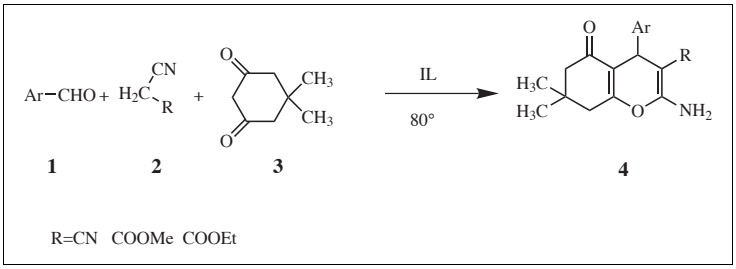
Synthesis of 2-Amino-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran Derivatives in Ionic Liquid Medium

Yuling Li*, Baixiang Du, Xiangshan Wang, Daqing Shi, Shujiang Tu

Department of Chemistry, Xuzhou Normal University, Key Laboratory of Biotechnology on Medical Plant of Jiangsu Province, Xuzhou, Jiangsu, 221116, P. R. China

E-mail: ylli1972@yahoo.com

Received September 1, 2005



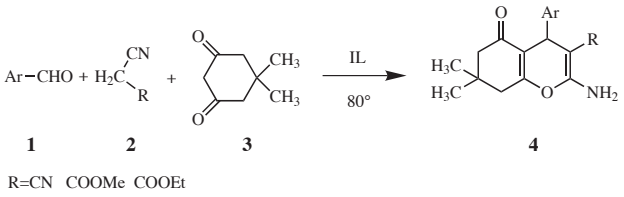
In this paper, preparation of 2-Amino-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives from aromatic aldehyde, malononitrile or cyanoacetate and 5,5-dimethyl-1,3-cyclohexanedione in ionic liquid [bmim$^+$][BF_4^-] was described. Compared with other methods, this new method has the advantages of easier work-up, milder reaction conditions, high yields and environmentally benign procedure.

J. Heterocyclic Chem., **43**, 685 (2006).

Heterocycles are of great value in the design and discovery of new biologically active compounds. Among them, benzopyran pharmacophore constitutes an important core structure of many natural products showing antibacterial [1], antitumor [2], antiallergic [3], antioxidant [4], potassium channel activator [5] and insulin-sensitizing activity [6]. 4*H*-Benzo[*b*]pyrans are the structural unit of a number of natural products and are used as versatile synthons because of the inherent reactivity of the inbuilt pyran ring [7]. The usual method for 4*H*-benzo[*b*]pyrans synthesis is from cinnamonitrile derivatives with dimedone catalyzed by acid or base [8]. Recently there are many methods available for the synthesis of compounds containing the benzo[*b*]pyran, from aldehyde, malononitrile or cyanoacetate and dimedone *via* traditional heating in organic solvents [9], or in water catalyzed by TEBA [10], or improved under microwave and ultrasonic irradiation [11], but they were reacted in the organic solvents or low solubility in water, which inspired us to explore new reaction media for synthesis the benzo[*b*]pyrans. Ionic liquids have been used as green solvents in recent years with unique properties such as a wide liquid range, high thermal and chemical stability, negligible vapor pressure, nonflammability, and high capacity. Room temperature ionic liquids, especially those based on the 1,3-dialkyl-imidazolium cations, have been shown to be good 'solvents' for a wide range of inorganic and organic reactions [12]. A nice feature of ionic liquid is that yields can be optimized by changing the anions or properties of the cation. In addition, several ionic liquids show enhancement in reaction rates and selectivity, compared to organic solvents with the added benefit of the ease of recovery and reuse of these ionic liquids.

In view of the emerging importance of room temperature ionic liquids as novel reaction media, we report in this paper a novel three-component one-pot synthesis of well functionalised 2-amino-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives in ionic liquid medium (Scheme 1). When three components of aromatic aldehyde **1**, malononitrile or cyanoacetate **2** and 5,5-dimethyl-1,3-cyclohexanedione (*i.e.* dimedone) **3** were treated in ionic liquid [bmim$^+$][BF_4^-] at 80° for a short time (0.5-2 h), the 4*H*-benzo[*b*]pyrans derivatives **4** were obtained in high yields (85~95%) (Table 1).

Scheme 1



First, we carried out a series of experiments shown in Scheme 1 to select an optimum reaction media for preparation of **4**. The results are summarized in Table 1. It turned out that at room temperature the reaction did not yield any product even after a long reaction time (5 h) (Table 1, entries 1 and 2). In this reaction, the efficiency of ionic liquid was strongly influenced by the nature of the anion. Among these ionic liquids, [bmim$^+$][BF_4^-] was

found to be the best reaction media in terms of yields and reaction rates (Table 1).

Table 1

Synthesis of **4a** in ionic liquid under different reaction conditions [a].

Entry	Temperature /°C	ionic liquid	Time /h	Yield [*b*]/(%)
1	r.t.	[bmim$^+$][BF_4^-] [*c*]	5	0
2	r.t.	[bmim$^+$]Br^-	5	0
3	80	[bmim$^+$]Br	3	70
4	80	[emim$^+$]Br^- [*d*]	3	54
5	80	[emim$^+$][BF_4^-]	3	82
6	**80**	**[bmim$^+$][BF_4^-]**	**0.5**	**91**

[a] Reaction condition: 10 mL ionic liquid, 2 mmol 3-chlorobenzaldehyde, 2 mmol malononitrile and 2 mmol dimedone; [b] Isolated yields; [c] bmim (i.e. 1-n-butyl-3-methylimidazolium); [d] emim (i.e. 1-ethyl-3-methylimidazolium).

