One-Pot Eco-Safe Saccharin-Catalyzed Procedure for Expedient and Convenient Synthesis of Dihydropyrano[2,3-*c*]pyrazole, Tetrahydrobenzo[*b*]pyran and Pyrano[2,3-*d*]pyrimidinone Scaffolds as a Green and Versatile Catalyst

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ABSTRACT

*A green and facile saccharin-catalyzed procedure is developed for the one-pot convenient synthesis of dihydropyrano[2,3-*c*]pyrazole, tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone scaffolds via multi-component tandem Knoevenagel cyclocondensation reaction. This procedure has the chief advantages of green, inexpensive and readily available catalyst, high atom-economy, high to quantitative yields and the reaction procedure is mild and involves facile workup procedure to obtain the desired products in short reaction times.*

Keywords: *green procedures; saccharin; dihydropyrano[2,3-*c*]pyrazoles; tetrahydrobenzo[*b*]pyrans; pyrano[2,3-*d*]pyrimidinones*

ABSTRAK

*Metode sintesis yang mudah dan green, yakni sintesis one-pot terkatalisis sakarin, telah dikembangkan untuk menghasilkan kerangka dihydropyrano[2,3-*c*]pyrazole, tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone melalui reaksi multikomponen beruntun yang terdiri dari reaksi Knoevenagel dan siklokondensasi. Metode ini memiliki kelebihan yaitu bersifat green, tidak mahal, katalis mudah didapat, dan atom ekonomi yang tinggi. Selain itu, reaksi ini dapat dilakukan pada kondisi ringan dan serta memiliki prosedur work-up yang mudah, sehingga berbagai senyawa target dapat dihasilkan dalam waktu reaksi yang singkat dengan rendemen yang tinggi.*

Kata Kunci: *metode sintesis green; sakarin; dihydropyrano[2,3-*c*]pyrazoles; tetrahydrobenzo[*b*]pyrans; pyrano[2,3-*d*]pyrimidinones*

INTRODUCTION

Multicomponent reactions (MCRs) are processes ‘‘in which more than two educts directly get converted into their products by one-pot reaction’’ [1-2]. MCRs [3-7] play an important role in modern organic chemistry, because they generally exhibit higher atom economy and selectivity as well as produce fewer by-products compared to classical multistep synthesis [8]. The development of environmentally friendly catalysts and solvents for organic reactions is one of the major minatory factors to environmental and human health. Thus, removal or reduction of the use of non-volatile solvents and non-metallic is one of the major goals of green chemistry.

Structures containing the pyran derivatives have attracted synthetic organic chemists and biochemists because of their pharmaceutical and biological activities. Literature reports have already established pyrans as Chk1 kinase inhibitory activity [9], analgesic properties [10], anticancer [11], vasodilatory activities [12], spamolytic [13] antihypertensive, hepatoprotective, cardiotonic [14], vasodilator [15], anti-leukemic [16-17], emetic [18], anti-anaphylactic activities [19], diuretic [20], anti-alzheimer [21].

Because of the above mentioned applications, many methods using different types of catalysts are reported for the preparation of these compounds which of them ZrO_2 NPs [22], choline chloride/Urea deep [23], isonicotinic [24], molecular sieves [25], meglumine [26], CAPB [27], L-proline/KF-alumina [28], CTACl [29], lipase [30], $CaHPO_4$ [31], SiO_2 NPs [32], Glycerol [33], SBPPSP [34], DBSA [35], $NH_4Al(SO_4)_2•12H_2O$ [36], $NH_4H_2PO_4/Al_2O_3$ [37], ACoPc-MNPs [38], ZnO NPs [39], Fe_3O_4@SiO_2-imid-PMA [40], DABCO-based ionic liquids [41], L-proline [42], Iron ore pellet [43], nano-sawdust-OSO_3H [44], Al-HMS-20 [45], TSA/$B(OH)_3$ [46], Mn/ZrO_2 [47], Green cellulose-based nanocomposite [48],

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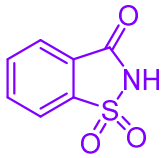


Fig 1. Structure of saccharin

DBA [49]. However, many of these methods suffer from disadvantages such as low yields, long reaction times, harsh reaction conditions, tedious work-up and requirement of excess amounts of reagents or catalysts. Therefore, it is important to find green and convenient methods for the synthesis of these types of compounds.

As part of our program aimed at developing green synthetic procedures with readily available and green saccharin-catalyzed [50] (Fig. 1), preparation of various biologically active pyran derivatives is of considerable interest and we report herein an eco-safe, highly efficient and inexpensive saccharin-catalyzed procedure for synthesis of dihydropyrano[2,3-*c*]pyrazole, tetrahydrobenzo[*b*]pyran and pyrano[2,3-*d*]pyrimidinone scaffolds *via* multicomponent tandem Knoevenagel cyclocondensation reaction, which might solve some cost problems in industry.

EXPERIMENTAL SECTION

Instrumentation

Melting points and IR spectra all compounds were determined using an Electro thermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer. Also, nuclear magnetic resonance, ^{1}H-NMR spectra were recorded on a Bruker DRX-400 Avance and Bruker DRX-300 Avance instruments and ^{13}C-NMR spectra were recorded on a Bruker DRX-100 Avance with $CDCl_3$ or DMSO-d_6 as solvents. Elemental analyses (C, H, N) were performed on a Heraeus CHN-O-Rapid analyzer. In this article, all reagents and solvents were purchased from Merck, Fluka and Acros chemical companies were used without further purification.

