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Organocatalyzed domino reactions: diversity oriented synthesis of pyran-annulated scaffolds using in situ-developed benzylidenemalononitriles

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Abstract Molecular diversity for the synthesis of pyran annulated heterocyclic scaffolds has been achieved from the multicomponent reaction of aldehyde, malonitrile and a third participant such as dimedone, barbituric acid and 3-methyl-1H-pyrazol-5(4H)-one. The reactions completed successfully using in situ-developed benzylidenemalononitriles via Knoevenagel reaction catalyzed by aspartic acid as a new efficient organo-catalyst in aqueous ethanol as a green medium at ambient conditions.

Keywords Multicomponent reactions · Pyran annulated heterocyclic scaffolds · Aqueous ethanol · Aspartic acid

Introduction

Pyran annulated molecules are the core fragment of many natural products [1]. These potentially active scaffolds have a broad spectrum of physiological activities [2, 3]. The "privileged" motif containing structures exhibits activities like diuretic [4], anticancer [5], anticoagulant [6], anticonvulsant [7], antimicrobial [8], anti-HIV [9], antimalarial [10], anti-tumour [11] antihyperglycemic and antidyslipidemic [12]. Also, many of them are used in Huntington's and Alzheimer's, Parkinson disease [13] and many more [14, 15]. Moreover, different substituted 4H-pyran derivatives have played increasing roles in synthetic approaches to promising molecules in the field of agrochemicals [16], medicinals [17, 18], and the cosmetics industries [19]. Some of the naturally occurring and synthetic pyran annulated

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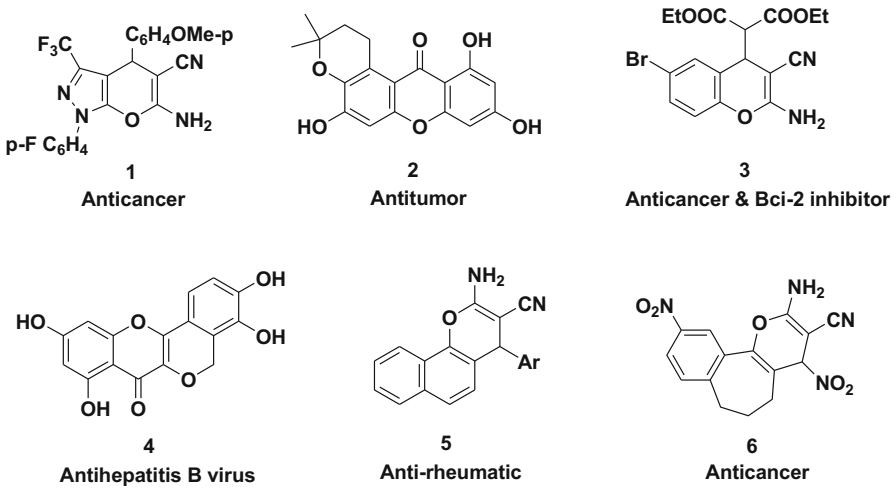
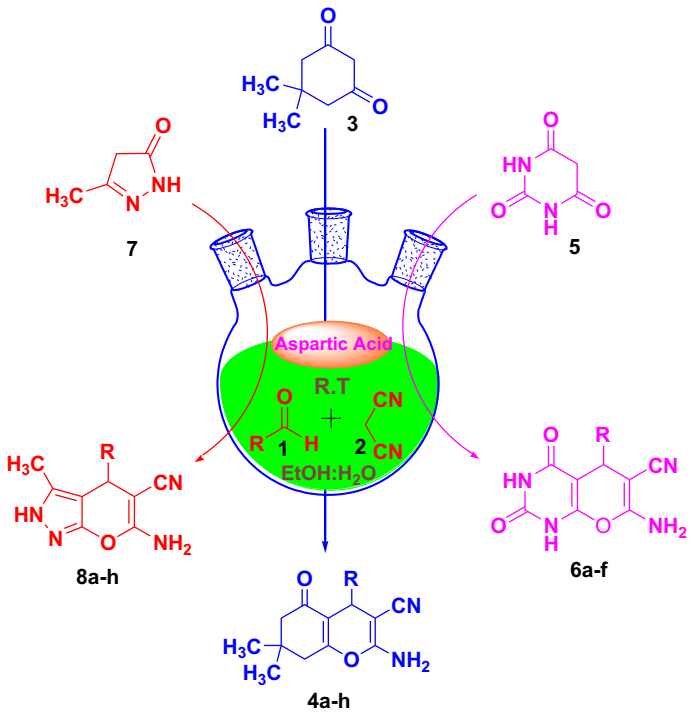


