One-Pot Multicomponent Synthesis of Novel 2-Tosyloxyphenylpyrans under Green and Conventional Condition with Anti-inflammatory Activity

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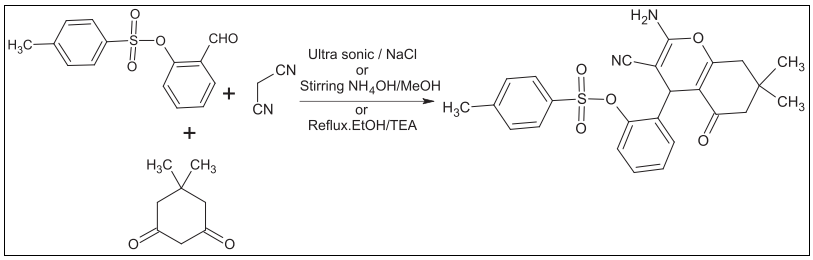

A mild, efficient, and environmentally green protocol for the synthesis of 2-tosyloxyphenylpyran derivatives **3-11** *via* reaction of 2-tosyloxybenzaldehyde (**1**) with malononitrile and some ketonic reagents in one-pot, three component reaction within few minutes under stirring in methanol in presence of ammonium hydroxide solution or ultrasonic irradiation. On the other hand, the same products **3-11** were obtained by traditional method, on treatment of 2-tosyloxybenzilidinemalononitrile (**2**) with the same ketonic reagents in refluxing ethanol in presence of TEA. 2-Tosyloxyphenylpyranopyrazoles **12** and **13** were obtained *via* treatment of compound **1** with malononitrile, hydrazine hydrate or phenyl hydrazine and ethyl acetoacetate, in one-pot, multicomponent reaction (MCRs). The structures of the new compounds were elucidated by elemental and spectral analyses. The newly synthesized compounds showed promising anti-inflammatory activity.

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INTRODUCTION

4*H*-Pyran derivatives comprise an important class of heterocyclic compounds because of their interesting biological and pharmacological activities [1], such as antimicrobial [2], anti-inflammatory [3], anticancer [4], anti-HIV [5], antidyslipidemic [6], antimalarial [7], antihyperglycemic, and cytotoxic [8]. Multicomponent reactions (MCRs) are defined as those reactions in which three or more compounds react together in one pot to form a new product [9] and have proved to be very influential and efficient bond-forming tools in organic synthesis and medicinal chemistry [10]. In recent years, the focus on green chemistry using environmentally benign reagents and conditions is one of the most fascinating developments in the synthesis of widely used organic compounds [11]. The use of water as a promising solvent for organic reactions has received considerable attention in the area of organic synthesis owing to its green credentials [11–14] and has been used for MCRs [15,16]. Over the last two decades, sonichemical methods have become widely used in heterocyclic synthesis [17–19] because they can be carried out in a higher yield, shorter reaction time and milder conditions [20–24].

Therefore, in view of these observations and in conjunction with our previous interest in synthesis heterocyclic rings [11,25,26], we report herein the synthesis of novel 2-tosyloxyphenylpyrans and 2-tosyloxyphenylpyranopyrazoles using green or conventional conditions and screen their anti-inflammatory activity.

RESULTS AND DISCUSSION

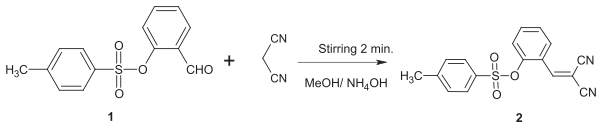
2-Tosyloxybenzaldehyde (**1**) was simply prepared *via* the reaction of salicylaldehyde with tosyl chloride under reflux acetonitrile in the presence of sodium carbonate [9] (Scheme 1).

Stirring of 2-tosyloxybenzaldehyde (**1**) with malononitrile in the presence NH_4OH solution afforded 2-tosyloxybenzylidinemalononitile (**2**) (Scheme 1). IR spectrum of compound **2** showed an absorption band at 2215 cm^{-1} because of CN group. Its ^1H NMR (δ DMSO-d_6) spectrum showed the disappearance of CHO group signal and appearance of two singlet signals at δ 8.11 and 2.47 ppm attributed to C=H and CH_3 groups, respectively.

2-Tosyloxyphenylpyran derivatives **3–6** were prepared *via* MCR of 2-tosyloxybenzaldehyde (**1**) with malononitrile and ketonic derivatives, namely acetylacetone, ethyl acetoacetate, benzoylacetone, and ethyl benzoylacetate *via* stirring in a mixture of ammonium hydroxide and methanol or under ultrasonic wave irradiation in sodium chloride solution (0.5 M) (Scheme 2).

Excellent yields were obtained in both methods (81–91%) within short reaction times (2–5 min) and problems associated

Scheme 1. Synthesis of 2-tosyloxybenzylidine malononitile.



with toxic solvent used (cost, safety, and pollution) were avoided (Table 1**)**.

