Synthesis of 4*H*,5*H*-pyrano[3,2-*c*]pyrano-5-ones in aqueous media

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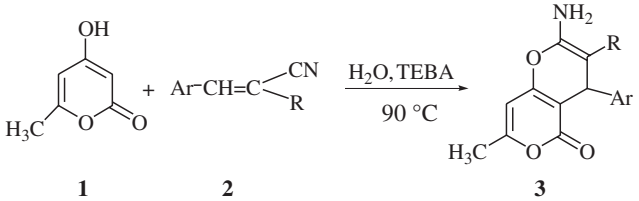
The reaction of 4-hydroxy-6-methylpyran-2-one with substituted cinnamonitriles in water in the presence of triethylbenzylammonium chloride (TEBA) provide an efficient route to 2-amino-4-aryl-4*H*,5*H*-pyrano[3,2-*c*]pyran-5-one derivatives. The products were characterised by IR, ^{1}H NMR, elemental analysis and were further confirmed by the X-ray crystal structure analysis.

Keywords: 4*H*,5*H*-pyrano[3,2-*c*] pyran-5-one, reaction in water, green chemistry

The need to reduce the amount of toxic waste and by products arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatiable materials in the design of new synthetic methods.[1-3] One of the most promising approaches uses water as a reaction medium.[4-6] Breslow,[7-8] who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic reactions in the 1980s. In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions.[9-14] The aqueous medium is cheaper, safer and environmentally friendly in comparison with organic solvents. Generally, the low solubility[15] of most reagents in water is not an obstacle to the reactivity, which, on the contrary, is reduced by the use of cosolvents.

In recent years, the synthesis of benzopyran derivatives has attracted great interest. Since the discovery of cromakalim as a typical ATP-sensitive potassium channel opener (PCO), a large number of benzopyran derivatives have been synthesised and demonstrated to possess potent relaxant activity on blood vessels, cardiac muscles, and other smooth muscles.[16-20] These agents may find use in the treatment of a variety of diseases such as hypertension, asthma, ischemia and urinary incontinence. Benzopyrans with amino and cyano groups are also synthons of some special natural products.[21-22] Benzopyran derivatives are generally prepared by the reaction of substituted cinnamonitriles and active methylene carbonyl compounds in an organic solvent (*e.g.* ethanol) in the presence of organic bases like piperidine or triethylamine.[23-25] Based on our previous studies on the use of water as solvent for carrying out carbon–carbon bond forming reactous under heterogeneous catalysis,[26-34] we now report the synthesis of 4*H*,5*H*-pyrano[3,2-*c*] pyran-5-ones in aqueous media.

When 4-hydroxy-6-methylpyran-2-one (**1**) and substituted cinnamonitriles (**2**) were stirred for 4–15 h at 90 °C in aqueous suspension in the presence of triethylbenzyl-ammonium chloride(TEBA),2-amino-4-aryl-4*H*,5*H*-pyrano[3,2-*c*]-pyran-5-ones (**3**) were obtained in excellent yields (see Scheme). The results are showed in Table 1.



1 **2** **3**

Scheme

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Table 1 Synthetic results for compounds **3**

Entry	Ar	R	Time/h	Yield/%[a]
3a	4-ClC_6H_4	CN	7	80
3b	4-$NO_2C_6H_4$	CN	8	91
3c	2-ClC_6H_4	CN	6	98
3d	2,4-$Cl_2C_6H_3$	CN	5	91
3e	4-BrC_6H_4	CN	8	95
3f	3,4-$OCH_2OC_6H_3$	CN	12	95
3g	4-FC_6H_4	CN	4	88
3h	3,4-$(CH_3O)_2C_6H_3$	CN	10	91
3i	3-$NO_2C_6H_4$	CN	6	86
3j	3,4-$(CH_3)_2C_6H_3$	CN	8	75
3k	2,4-$Cl_2C_6H_3$	CO_2Et	12	77
3l	4-$CH_3OC_6H_4$	CO_2Et	10	87
3m	4-FC_6H_4	CO_2Et	15	83
3n	2-ClC_6H_4	CO_2Et	7	76
3o	C_6H_5	CO_2Et	10	95
3p	4-ClC_6H_4	CO_2Et	15	76
3q	C_6H_5	CO_2Me	12	75
3r	4-ClC_6H_4	CO_2Me	12	84

[a]Isolated yield based on the amount of 4-hydroxy-6-methylpyran-2-one **1**.