Procedure

General procedure for preparation of dihydropyrano [2,3-c]pyrazoles (5a-q)

Saccharin (25 mol%) was added to a mixture of ethyl acetoacetate (1, 1.0 mmol), hydrazine hydrate (2, 1.0 mmol), aryl aldehyde derivatives (3, 1.0 mmol) and malononitrile (4, 1.0 mmol) in EtOH at 60 °C. After completion of the reaction (by thin layer chromatography TLC) the mixture was cooled to rt, the precipitated product was filtered and washed with aqueous ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product (5a-q). Spectra data of selected and known are represented below:

6-amino-1,4-dihydro-3-methyl-4-(2-chlorophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (5b). Solid powder; Yield: 81%; M.p. 245–247 °C; IR (KBr): v 3391, 3357, 3314, 3169, 2190, 1609, 1489, 1408, 1350, 1052, 763; cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): 1.78 (3H, s, CH_3), 5.08 (1H, s, CHAr), 6.96 (2H, s, NH_2), 7.19–7.54 (4H, m, ArH), 12.14 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): 10.0, 33.9, 56.2, 97.3, 120.9, 128.2, 129.0, 129.9, 131.2, 132.4, 135.8, 141.4, 155.4, 161.7. Anal. Calcd for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54%. Found: C, 57.68; H, 3.78; N, 20.15%.

6-amino-1,4-dihydro-3-methyl-4-(2-nitrophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (5e). Solid powder; Yield: 89%; M.p. 244–246 °C; IR (KBr): v 3477, 3228, 3120, 2196, 1651, 1595, 1493, 1401, 1353, 1107, 744 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): 1.78 (3H, s, CH_3), 5.11 (1H, s, CHAr), 7.04 (2H, s, NH_2), 7.34 (1H, d, *J* = 6.8 Hz, ArH), 7.50 (1H, t, *J* = 7.2 Hz, ArH), 7.67 (1H, *t*, *J* = 7.2 Hz, ArH), 7.86 (1H, d, *J* = 7.6 Hz, ArH), 12.22 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): 9.9, 31.8, 56.5, 96.8, 120.6, 124.0, 128.7, 131.7, 133.8, 136.1, 138.0, 149.6, 155.4, 161.6. Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56%. Found: C, 56.65; H, 3.58; N, 23.45%.

6-amino-1,4-dihydro-3-methyl-4-(4-methoxyphenyl) pyrano [2,3-*c*] pyrazole-5-carbonitrile (5m). Solid powder; Yield: 83%; M.p. 208–210 °C; IR (KBr): v 3455, 3320, 2190, 1654; ^{1}H-NMR (300 MHz, (DMSO-d6): d = 1.79 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 4.55 (1H, s, CHAr), 6.85 (2H, br, NH_2), 6.88 (2H, d, *J* = 9.0 Hz, ArH), 7.07 (2H, d, *J* = 9.0 Hz, ArH), 12.03 (1H, s, NH).

6-amino-1,4-dihydro-3-methyl-4-(4-nitrophenyl)pyrano[2,3-*c*]pyrazole-5-carbonitrile (5n). Solid powder; Yield: 88%; M.p. 246–248 °C; IR (KBr): v 3414, 3374, 3316, 3175, 2186, 1654, 1598, 1529, 1492, 1412, 1350, 1072, 872, 791 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): 1.82 (3H, s, CH_3), 4.84 (1H, s, CHAr), 7.06 (2H, s, NH_2),7.48 (2H, d, *J* = 8.4 Hz, ArH), 8.22 (2H, d, *J* = 8.4 Hz, ArH), 12.22 (1H, s, NH); ^{13}C-NMR (100 MHz, DMSO-d_6): 10.2, 31.1, 56.4, 97.0, 120.9, 124.3, 129.3, 136.3, 146.8, 152.5, 155.1, 161.6. Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56%. Found: C, 56.68; H, 3.68; N, 23.55%.

6-amino-1,4-dihydro-3-methyl-4-(4-bromophenyl) pyrano[2,3-*c*]pyrazole-5-carbonitrile (5o). Solid powder; Yield: 75%; M.p. 181–183 °C; IR (KBr): v 3470, 3227, 3120, 2194, 1735, 1650, 1595, 1560, 1401, 1353, 1107, 883, 810, 744, 543 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): 1.60 (3H, s, CH_3), 4.69 (1H, s, CHAr), 6.96 (2H, s, NH_2), 7.15 (2H, d, *J* = 8.0 Hz, ArH), 7.51 (2H, d, *J* = 8.0 Hz, ArH), 12.16 (1H, s, NH).

6-amino-1,4-dihydro-3-methyl-4-(4-hydroxyphenyl) pyrano[2,3-*c*]pyrazole-5-carbonitrile (5p). Solid powder; Yield: 79%; M.p. 219–221 °C; IR (KBr): v 3766, 3491, 3357, 3214, 3169, 2803, 2710, 2351, 2190, 1489, 1408, 1350, 1052, 763 cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): 1.77 (3H, s, CH_3), 4.45 (1H, s, CHAr), 6.62–6.98 (6H, m, ArH and NH_2), 9.23 (1H, s, OH), 12.02 (1H, s, NH).