Fig. 1 Some pyran-containing pharmaceutical drug scaffolds

molecules are shown in Fig. 1 **1**–**6**, which shows a diverse and wide range of pharmaceutical potentials [20–27].

Such a numerous application of pyran annulated heterocyclic compounds in medicinal chemistry have produced substantial interest among synthetic chemists during the last few years to develop efficient and convenient synthetic protocols for these privileged scaffolds. Consequently, so many methods and strategies are already reported, which includes use of ultrasonic irradiation [28], microwaves [29] and a variety of catalysts and reagents such as DBU [30], heteropolyacids [31], diammonium hydrogen phosphate [32], DMAP [33], basic ionic liquids [34], ZnO-β-Zeolite [35], tetrabutylammonium bromide [36], iodine [37], nano MgO [38], phenylboronic acid [39], β-cyclodextrin [40], alum [41], Zn[(L)proline] [42], Amberlyst A21 [43], aminopro-pylated-SiO_2 [44], magnetic nanocatalyst [45], (S)-proline [46], Amberlite IRA-40 (OH) [47] and urea [48]. However some of these methods suffer from limitations such as elevated temperatures, use of strong corrosive acids, unsatisfactory yields, long reaction time, high catalytic loading and use of hazardous solvents and, in some cases, the need to use ultrasonic or microwave irradiation. However, some of the heterogeneous catalysts and nano-particles promoted methods that provide better results, but they are not only costly, their preparation requires tiresome methods and results in low yields. Thus, the development of a new, convenient and readily available procedure that avoids many of these problems is extremely desirable.

Aspartic acid is an amino acid broadly used in different sectors such as the pharmaceutical, agriculture, cosmetics industries, and they are used as nutrition supplements in the food and beverage industries [49–52]. Aspartic acid is safe, readily available, nontoxic and of low cost. Our literature search at this stage revealed that there are no reports on the synthesis of 2-amino-3-cyano-4H-pyrans, 1H-Pyrano[2,3-d] pyrimidine-2,4(3H,5H)-diones and 1,4-dihydropyrano [2,3-c] pyrazoles catalyzed by aspartic acid as an efficient organo-catalyst in an aqueous ethanol medium. As part of our investigations aimed at developing newer



Scheme 1 Diversity oriented synthesis of pyrans using aspartic acid as a catalyst

convenient, efficient and environmentally friendly methodologies for some diverse heterocyclic scaffolds [53–56], and following our interest in organo-catalysis herein, we wish to report an efficient and simple protocol for the diversity oriented synthesis of 2-amino-3-cyano-4H-pyrans, 1H-pyrano [2,3-d] pyrimidine-2, 4 (3H,5H)-diones and 1,4-dihydropyrano[2,3-c] pyrazoles (Scheme 1).

Experimental

All the chemicals were obtained from commercial sources and used without further purification. To monitor progress of the reaction by TLC, silica gel-coated aluminum sheets (Merck made) were used. Melting points were determined in an open glass capillary tube and are uncorrected. The NMR spectra were recorded on a Bruker Advance DPX-250. Mass spectra were recorded on a Waters Mass spectrometer.