Table 1 shows the results using a series of aromatic aldehydes that undergo the reaction to give excellent yields (75–98 %) of the products. This procedure does not require the use of any organic solvent. In fact the target compounds **3** were isolated in a practically pure form by simple Büchner filtration of the final aqueous mixture. In this reaction TEBA is necessary. If no TEBA is added the reaction takes a long time and the yield will very low. The role of the TEBA is to from micelles.

Product structures were established on the basis of spectroscopic data, particularly ^{1}H NMR analysis, and were further confirmed by the X-ray crystal structure analysis of the products **3f**[35] (Fig. 1) and **3l**[36] (Fig. 2).

In summary, the conversion of substituted cinnamonnitriles and 4-hydroxy-6-methylpyran-2-one into 2-amino-4-aryl-4*H*,5*H*-pyrano[3,2-*c*]pyran-5- ones can be efficiently performed in water as a solvent using a catalytic amount of TEBA. Compared to the previous methods in an organic solvent,[37] this new protocol has the advantages of good yields, low cost, and simple operation.

Experimental

IR spectra were recorded on a FT IR-8101 spectrometer in KBr. ^{1}H NMR spectra were determined on a Inova-400 MHz spectrometer using DMSO-d_6 solutions. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Microanalyses were carried out on a Perkin-Elmer 2400 II elemental analyser. X-ray diffraction was recorded using a Rigaku Mercury diffactometer.

General procedure for the synthesis of 2-amino-4-aryl-4H,5H-pyrano[3,2-c]pyran- 5-one derivatives (**3**)

A mixture of 4-hydroxy-6-methylpyran-2-one **1** (2 mmol), the substituted cinnamonitrile **2** (2 mmol) and TEBA (0.15 g, 0.66 mmol) in H_2O (10 ml) was stirred for 4–15 h at 90 °C and then cooled to

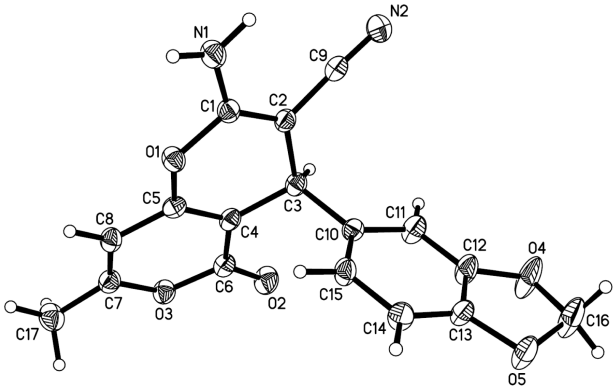

Fig. 1 The X-ray crystal structure of compound **3f.**

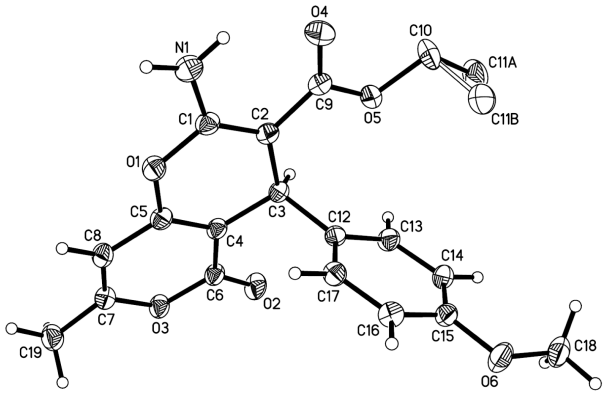

Fig. 2 The X-ray crystal structure of compound **3l**. The ethyl group is disordered.

room temperature. The solid material formed was collected by filtration, washed with water and recrystallised from 95 % ethanol to give pure **3**.

For **3a**, **3b 3l**, **3p** and **3r** the AA'XX' systems of the aromatic groups give apparent pairs of doublets in the ^{1}H NMR spectra.

