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Green One-Pot Pseudo-Four Component Synthesis of Substituted 5-Cyano-2-imino-4-aryl/heteroaryl-6-(phenylthio)-2*H*-pyran-3-carboxylic Acid Catalyzed by Montmorillonite K-10 Clay

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A synthetic method of substituted 5-cyano-2-imino-4-aryl/heteroaryl-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (**4a-d**) using Montmorillonite K-10 clay as catalyst was developed *via* one-pot pseudo-four-component reaction. Various aldehydes and thiophenols exhibit swift reactivity with cyanoacetic acid, resulting in satisfactory to exceptional yields (ranging from 70% to 90%) within an exceptionally short reaction duration of 0.75 to 1.5 h. The structural characterization of the synthesized compounds was conducted through IR, ^{1}H, ^{13}C NMR and elemental analysis. Safer technique, simple work-up as well as reusability of the catalyst for two runs are the characteristic features of this method. This multicomponent one-pot reaction approach demonstrates a straightforward synthetic strategy for the formation of two novel C-C bonds, one C-S bond, one C-O bond, and the formation of a new ring structure. Additionally, this reaction exhibits high efficiency as all the reactants are completely utilized.

Keywords: Green chemistry, Multicomponent reaction, Substituted 2*H*-pyran, Montmorillonite K-10 clay, Recoverable catalyst.

INTRODUCTION

Green chemistry has laid a sturdy groundwork providing essential design criteria for the development of most effective reactions and methodologies to generate a library of new biologically active motifs in more sustainable and eco-friendly conditions [1]. Prevention of waste and catalysis are two of the most vital aspects of green chemistry protocols that play a distinctive part in a broad array of organic conversions [2].

Considering the above facts, multicomponent reactions (MCRs) have been recently recognized as a vital methodological device in the synthetic and medicinal chemist's toolbox [3]. MCRs offer many advantages, thus there has been a dramatic rise in its applications in all fields of organic synthesis. As of today, initiatives have been ramped up to formulate an original and multifaceted library of compounds *via* MCRs, for which a catalyst is often required [4]. The integration of metal-organic frameworks (MOFs) with heterogeneous catalysts has been seen to result in a wide range of methodologies that effectively merge the advantages of a highly atom-efficient and potentially reusable heterogeneous catalytic system. On account of its affordability, versatility and sustainability, Montmorillonite K-10 clay (Mont-K10 clay) ranks top among the catalysts of heterogeneous catalytic reactions that have been explored most extensively [5,6].

Heterocyclic compounds play a critical role in various fields from medicinal to chemo sensing due to the fact that they constitute the fundamental components of several physiologically active frameworks in addition to many commercial compounds [7-13]. Significantly, heterocyclic motifs containing nitrile and sulfur are the prevalent structural components that are abundantly present in the natural and medicinal compounds. Since these molecules are capable of essentially every recognized biological activity [14], they are often referred to as a 'mystic moiety. As a result of potential improvements in binding affinity to the target, the pharmacokinetic profile of the parent drugs and the suppression of drug resistance, the incorporation of a nitrile [15] or sulphur [16] group into heterocyclic compounds has emerged as an intriguing option in rational drug formulation.

Pyran, an oxygen heterocyclic compound, exhibits a wide distribution in both the animal and plant worlds and encompasses a diverse range of medicinal attributes [17]. 2*H*-pyrans are more prominent since they constitute an integral part of natural products with biological significance [18]. Additionally, they act as a vital strategic intermediate for the synthesis of natural compounds such as steroids [19]. Pyran analogues have numerous applications as antibacterial [20], anticancer [21], anticoagulant [22], sex pheromone [23] and anti-proliferative agents [24]. Pyrans also have the potential to treat neurological disorders, namely Alzheimer's, Parkinson's and Huntington's [25].

In continuation to our work for the synthesis of Mont-K10 catalyzed substituted 2-aminopyridines using pseudo-four component reactions [26,27], herein, a design approach to synthesize highly functionalized pyran derivatives by using one pot pseudo- four- components synthesis of substituted 5-cyano-2-imino-4-aryl/heteroaryl-6-(phenylthio)-2*H*-pyran-3-carboxylic acid using Mont-K10 clay has been devised.

