, s, NH_2), 7.791–7.817 (4 H, m, C8', C12', C14', and C18'-H), 7.298–7.379 (9 H, m, C2' to C6', C9', C11', C15', and C17'-H), 7.236 (2 H, t, $J = 7.5$ Hz, C10', and C16'-H), 6.180 (1H, s, C1-H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 61.23 (C1), 63.97 (C2), 116.51 (-CN), 126.97 (C4'), 127.51 (C2' and C6'), 128.47 (C10' and C16'), 129.02 (C3' and C5'), 130.09 (C8', C12', C14' and C18'), 131.08 (C9', C11', C15' and C17'), 136.28 (C7' and C13'), 137.57 (C6 and C7), 139.81 (C1'), 158.12 (C3), 161.97 (C5), 164.23 (C8).

HRLC-MS *m/z* (ESI): Calcd for $C_{26}H_{19}N_4O_2$ $(M + H)^+$: 419.1503, found: 419.1501

Conclusion

In summary, novel 1H-pyrazolo[1,2-a]pyridazine-2-carbonitrile derivatives substituted with electron donating or withdrawing groups were designed and synthesized by an efficient, green, and sustainable one-pot three-component methodology. The biocompatibility, inexpensiveness, and recyclability of the choline hydroxide catalyst, mild reaction conditions, operational simplicity, lower loading of catalyst, solvent-free condition, short reaction time, high atom economy, column chromatography-free protocol, and excellent yields make this strategy a green alternative to the existing protocols.

Full experimental details and data pertaining to the characterization of the compounds **7a** to **7i** using ^{1}H NMR, ^{13}C MNR spectra and HRLC-MS are given in the Supplementary information which can be seen via the "Supplementary Content" section of this article's webpage.

Acknowledgments

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Disclosure statement

All authors declare that they have no conflict of interest to disclose.

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