On treatment of 2-tosyloxybenzylidinemalononitile (**2**) with the previous ketonic reagents under reflux ethanol in the presence of TEA, the same products **3–6** were obtained in moderate yields (67–79%) and longer reaction times (3 – 5 h) (Scheme 2; Table 1**)**.

IR spectra of compounds **3–6** revealed the appearance of two new bands in the range 3391–3224 cm^{-1} for NH_2 groups, CN groups in the range 2202–2189 cm^{-1}, and carbonyl groups at 1661_{acetyl}, 1701_{ester}, and 1703_{ester} cm^{-1}, respectively. ^1H NMR (δ-DMSO-d_6) spectra showed, in addition to the expected aromatic proton signals, a singlet signal corresponding to NH_2 groups in the region δ 7.05–6.77 ppm which disappeared on deuteration and a

Scheme 2. Synthesis of 2-tosyloxyphenylpyrans.

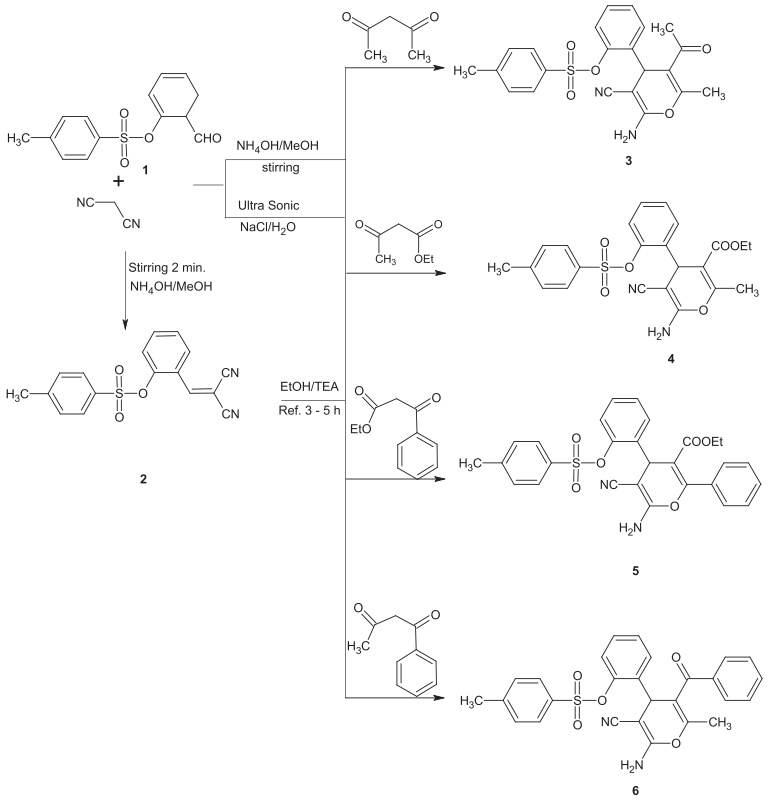


Table 1

Comparison of the reaction times and yields for synthesis 2-Tosyl-oxyphenylpyrans (green and traditional methods).

Comp. No.	Conventional method/EtOH/TEA		Stirrer in MeOH/NH_4OH		Ultra sonic wave/H_2O/NaCl	
	Yield %	Time (h)	Yield %	Time (min)	Yield %	Time (min)
3	79	4	89	3	86	3
4	78	5	84	2	81	5
5	71	3	83	5	82	3
6	67	3	91	4	84	2
7	69	5	86	3	79	3
8	71	4	92	5	90	3
9	66	5	94	4	89	5
10	74	4	88	7	87	3
11	42	4	87	7	85	5

new singlet signal in the region δ 4.75–4.37 ppm consistent with the CH $_{pyran}$. Furthermore, ^{1}H NMR (δ DMSO-d_6) of compounds **4** and **5** showed quartet and triplet signals in the region δ 3.97–3.80 and 0.99–0.76 ppm for CH_2 and CH_3 of the ester groups, respectively. ^{13}C NMR spectrum of compound **4** showed the appearance of new signals at δ 21.61, 18.58, and 14.02 ppm because of the three methyl groups, a new signal at 165.67 ppm because of the CO group, and negative signal at δ 56.62 ppm for CH_2 group in DEPT 135.

The formation of compound **4** can be explained by the possible mechanism presented in Scheme 3. The reaction can occur *via* initial formation of the α,β-unsaturated compound **2** *via* Knoevenagel condensation reaction between aldehyde **1** and malononitrile, which undergoes nucleophilic attack of ethyl acetoacetate anion to give the Michael adduct. Then, the latter promotes, cyclization to compound **4** *via* nucleophilic attack of enolized OH group to CN group. However, an alternative mechanism cannot be ruled out, in which the pathway starts from the reaction between **1** and ethyl acetoacetate to generate the α,β-unsaturated compound **A**, which in turn undergoes an addition of malononitrile anion to afford adduct **B**. Then nucleophilic attack of enolized OH group to CN group.