General procedure for the synthesis of 2-amino-3-cyano-4H-pyrans(4a–4h), 1H-pyrano[2,3-d]pyrimidine-2,4(3H,5H)-diones (6a–6f) and 1,4-dihydropyrano [2,3-c]pyrazoles (8a–8h)

A 25 mL round bottom flask was charged with aldehyde **1** (1 mmol), malononitrile **2** (1.1 mmol) and aspartic acid (20 mol%) in 4 mL EtOH: H_2O (1:1), the reaction mixture

was then stirred vigorously at room temperature for about 10 min. After that, the third reactant, dimedone **3**/barbituric acid **5**/3-methyl-1H-pyrazol-5(4H)-one **7** (1 mmol) was added to the reaction mixture, and stirring was continued for an appropriate time at ambient temperature as mentioned in respective tables in the text. On completion of the reaction (as monitored by TLC), water(5 mL) was added and stirring was continued until a solid mass precipitated out that was filtered off and washed with water to obtain a crude product. The dried crude product was successively washed by a mixture of hexane: ethyl acetate (80:20) and then dried, to obtained the desired pure product.

Selected spectral data

2-amino-7, 7-dimethyl-5-oxo-4-phenyl-5, 6, 7, 8-tetrahydro-4H-chromene-3-carbonitrile (4a) M P. 230–232 °C; ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.24–7.27 (m, 2H), 7.15–7.18 (m, 3H), 6.82 (brs, 2H), 4.20 (s, 1H), 2.52 (2H, s) 2.44–2.54 (d, 2H), 2.25 (d, 1H), 2.09 (d, 1H), 1.07 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 195.6, 162.4, 158.4, 144.7, 128.3, 127.1, 126.5, 119.7, 112.6, 58.31, 49.9, 35.5, 31.7, 28.3, 26.7.; Mass (*m*/*z*) = 295.1 [M + 1].

2-amino-4-(4-methoxyphenyl)-7, 7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile (4f) M P. 201–203 °C; ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.04–7.07 (d, 2H), 6.83 (s, 2H), 6.79–6.82 (d, 2H), 4.14 (s, 1H), 3.72 (s, 3H), 2.22 (d, 1H), 2.08 (d, 1H), 1.08 (s, 3H), 0.97 (s, 3H).; ^{13}C NMR (100 MHz, DMSO) δ (ppm): 196.1, 162.5, 158.8, 158.3, 137.2, 128.6, 120.2, 114.0; Mass (*m*/*z*) = 323.2 [M − 1].

7-Amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-d]pyrimidine-6-carbonitrile (6b) M P. 232–234 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 11.12 (s, 1H), 7.35(d, 2H), 7.25 (d, 2H), 7.19 (s, 2H) 4.25 (s, 1H); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 162.9,158.0, 152.8, 149.8, 143.4, 131.6, 129.6, 128.5, 119.4, 88.3, 58.6, 35.5. Mass (*m*/*z*) = 315.1 [M − 1].

6-amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (8b) M P. 172–174 °C; ^{1}H NMR (400 MHz, DMSO) δ (ppm): 12.00 (s, 1H), 7.07 (d, 2H), 6.83(d, 2H), 6.71 (s, 2H), 4.51 (s, 1H), 3.74 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 160.6, 157.8, 154.7, 136.3, 135.3, 128.3, 120.7, 113.5, 97.6, 57.6, 54.8, 35.5, 9.7; Mass (*m*/*z*) = 283.2 [M + 1].