General procedure for preparation of tetrahydro benzo[b]pyrans (8a-r)

A mixture of aryl aldehyde derivatives (7, 1.0 mmol), malononitrile (4, 1.0 mmol), dimedone (6, 1.0 mmol) was well heated with saccharin (15 mol%) in 3 mL EtOH at 50 °C for appropriate time. The completion of reaction was also indicated by TLC. After completion of the reaction, the mixture was cooled to rt, the precipitated product was filtered and washed with ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product (8a-r). Spectra data of selected and known are represented below:

2-amino-3-cyano-4-phenyl-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (8a). Solid powder; Yield: 92%; M.p. 225–227 °C; IR (KBr): v 3395, 3323, 3027, 2960, 2199, 1680; ^{1}H-NMR (400 MHz, $CDCl_3$): 1.04 (3H, s, CH_3), 1.13 (3H, s, CH_3), 2.16 (1H, d, *J* = 16.0 HZ, CH_2), 2.28 (1H, d, *J* = 16.0 HZ, CH_2), 2.58 (2H, s, CH_2), 4.30 (1H, s, CHAr), 6.25 (2H, br s, NH_2), 7.19 (1H, m, ArH), 7.28 (4H, m, ArH).

2-amino-3-cyano-4-(2,3-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (8d). Solid powder; Yield: 87%; M.p. 216–218 °C; IR (KBr): v 3305, 3205, 2945, 2175, 1676, 1212; ^{1}H-NMR (400 MHz, $CDCl_3$): 1.08 (3H, s, CH3), 1.12 (3H, s, CH_3), 2.21 (2H, dd, *J* = 20.0, 16.0 Hz, CH_2), 2.39-2.51 (2H, m, CH_2), 3.85 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.52 (1H, s, CHAr), 4.74 (2H, s, NH_2), 6.72 (1H, dd, *J* = 8.0, 1.2 Hz, ArH), 6.79 (1H, dd, *J* = 1.6, 8.0 Hz, ArH), 6.97 (1H, t, *J* = 8.0 Hz, ArH).

2-amino-3-cyano-4-(4-hydroxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (8o). Solid powder; Yield: 81%; M.p. 211–213 °C; IR (KBr): v 3285, 3160, 2960, 2185, 1675, 1209; ^{1}H-NMR (400 MHz, $CDCl_3$): 1.05 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.24 (2H, dd, *J* = 20.0, 16.4 Hz, CH_2), 2.46 (2H, t, *J* = 19.2 Hz, CH_2), 4.36 (1H, s, CHAr), 4.53 (2H, s, NH_2), 5.26 (1H, s, OH), 6.71-6.74 (2H, m, ArH), 7.08-7.12 (2H, m, ArH).

2-amino-3-cyano-4-(4-methylphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[*b*]pyran (8r). Solid powder; Yield: 88%; M.p. 221–223 °C; IR (KBr): v 3465, 3320, 2955, 2190, 1676, 1247; ^{1}H-NMR (400 MHz, $CDCl_3$): 1.06 (3H, s, CH_3), 1.12 (3H, s, CH_3), 2.23 (2H, dd, *J* = 20.0, 16.4 Hz, CH_2), 2.30 (3H, s, CH_3), 2.46 (2H, s, CH_2), 4.38 (1H, s, CHAr), 4.54 (2H, s, NH_2), 7.10 (2H, d, *J* = 7.6 Hz, ArH), 7.12-7.14 (2H, m, ArH).

General procedure for preparation of pyrano[2,3-d]pyrimidinones (11a-q)

A mixture of barbituric acid derivatives (9, 1.0 mmol), aryl aldehyde derivatives (10, 1.0 mmol), malononitrile (4, 1.0 mmol), saccharin (20 mol%) and 3 mL EtOH was heated at 60 °C for appropriate time. After completion of the reaction, as monitored by TLC, the mixture was cooled to rt, the precipitated product was filtered and washed with ethanol. The crude product was purified by recrystallization from ethanol to afford the desired product (11a-q). The products have been characterized by melting points and ^{1}H-NMR spectroscopy. Spectra data of selected and known products are represented below:

7-Amino-5-(4-chlorophenyl)-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-*d*]-pyrimidine-6-carbonitrile (11j). Solid powder; Yield: 81%; M.p. 237–239 °C; IR (KBr): v 3415, 3311, 3203, 3102, 3022, 2193, 1710 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): 4.48 (1H, s, CHAr), 7.30 (2H, s, NH_2), 7.60 (1H, t, ArH), 7.70 (1H, m, ArH), 8.0 (2H, t, ArH), 11.12 (1H,s, NH), 12.18 (1H, s, NH).

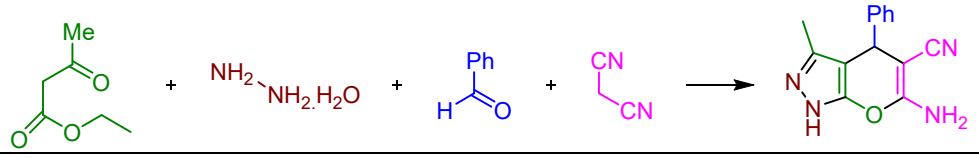
7-Amino-5-(4-bromophenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-*d*]-pyrimidine-6-carbonitrile (11o). Solid powder; Yield: 78%; M.p. 209–211 °C; IR (KBr): v 3375, 3260, 2275, 1705, 1601, 1632 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): 3.07 (3H, s, CH_3), 3.34 (3H, s, CH_3), 4.32 (1H, s, CHAr), 7.21 (2H, d, *J* = 8.4 Hz, ArH), 7.38 (2H, s, NH_2), 7.93 (2H, d, *J* = 8.4 Hz, ArH).