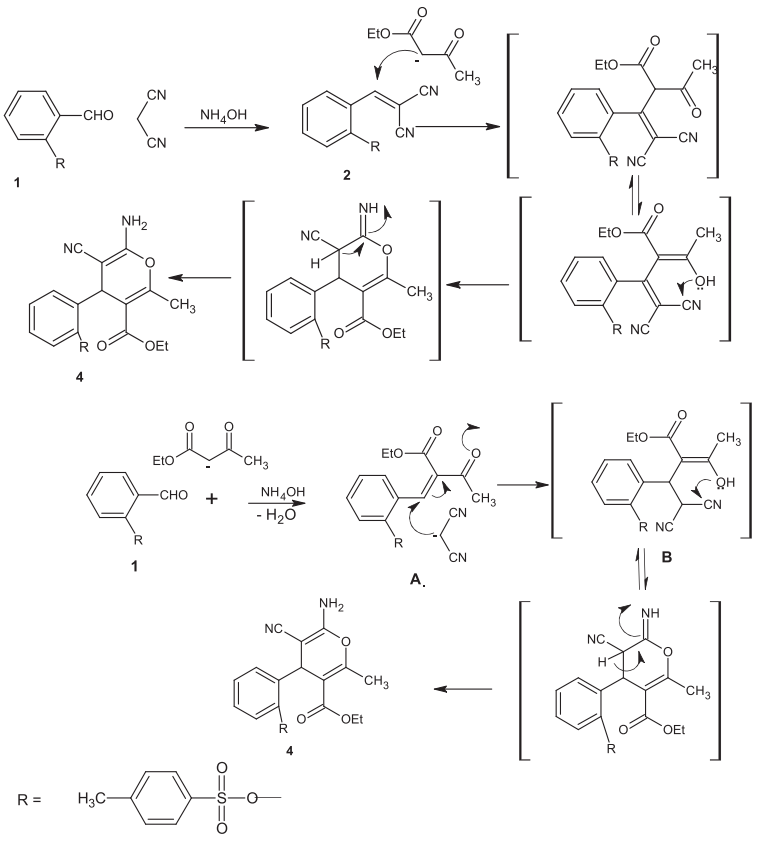
By the same ways, MCR between compound **1** with malononitrile and some cyclic ketones namely; cyclopentanone, cyclohexanone, 1,3-cyclohexanedione, cycloheptanone, or dimidone under stirring in methanol in the presence of ammonium hydroxide solution or ultrasonic irradiation technique within few minutes afford 2-tosyloxyphenylpyran derivatives **7–11**, respectively (Scheme 4).

Excellent yields were obtained in (85–92%) within short reaction times (3–7 min) (Table 1**)**.

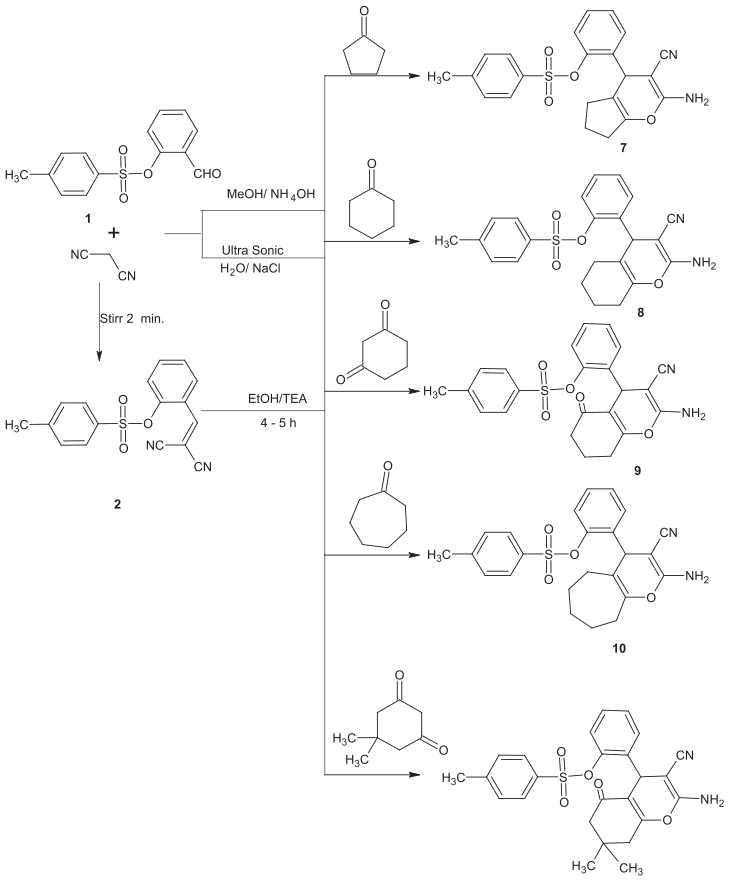
On the other hand, the same products **7–11** were obtained on treatment of compound **2** with the previous cyclic ketones under reflux in ethanol and TEA. Moderate yields (66–74%) were obtained in longer reaction times (3–5 h) (Table 1**)**.