EXPERIMENTAL

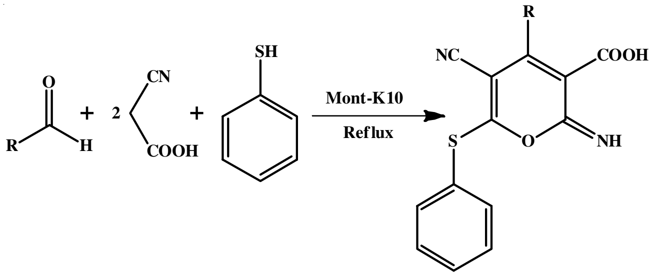
The chemicals and reagents were purchased from Sigma Aldrich and used without additional purification. Freshly dried as well as distilled solvents were used. The Montmorillonite K10 clay (Mont-K10 clay) was heated prior to its use in the reaction. TLC was used to monitor the progress of the reaction using a solvent mixture of ethyl acetate and hexane (20:80 v/v). The melting points were measured with KGX equipment in open capillaries and are uncorrected.

The infrared spectra in KBr pellets were acquired by employing a Bruker FT IR spectrometer, Alpha II. At the frequencies of 400 MHz and 100 MHz, the ^{1}H & ^{13}C NMR spectra were obtained by a Jeol Resonance 400 MHz spectrometer with TMS as an internal reference. A Xevo G2-S QTof (Waters, USA) instrument was used for recording high resolution mass spectra (HRMS).

General procedure of the multicomponent synthesis of 5-cyano-2-imino-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (4a-d): A mixture of aromatic aldehyde, cyanoacetic acid and thiophenol were mixed thoroughly in the ratio of 1:2:1 mmol followed by the addition of Montmorillonite K10 clay (20 mol%) in 25 mL round-bottom flask fitted with a condenser and then refluxed in ethanol. Throughout the reflux process, the reaction mixture was kept exposed to air where the progression of the reaction was monitored through TLC techniques. Following the completion, the mixture was left to cool down at ambient temperature. The Mont-K10 clay was subsequently sieved out while the solvent collected after filtration was extracted at reduced pressure. The solid product was subsequently rinsed with 3 × 10 mL of EtOAc and then dried (**Scheme-I**). Recrystallization using absolute ethanol was carried out to purify the crude product. The separated Mont-K10 clay was rinsed twice with 10 mL of EtOH and EtOAc, respectively, dried and reused in later experiments.

Characterization data

4-(4-Chlorophenyl)-5-cyano-2-imino-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (4a): White solid; m.p.: 230-232 ºC; yield: 90%; IR (KBr, ν_{max}, cm^{-1}): 3569, 2982, 2266, 1742, 1585, 1476, 1389, 1270, 1201, 1068, 1017, 928, 832, 753, 687. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.32 (bs, 1H, COOH), 8.00 (d, J = 8 Hz, 2H, Ar-H), 7.90 (d, J = 8 Hz, 2H, Ar-H), 7.65 (t, J = 8 Hz, 2H, Ar-H), 7.53-7.46 (m, 2H, Ar-H), 7.34-7.26 (m, 2H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 192.71, 174.63, 173.51, 165.24, 138.31, 138.04, 132.73, 131.72, 131.54, 130.01, 129.97, 129.91, 129.31, 128.12, 127.69, 125.97, 116.04, 106.90, 80.51. HRMS (ESI/Q-TOF) *m/z*: [M+H] calcd. for $C_{19}H_{11}N_2O_3SCl$: 382.01789; found: 382.8472.



Scheme-I: One pot pseudo-four-component reaction of aldehyde, cyanoacetic acid and thiophenol catalyzed by Mont-K10 clay

4-(4-Bromophenyl)-5-cyano-2-imino-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (4b): White solid; m.p.: 258-260 ºC; yield: 88%; IR (KBr, ν_{max}, cm^{-1}): 3571, 2983, 2266, 1742, 1588, 1474, 1391, 1202, 1072, 1016, 928, 831, 753, 689. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.45 (dd, J = 8 Hz, 1H, Ar-H), 7.39-7.33 (m, 4H, Ar-H), 7.27-7.18 (m, 5H, Ar-H), 6.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 166.19, 164.83, 139.06, 134.21, 134.20, 134.18, 131.89, 131.54, 130.51, 129.58, 129.56, 129.55, 129.54, 128.09, 121.65, 116.27, 115.62, 62.46, 55.90. HRMS (ESI/Q-TOF) *m/z*: [M+H] calcd. for $C_{19}H_{11}N_2O_3SBr$: 425.96738; found 426.5941.