7-Amino-5-(4-methylphenyl)-1,3-dimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-pyrano[2,3-*d*]-pyrimidine-6-carbonitrile (11q). Solid powder; Yield: 88%; M.p. 207–209 °C; IR (KBr): v 3425, 3298, 3180, 2180, 1698, 1674, 1607 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): 2.25 (3H, s, CH_3), 3.07 (3H, s, CH_3), 3.34 (3H, s, CH_3), 4.27 (1H, s, CHAr), 7.09 (4H, dd, *J* = 8.4 Hz, *J* = 8.4 Hz, ArH), 7.30 (2H, s, NH_2).

RESULT AND DISCUSSION

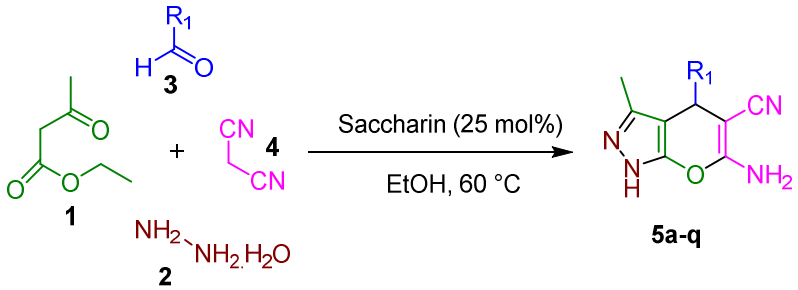
In the beginning, the optimal conditions for this reaction were investigated. Conducting reaction between ethyl acetoacetate (1, 1.0 mmol), hydrazine hydrate (2, 1.0 mmol), aryl aldehyde derivatives (3, 1.0 mmol) and malononitrile (4, 1.0 mmol) in the presence of saccharin as catalyst was selected as model. Variation of the amount of saccharin from 5 to 10, 15, 20 and 25 mol% led to 27, 41, 58, 73, and 88% of yields, respectively (Table 1, entries 3-7). When 5 mol% of catalyst was used, the reaction needed more time to furnish, and yield also decreased (Table 1, entry 3).

Table 1. Optimization of the reaction condition on the synthesis of **5a**[a]



Entry	Saccharin (mol%)	Solvent/Conditions	Time (min)	Isolated Yields (%)
1	Catalyst free	EtOH, rt	120	trace
2	Catalyst free	EtOH, 60 °C	120	trace
3	5	EtOH, 60 °C	80	27
4	10	EtOH, 60 °C	65	41
5	15	EtOH, 60 °C	40	58
6	20	EtOH, 60 °C	25	73
7	**25**	**EtOH, 60 °C**	**15**	**88**
8	25	EtOH/H_2O, 60 °C	55	67
9	25	Solvent free, 60 °C	120	35
10	25	MeOH,60 °C	45	62
11	25	EtOH, 40 °C	35	69
12	25	EtOH, rt	60	53
13	25	EtOH/H_2O, rt	95	44
14	25	CH_3CN, rt	75	46
15	25	H_2O, rt	140	28
16	25	CH_2Cl_2, rt	180	32
17	25	$CHCl_3$, rt	180	27
18	25	MeOH, rt	80	41
19	30	EtOH, 60 °C	15	89

[a] Reaction conditions benzaldehyde (1 mmol), hydrazine hydrate (1 mmol), malononitrile (1 mmol) and ethyl acetoacetate (1 mmol) and catalyst in various solvents and temperatures