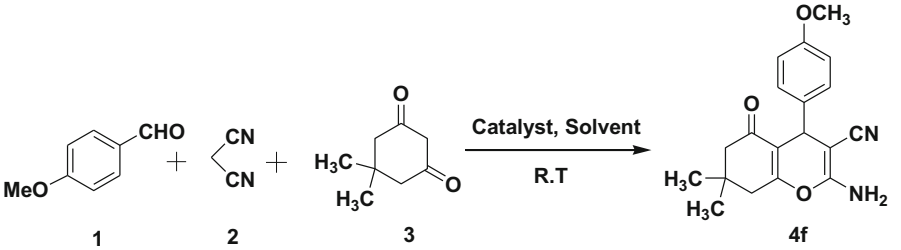
6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (8e) M P. 170–172 °C; ^{1}H NMR (400 MHz, DMSO): δ (ppm): 12.06 (s, 1H), 7.34 (d, 2H), 7.19 (d, 2H), 6.82 (s, 2H), 4.59(s, 1H), 1.80 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ (ppm): 160.8, 154.6, 143.2, 135.4, 131.3, 129.1, 128.2, 120.5, 96.9, 56.8, 35.7, 9.7; Mass (*m*/*z*) *m*/*z* = 287.1 [M + 1].

Results and discussion

Herein, we wish to report a convenient and facile access to some highly substituted 2-amino-3-cyano-4H-pyrans, 1H-pyrano[2,3-d]pyrimidine-2,4(3H,5H)-diones and 1,4-dihydropyrano[2,3-c]pyrazoles via one-pot three component reaction of

aldehydes, malonitrile and dimedone/barbaturic acid/3-methyl-1H-pyrazol-5(4H)-one in aqueous ethanol medium promoted by aspartic acid. Preliminary observations were mainly conducted on a number of trial reactions of dimedone (1 mmol), anisaldehyde (1 mmol) and malonitrile (1.1 mmol) in the presence of different catalysts in ethanol at room temperature for the synthesis of 2-amino-3-cyano-4H-pyrans. The catalyst-free reaction gave a mixture of products that included some amounts of the desired product (Table 1, entry 1). Sodium azide, sodium saccharin, and alanine afforded the desired product in moderate yield (Table 1, entry 2–4). The reaction furnished the product in 80 % yield within 1 h (Table 1, entry 5) when aspartic acid as a catalyst was used. Aspartic acid is an amino acid with two carboxylic groups in its structure whereas alanine has one, and the presence of two carboxylic groups may be relevant to the unique role of aspartic acid for maximum yield than does alanine. The yield and the rate of the aspartic acid-catalyzed reaction were quite better when ethanol was used as a solvent (Table 1, entry 5). This shows that the aspartic acid exhibited a good catalytic activity for the synthesis of 2-amino-3-cyano-4H-pyrans.

Table 1 Optimization of the reaction conditions for the synthesis of 2-amino-3-cyano-4H-pyrans



1 2 3 4f

Entry	Catalyst (20 mol%)	Solvent	Time (h)	Yield (%)[a]
1	None	EtOH	10	20
2	Sodium azide	EtOH	9	38
3	Sodium saccharin	EtOH	8	52
4	Alanine	EtOH	6	50
5	Aspartic acid	EtOH	1	80
6	Aspartic acid	MeOH	3	40
7	Aspartic acid	Dioxane	3	25
8	Aspartic acid	Acetonitrile	2	60
9	Aspartic acid	DCM	2	55
10	Aspartic acid	Toulene	4	45
11	Aspartic acid	H_2O	3	65
12	Aspartic acid	ACN:H_2O	3	70
13	Aspartic acid	EtOH:H_2O	1	96
14	Aspartic acid (10 %)	EtOH:H_2O	1	89
15	Aspartic acid (25 %)	EtOH:H_2O	1	94

