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Synthesis of 4-substituted pyrano[4,3-*b*]pyran-2,5-diones in an ionic liquid

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ABSTRACT

The mildly basic ionic liquid *N*,*N*,*N*,*N*-tetramethylguanidinium triflate (TMGTf) was found to be a very effective solvent for the reaction between 4-hydroxy-6-methyl-2*H*-pyran-2-one, Meldrum's acid, and aldehydes to afford some novel pyrano[4,3-*b*]pyran-2,5-diones in high yields at room temperature. The stages, through which these reactions might proceed, depend largely on the nature of the aldehyde substrates. The reaction of aliphatic aldehydes has given access to some novel carboxylated products.

1. Introduction

Pyran derivatives represent the key building blocks of many natural products,[1–3] and constitute the core of valuable compounds exhibiting a broad spectrum of biological activities.[4–8] Certain pyran-based motifs are often found as recurring structures in a variety of natural and biologically relevant products. Arisugacins, davallialactone, clavilactone, pyripyropenes, philigridrins, and territrems are representatives of natural and secondary metabolites being characterized by the presence of pyrano[4,3-*b*]pyran-5*H*-one nucleus in their structures. Pyripyropenes[9] are the most potent naturally occurring biologically available inhibitors of acyl–CoA:cholesterol acyltransferase (ACAT). The inhibition of ACAT represents a promising new approach to prevention of atherosclerosis. Arisugacins, and territrems are inhibitors of acetylcholinesterase, making them potential drugs for treatment of dementia diseases, such as Alzheimer's disease.[10,11] Davallialactone[12] downregulates LPS-induced macrophage inflammatory responses, and clavilactone[13] was identified as an antifungal, and antibacterial agent, as well as being a potent inhibitor of tyrosine kinases. These interesting features have projected the pyrano[4,3-*b*]pyran-5*H*-one framework as a valuable lead pharmacophore and inspired much efforts toward the synthesis of its derivatives.[14–16] This interest is further intensified by the fact that the 2*H*-pyranone ring is prone to conversion to carbocyclic or even to other heterocyclic systems.[17–19] However, little efforts have been paid to the synthesis of 3,4-dihydro-pyrano[4,3-*b*]pyran-2,5-dione derivatives.[20–22]

With this background in mind and in line with our interest in the synthesis of pyranopyranone compounds, and also in performing reactions with the aid of ionic liquids,[23–25] herein we report an efficient one-pot synthesis of 4-aryl-3,4-dihydro-7-methyl-pyrano[4,3-*b*]pyran-2,5-diones 4 in ionic liquid medium. Recently, ionic liquids (ILs) have received recognition as a new generation of solvents having unique chemical and physical properties, such as nonvolatility, nonflammability, and thermal stability. Their dual organic and ionic nature allows them to establish ion–ion and ion–dipole as well as van der Waals interactions with reacting species, including transition states; hence they sometimes give rise to improved yields and rate enhancements. Structural variation of ILs gives more flexibility to their applications and provides fine tunning of their miscibility, promoting phase-separation of products. Moreover, functionalized ILs offer task-specific types for catalysis applications, or serve as solution phase supports for elegant combinatorial syntheses.[26]

2. Result and discussion

To approach the synthesis, we first focused our studies on two model reactions, involving 4-hydroxy-6-methylpyran-2*H*-one **1**, Meldrum's acid **2**, and 4-methylbenzaldehyde **3d**/2-chlorobenzaldehyde **3b**, with the expected production of the desired pyrano[4,3-*b*]pyran-2,5-diones **4d** and **4b**, respectively. In this regard, we attempted to determine the optimum conditions by examining the influence of IL (Table 1), temperature, and solvent (Table 2) variations on the progress of the trial reactions. It can be