4-(4-Nitrophenyl)-5-cyano-2-imino-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (4c): Yellow solid; m.p.: 294-296 ºC; yield: 85%; IR (KBr, ν_{max}, cm^{-1}): 3576, 2983, 2265, 1740, 1587, 1475, 1391, 1202, 1072, 1016, 929, 832, 753, 689. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.33-8.09 (m, 3H, Ar-H), 7.89-7.25 (m, 6H, Ar-H), 6.82 (bs, 1H, COOH), 6.30 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 172.59, 171.44, 171.11, 166.47, 148.81, 147.74, 147.40, 147.23, 147.12, 131.92, 130.07, 130.01, 129.66, 129.51, 129.44, 124.62, 116.33, 101.91, 55.69. HRMS (ESI/Q-TOF) *m/z*: [M+H] calcd. for $C_{19}H_{11}N_3O_5S$: 393.04194; found 394.9518.

4-(Thiophen-2-yl)-5-cyano-2-imino-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (4d): Yellow solid; m.p.: 212-214 ºC; yield: 70%; IR (KBr, ν_{max}, cm^{-1}): 3455, 3033, 2223, 1599, 1510, 1341, 1176, 1106, 984, 837, 743, 683. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 8.50 (s, 3H, Ar-H), 8.13 (d, J = 8 Hz, 2H, Ar-H), 7.97 (dd, J = 4 Hz, 3H, Ar-H), 7.30 (dd, J = 4 Hz, 3H, Ar-H). ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 164.02, 148.30, 147.72, 147.62, 140.92, 140.12, 137.76, 137.01, 136.19, 131.60, 129.53, 129.25, 116.82, 99.59, 98.01, 53.69. HRMS (ESI/Q-TOF) *m/z*: [M+H] calcd. for $C_{17}H_{10}N_2O_3S_2$: 354.01328; found 354.0266.

RESULTS AND DISCUSSION

Optimization of reaction conditions: For optimizing the reaction conditions, chlorobenzaldehyde, cyanoacetic acid and thiophenol were selected as benchmark substrates to refine the reaction conditions. Indeed, after the experimentation with different solvents, catalyst dosage and reaction temperatures,

TABLE-1
OPTIMIZATION OF REACTION CONDITIONS FOR ONE POT MULTICOMPONENT REACTION[a]

Entry	Mont K10 (mol %)	Solvent	Temperature (°C)	Time (h)	Yield (%)[b]
1	–	Ethanol	Reflux	10.00	Nil
2	5	Ethanol	Reflux	6.00	23
3	10	Ethanol	Reflux	3.00	43
4	15	Ethanol	Reflux	1.50	60
5	20	Ethanol	Reflux	0.75	90
6	25	Ethanol	Reflux	0.75	90
7	20	Ethanol	65	1.00	50
8	20	Ethanol	55	1.00	40
9	20	Ethanol	RT	3.00	< 5
10	20	–	Reflux	1.00	10
11	20	Water	Reflux	1.00	10
12	20	Water:ethanol	Reflux	1.00	30
13	20	Methanol	Reflux	1.00	75
14	20	Acetonitrile	Reflux	1.00	53
15	20	Tetrahydrofuran	Reflux	1.00	45
16	20	Toluene	Reflux	1.00	23

[a]Reaction scale: Chlorobenzaldehyde (1 mmol), cyanoacetic acid (2 mmol), thiophenol (1 mmol); [b]Isolated yields.

it was observed that the refluxing of three reactants with Mont-K10 clay in ethanol for a duration of 0.75-2.0 h resulted in the synthesis of various substituted pyrans (Table-1).

Even after an extended reaction period, the reaction failed to continue in the absence of catalyst (entry 1, Table-1). In contrast, when the reaction was performed in the vicinity of 20 mol% of Mont-K10 clay the reaction took 0.75 h and the product yield was 90% (entry 5, Table-1). Higher loadings of catalyst over 20 mol% neither afforded a marked influence on the product yield nor reaction rate (entry 6, Table-1). Entries 7-9 illustrated the effect of varying temperatures on the reaction. At lower temperature, the reaction time was increased while the yields of the product were slightly decreased (entry 7-8, Table-1). However, at room temperature only traces of the desired product were isolated (< 5%) (entry 9, Table-1).

Upon determining the appropriate quantity of catalyst as well as temperature for this process, the screening of solvents such as water, water-ethanol mixture, ethanol, methanol, acetonitrile, tetrahydrofuran and toluene were also tested (entries 11-16, Table-1). With ethanol mediated reaction, the result was found to be the best (entry 5, Table-1). Just before employing solvents, the reaction was additionally examined under solventless condition, but it could offer only 10% yield in 1 h (entry 10, Table-1). In a similar fashion, the reactions were carried out with the aforementioned solvents, unfortunately, the product was obtained with reduced yields. In accordance with ethanol, the reaction in methanol also went smoothly (entry 13, Table-1), since methanol is much toxic and hazardous than ethanol, we constrained its application for this one pot pseudo-four-component reaction. As a result, ethanol as solvent was chosen for ongoing research.