The IR spectra of compounds **7–11** showed two absorption bands at 3359–3215 cm^{-1} because of NH_2 groups, 2206–2183 cm^{-1} for CN groups, and 1678 cm^{-1} because of CO group in compound **9**. The ^{1}H NMR (δ DMSO-d6) spectra of compounds **7–11** showed, besides the expected aromatic protons signals, new singlet signal in the region δ 7.19 – 6.98 ppm consistent with the NH_2 groups which disappeared on deuteriation, in addition to a singlet signal corresponding to CH $_{pyran}$ in the region δ

Scheme 3. Proposed mechanisms for the synthesis of pyrans.



Scheme 4. Synthesis of 2-tosyloxyphenylpyrans.



4.44–4.16 ppm. Furthermore, ^{13}C NMR spectrum of compound **9** showed C=O group signal at δ 195.93 ppm.

It was shown that, the green method is considered as environment-friendly and economically for synthesis of 2-tosyloxyphenylpyran derivatives.

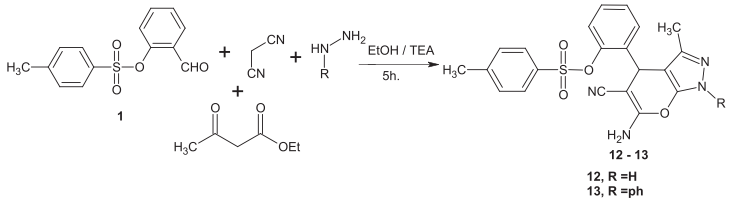
On treatment of 2-tosyloxybenzaldehyde (**1**) with malononitrile, hydrazine hydrate or phenyl hydrazine, and ethyl acetoacetate, in one-pot, four component process in refluxing ethanol in the presence of TEA, 2-tosyloxyphenylpyranopyrazoles **12** and **13**, were yielded (Scheme 5).

IR spectra of compounds **12** and **13** revealed two absorption bands in the range 3369–3219 cm^{-1} because of NH_2 groups, in addition to CN groups at 2196 and 2203 cm^{-1}. ^{1}H NMR (δ-DMSO-d_6) spectra of compounds **12** and **13** showed, new singlet signals corresponding to NH_2 groups in the region δ 6.81 ppm and 7.09 ppm, respectively, which disappeared on deuteriation, in addition to singlet signal at δ 4.92 and 4.85 ppm consistent with the CH_{pyran}, and new signals at δ 1.74 and 1.76 ppm because of the $CH_{3\ pyrazole}$ groups, respectively. Furthermore, compound **12** showed, new singlet signal at δ 12.10 ppm because of NH group. ^{13}C NMR spectrum of compound **12** showed a new signal at δ 9.98 ppm because of the $CH_{3\ pyrazole}$ group and at δ 30.61 ppm for CH_{pyran} group.

ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory activity screening for the selected compounds **3**, **4**, **5**, **6**, **7**, **9**, **10**, and **11** was determined in

Scheme 5. Synthesis of 2-tosyloxyphenylpyranopyrazoles.



vivo by the acute carrageenan-induced paw edema standard method in rats Winter *et al.* [27]. Adult albino rats of either sex (pregnant female animals were excluded) weighing 160–190 g were divided into **11** groups of **8** animals, all rats were fasted overnight, then on the next day (day of experiment), animals were uniformly hydrated by giving 3 mL of water per rat orally. Indomethacin, celecoxib (reference standards), and the tested compounds (100 mg/kg body weight) were suspended in saline solution by the aid of few drops of Tween 80 and given orally 1 h before induction of inflammation. The control group was given saline solution containing few drops of Tween 80. Carrageenan paw edema was induced according to a modified method of Winter *et al.* [27] by subcutaneous injection of 1% solution of carrageenan in saline (0.1 mL/rat) into the sub planter region of the right hind paw of rats. The thickness of rat paw was measured by mercury digital micrometer at different time intervals, at zero time and after 1, 2, and 3 h of carrageenan injection. The edema was determined from the difference between the thickness of injected and non-injected paws. Data were collected, revised, and analyzed. Quantitative variables from normal distribution were expressed as means ± SE "standard error". The significant difference between groups was tested by using *one-way* ANOVA followed by post hoc test at $p < 0.05$ and $p < 0.01$ (Table 2**)**. The results of the anti-inflammatory activity were expressed as percentage inhibition of edema thickness in treated animals in comparison with the control group according to the following equation:

$$\%\ \text{of edema inhibition} = \frac{(V_R\text{-}V_L)\,\text{control} - (V_R\text{-}V_L)\,\text{treated} \times 100}{(V_R\text{-}V_L)\,\text{control}}$$

where V_R represents the mean right paw thickness, V_L represents the mean left paw thickness $(V_R - V_L)_{control}$ represents the mean increase in paw thickness in the control group of rats, and $(V_R - V_L)_{treated}$ represents the mean increase in paw thickness in rats treated with the tested compounds [28–30].

Table 2

Anti-inflammatory activity of tested compounds using carrageenan-induced paw edema in rats.