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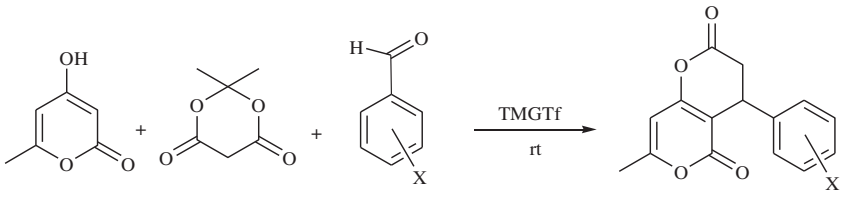
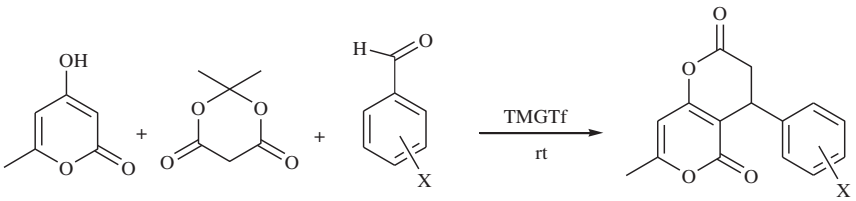
Table 1
Evaluation of three ionic liquids, having different acid-base characteristics, on progress of the reaction at room temperature



1 2 3 X= 4-Me /2-Cl 4

Entry	X	Ionic liquids	Reaction time	Yield(%) of 4
1	2-Cl	—	24 h	—
2	4-Me	—	24 h	—
3	2-Cl	$[BMIm]BF_4$	24 h	—
4	4-Me	$[BMIm]BF_4$	24 h	—
5	2-Cl	$[BMIm]BF_4$–LiCl	24 h	Trace
6	4-Me	$[BMIm]BF_4$–LiCl	24 h	Trace
7	2-Cl	TMGTf	30 min	95
8	4-Me	TMGTf	50 min	83

Table 2
Effect of solvent on synthesis of 4-aryl-3,4-dihydro-pyrano[4,3-*b*]pyran-2,5-diones **4a** and **4b**



1 2 3 X= 4-OMe /2-Cl 4

Entry	X	Conditions	Reaction time	Yield (%) of **4**[a]
1	4-Me	H_2O-rt	24 h	—
2	2-Cl	H_2O-rt	24 h	—
3	4-Me	H_2O-reflux	24 h	—-
4	2-Cl	H_2O-reflux	24 h	—
5	4-Me	H_2O–EtOH-rt	24 h	Trace
6	2-Cl	H_2O–EtOH-rt	24 h	Trace
7	4-Me	H_2O–EtOH-reflux	24 h	Trace
8	4-Me	EtOH-rt	24 h	<30
9	2-Cl	EtOH-rt	24 h	<30
10	4-Me	EtOH-reflux	24 h	<30
11	2-Cl	EtOH–TMGTf-rt	24 h	<20

[a] Isolated yields.

seen that the best yields of the expected products were obtained in *N*,*N*,*N*,*N*-tetramethylguanidinium triflate (TMGTf) at room temperature (Table 1, entries 7 and 8).

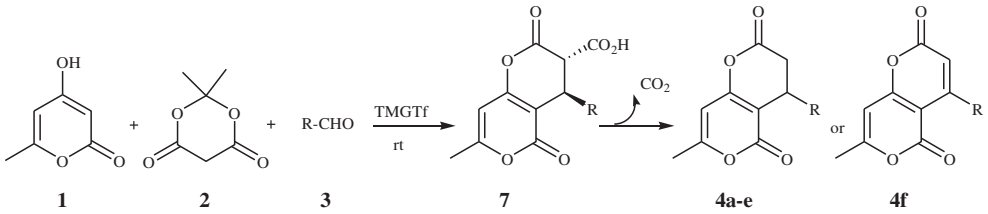
The ionic liquid, TMGTf, could be recovered from the aqueous extracts of the reaction mixtures by evaporation of water under reduced pressure. It retains almost all the initial activity after recovery, when reused in the next successive cycles. For instance running the model reaction of 4-hydroxy-6-methylpyran-2*H*-one **1**, Meldrum's acid **2**, and 2-chlorobenzaldehyde **3** in 1 mL of fresh, first recycled, and second recycled TMGTf at ambient temperature has given, respectively, 95%, 94%, and 92% of the product **4b**.