2-Amino-3-cyano-4-(4-chlorophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-5-one (**3a**):[37] M.p. 230–231 °C; IR: ν/cm^{-1} 3384, 3324, 3031, 2201, 1711, 1673, 1645, 1614, 1585, 1489, 1445, 1413, 1384, 1261, 1195, 1142, 1094, 1042, 1009, 981, 829, 778; ^{1}H NMR (DMSO-d_6): δ 2.23 (3H, s, CH_3), 4.32 (1H, s, C^4-H), 6.28 (1H, s, C^8-H), 7.22 (2H, d, J = 8.8 Hz, ArH), 7.24 (2H, s, NH_2), 7.37 (2H, d, J = 8.8 Hz, ArH); Anal. calcd for $C_{16}H_{11}ClN_2O_3$: C 61.1, H 3.5, N 8.9; found C 61.2, H 3.4, N 8.9.

2-Amino-3-cyano-4-(4-nitrophenyl)-7-methyl-4H,5H-pyrano[3,2-c] pyran-5-one (**3b**): M.p. 219–220 °C; IR: ν/cm^{-1} 3398, 3297, 3083, 2203, 1707, 1670, 1642, 1605, 1518, 1445, 1412, 1379, 1332, 1264, 1198, 1178, 1138, 1111, 1044, 984, 872, 823, 742, 693; ^{1}H NMR (DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.51 (1H, s, C^4–H), 6.32 (1H, s, C^8–H), 7.35 (2H, s, NH_2), 7.51 (2H, d, J = 6.8 Hz, ArH), 8.18 (2H, d, J = 6.8 Hz, ArH); Anal. calcd for $C_{16}H_{11}N_3O_5$: C 59.1, H 3.4, N 12.9; found C 59.2, H 3.25, N 12.8.

2-Amino-3-cyano-4-(2-chlorophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-5-one (**3c**): M.p. 267–268 °C; IR: ν/*cm*$^{-1}$ 3471, 3344, 2192, 1700, 1669, 1638, 1602, 1579, 1473, 1443, 1376, 1322, 1262, 1196, 1180, 1139, 1043, 982, 963, 820, 762; ^{1}H NMR (DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.80 (1H, s, C^4–H), 6.29 (1H, s, C^8–H), 7.22 (2H, s, NH_2), 7.23–7.32 (3H, m, ArH), 7.38–7.41 (1H, m, ArH); Anal. calcd for $C_{16}H_{11}ClN_2O_3$: C 61.1, H 3.5, N 8.9; found C 61.2, H 3.4, N 8.7.

2-Amino-3-cyano-4-(2,4-dichlorophenyl)-7-methyl-4H,5H-pyrano[3,2-c]pyran-5-one (**3d**): M.p. 230–231 °C; IR: ν/cm^{-1} 3347, 3141, 2972, 2921, 2197, 1715, 1669, 1640, 1611, 1472, 1388, 1265, 1200, 1179, 1103, 1042, 975, 859, 813, 790, 737; ^{1}H NMR (DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.80 (1H, s, C^4–H), 6.29 (1H, s, C^8–H), 7.27 (2H, s, NH_2), 7.29 (1H, d, J = 8.8 Hz, ArH), 7.38 (1H, m, J = 8.8 Hz, ArH), 7.55 (1H, s, ArH); Anal. calcd for $C_{16}H_{10}Cl_2N_2O_3$: C 55.0, H 2.9, N 8.0; found C 55.3, H 2.6, N 8.1.

2-Amino-3-cyano-4-(4-bromophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-5-one (**3e**): M.p. 223–224 °C; IR: ν/cm^{-1} 3388, 3325, 2201, 1708, 1680, 1644, 1609, 1486, 1445, 1408, 1385, 1314, 1283, 1261, 1196, 1176, 1142, 1098, 1074, 1043, 982, 854, 829, 776; ^{1}H NMR (DMSO-d_6): δ 2.30 (3H, s, CH_3), 4.31 (1H, s, C^4–H), 6.28 (1H, s, C^8–H), 7.17 (2H, d, J = 8.4 Hz, ArH), 7.25 (2H, s, NH_2), 7.51 (2H, d, J = 8.4 Hz, ArH); Anal. calcd for $C_{16}H_{11}BrN_2O_3$: C 53.5, H 3.1, N 7.8; found C 53.7, H 2.9, N 8.0.