[a] Isolated yields

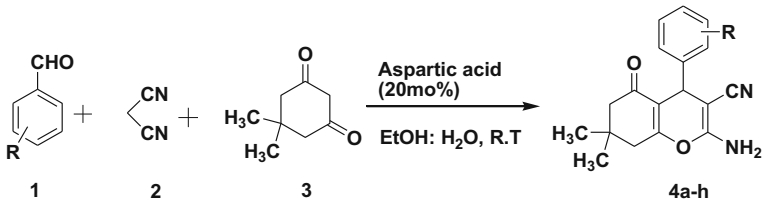
Next, we studied the effects of other solvent systems on the model reaction;, we used different solvents, such as MeOH, dioxane, acetonitrile, DCM, toulene, water, ACN: water (1:1) and EtOH: Water (1:1) in presence of a catalytic amount (20 mol%) of aspartic acid at room temperature. Water alone as a reaction medium provided considerably better yield (Table 1, entry 11), but the product was obtained as a sticky solid material. As can been seen in (Table 1, entry 13), the aspartic acid catalyzed reaction in ethanol: Water (1:1, v/v) led to higher yields in shorter reaction times than the others. As a consequence, ethanol: Water (1:1, v/v) was nominated as the suitable solvent. Recently, we have reported an organo-catalyzed synthesis of isoxazoles in aqueous ethanol medium at room temperature [55]. In pursuance of making the methodology economical and green, water: ethanol (1:1, v/v) was found to be an ideal medium. Moreover, we tried to optimize the reaction by varying the amount of aspartic acid. When 20, 10 and 25 mol% of aspartic acid were used, the yields were 96, 89 and 94 %, respectively (Table 1, entry 13–15). Therefore, 20 mol% of aspartic acid was found to be an optimal amount for the reaction completion. To explore the effectiveness and generality of the protocol, the present observations were extended to different aromatic aldehydes having electron releasing/withdrawing substituents such as methoxy, nitro, hydroxyl, methyl, halogens and so on (Table 2, entry 1–8). All the reactions smoothly resulted in the formation of corresponding 2-amino-3-cyano-4H-pyrans in greater yields (90–96 %). The pure products were isolated without chromatographic purification just by washing with water and then a mixture of hexane: Ethyl acetate, as on completion of the reaction most of the products come out as solid precipitate in the reaction vessel. All the products are quite stable in aqueous media (Scheme 2).

Encouraged by these results and to illustrate the applicability of our procedure, we endeavored to continue the aspartic acid catalyzed protocol to find out whether the protocol could explore similar results in the case of other multicomponent reactions, which involved an in situ formed benzylidene malononitrile intermediate. Here we used barbaturic acid as an active methylene compound instead of dimedone along with anisaldehyde and malonitrile as the model substrates (Scheme 3).

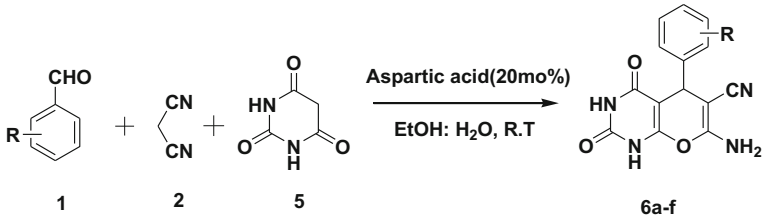
Table 2 Multicomponent condensation of aromatic aldehydes, dimedone, and malononitrile

Entry	*R*	Product	Time (h)	Yield (%)[a]	M. p. (°C)	
					Observed	Literature
1	C_6H_5	**4a**	1	93	230–232	224–226 [48]
2	4-Cl–C_6H_4	**4b**	1.5	95	212–214	215–217 [29]
3	3-NO_2–C_6H_4	**4c**	2	92	216–218	204–206 [48]
4	2-Cl–C_6H_4	**4d**	1.5	94	200–202	201–203 [44]
5	4-Me–C_6H_4	**4e**	1	95	217–220	208–210 [34]
6	4-MeO–C_6H_4	**4f**	1	96	201–203	199–201 [29]
7	4-OH–C_6H_4	**4g**	1.5	94	218–220	223–225 [44]
8	4-(Br)–C_6H_4	**4h**	1.5	95	200–202	193–195 [34]