With the intention to demonstrate the scope and versatility of the present method, the one-pot multi component reaction (**Scheme-I**) with a variety of aldehydes under optimized reaction conditions was carried out. Table-2 reveals that the aromatic aldehydes having the electron-withdrawing or electron-donating groups with cyanoacetic acid and thiophenols smoothly giving excellent yields (entries 1-3, Table-2). Moreover, heteroaryl aldehyde (thiophene-2-carbaldehyde) gave the desired products in good yield (entry 4, Table-2). When aliphatic aldehydes and aliphatic thiols were utilized in place of aryl aldehydes and aryl thiols, black sticky and greasy products appeared, which is a drawback of the reaction.

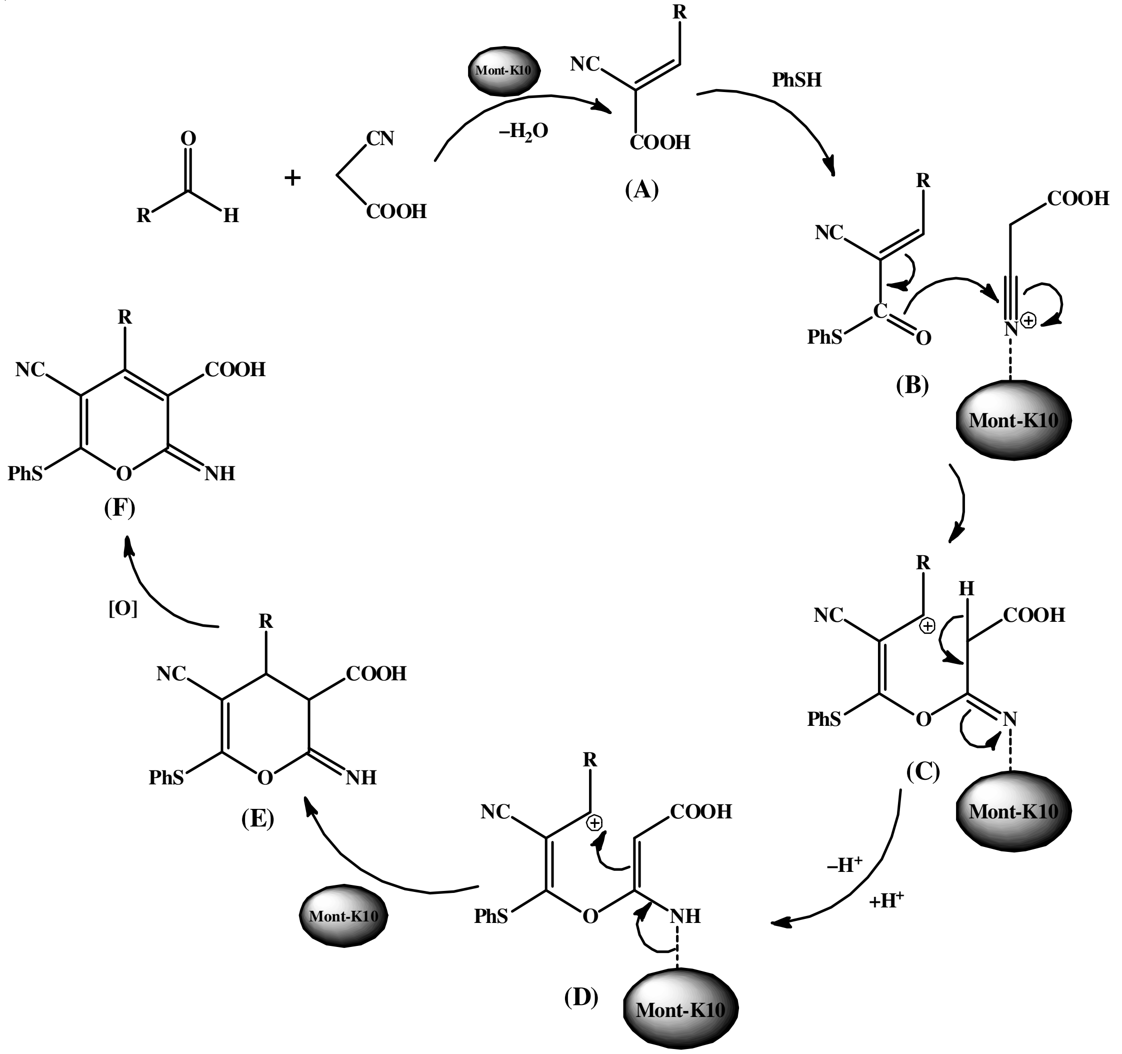
TABLE-2
SYNTHESIS OF PYRAN DERIVATIVES *via* Mont-K10 CLAY PROMOTED REACTION OF ALDEHYDE, CYANOACETIC ACID AND THIOPHENOLS USING ETHANOL AS SOLVENT[a]