2-Amino-3-cyano-4-(3,4 methylenedioxyphenyl)-7-methyl-4H,5H-pyrano[3,2-c]pyran-5-one (**3f**): M.p. 228–230 °C; IR: ν/cm^{-1} 3400, 3328, 2885, 2202, 1706, 1670, 1644, 1613, 1592, 1502, 1485, 1443, 1382, 1259, 1193, 1139, 1038, 984, 922, 796, 784; ^{1}H NMR (DMSO-d_6): δ 2.23 (3H, s, CH_3), 4.22 (1H, s, C^4–H), 5.99 (2H, s, OCH_2O), 6.26 (1H, s, C^8–H), 6.66 (1H, d, J = 8.0 Hz, ArH), 6.72 (1H, s, ArH), 6.83 (1H, m, J = 8.0 Hz, ArH), 7.16 (2H, s, NH_2); Anal. calcd for $C_{17}H_{12}N_2O_5$: C 63.0, H 3.7, N 8.6; found C 62.7, H 3.5, N 8.85.

2-Amino-3-cyano-4-(4-fluorophenyl)-7-methyl-4H,5H-pyrano[3,2-c]pyran-5-one (**3g**):[37] M.p. 242–243 °C; IR: ν/cm^{-1} 3399, 3326, 2885, 2197, 1711, 1672, 1644, 1613, 1508, 1445, 1415, 1383, 1323, 1261, 1220, 1177, 1139, 1097, 1043, 980, 854, 827, 785, 747; ^{1}H NMR (DMSO-d_6): δ 2.22 (3H, s, CH_3), 4.32 (1H, s, C^4–H), 6.27 (1H, s, C^8–H), 7.11–7.15 (2H, m, ArH), 7.21 (2H, s, NH_2), 7.22–7.26 (2H, m, ArH); Anal. calcd for $C_{16}H_{11}N_2O_3$: C 64.4, H 3.7, N 9.4; found C 64. 7, H 3.5, N 9.5.

2-Amino-3-cyano-4-(3,4-dimethoxyphenyl)-7-methyl-4H,5H-pyrano[3,2-c]pyran-5-one (**3h**): M.p. 207–209 °C; IR: ν/cm^{-1} 3397, 3328, 2962, 2197, 1708, 1666, 1643, 1611, 1515, 1463, 1422, 1380, 1262, 1143, 1021, 969, 854, 819, 761; ^{1}H NMR (DMSO-d_6): δ 2.23 (3H, s, CH_3), 3.73 (6H, s, 2×CH_3O), 4.24 (1H, s, C^4–H), 6.26 (1H, s, C^8–H), 6.67 (1H, d, J = 8.4 Hz, ArH), 6.78 (1H, s, ArH), 6.89 (1H, d, J = 8.4 Hz, ArH), 7.14 (2H, s, NH_2); Anal. calcd for $C_{18}H_{16}N_2O_5$: C 63.5, H 4.7, N 8.2; found C 63.8, H 4.5, N 8.5.

2-Amino-3-cyano-4-(3-nitrophenyl)-7-methyl-4H,5H-pyrano[3,2-c]pyran-5-one (**3i**): M.p. 234–235 °C; IR: ν/cm^{-1} 3400, 3327, 2199, 1717, 1673, 1646, 1610, 1526, 1477, 1448, 1378, 1344, 1263, 1200, 1143, 1095, 1042, 977, 822, 733, 685; ^{1}H NMR (DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.57 (1H, s, C^4–H), 6.32 (1H, s, C^8–H), 7.35 (2H, s, NH_2), 7.62–7.66 (1H, m, ArH), 7.72–7.75 (1H, m, ArH), 8.05–8.06 (1H, m, ArH), 8.11–8.14 (1H, m, ArH); Anal. calcd for $C_{16}H_{11}N_3O_5$: C 59.1, H 3.4, N 12.9; found C 59.3, H 3.2, N 12.9.