	% inhibition of edema (% mean ± SE)		
Compound. no	1 h	2 h	3 h
Control	0.00	0.00	0.00
Indomethacin	31.51 ± 2.32	40.12 ± 2.91	60.81 ± 3.15
Celecoxib	31.43 ± 2.87	45.75 ± 3.41	63.78 ± 3.30
3	31.00 ± 1.03*	40.96 ± 2.27*	57.93 ± 2.22*
4	32.79 ± 1.48*	45 ± 1.02*	57.12 ± 0.92*
5	30.86 ± 1.57*	41.38 ± 3.47*	47.41 ± 3.10*
6	26.61 ± 2.92*	37.15 ± 2.93*	44.38 ± 2.31*
7	29.18 ± 2.19*	40.43 ± 2.40*	58.67 ± 1.18*
9	26.86 ± 1.86*	35.25 ± 1.22**	52.81 ± 1.17*
10	32.79 ± 1.48*	45.14 ± 1.12*	57.12 ± 0.92*
11	31.21 ± 1.67*	41.22 ± 3.19*	55.03 ± 1.99*

*Significant difference from the control value at $p < 0.01$.
**Significant difference from the control value at $p < 0.05$.

From the obtained results, we observed that all the tested compounds show considerable anti-inflammatory activity; compounds **3**, **4**, **7**, **10**, and **11** exhibit excellent anti-inflammatory properties.

EXPERIMENTAL

All melting points were recorded on Melt-Temp II melting point apparatus. IR spectra were measured as KBr pellets on a Shimadzu DR-8001 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker at 400 MHz and 100 MHz using TMS as an internal reference and DMSO-*d6* as a solvent. The elemental analyses were carried out on a Perkin-Elmer 240C Micro analyzer. The ultrasonic irradiation was performed by using a Branson ultrasonic cleaner bath, model 1510, AC input 115 V, output 50 W, and 1.9 L with a mechanical timer (60 min with continuous hold). All compounds were checked for their purity on TLC plates.

Synthesis of 2-tosyloxybenzylidenemalononitrile (2). A mixture of 2-tosyloxybenzaldehyde (**1**) (0.002 mol, 0.55 g) and malononitrile (0.002 mol, 0.13 g), in methanol (5 mL), containing drops of NH_4OH was stirred for 2 min. The formed solid product was filtered off, washed with small amounts of water, dried, and crystallized from ethanol. m. p. 152–153°C, IR (KBr) 2215 (C≡N), 1378, 1146 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 8.11 (s, 1H=CH), 7.91 (d, 1H, *J* = 4 Hz, Ar—H), 7.80 (t, 1H, Ar—H), 7.69 (d, 2H, *J* = 8 Hz, Ar—H), 7.60 (t, 1H, Ar—H), 7.51–7.45 (m, 3H, Ar), 2.47 (s, 3H, CH_3); ^{13}CNMR: δ 156.12, 153.09, 138.45, 132.57, 130.65, 129.24, 128.11, 126.13, 121.01, 116.42, 114.23, 112.23, 83.14, 21.04,: *Anal.* Calcd. for $C_{17}H_{12}N_2O_3S$ (324.45): C (62.95%), H (3.73%), N (8.64%), S (9.89%) Found: C (63.02%), H (3.67%), N (8.59%), S (9.96%).

General procedure for preparation of 2-tosyloxyphenylpyrans 3 – 11. ***Method A.*** A mixture of compound **1** (0.002 mol, 0.55 g), malononitrile (0.002 mol, 0.13 mL), and appropriate ketonic reagents (0.002 mol), namely acetylacetone (0.21 mL), ethyl acetoacetate (0.26 mL), benzoylacetone (0.30 gm), ethyl benzoylacetate (0.34 mL), cyclopentanone (0.18 mL), cyclohexanone (0.21 mL), 1,3-cyclohexandione (0.22 gm), cycloheptanone (0.24), or dimidone, (0.28 gm), was stirred in a mixture of methanol (5 mL) and 5 drops of NH_4OH at room temperature for 3–5 min. After completion of the reaction (monitored by TLC), the formed product was filtered off, washed with small amounts of water (10 mL) and then cold methanol (5 mL), dried, and crystallized from ethanol.

Method B. Exposed a mixture of compound **1** (0.002 mol, 0.55 g), malononitrile (0.002 mol, 0.13 mL),

and previous ketonic reagents (0.002 mol) in sodium chloride solution (0.5 M, 10 mL) to ultrasonic irradiation until dissolve and continuous for the appropriate time (Table 1). The progress of the reaction was monitored by TLC, the formed product was filtered off, washed with small amount of water, dried, and crystallized from ethanol.

Method C. A mixture of compound **2** (0.001 mol, 0.33 g), and selected ketonic reagent (0.001 mol) was refluxed in ethanol (20 mL) in the presence of drops of TEA for 4–7 h (TLC monitoring). The reaction mixture was allowed to cool to room temperature and the formed precipitate was filtered off and crystallized from ethanol.