Interestingly, no by-products formed via condensation of 2 equiv of either carbon acids (**1** or **2**) with an aldehyde substrate. After optimization of the conditions for the model reactions, a range of different aldehydes were screened to explore the scope of this protocol. As shown in Table 3, the reaction is compatible with an array of arylaldehydes bearing either electron-withdrawing or electron-donating substituents. It also proceeds well with sterically hindered 2-chlorobenzaldehyde and enolizable aliphatic aldehydes to afford fairly high yields of the corresponding products.

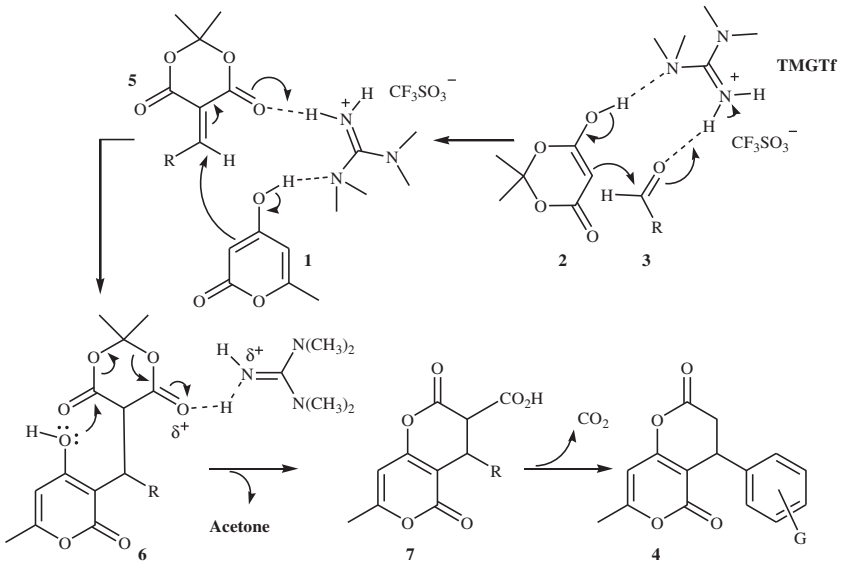
The mechanism of the reaction has not been determined. A possible pathway is proposed in Scheme 1. The synthesis is likely initiated by TMGTf, which upon removing a proton from Meldrum's acid **2** promotes a Knoevenagel condensation with the aldehyde **3**, resulting in formation of the intermediate 5. This intermediate subsequently undergoes a Michael type addition with 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** to produce the adduct 6. Cyclization of **6** via a translactonization reaction leads to liberation of an acetone molecule leaving the initial product **7** bearing a carboxyl group at the 3-position. Spontaneous decarboxylation of the product **7** affords the 4-aryl-product **4**. The initial condensation during the three-component reaction appears to be influenced by the different pKa values of the two dicarbonyl substrates, such that the Knoevenagel condensation of Meldrum's acid predominates, due to its stronger acidity. This consideration was in fact confirmed by isolation of intermediate **5** from the reaction media.

The activity of TMGTf is better conceived by considering its acid-base bifunctional nature, providing both proton donating and accepting functions during the catalysis process. Under this hydrogen bonding network and the mildly basic conditions, the

Table 3
Reaction of 4-hydroxy-6-methyl-2*H*-pyran-2-one **1** with Meldrum's acid **2** and various aldehydes **3** in the presence of (TMGTf)