2-Amino-3-cyano-4-(3,4-dimethylphenyl)-7-methyl-4H,5H-pyrano[3,2-c]pyran-5-one (**3j**): M.p. 228–230 °C; IR: ν/cm^{-1} 3417, 3324, 3098, 2920, 2200, 1706, 1678, 1644, 1644, 1613, 1587, 1503, 1446, 1413, 1379, 1260, 1195, 1135, 1091, 1038, 964, 819, 791, 780; ^{1}H NMR (DMSO-d_6): δ 2.17 (3H, s, CH_3), 2.19 (3H, s, CH_3), 2.22 (3H, s, CH_3), 4.18 (1H, s, C^4–H), 6.26 (1H, s, C^8–H), 6.68 (2H, d, J = 8.4 Hz, ArH), 6.92 (1H, s, ArH), 7.05 (1H, d, J = 8.4 Hz, ArH), 7.13 (2H, s, NH_2); Anal. calcd for $C_{18}H_{16}N_2O_3$: C 70.1, H 5.2, N 9.1; found C 70.3, H 5.0, N 9.3.

Ethyl2-amino-5-oxo-4-(2,4-dichlorophenyl)-7-methyl-4H,5H-pyrano [3,2-c] pyran-3- carboxylate (**3k**): M.p. 204–205 °C; IR: ν/cm^{-1} 3435, 3299, 3064, 2985, 1714, 1679, 1614, 1504, 1471, 1380, 1289, 1174, 1079, 1046, 956, 863, 849, 731; ^{1}H NMR (DMSO-d_6) δ: 1.04 (3H, t, J = 7.2 Hz, CH_3), 2.22 (3H, s, CH_3), 3.93 (2H, q, J = 7.2 Hz, CH_2O), 4.88 (1H, s, C^4–H), 6.18 (1H, s, C^8–H), 7.25 (1H, d, J = 8.4 Hz, ArH), 7.31 (1H, d, J = 8.4 Hz, ArH), 7.42 (1H, m, ArH), 7.83 (2H, s, NH_2); Anal. calcd for $C_{18}H_{15}Cl_2NO_5$: C 54. 6, H 3.8, N 3.5; found C 54.8, H 3.7, N 3.7.

Ethyl 2-amino-5-oxo-4-(4-methoxyphenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-3-carboxylate (**3l**):[37] M.p. 173–174 °C; IR: ν/cm^{-1} 3426, 3296, 3064, 3088, 2984, 1715, 1684, 1616, 1508, 1457, 1379, 1290, 1172, 1082, 1027, 957, 827, 735; ^{1}H NMR (DMSO-d_6) δ: 1.09 (3H, t, J = 7.2 Hz, CH_3), 2.21 (3H, s, CH_3), 3.69 (3H, s, CH_3O), 3.97 (2H, q, J = 7.2 Hz, CH_2O), 4.48 (1H, s, C^4–H), 6.28 (1H, s, C^8–H), 6.79 (2H, d, J = 8.8 Hz, ArH), 7.07 (2H, d, J = 8.8 Hz, ArH), 7.66 (2H, s, NH_2); Anal. calcd for $C_{19}H_{19}NO_6$: C 63.9, H 5.4, N 3.9; found C 63.95, H 5.1, N 3.8.

Ethyl 2-amino-5-oxo-4-(4-fluorophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-3-carboxylate (**3m**): M.p. 162–163 °C; IR: ν/cm^{-1} 3434, 3307, 3099, 3088, 2984, 1708, 1681, 1625, 1504, 1382, 1290, 1250, 1221, 1141, 1095, 834, 743; ^{1}H NMR (DMSO-d_6) δ: 1.06 (3H, t, J = 7.2 Hz, CH_3), 2.22 (3H, s, CH_3), 3.96 (2H, q, J = 7.2 Hz, CH_2O), 4.53 (1H, s, C^4–H), 6.29 (1H, s, C^8–H), 7.03–7.08 (2H, m, ArH), 7.18–7.21 (2H, m, ArH), 7.73 (2H, s, NH_2); Anal. calcd for $C_{18}H_{16}FNO_5$: C 62.6, H 4.7, N 4.1; found C 62.85, H 4.5, N 4.2.

Ethyl 2-amino-5-oxo-4-(2-chlorophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-3-carboxylate (**3n**): M.p. 203–205 °C; IR: ν/cm^{-1} 3422, 3296, 3093, 2988, 1709, 1687, 1617, 1511, 1440, 1378, 1286, 1250, 1176, 1143, 1077, 1039, 956, 815, 773; ^{1}H NMR (DMSO-d_6)

δ: 1.03 (3H, t, J = 7.2 Hz, CH_3), 2.21 (3H, s, CH_3), 3.91 (2H, q, J = 7.2 Hz, CH_2O), 4.90 (1H, s, C^4–H), 6.27 (1H, m, ArH), 7.18–7.29 (4H, m, ArH), 7.78 (2H, s, NH_2); Anal. calcd for $C_{18}H_{16}ClNO_5$: C 59.8, H 4.5 N 3.9; found C 60.0, H 4.25, N 3.7.