2-(3-Acetyl-6-amino-5-cyano-2-methyl-4H-pyran-4-yl)phenyl-4-methylbenzene sulfonate (3). Mp. 178–180; IR (KBr) cm^{-1} 3348, 3224 (NH_2), 2192 (C≡N), 1661 (C=O), 1351, 1129 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 7.83 (d, 2H, *J* = 8 Hz, Ar—H), 7.42 (d, 2H, *J* = 8.0 Hz, Ar—H), 7.24–7.17 (m, 4H, Ar—H), 6.79 (s, 2H, NH_2, D_2O exchangeable), 4.37 (s, 1H, CH-pyran), 2.41 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.11 (s, 3H, CH_3); ^{13}C NMR: δ 193.91, 157.03, 135.38, 135.16, 131.42, 131.08, 129.67, 129.39, 126.71, 126.09, 123.01, 117.24, 112.13, 57.17, 36.10, 28.31, 21.04, 18.12: *Anal.* Calcd. for $C_{22}H_{20}N_2O_5S$ (424.48): C (62.25%), H (4.75%), N (6.60%), S (7.55%) Found: C (62.39%), H (4.71%), N (6.82%), S (7.43%).

Ethyl-6-amino-5-cyano-2-methyl-4-(2-tosyloxyphenyl)-4H-pyran-3-carboxylate (4). Mp.161–163°C; IR (KBr) cm^{-1} 3375, 3257 (NH_2), 2190 (C≡N), 1703 (C=O), 1364, 1184 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 7.93 (d, 2H, *J* = 8 Hz, Ar—H), 7.53 (d, 2H, *J* = 8.0 Hz, Ar—H), 7.26–7.16 (m, 4H, Ar—H), 6.77 (s, 2H, NH_2, D_2O exchangeable), 4.62 (s, 1H, CH-pyran); 3.97–3.92 (q, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 0.99–0.95 (t, 3H, CH_3); ^{13}C NMR: δ 165.67, 157.51, 156.97, 147.84, 146.02, 145.56, 143.67, 131.58, 130.11, 128.69, 127.18, 124.12, 121.79, 118.28, 106.31, 59.61, 56.12, 36.84, 21.61, 18.58, 14.02: *Anal.* Calcd. for $C_{23}H_{22}N_2O_6S$ (454.49): C (60.78%), H (4.88%), N (6.16%), S (7.06%) Found: C (60.87%), H (4.69%), N (6.32%), S (7.19).

Ethyl-6-amino-5-cyano-2-phenyl-4-(2-(tosyloxy)phenyl)-4H-pyran-3-carboxylate (5). Mp. 162–164°C; IR (KBr) cm^{-1} 3322, 3230 (NH_2), 2202 (C≡N), 1701 (C=O), 1354, 1155 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 7.93 (d, 2H, *J* = 8 Hz, Ar—H), 7.52 (d, 2H, *J* = 8.0 Hz, Ar—H), 7.50–7.44 (m, 4H, Ar—H), 7.34–7.33 (t, 1H, Ar—H), 7.31–7.29 (t, 3H, Ar—H), 7.20–7.17 (t, 1H, Ar—H), 6.90 (s, 2H, NH_2, D_2O exchangeable), 4.75 (s, 1H, CH-pyran); 3.80–3.75 (q, 2H, CH_2), 2.45 (s, 3H, CH_3), 0.79–0.76 (t, 3H, CH_3);^{13}CNMR: δ 165.87, 159.12, 155.41, 146.97, 138.57, 137.27, 134.68, 132.58, 131.99, 130.96, 129.67, 128.18, 126.28, 126.51, 121.87, 119.22, 108.29, 60.17, 56.68, 35.81, 21.15, 14.26: *Anal*. Calcd. for $C_{28}H_{24}N_2O_6S$ (516.56): C (65.10%), H (4.68%), N (5.42%), S (6.21%) Found: C (65.13), H (4.56%), N (5.51%), S (6.29%).

2-(2-Amino-5-benzoyl-3-cyano-6-methyl-4H-pyran-4-yl)phenyl-4-methylbenzene sulfonate (6). Mp. 167–169°C; IR (KBr) cm^{-1} 3391, 3272 (NH_2), 2189 (C≡N), 1657 (C=O), 1368, 1165 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 7.91 (d, 2H, *J* = 8 Hz, Ar—H), 7.67–7.07 (m, 11H, Ar—H), 7.05 (s, 2H, NH_2, D_2O exchangeable), 4.61 (s, 1H, CH-pyran); 2.41 (s, 3H, CH_3), 1.69 (s, 3H, CH_3): ^{13}C NMR: δ 193..5, 159.41, 155.14, 146.98, 140.09, 137.96, 136.21, 134.52, 133.01, 132.52, 131.15, 130.61, 127.63, 126.57, 121.25, 118.36, 104.86, 57.19, 35.92, 21.38, 18.47: *Anal*. Calcd. for $C_{27}H_{22}N_2O_5S$ (486.53): C (66.65%), H (4.56%), N (5.76%), S (6.59%) Found: (66.72%), H (4.61%), N (5.57%), S (6.92%)