Product	R	Reaction time	Yield (%)
4a	4-MeO·C_6H_4	55	85
4b	2-Cl·C_6H_4	30	95
4c	3-Br·C_6H_4	35	92
4d	4-Me·C_6H_4	50	83
4e	4-NO_2·C_6H_4	35	79
4f	Thiophene-2-yl	45	90
7a	Methyl	40	82
7b	Ethyl	45	80
7c	*n*-Propyl	45	84
7d	*n*-Butyl	50	85



Scheme 1. A plausible sequence of events resulting in production of compounds **4** and **7**.

employed arylaldehydes proceeded entirely through decarboxylation of the intermediates **7** to give the products **4a**–**f**, while the reaction of aliphatic aldehydes stopped at this stage to give the corresponding 3-carboxylic acid products **7a**–**d**. Presumably, decarboxylation of the intermediates **7** are facilitated by the presence of an aryl group at the 4-position. In the case of **4f**, the sequence of reactions is followed by an aerobic dehydrogenation to give the corresponding dehydrogenated product **4f**.

The NMR spectra and the mass spectrometric data as well as elemental analyses of all the products are consistent with their structures. For example, the ^{1}H NMR spectrum of **4a** displayed an AMX spin system for the CH_2CH protons (at δ_H 3.11, 3.47, and 4.67 ppm). A relatively large coupling between a vicinal pair of protons of this system (^3J=9.6 Hz) can be attributed to their axial orientation in the molecule and consequently to restricted inversion of the dihydropyranone ring bearing the aryl substituent at the equatorial position. Compounds **7a**–**d** exhibited a precise pattern of ^{1}H-resonances embedding an AX spin system in the aliphatic region along with a singlet signal at low field, which are best interpreted as arising from the R–CH–CH–CO_2H congestion. Here also, the alkyl substituents (R) occupy the pseudo-equatorial position, as the two methine protons gain nearly anti-orientation and establish the coupling of about 8.9 Hz. Presumably, the diastereoselective formation of **7a**–**d** arises from a biased conformation that adducts **5** adopt, as in Fig. 1, during cyclization transition. This likely conformation is the requirement of repulsive steric interactions between the bulky aryl or pyranyl substituents and the axial methyl group rendering the two vicinal protons to achieve an anti arrangement.

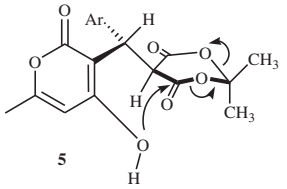


Fig. 1. The prescribed conformation of adduct **5** during cyclization.

3. Conclusion

In summary, a one-pot three-component reaction for synthesis of 4-aryl-7-methyl-3,4-dihydro-pyrano[4,3-*b*]pyran-2,5-diones using the reaction of arylaldehydes with 4-hydroxy-2*H*-pyranone **1** and Meldrum's acid in the ionic liquid *N*,*N*,*N*,*N*-tetramethylguanidinium triflate was introduced. Aliphatic aldehydes go through a similar reaction, however in TMGTf their products resist toward decarboxylation process, leading to production of 4-alkyl-7-methyl-2,5-dioxo-2,3,4,5-tetrahydro-pyrano[4,3-*b*]pyran-3-carboxylic acids. The ionic liquid acts as a catalyst in these reactions, enabling for the first time to control the progress of reaction of aliphatic aldehydes, and can be recovered for reuse several times. Another advantage of the present method is that it requires no metal catalysts or additional solvent.

4. Experimental section

4.1. General

All of the solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were measured on an electrothermal apparatus. IR spectra were obtained in KBr disks on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with Brucker DRX-400 AVANCE spectrometers. Chemical shifts of ^{1}H and ^{13}C NMR spectra were expressed in parts per million downfield from tetramethylsilane. Mass spectra were recorded on a Shimadzu QP1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N were performed using a Foss Heraus CHN-*O*-rapid analyzer.