Ethyl 2-amino-5-oxo-4-phenyl-7-methyl-4H,5H-pyrano[3,2-c]pyran-3-carboxylate (**3o**):[37] M.p. 182–183 °C; IR: ν/ cm^{-1} 3428, 3304, 3094, 2986, 1710, 1687, 1612, 1507, 1443, 1382, 1286, 1213, 1140, 1079, 957, 817, 753, 703; ^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, t, J = 7.2 Hz, CH_3), 2.21 (3H, s, CH_3), 3.96 (2H, q, J = 7.2 Hz, CH_2O), 4.54 (1H, s, C^4–H), 6.29 (1H, s, C^8–H), 7.12–7.26 (5H, m, ArH), 7.71 (2H, s, NH_2); Anal. calcd for $C_{18}H_{17}NO_5$: C 66.05, H 5.2, N 4.3; found C 66.2, H 5.0, N 4.4.

Ethyl 2-amino-5-oxo-4-(4-chlorophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-3-carboxylate (**3p**):[38] M.p. 156–157 °C; IR: ν/cm^{-1} 3431, 3307, 3064, 2980, 1718, 1688, 1618, 1504, 1442, 1410, 1375, 1290, 1213, 1140, 1076, 1013, 980, 955, 818, 758, 703; ^{1}H NMR (DMSO-d_6) δ: 1.07 (3H, t, J = 7.2 Hz, CH_3), 2.22 (3H, s, CH_3), 3.96 (2H, q, J = 7.2 Hz, CH_2O), 4.52 (1H, s, C^4–H), 6.30 (1H, s, C^8–H), 7.19 (2H, d, J = 8.4 Hz, ArH), 7.30 (2H, d, J = 8.4 Hz, ArH), 7.75 (2H, s, NH_2); Anal. calcd for $C_{18}H_{16}ClNO_5$: C 59.8, H 4.5, N 3.9; found C 59.9, H 4.3, N 3.7.

Methyl 2-amino-5-oxo-4-phenyl-7-methyl-4H,5H-pyrano[3,2-c] pyran-3-carboxylate (**3q**): M.p. 195–196 °C; IR: ν/cm^{-1} 3436, 3307, 3093, 3001, 1709, 1691, 1614, 1502, 1436, 1378, 1382, 1293, 1214, 1194, 1140, 1079, 980, 816, 729, 702; ^{1}H NMR (DMSO-d_6) δ: 2.21 (3H, s, CH_3), 3.52 (3H, s, CH_3O), 4.54 (1H, s, C^4–H), 6.29 (1H, s, C^8–H), 7.16–7.24 (5H, m, ArH), 7.72 (2H, s, NH_2); Anal. calcd for $C_{17}H_{15}NO_5$: C 65.2, H 4.8, N 4.5; found C 65.4, H 4.7, N 4.6.

Methyl 2-amino-5-oxo-4-(4-chlorophenyl)-7-methyl-4H,5H-pyrano [3,2-c]pyran-3-carboxylate (**3r**): M.p. 145–146 °C; IR: ν/cm^{-1} 3401, 3295, 3087, 2946, 1734, 1690, 1618, 1523, 1489, 1435, 1378, 1381, 1267, 1196, 1137, 1086, 1013, 970, 936, 827, 783; ^{1}H NMR (DMSO-d_6) δ: 2.22 (3H, s, CH_3), 3.51 (3H, s, CH_3O), 4.53 (1H, s, C^4–H), 6.29 (1H, s, C^8–H), 7.19 (2H, d, J = 8.4 Hz, ArH), 7.29 (2H, d, J = 8.4 Hz, ArH), 7.76 (2H, s, NH_2); Anal. calcd for $C_{17}H_{14}ClNO_5$: C 58.7, H 4.1, N 4.0; found C 59.0, H 4.0, N 3.95.

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