Entry	R	Product	Yield (%)[b]	Time (h)
1	4-ClC_6H_4	I	90	0.75
2	4-BrC_6H_4	II	88	1.00
3	$4\text{-O}_2NC_6H_4$	III	85	1.00
4	SC_4H_3	IV	70	1.50

[a]Reaction conditions: Aromatic aldehydes (4 mmol), cyanoacetic acid (8 mmol), thiophenol (4 mmol); Catalyst: 20 mol%; solvent: 15 mL of EtOH; [b]Isolated yields.

Synthesized compounds were completely ascertained with various spectroscopic techniques *viz.* FT-IR, ^{1}H & ^{13}C NMR, mass spectrometry and elemental analysis. The FT-IR of the products displayed a wide absorption band at 3571-3455 cm^{-1} indicating O-H group. The overlap between the O-H and N-H stretching vibrations may result in the concealing of the N-H band [28]. One absorption band at 2269-2223 cm^{-1} implies the presence of -C≡N stretching along with absorption band of carbonyl group at 1742-1740 cm^{-1}. Additionally, a peak at 1599-1585 cm^{-1} is attributed to the C=C stretching and peak at 753-735 cm^{-1} is primarily due to the thioether bond. In ^{1}H NMR spectra, all the aromatic ring protons were observed as multiplet between δ 7.5-8.5 ppm. However, in certain cases, -NH and -OH protons were not detected, which may be due to their peaks merging with DMSO as solvent [29,30]. Moreover, in ^{13}C NMR spectra signal for nitrile group carbon appears at δ 116 ppm. All of the remaining aromatic carbon atoms elicited signals between δ 125 and 172 ppm.

Mechanism: Scheme-II proposes a feasible mechanism for the synthesis of pyran analogues (**4a-d**). Mont-K10 clay initiates the Knoevenagel condensation of aldehyde with cyano-



Scheme-II: Proposed mechanism for the Mont-K10 clay catalyzed synthesis of substituted 5-cyano-2-imino-4-aryl(or heteroaryl)-6-(phenylthio)-2*H*-pyran-3-carboxylic acid

acetic acid yielding Knoevenagel adduct. Intermediate (B) appears through the nucleophilic addition of thiolate to the carboxylic acid group of the Knoevenagel adduct. At the same time, second molecule of cyanoacetic acid is activated by Mont-K10 clay, facilitating its Michael addition, which leads to the formation of intermediate (C). Then the formed intermediate (C) passes through a proton shift, intramolecular cyclization (D) and finally oxidative aromatization (E), leading to the desired substituted 2*H*-pyrans (F).

Recyclability studies: For practical catalytic applications, the reusability and stability of heterogeneous catalysts is essential since it facilitates separation and recovery. Hence, the reusability of Mont-K10 clay was also investigated for this about five consecutive cycles of experiments was conducted. As it can be deduced from Table-3, the catalyst can be successfully reused up to two runs without loss of activity.

TABLE-3
RECYCLABILITY STUDIES OF Mont K10 CLAY[a]

Number of cycles	Yield (%)[b]	Time (h)
Native	90	0.75
Run 1	90	0.75
Run 2	90	0.75
Run 3	88	0.75
Run 4	84	0.75
Run 5	80	0.75

[a]Reaction conditions: Chlorobenzaldehyde (1 mmol), cyanoacetic acid (2 mmol), thiophenol (1 mmol); Catalyst: Mont K10 clay (20 mol%); Solvent: ethanol (5 mL); [b]Isolated yields.

Conclusion

An efficient synthetic method for substituted 5-cyano-2-imino-4-aryl/heteroaryl)-6-(phenylthio)-2*H*-pyran-3-carboxylic acid (**4a-d**) by one pot pseudo-four-component reactions of substituted aldehydes, thiophenol and cyanoacetic acid in the presence of Montmorillonite K10 clay as an environmentally benign catalyst has been developed. Expedient reactions, safe process, good to excellent yields, easy work-up (without any hazardous solvents), reusability of the catalyst up to two runs make this method a viable approach in the arena of synthetic methods to access diversely substituted 2*H*-pyrans abiding green chemistry principles.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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