4.2. Typical experimental procedure

A mixture of the 4-hydroxy-6-methyl-2*H*-pyran-2-one (0.126 g, 1 mmol), Meldrum's acid (0.144 g, 1 mmol) and 4-methoxybenzaldehyde (0.121 mL, 1 mmol) was added to a vial containing a magnetic stirring bar and the ionic liquid (TMGTf, 1 mL). The reaction mixture was sealed and stirred at room temperature until disappearance of the starting materials (55 min as monitored by TLC). After completion of the reaction, the residue was washed with 4×7 mL of cold water to extract the ionic liquid. The solid residue was recrystallized from ethanol (95.5%) to obtain pure product **4a** (0.24 g, 85%). The ionic liquid was recovered from the aqueous extracts by evaporating of water under reduced pressure and reused in the next cycles.

*4.2.1. 4-(4-Methoxyphenyl)-7-methyl-3,4-dihydro-pyrano[4,3-b]pyran-2,5-dione (**4a**).* White powder (0.243 g, 85%). Mp 194–196 C. IR (KBr): 3000, 1724 (C=O), 1667 (C=O), 1580, 1510, 1410, 1245 cm^{-1} ^{1}H NMR (500.1 MHz, $CDCl_3$): δ_H 2.16 (s, 3H, 7-CH_3), 3.11 (dd, 1H, ^2J 17.0 and ^3J 4.6 Hz), 3.47 (dd, 1H, ^2J 17.0 and ^3J 9.6 Hz), 3.79 (s, 3H, OMe), 4.67 (dd, 1H, ^3J 9.6 and 4.6 Hz), 5.88 (s, 1H, 8-H), 6.83 (d, 2H, ^3J 8.7 Hz, Ar), 7.29 (d, 2H, ^3J 8.7 Hz, Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ_C 20.1, 35.5, 36.6, 55.6, 101.8, 105.1, 114.0, 129.2, 133.2, 158.6, 161.3, 165.3, 166.3, 175.6. MS (EI, 70 eV) *m*/*z*: 286 (M^+, 12), 279 (14), 258 (100), 243 (30), 207 (44), 165 (46), 149 (79), 134 (54), 43 (94). Anal. Calcd for $C_{16}H_{14}O_5$ (286.28): C, 67.13; H, 4.93%. Found: C, 67.20; H, 5.06%.

*4.2.2. 4-(2-Chlorophenyl)-7-methyl-3,4-dihydro-pyrano[4,3-b]pyran-2,5-dione (**4b**).* White powder (0.275 g, 95%). Mp 228–230 °C. IR (KBr): 3010, 1700 (C=O), 1590, 1100 cm^{-1} ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 2.29 (s, 3H, 7-CH_3), 2.76 (dd, 1H, *J* 16.0, 1.8 Hz), 3.53 (dd, 1H, ^2J 16.0 and ^3J 8.2 Hz), 4.58 (br d, 1H, *J* 6.8 Hz), 6.47 (s, 1H, 8-H), 6.96 (dd, 1H, ^3J 7.6 and ^4J 1.7 Hz, Ar), 7.27 (dt, 1H, ^3J 7.5 and ^4J 1.3 Hz, Ar), 7.32 (dt, 1H, ^3J 7.5 and ^4J 1.7 Hz, Ar), 7.52 (dd, 1H, ^3J 7.8 and ^4J 1.3 Hz, Ar). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 22.6, 35.5, 37.8, 101.8, 104.0, 130.3, 131.1, 132.6, 133.3, 135.5, 140.1, 164.8, 166.0, 167.1, 167.9. MS (EI, 70 eV) *m*/*z*: 291 (M^++1, ^{35}Cl, 0.8), 255 (M^+–Cl, 95), 227 (M^+–Cl–HCO, 25), 213 (M^+–Cl–CO_2, 100), 173 (58), 136 (28), 101 (26). Anal. Calcd for $C_{15}H_{11}ClO_4$ (290.70): C, 61.98; H, 3.81%. Found: C, 62.11; H, 3.77%.