[a] Isolated yields



Scheme 2 The efficient synthesis of 2-amino-3-cyano-4H-pyrans



Scheme 3 The efficient synthesis of 1H-Pyrano [2, 3-d] pyrimidine-2, 4(3H, 5H)-diones

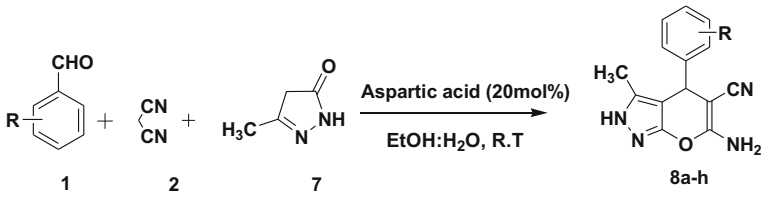
The C–H activated barbituric acid underwent reaction very smoothly with malonitrile and anisaldehyde under the similar optimized reaction conditions. The desired products 1H-Pyrano [2, 3-d] pyrimidine-2, 4(3H, 5H)-diones (Table 3, entries 1–6) with other aldehydes were equally formed in maximum yields (80–90 %) within the limited time period. As it can be seen from Table 3, the electronic nature of the groups on benzaldehyde has an insignificant effect on the conversion.

After developing a general and common procedure for the synthesis of 2-amino-3-cyano-4H-pyrans, as well as 1H-Pyrano[2,3-d]pyrimidine-2,4(3H,5H)-diones, we focused our interest towards another significant pyran-annulated heterocycle, namely pyrano [3,2-c] pyrazoles (Scheme 4), since the molecules belonging to this scaffold hold a position of eminence owing to their human chk1 inhibitor activity

Table 3 Synthesis of pyrano [2, 3-d] pyrimidinones

Entry	*R*	Product	Time (h)	Yield (%)[a]	M.p. (°C)	
					Observed	Literature
1	C_6H_5	**6a**	2	90	218–220	223–224 [42]
2	4-Cl–C_6H_4	**6b**	2.5	92	232–234	236–238 [48]
3	3-NO_2–C_6H_4	**6c**	2.5	90	270–272	271–273 [41]
4	4-Me–C_6H_4	**6d**	1.5	93	225–226	225–226 [42]
5	4-MeO–C_6H_4	**6e**	1.5	94	276–278	280–281 [42]
6	4-(Br)–C_6H_4	**6f**	2	92	228–230	222–234 [41]

[a] Isolated yields



Scheme 4 The efficient synthesis of pyrano [3, 2- c] pyrazoles

[57, 58]. Here also the synthesis of 1, 4-dihydropyrano [2, 3-c] pyrazoles was accomplished successfully by a one-pot model reaction of anisaldehyde, malononitrile and 3-methyl-1H-pyrazol-5(4H)-one in the presence of 20 mol% aspartic acid in ethanol: water at room temperature conditions.