2-(2-Amino-3-cyano-4,5,6,7-tetrahydrocyclopenta[b]pyran-4-yl)phenyl-4-methyl benzenesulfonate (7). Mp. 182–184°C; IR (KBr) cm^{-1} 3321, 3264 (NH_2), 2201 (C≡N), 1351, 1189 (SO_2) cm^{-1}; 7.79 (d, 2H, Ar—H), 7.54–7.34 (m, 5H, Ar—H), 7.07 (m, 1H, Ar—H), 6.98 (s, 2H, NH_2, D_2O exchangeable), 4.16 (s, 1H, CH-pyran); 2.94–2.74 (m, 4H, $2CH_2$) 2.44 (s, 3H, CH_3), 1.83–1.52 (m, 4H, $2CH_2$): ^{13}C NMR: δ 157.59, 146.09, 145.14, 135.46, 134.82, 133.67, 131.56, 131.68, 127.29, 123.34, 119.13, 107.28, 56.36, 38.59, 30.19, 26.03, 21.26, 18.04 *Anal*. Calcd. for $C_{22}H_{20}N_2O_4S$ (408.47) C (64.69%), H (4.94%), N (6.86%), S (7.85%) Found: C (64.57%), H (4.79%), N (6.65%), S (7.43%).

2-(2-Amino-3-cyano-5,6,7,8-tetrahydro-4H-chromen-4-yl)phenyl-4-methylbenzene sulfonate (8). Mp.174–176°C; IR (KBr) cm^{-1} 3342, 3246 (NH_2), 2196 (C≡N), 1381–1175 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 7.89 (d, 2H, Ar—H), 7.84–7.24 (m, 6H Ar—H), 7.19 (s, 2H, NH_2, D_2O exchangeable), 4.36 (s, 1H, CH-pyran), 2.46 (s, 3H, CH_3), 2.41–2.19 (m, 6H, $3CH_2$), 1.66–1.55 (m, 2H, CH_2), ^{13}C NMR: δ 158.07, 147.41, 145.26, 136.70, 135.42, 133.14, 131.24, 131.51, 127.55, 119.21, 118.91, 109.01, 51.63, 36.68, 26.36, 22.61, 22.23, 22.02, 21.09: *Anal*. Calcd. for $C_{23}H_{22}N_2O_4S$ (422.49) C (65.38%), H (5.25%), N (6.63%), S (7.59%) Found: C (65.52%), H (5.36%), N (6.51%), S (7.73%).

2-(2-Amino-3-cyano-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)phenyl-4-methyl benzenesulfonate (9). Mp. 198–200°C; IR (KBr) cm^{-1} 3347, 3215 (NH_2), 2183 (C≡N), 1678 (C=O), 1360, 1155 (SO_2) cm^{-1}; ^{1}H NMR (DMSO-*d6*): 7.96 (d, 2H, *J* = 8 Hz, Ar—H), 7.53 (d, 2H, *J* = 8.0 Hz, Ar—H), 7.23–7.19 (t, 3H, Ar—H), 7.03(d, 1H, Ar—H), 7.02 (s, 2H, NH_2, D_2O exchangeable), 4.44 (s, 1H, CH-pyran), 2.56–2.45 (t, 2H, CH_2), 2.30–2.24 (q, 2H, CH_2), 1.96 (d, 2H, CH_2): ^{13}C NMR: δ 195.93, 165.16, 159.22, 148.37, 145.95, 136.05, 133.93, 131.18, 130.71, 128.42, 128.32, 126.77, 119.88, 119.62, 11.15, 57.67, 36.75, 27.05, 21.61, 20.13; *Anal*. Calcd. for $C_{23}H_{20}N_2O_5S$ (436.48); C (63.29%), H (4.62%), N (6.42%), S (7.35%) Found: C (63.42%), H (4.56%), N (6.48%), S (7.26%).

2-(2-Amino-3-cyano-4,5,6,7,8,9-hexahydrocyclohepta[b]pyran-4-yl)phenyl-4-methyl benzenesulfonate (10). Mp. 193–195°C; IR (KBr) cm^{-1} 3359, 3241 (NH_2), 2206 (C≡N), 1368, 1187 (SO_2) cm^{-1}; ^1H NMR (DMSO-*d6*): 7.87 (d, 2H, Ar—H), 7.56–7.34 (m, 6H, Ar—H), 7.11 (s, 2H, NH_2, D_2O exchangeable), 4.19 (s, 1H, CH-pyran), 2.47 (s, 3H, CH_3), 1.73 –1.59 (m, 2H, CH_2), 1.31–1.28 (m, 4H, CH_2), 1.09–99 (m, 4H, CH_2): ^{13}C NMR: δ 159.15, 147.37, 146.41, 140.42, 134.60, 133.43, 131.12, 131.38, 128.85, 127.31, 122.28, 119.11, 108.35, 54.13, 36.81, 31.27, 31.55, 27.31, 27.59, 25.67, 21.12 *Anal*. Calcd. for $C_{24}H_{24}N_2O_4S$ (436.52) C (66.03%), H (5.54%) N (6.42%) S (7.35%) Found: C (66.09%), H (5.31%), N (6.63%), S (7.27%).