*4.2.3. 4-(3-Bromophenyl)-7-methyl-3,4-dihydro-pyrano[4,3-b]pyran-2,5-dione **4c**.* White powder (0.308 g, 92%). Mp 216–218 °C. IR (KBr): 3070, 1670 (C=O), 1560, 1440, 1408 (C=C), 1280 cm^{-1} ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 1.93 (s, 3H, 7-CH_3), 2.88 (br s, 1H, 3-H_B), 3.04 (br s, 1H, 3-H_A), 4.58 (br s, 1H, 4-H), 5.72 (s, 1H, 8-H), 7.14 (t, 1H, ^3J 7.7 Hz, 5′-H), 7.27 (d, 2H, ^3J 7.7 Hz, Ar), 7.50 (s, 1H, 2′-H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 20.1, 36.2, 36.8, 100.8, 102.9, 122.1, 127.4, 129.8, 129.9, 130.8, 131.1, 164.5, 164.6, 166.6, 166.8. MS (EI, 70 eV) *m*/*z*: 336 (M^++2, ^{81}Br, 9), 334 (M^+, ^{79}Br, 8) 308 (336–CO, 36), 306 (334–CO, 35), 227 (15), 202 (29), 200 (32), 185 (32), 183 (32), 157 (C_6H_4–^{81}Br, 23), 155 (C_6H_4–^{79}Br, 23), 149 (62), 115 (27), 43 (100). Anal. Calcd for $C_{15}H_{11}BrO_4$ (335.15): C, 53.76; H, 3.31%. Found: C, 53.71; H, 3.42%.

*4.2.4. 4-(4-Methylphenyl)-7-methyl-3,4-dihydro-pyrano[4,3-b]pyran-2,5-dione (**4d**).* White powder (0.224 g, 83%). Mp 183–185 C. IR (KBr): 3080, 2955, 2920, 1724 (C=O), 1668 (C=O), 1277 cm^{-1} ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 2.05 (s, 3H, 7-CH_3), 2.31 (s, 3H, 4′-CH_3), 3.16 (dd, 1H, ^3J 4.9 and ^2J 16.6 Hz, 3-H_B), 3.43 (dd, 1H, ^3J 9.3 and ^2J 16.6 Hz, 3-H_A), 4.73 (dd, 1H, *J* 9.3 and 4.9 Hz, 4-H), 5.83 (s, 1H, 8-H), 7.08 (d, 2H, *J* 7.6 Hz, Ar), 7.29 (d, 2H, *J* 7.6 Hz, Ar). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 19.9, 21.4, 30.0, 35.4, 102.5, 106.1, 127.3, 128.3, 128.9, 134.1, 159.2, 159.3, 167.9, 174.2. MS (EI, 70 eV) *m*/*z*: 270 (M^+, 9), 242 (M^+–CO, 12), 227 (M^+–CH_3CO, 35), 213 (94), 185 (19), 149 (23), 115 (70), 98 (39), 91 (36), 43 (100). Anal. Calcd for $C_{16}H_{14}O_4$ (270.28): C, 71.10; H, 5.22%. Found: C, 71.14; H, 5.33%.

*4.2.5. 4-(4-Nitrophenyl)-7-methyl-3,4-dihydro-pyrano[4,3-b]pyran-2,5-dione (**4e**).* Pale yellow powder (0.237 g, 79%). Mp 193–195 C. IR (KBr): 3080, 2925, 1704 (C=O), 1667 (C=O), 1518, 1340, 842 cm^{-1} ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 2.07 (s, 3H, 7-CH_3), 2.89 (br s, 3-H_B), 3.13 (br s, 3-H_A), 4.75 (br s, 1H, 4-H), 5.65 (s, 1H, 8-H), 7.53 (d, 2H, *J* 7.7 Hz, Ar), 8.05 (d, 2H, *J* 7.7 Hz, Ar). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 19.9, 34.1, 36.5, 101.6, 105.8, 123.8, 128.6, 146.0, 153.3, 159.6, 166.3, 167.2, 174.1. MS (EI, 70 eV) *m*/*z*: 301 (M^+, 24), 273 (M^+–CO, 76), 256 (8), 230 (12), 189 (9), 115 (17), 101 (18), 85 (52), 43 (100). Anal. Calcd for $C_{15}H_{11}NO_6$ (301.25): C, 59.80; H, 3.68; N, 4.65%. Found: C, 59.85; H, 3.73% N, 4.59%.