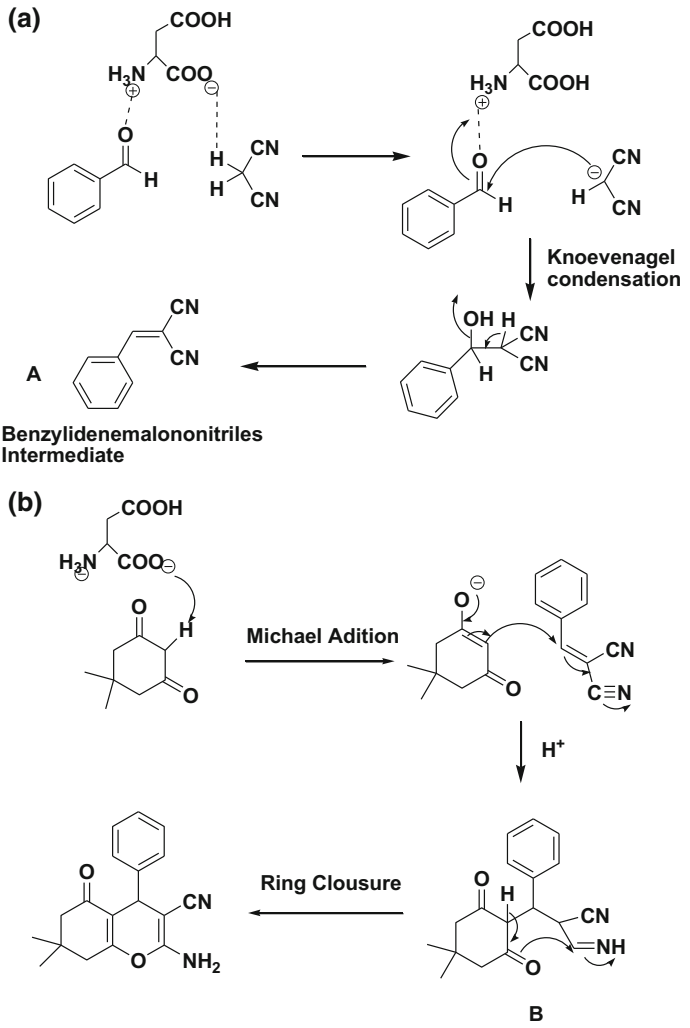
This success led us to apply these conditions to other aldehydes; to our delight, all the aldehydes afforded the corresponding pyrano pyrazoles in excellent yields (Table 4, entries 1–8). All the products **(4a–h), (6a–6f), (8a–8h)** are known compounds, and their structures were confirmed by comparison of their physical and spectral data with those reported previously [29, 34, 40–44], [48]. From all these observations, we have found that aspartic acid is a versatile organocatalyst for multicomponent reactions using in situ-developed benzylidene malononitrile with various C–H-activated compounds.

To rationalize the synthesis of various pyran annulated heterocyclic scaffolds, a possible mechanism of the reaction among aldehyde, malonitrile and dimedone catalyzed by aspartic acid is explained in Scheme 5 based on previous reports of an amino acid (glycine) catalyzed protocol for the synthesis of 2-amino-4H-chromenes [59]. The knoevenagel intermediate benzylidine malonitrile **A** was formed in situ by the reaction of aldehyde and malonitrile in the presence of aspartic acid. This knoevenagel intermediate **A** reacts with an in situ formed carbanion of the C–H activated dimedone by a Michael addition reaction to give rise to intermediate

Table 4 Synthesis of dihydropyrano pyrazoles

Entry	*R*	Product	Time (h)	Yield (%)[a]	M. p. (°C)	
					Observed	Literature
1	H	**8a**	6	88	242–244	244–246 [40]
2	4-OCH_3	**8b**	5	90	172–174	174–175 [43]
3	4-OH	**8c**	7	87	220–222	218–220 [40]
4	3-NO_2	**8d**	5	84	192–194	194–196 [48]
5	4-Cl	**8e**	5	90	170–172	175–176 [43]
6	4-Br	**8f**	6	85	202–204	206–208 [40]
7	2-Cl	**8g**	7	88	244–246	240–242 [40]
8	4-Me	**8h**	6	91	208–210	206–208 [40]

[a] Isolated yields



Scheme 5 Proposed mechanism for the aspartic acid catalyzed synthesis of 2-Amino-4 H-benzo [b] pyrans

B. The intermediate **B** after ring closure affords the desired 2-amino-3-cyano-4H-pyrans.

Conclusion

In conclusion, we have described, for the first time, aspartic acid catalyzed an alternative and facile protocol for easy access to functionalized pyran-annulated heterocycles via multicomponent domino Knoevenagel-cyclocondensation of

substituted aldehydes, malononitrile, and C–H-activated compounds in aqueous ethanol at room temperature. Simple procedures, easy workup, maximum products yields, mild reaction conditions, the avoidance of toxic reagents and organic solvents are significant advantages of the present protocol compared to the reported ones.

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