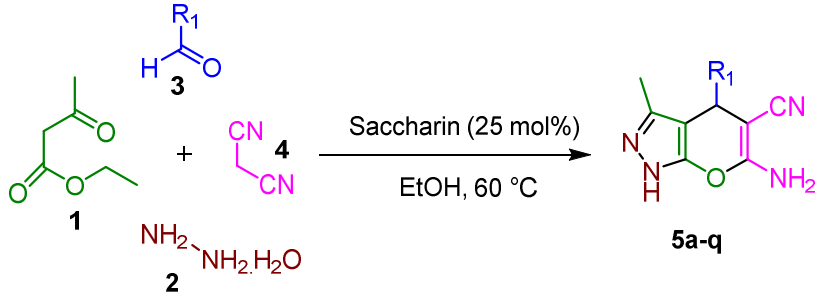


Scheme 1. Synthesis of dihydropyrano[2,3-*c*]pyrazoles

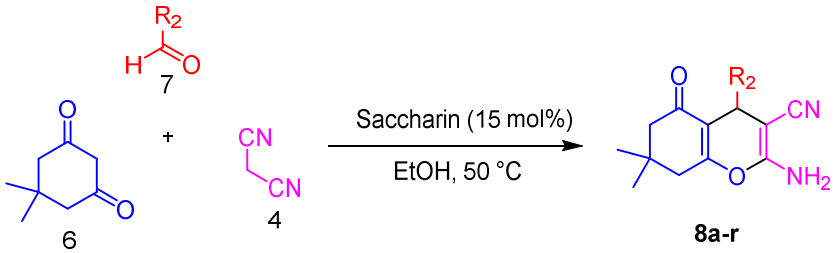
The amount of saccharin required for this transformation in a range of different temperatures (rt, 40 and 60 °C) was also evaluated. These results indicated that, 25 mol% saccharin at 60 °C gives high yield of the product in duration of reaction. The use of different solvents such as EtOH, EtOH/H_2O, MeOH, CH_3CN, H_2O, CH_2Cl_2 and $CHCl_3$ were investigated and among all these solvents, EtOH was found to be the best in terms of the yield of the product and time of completion in comparison with other solvents (Table 1, entry 7). The best result was obtained with 25 mol% of saccharin as catalyst at 60 °C in EtOH and afforded 6-amino-1,4-dihydro-3-methyl-4 (phenyl) pyrano[2,3-*c*]pyrazole-5-carbonitrile (**5a**) in 15 min with 88% of yield (Table 1, entry 7). After optimizing the conditions, the broad view of this process was studied by the reaction of ethyl acetoacetate (1, 1.0 mmol), hydrazine hydrate (2, 1.0 mmol), aryl aldehyde derivatives (3, 1.0 mmol) and malononitrile (4, 1.0 mmol) in the presence of 25 mol% saccharin in EtOH at 60 °C (Scheme 1). The results of this study are presented in Table 2. The reaction was clean, and no chromatographic separation was performed because no impurities were observed. After completion of the reaction, the solid product was collected by simple filtration.

After the successful synthesis of dihydropyrano[2,3-*c*]pyrazoles, we turned our attention toward the synthesis of tetrahydrobenzo[*b*]pyrans. In continuation of our studies on the development of new strategies for the synthesis of organic compounds, herein, we wish to report a green access high efficient condensation between aromatic aldehydes derivatives (7, 1.0 mmol) and malononitrile (4, 1.0 mmol) and dimedone (6, 1.0 mmol) to tetrahydrobenzo[*b*]pyrans

Table 2. Saccharin catalyzed synthesis of dihydropyrano[2,3-*c*]pyrazoles



Entry	R^1	Product	Time (min)	Isolated Yields (%)	M.p. °C	Lit. M.p. °C
1	C_6H_5	**5a**	15	88	242-244	244-246[27]
2	2-Cl-C_6H_4	**5b**	25	81	245-247	245-246[26]
3	2,4-$(Cl)_2$-C_6H_3	**5c**	35	76	227-229	229-230[26]
4	2-OMe-C_6H_4	**5d**	20	84	248-250	249-250[26]
5	2-O_2N-C_6H_4	**5e**	15	89	244-246	243-244[26]
6	3-Cl-C_6H_4	**5f**	25	78	230-232	230-231[26]
7	3,4-$(OMe)_2$-C_6H_3	**5g**	25	82	190-192	188-191[25]
8	3-O_2N-C_6H_4	**5h**	15	87	189-191	190-193[27]
9	3-Br-C_6H_4	**5i**	30	79	224-226	223-224[27]
10	3-OH-C_6H_4	**5j**	35	77	226-228	225-228[27]
11	3-F-C_6H_4	**5k**	10	91	243-245	242-243[26]
12	4-Cl-C_6H_4	**5l**	30	80	232-234	234-235[26]
13	4-OMe-C_6H_4	**5m**	25	83	208-210	210-212[26]
14	4-O_2N-C_6H_4	**5n**	15	88	246-248	248-249[26]
15	4-Br-C_6H_4	**5o**	35	75	181-183	180-181[22]
16	4-OH-C_6H_4	**5p**	35	79	219-221	220-223[25]
17	4-Me-C_6H_4	**5q**	15	87	204-206	205-208[27]

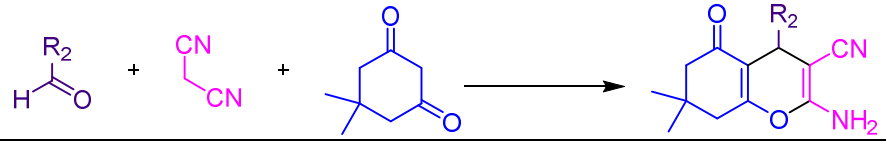


Scheme 2. Synthesis of tetrahydrobenzo[*b*]pyrans

synthesis in the presence of saccharin as a green catalyst (Scheme 2).

At first, in order to optimize reaction conditions, the reaction of benzaldehyde (1.0 mmol) with malononitrile (1.0 mmol) and dimedone (1.0 mmol) was chosen as a model (compound **8a**). We firstly evaluated required amount of the catalyst for this transformation. In the absence of catalyst, a trace product was obtained after 60 min at 50 °C (Table 3, entry 2). By adding 5 mol% of the catalyst, the reaction showed an appreciable progress and completed in about 40 min (Table 3, entry 3). When 15 mol% of catalyst was used, the reaction efficiently proceeded and completed in less reaction time (10 min) (Table 3, entry 5). By further increasing catalyst amount no appreciable improvement in the product yield and reaction time was observed (Table 3, entry 17). Next, the model reaction was established at room temperature in the presence of saccharin (15 mol%) as catalyst, but the reaction rate decreased (Table 3, entry 6). A number of solvents such as MeOH, EtOH/H_2O, H_2O, CH_3CN, CH_2Cl_2 and $CHCl_3$ were also tried with catalytic amount of saccharin (15 mol%) and it was found that the use of protic solvents such as EtOH and MeOH dramatically reduces the reaction time with improved product yield. From the economic and environmental point of view, EtOH was selected as medium for all further reactions. Therefore, the best reaction conditions were obtained by using 15 mol% of saccharin as the catalyst in EtOH at 50 °C (Table 3, entry 5). By loading the reaction in achieved optimal conditions, a variety of known tetrahydrobenzo[*b*]pyrans were successfully synthesized and results of this new