*4.2.6. 4-(Thiophene-2-yl)-7-methyl-pyrano[4,3-b]pyran-2,5-dione (**4f**).* Pale yellow powder (0.234 g, 90%). Mp 188–189 °C. IR (KBr): 3097, 1716 (C=O), 1558, 1397, 1190 cm^{-1} ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 2.08 (s, 3H, 7-CH_3), 5.64 (s, 1H, 8-H), 6.00 (s, 1H, 3-H), 6.45 (br s, 1H, Thiophenyl 3-H), 6.75 (t, 1H, *J* 3.7 Hz, Thiophenyl 4-H), 7.08 (d, 1H, *J* 4.9 Hz, Thiophenyl 5-H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 19.9, 102.6, 105.9, 106.0, 123.1, 123.4, 126.7, 150.0, 159.2, 165.8, 166.9, 172.7, 173.9. MS (EI, 70 eV) *m*/*z*: 260 (M^+, 3), 239 (10), 220 (100), 191 (15), 177 (43), 136 (78), 108 (70), 98 (59), 85 (35), 69 (95), 43 (86). Anal. Calcd for $C_{13}H_8O_4S$ (260.27): C, 59.99H, 3.10%. Found: C, 60.14; H, 3.15%.

*4.2.7. 2,3,4,5-Tetrahydro-4,7-dimethyl-2,5-dioxopyrano[4,3-b]pyran-3-carboxylic acid (**7a**).* White powder (0.195 g, 82%). Mp 130–132 C. IR (KBr): mp 126–128 C. IR (KBr): 3100, 2995, 2600 (broad and strong), 1720 (C=O), 1635, 1580, 1540, 1300, 1250 cm^{-1} ^{1}H NMR (500.1 MHz, DMSO-d_6): δ_H 0.82 (t, 3H, ^3J 7.2 Hz, 1′-CH_3), 2.14 (s, 3H, 7-CH_3), 3.52 (dt, 1H, ^3J 8.9 and ^3J 5.7 Hz, 4-H), 4.14 (d, 1H, ^3J 8.9 Hz, 3-H), 5.96 (s, 1H, 8-H), 11.46 (s, 1H, CO_2H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 14.7, 20.0, 29.0, 48.0, 100.7, 105.7, 161.6, 164.6, 165.1, 165.9, 166.9. MS (EI, 70 eV) *m*/*z*: 238 (M^+, 40), 230 (20), 222 (22), 179 (85), 153

(31), 121 (68), 95 (50), 69 (67), 43 (100). Anal. Calcd for $C_{11}H_{10}O_6$ (238.19): C, 55.47; H, 4.23%. Found: C, 55.35; H, 4.39%.

*4.2.8. 4-Ethyl-2,3,4,5-tetrahydro-7-methyl-2,5-dioxo-pyrano[4,3-b] pyran-3-carboxylic acid (**7b**).* White powder (0.201 g, 80%). Mp 128–130 °C. IR (KBr): 3000, 2980, 2600 (broad and strong), 1790, 1740 (C=O), 1620, 1540, 1400, 1350 cm^{-1} ^1H NMR (500.1 MHz, DMSO-d_6): δ_H 0.82 (t, 3H, ^3J 7.2 Hz, 2′-CH_3), 1.75–1.81 (m, 1H, 1′-H_B), 1.88–1.91 (m, 1H, 1′-H_A), 2.14 (s, 3H, 7-CH_3), 3.48 (dt, 1H, ^3J 8.9 and 5.7 Hz, 4-H), 4.14 (d, 1H, ^3J 8.9 Hz, 3-H), 5.96 (s, 1H, 8-H), 11.46 (s, 1H, CO_2H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 14.7, 20.0, 22.8, 36.0, 48.0, 100.8, 105.7, 161.6, 164.6, 165.0, 166.0, 166.8. MS (EI, 70 eV) *m/z*: 252 (M^+, 50), 237 (22), 222 (23), 205 (43), 179 (84), 154 (29), 123(59), 94 (50), 69 (43), 43 (100). Anal. Calcd for $C_{12}H_{12}O_6$ (252.22): C, 57.14; H, 4.80%. Found: C, 57.28; H, 4.93%.