4-(2-Amino-3-cyano-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4H-chromen-4-yl)phenyl 4-methylbenzenesulfonate (11). Mp. 243–245°C; IR (KBr) cm^{-1} 3334, 3259 (NH_2), 2197 (C≡N), 1678 (C=O), 1375–1163 (SO_2) cm^{-1}; ^1H NMR (DMSO-*d6*): 7.76–7.68 (m, 3H, Ar—H), 7.46–7.26 (m, 3H, Ar—H), 7.18–7.01 (m, 4H, Ar—H + 2H, NH_2, D_2O exchangeable), 4.24 (s, 1H, CH-pyran), 2.41 (s, 3H, CH_3), 2.23 (s, 2H, CH_2), 2.20 (s, 2H, CH_2), 1.17 (s, 3H, CH_3), 0.98 (s, 3H, CH_3): ^{13}CNMR: δ 193.91, 161.02, 156.39, 147.27, 146.98, 145.13, 136.19, 133.46, 131.93, 127.06, 126.51, 124.63, 116.19, 111.09, 59.63, 51.76, 33.58, 32.42, 27.83, 26.53, 21.42: *Anal*. Calcd. for $C_{25}H_{24}N_2O_5S$ (464.48) C (64.64%), H (5.21%), N (6.03%), S (6.90%) Found: C (64.56%), H (5.43%), N (6.06%), S (6.61%).

General procedure for preparation of 2-tosyloxyphenyl[pyrano[2–3c]pyrazole derivatives 12 and 13. A mixture of 2-tosyloxybenzaldehyde (**1**) (0.002 mol, 0.55 g), malononitrile (0.002 mol, 0.13 mL), and appropriate reagent (0.002 mol), namely hydrazine hydrate (0.10 mL) or phenyl hydrazine (0.20 mL), and ethyl acetoacetate (0.26 mL) was refluxed in ethanol (20 mL) containing drops of TEA for 5 h (TLC monitoring). The reaction mixture was allowed to cool to room temperature and the formed precipitate was filtered off and crystallized from ethanol.

2-(6-Amino-5-cyano-3-methyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl)phenyl-4-methylbenzenesulfonate (12). Mp. 217–219°C; IR (KBr) cm^{-1} 3369, 3219, 3203 (NH_2 + NH), 2196 (C≡N), 1396, 1182 (SO_2) cm^{-1}; ^1H NMR (DMSO-*d6*): 12.10 (s, 1H, NH, D_2O exchangeable), 7.85 (d, 2H, Ar—H), 7.53 (d, 2H, Ar—H), 7.28–7.09 (m, 4H, Ar—H), 6.81 (s, 2H,NH_2, D_2O exchangeable), 4.92 (s, 1H, CH-pyran), 2.44 (s, 3H, CH_3), 1.74 (s, 3H, CH_3); ^{13}C NMR: ^{13}C NMR: 161.65, 155.65, 147.32, 146.35, 136.92, 136.06, 132.69, 130.84, 130.51, 128.77, 128.48, 128.07, 121.50, 120.42, 96.89, 56.67, 30.62, 21.64, 9.98; DEPT 135 δ 130.84, 130.51, 120.77, 120.07, 121.51, 36.52, 21.64, 9.58 *Anal*. Calcd. For $C_{21}H_{18}N_4O_4S$ (422.52) C (59.70%), H (4.29%), N (13.26%), S (7.59%); Found C (59.64%), H (4.42%), N (13.19%). S (7.63%).

2-(6-Amino-5-cyano-3-methyl-1-phenyl-1,4-dihydropyrano[2,3-c]pyrazol-4-yl) phenyl 4-methylbenzenesulfonate (13). Mp. 231–233°C; IR (KBr) cm^{-1} 3362, 3289 (NH_2), 2203 (C≡N), 1372, 1173 (SO_2) cm^{-1}; ^1H NMR (DMSO-*d6*): 7.88 (d, 2H, Ar—H), 7.67 (d, 2H, Ar—H), 7.59–7.18 (m, 7H, Ar—H), 7.09 (s, 2H, NH_2, D_2O exchangeable), 7.06 (d, 2H, Ar—H), 4.85 (s, 1H, CH-pyran), 2.46 (s, 3H, CH_3), 1.76 (s, 3H, CH_3); ^{13}C NMR: δ 160.98, 155.87, 147.05, 146.69, 138.21, 137.53, 137.12, 131.96, 130.76, 130.08, 129.21, 129.06, 128.57, 128.23, 126.78, 123.23, 122.25, 120.32, 97.76, 57.36, 30.18, 21.65, 10.14: *Anal*. Calcd. For $C_{27}H_{22}N_4O_4S$ (498.68) C (65.05%), H (4.45%), N (11.24%), S (6.43%) Found C (65.21%), H (4.62%), N (11.39%), S (6.57%).

CONCLUSION

2-Tosyloxybenzaldehyde can be used for synthesis of 2-tosyloxyphenylpyrans and 2-tosyloxyphenylpyranopyrazoles *via* one-pot, MCR under green and conventional conditions. In general, the products were obtained in high yield and short reaction time using green methods. Some selected compounds were screening anti-inflammatory activity and showed good activity.

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