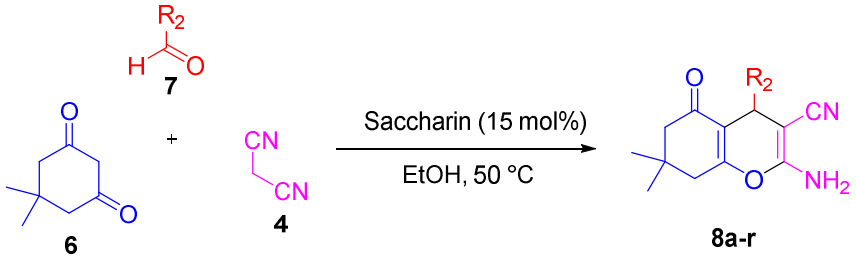
Table 3. Optimization of the reaction condition on the synthesis of **8a**[a]



Entry	Saccharin (mol%)	Solvent/Conditions	Time (min)	Isolated Yields (%)
1	Catalyst free	EtOH, rt	60	trace
2	Catalyst free	EtOH, 50 °C	60	trace
3	5	EtOH, 50 °C	40	48
4	10	EtOH, 50 °C	20	76
5	**15**	**EtOH, 50 °C**	**10**	**92**
6	15	EtOH, rt	45	72
7	15	EtOH, 40 °C	20	80
8	15	EtOH, 60 °C	10	92
9	15	Solvent free, 50 °C	40	64
10	15	MeOH, 50 °C	35	62
11	15	MeOH, rt	55	41
12	15	EtOH/H_2O, 50 °C	35	63
13	15	H_2O, rt	50	47
14	15	CH_3CN, rt	60	36
15	15	CH_2Cl_2, rt	70	32
16	15	$CHCl_3$, rt	70	24
17	20	EtOH, 50 °C	10	94

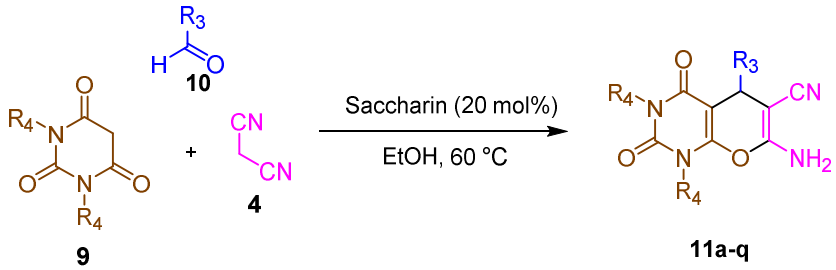
[a] Reaction conditions benzaldehyde (1 mmol), malononitrile (1 mmol), dimedone (1 mmol) and catalyst in various solvents and temperatures

Table 4. Saccharin catalyzed synthesis of tetrahydrobenzo[*b*]pyrans



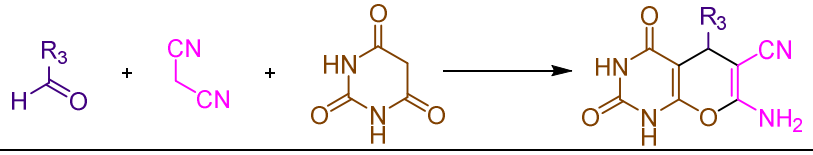
Entry	R^2	Product	Time (min)	Isolated Yields (%)	M.p. °C	Lit. M.p. °C
1	C_6H_5	**8a**	10	92	225-227	226-228[31]
2	2-Cl-C_6H_4	**8b**	15	84	208-210	208-210[32]
3	2,4-$(Cl)_2$-C_6H_3	**8c**	20	81	183-185	182-184[31]
4	2,3-$(OMe)_2$-C_6H_3	**8d**	15	87	216-218	217-219[32]
5	2-O_2N-C_6H_4	**8e**	10	92	222-224	223-226[31]
6	3-Cl-C_6H_4	**8f**	20	86	229-231	228-230[31]
7	3,4-$(OMe)_2$-C_6H_3	**8g**	15	85	225-227	227-229[39]
8	3-O_2N-C_6H_4	**8h**	10	89	210-212	210-211[32]
9	3-Br-C_6H_4	**8i**	25	85	227-229	228-230[32]
10	3-OH-C_6H_4	**8j**	25	83	228-230	226-228[38]
11	3-Me-C_6H_4	**8k**	10	90	200-202	198-200[34]
12	4-OMe-C_6H_4	**8l**	15	89	203-205	202-205[31]
13	4-O_2N-C_6H_4	**8m**	15	88	176-178	175-176[33]
14	4-Br-C_6H_4	**8n**	25	83	206-208	204-206[31]
15	4-OH-C_6H_4	**8o**	25	81	211-213	210-212[38]
16	4-OH-3-OMe-C_6H_3	**8p**	20	86	229-231	227-229[39]
17	4-F-C_6H_4	**8q**	10	93	199-201	198-200[34]
18	4-Me-C_6H_4	**8r**	10	88	221-223	221-223[34]

procedure were shown in Table 4. It is worthwhile to note that for purification of products (**8a-r**), a simple filtration and recrystallization from boiling EtOH is needed. Reactions of aromatic aldehydes bearing electron withdrawing/donating group (7, 1.0 mmol), with malononitrile (4, 1.0 mmol) and dimedone (6, 1.0 mmol)