*4.2.9. 4-Propyl-2,3,4,5-tetrahydro-7-methyl-2,5-dioxo-pyrano[4,3-b] pyran-3-carboxylic acid (**7c**).* White powder (0.223 g, 84%). Mp 130–132 °C. IR (KBr): 3097, 2940, 2600 (broad and strong), 1780. 1740 (C=O), 1656 (C=O), 1545, 1403, 1336 cm^{-1} ^1H NMR (500.1 MHz, DMSO-d_6): δ_H 0.82 (t, 3H, ^3J 7.2 Hz, 3′-CH_3), 1.12–1.21 (m, 2H, 2′-H), 1.67–1.75 (m, 1H, 1′-H_B), 1.87–1.90 (m, 1H, 1′-H_A), 2.14 (s, 3H, 7-CH_3), 3.51 (dt, 1H, ^3J 8.9 and 5.7 Hz, 4-H), 4.14 (d, 1H, ^3J 8.9 Hz, 3-H), 5.96 (s, 1H, 8-H), 11.46 (s, 1H, CO_2H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 14.7, 20.0, 28.4, 29.0, 35.7, 48.1, 100.7, 105.7, 161.6, 164.6, 165.1, 166.0, 166.9. MS (EI, 70 eV) *m/z*: 263 (M^+–3, 13), 240 (4), 222 (22), 205 (13), 179 (80), 165 (8), 152 (27), 122 (74), 94 (36), 68 (43), 43 (100). Anal. Calcd for $C_{13}H_{14}O_6$ (266.25): C, 58.64; H, 5.30%. Found: C, 58.75; H, 5.23%.

*4.2.10. 4-Butyl-2,3,4,5-tetrahydro-7-methyl-2,5-dioxo-pyrano[4,3-b] pyran-3-carboxylic acid (**7d**).* White powder (0.238 g, 85%). Mp 128–130 °C. IR (KBr): 3100, 2992, 2610 (broad and strong), 1782, 1741 (C=O), 1660 (C=O), 1610, 1542, 1410, 1328 cm^{-1} ^1H NMR (500.1 MHz, DMSO-d_6): δ_H 0.81 (t, 3H, ^3J 7.0 Hz, 3′-CH_3), 1.13–1.30 (m, 4H, 2CH_2), 1.75–1.81 (m, 1H, 1′-H_B), 1.87–1.95 (m, 1H, 1′-H_A), 2.14 (s, 3H, 7-CH_3), 3.49 (dt, 1H, ^3J 9.0 and 5.7 Hz, 4-H), 4.14 (d, 1H, ^3J 9.0 Hz, 3-H), 5.95 (s, 1H, Ar), 11.46 (s, 1H, CO_2H). ^{13}C NMR (125.7 MHz, DMSO-d_6): δ_C 14.7, 20.0, 28.4, 29.0, 30.0, 35.9, 48.1, 100.7, 105.7, 161.6, 164.6, 165.0, 166.0, 166.9. MS (EI, 70 eV) *m/z*: 280 (M^+, 2), 237 (18), 223 (57), 205 (43), 179 (91), 137 (57), 108 (41), 98 (39), 69 (60), 53 (34), 43 (100). Anal. Calcd for $C_{14}H_{16}O_6$ (280.27): C, 59.99; H, 5.75%. Found: C, 60.12; H, 5.63%.

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