Scheme 3. Synthesis of pyrano[2,3-*d*]pyrimidinones

Table 5. Optimization of the reaction condition on the synthesis of **11i**[a]



Entry	Saccharin (mol%)	Solvent/Conditions	Time (min)	Isolated Yields (%)
1	Catalyst free	EtOH, rt	180	trace
2	Catalyst free	EtOH, 60 °C	180	trace
3	5	EtOH, 60 °C	70	36
4	10	EtOH, 60°C	55	55
5	15	EtOH, 60 °C	40	72
6	**20**	**EtOH, 60 °C**	**25**	**89**
7	20	EtOH, rt	60	57
8	20	EtOH, 40 °C	45	68
9	20	Solvent free, 60 °C	80	52
10	20	EtOH/H_2O, 60 °C	65	58
11	20	MeOH, 60 °C	55	59
12	20	MeOH, rt	85	41
13	20	H_2O, rt	90	32
14	20	CH_3CN, rt	85	44
15	20	CH_2Cl_2, rt	95	16
16	20	$CHCl_3$, rt	95	19
17	25	EtOH, 60 °C	25	90

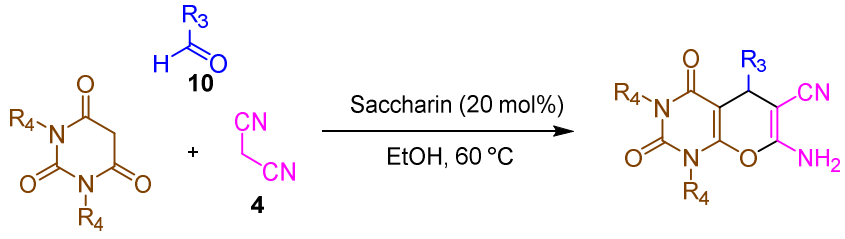
[a] Reaction conditions benzaldehyde (1 mmol), malononitrile (1 mmol), barbituric acid (1 mmol) and catalyst in various solvents and temperatures.

gave the expected products in high to excellent yields under the same reaction conditions (Table 4).

The saccharin also, is reported in preparation of pyrano[2,3-*d*]pyrimidinone derivatives. To optimize the reaction conditions the condensation reaction of benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), and barbituric acid (1.0 mmol) was selected as a typical and different amount of saccharin in rt, 40 and 60 °C and the optimization was confirmed. As exposed in Table 5, the best results were obtained when the reaction was achieved using 20 mol% of saccharin catalyst at 60 °C (Table 5, entry 6). No improvement was detected in the yield of reaction *via* increasing the amount of the catalyst (Table 5, entry 17). Table 5 obviously shows that in the absence of saccharin, the product was made in low efficiency (Table 5, entries 1 and 2). To compare the result of the solution with that of ethanol solvent, a mixture of benzaldehyde (1.0 mmol), malononitrile (1.0 mmol), and barbituric acid using 20 mol% of saccharin in numerous solvents such as EtOH/H_2O, MeOH, H_2O, CH_3CN, CH_2Cl_2, and $CHCl_3$ was studied. The results are presented in Table 5. As it can be seen in Table 5, EtOH is clearly the best selection for this reaction. Another purpose for choosing ethanol as a solvent for this reaction is that EtOH is a safe, cheap and benign solvent in comparison with organic solvents. Then, it was used in the model reaction and stimulated by the significant results, and with the intention of displaying the overview and scope of this new approach, a range of pyrano[2,3-*d*]pyrimidinone derivatives were produced from the one-pot three-component reaction of aryl aldehyde derivatives (10, 1.0 mmol), malononitrile (4, 1.0 mmol), with barbituric acid/1,3-dimethylbarbituric acid (9, 1.0 mmol) using a catalytic amount of saccharin (20 mol%) in EtOH solvent at 60 °C. The results are briefly shown in Table 6.

Comparison of catalytic ability some of catalysts reported in the literature for synthesis of dihydropyrano

Table 6. Saccharin catalyzed synthesis of pyrano[2,3-*d*]pyrimidinones



Entry	R^3	R^4	Product	Time (min)	Isolated Yields (%)	M.p. °C	Lit. M.p. °C
1	C_6H_5	H	**11a**	25	89	224-226	224-225[41]
2	C_6H_5	Me	**11b**	25	86	235-237	237-238[46]
3	2-Cl-C_6H_4	H	**11c**	30	80	213-215	211-214[46]
4	2,4-$(Cl)_2$-C_6H_3	H	**11d**	35	76	239-241	241-242[42]
5	2,4-$(OMe)_2$-C_6H_3	H	**11e**	30	82	225-227	227-228[43]
6	2-O_2N-C_6H_4	H	**11f**	20	90	256-258	254-256[41]
7	2-OH-C_6H_4	H	**11g**	35	79	169-171	169-170[43]
8	3-Cl-C_6H_4	H	**11h**	30	78	240-242	239-241[31]
9	3-OH-C_6H_4	H	**11i**	35	77	157-159	158-160[42]
10	4-Cl-C_6H_4	H	**11j**	35	81	237-239	235-237[46]
11	4-OMe- C_6H_4	H	**11k**	25	84	270-272	272-274[44]
12	4-O_2N-C_6H_4	H	**11l**	25	87	236-238	236-237[50]
13	4-O_2N-C_6H_4	Me	**11m**	25	84	215-217	214-216[46]
14	4-Br-C_6H_4	H	**11n**	30	81	243-245	240-245[43]
15	4-Br-C_6H_4	Me	**11o**	35	78	209-211	210-211[47]
16	4-Me-C_6H_4	H	**11p**	20	90	226-228	226[46]
17	4-Me-C_6H_4	Me	**11q**	20	88	207-209	205-207[46]

Table 7. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of dihydropyrano[2,3-*c*]pyrazoles[a]

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	ZrO_2 NPs	EtOH/H_2O, rt	5 min/95	[22]
2	Choline chloride	Urea Deep, 80 °C	10 min/95	[23]
3	Isonicotinic acid	Solvent-free, 85 °C	30 min/90	[24]
4	Molecular sieves	EtOH, Reflux	1 h/84	[25]
5	Meglumine	EtOH/H_2O, rt	15 min/95	[26]
6	CAPB	H_2O, 50-60 °C	4 min/96	[27]
7	L-proline	H_2O, Reflux	10 min/87	[28]
8	KF-alumina	EtOH, Reflux	12 min/80	[28]
9	CTACl	H_2O, 90 °C	240 min/89	[29]
10	Lipase	EtOH, 30°C	1h/90	[30]
11	**Saccharin**	**EtOH, 60°C**	**15 min/88**	**This work**

[a] Based on the four-component reaction of benzaldehyde, hydrazine hydrate, malononitrile and ethyl acetoacetate

Table 8. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of tetrahydrobenzo[*b*]pyrans[a]

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	$CaHPO_4$	H_2O/EtOH, 80 °C	2h/91	[31]
2	SiO_2 NPs	EtOH, rt	25 min/94	[32]
3	Glycerol	80 °C	60 min/93	[33]
4	SBPPSP	H_2O/EtOH, Reflux	25 min/90	[34]
5	DBSA	H_2O, Reflux	4h/90	[35]
6	$NH_4Al(SO_4)_2.12H_2O$	EtOH, 80 °C	120 min/92	[36]
7	$NH_4H_2PO_4/Al_2O_3$	EtOH, Reflux	15 min/86	[37]
8	ZnO NPs	H_2O/EtOH, rt	3 min/95	[39]
9	Fe_3O_4@SiO_2-imid-PMA	H_2O, Reflux	20 min/94	[40]
10	**Saccharin**	**EtOH, 50 °C**	**10 min/92**	**This work**

[a] Based on the three-component reaction of benzaldehyde, malononitrile and dimedone

Table 9. Comparison of catalytic ability some of catalysts reported in the literature for synthesis of pyrano[2,3-*d*]pyrimidinones[a]

Entry	Catalyst	Conditions	Time/Yield (%)	References
1	$[DABCO](SO_3H)_2(Cl)_2$	H_2O, Reflux	10 min/86	[41]
2	$[DABCO](SO_3H)_2(HSO_2)_2$	H_2O, 90 °C	7 min/90	[41]
3	Iron ore pellet	$EtOH/H_2O$, Reflux	8 min/73	[43]
4	nano-sawdust-OSO_3H	EtOH, Reflux	15 min/94	[44]
5	Al-HMS-20	EtOH, rt	12 h/92	[45]
6	TSA	$EtOH/H_2O$, Reflux	90 min/88	[46]
7	$B(OH)_3$	THF/H_2O, Reflux	125 min/81	[46]
8	Green cellulose-based nanocomposite	THF/H_2O, Reflux	35 min/90	[48]
9	DBA	$EtOH/H_2O$, Reflux	58 min/94	[49]
10	**Saccharin**	**EtOH, 60 °C**	**25 min/89**	**This work**

[a] Based on the three-component reaction of benzaldehyde, malononitrile and barbituric acid

[2,3-*c*]pyrazoles, tetrahydrobenzo[*b*]pyrans and pyrano[2,3-*d*]pyrimidinones are shown in Table 7, 8 and 9. This study reveals that saccharin has shown its extraordinary potential to be an alternative green, mild, inexpensive and highly efficient catalyst for synthesis of these biologically active heterocyclic compounds, in addition to the use of high to excellent yields and short reaction times in the reactions are the notable advantages this present methodology.

CONCLUSION

In conclusion, we have introduced a saccharin as a green, highly efficient and inexpensive catalyst for the synthesis of dihydropyrano[2,3-*c*]pyrazole, tetrahydro benzo[*b*]pyran, pyrano[2,3-*d*]pyrimidinone scaffolds. The promising reasons for the presented protocol is efficiency, generality, high to excellent yields of the products, short reaction times, cleaner reaction profile, simplicity, green, low cost and high catalytic activity of catalyst.

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