In order to demonstrate the efficiency and scope of the present method, we applied this ionic liquid to the reaction of a variety of aromatic aldehydes with malononitrile or cyanoacetate and dimedone. The results are summarized in Table 2. Data from Table 2 demonstrated that the reactions proceeded smoothly to give **4** in high yields under the above conditions. All the products were characterized by their melting points, ^{1}H nmr and ir spectra.

Table. 2

Synthesis of **4** in ionic liquid [bmim$^+$][BF_4^-] [a].

Entry	Ar	R	Time/h	Yields (%) [*b*]
4a	3-ClC_6H_4	CN	0.5	91
4b	2- NO_2- 4-ClC_6H_3	CN	0.5	95
4c	3-$NO_2C_6H_4$	CN	0.5	91
4d	3,4-$(CH_3)_2C_6H_3$	CN	1	90
4e		CN	0.5	85
4f	3,4-$Cl_2C_6H_3$	CN	0.5	90
4g	3,4-$(CH_3O)_2C_6H_3$	CN	1	90
4h	2,4-$Cl_2C_6H_3$	CN	0.5	93
4i	2,4-$Cl_2C_6H_3$	$CO_2CH_2CH_3$	1	92
4j	4-$CH_3OC_6H_4$	CO_2CH_3	1.5	90
4k	3-ClC_6H_4	CO_2CH_3	1	86
4l	2-$NO_2C_6H_4$	CO_2CH_3	1	87
4m	2-O_2N-3,4-$OCH_2OC_6H_2$	$CO_2CH_2CH_3$	2	85
4n	4-$CH_3OC_6H_4$	$CO_2CH_2CH_3$	2	88
4o	3,4-$(CH_3)_2C_6H_3$	$CO_2CH_2CH_3$	1.5	87

[a] Reaction condition: 10 mL ionic liquid, 2 mmol aromatic aldehyde, 2 mmol malononitrile or cyanoacetate and 2 mmol dimedone, 80°; [b] Isolated yields.

Finally the recovery and reuse of the ionic liquid were studied. Since the products were weakly soluble in ionic liquids, they were easily separated by simple filtration. The filtrate ionic liquid could be recovered easily by drying at 80° *in vacuo* for several hours. Investigations by using 3-chlorobenzaldehyde as model substrates showed that successive reuse of the recovery ionic liquid. A summary of the reuse of the ionic liquid is shown in Table 3. Even in the fourth round the yield of the product **4a** is fairly good.

Table. 3

Study on the reuse of ionic liquid [bmim$^+$][BF_4^-][a].

Round	Temperature/°	Reaction time/h	Yield/(%) [b]
1	80	0.5	91
2	80	0.5	90
3	80	0.5	90
4	80	0.5	88

[a] Reaction condition: 10 mL ionic liquid, 2 mmol 3-chlorobenzaldehyde, 2 mmol malononitrile and 2 mmol dimedone; [b] Isolated yields

In conclusion, the products were synthesized directly from aldehyde, malononitrile or cyanoacetate and dimedone *via* heating in ionic liquid [bmim$^+$][BF_4^-] without catalyst. A considerable increase in the reaction rate was observed in ionic liquid [bmim$^+$][BF_4^-] when compared to the reported conventional solvent. The present work describes here an efficient method for the preparation of 2-amino-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives. The process is also significant from the viewpoint of pollution control where volatile organic compounds (VOCs) and phase transfer catalysts (PTC) can be avoided while the ionic liquids can be recycled.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H nmr spectra were obtained for solution in $CDCl_3$ with Me_4Si as internal standard using a Bruker-400 spectrometer. Elemental analyses were carried out using Carlo Erba 1110 analyzer. [bmim$^+$][BF_4^-] and [bmim$^+$]Br^- ionic liquids were prepared according to the procedures reported in literature [13,14].

General Procedure for Preparation of 2-Amino-4-aryl-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran Derivatives **4**.

A dry 50 mL flask was charged with aromatic aldehyde **1** (2 mmol), 2 mmol malononitrile or cyanoacetate **2** (2 mmol), 5,5-dimethyl-1,3-cyclohexanedione **3** (2 mmol) and ionic liquid [bmim$^+$][BF_4^-] (10 mL). The mixture was stirred at 80° for 0.5~2 h to complete the reaction (indicated by TLC), then cooled to room temperature. The solid was collected by filtration and washed with water. The filtrate of ionic liquid [bmim$^+$][BF_4^-] was then recovered for reuse by drying at 80° several hours *in vacuo*. The crude product was purified by recrystallization from 95% EtOH to give **4**.

2-Amino-3-cyano-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4a**).

4a: m.p. 227-229° (lit. 15 224-225°); ^{1}H nmr ($CDCl_3$): δ 1.06 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.20 (d, J = 16.0 Hz, 1H, C8-H), 2.27 (d, J = 16.0 Hz, 1H, C8-H), 2.42-2.53 (m, 2H, CH_2), 4.40 (s, 1H, CH), 4.58 (s, 2H, NH_2), 7.17-7.22 (m, 4H, phenyl); ir (potassium bromide): 3347, 3169, 2965, 2191, 1683, 1656, 1606, 1471, 720, 698 cm^{-1}.

2-Amino-3-cyano-4-(2-nitro-4-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4b**).

4b: mp 228-230°; ^{1}H nmr ($CDCl_3$): δ 1.03 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.15 (d, J = 16.0 Hz, 1H, C8-H), 2.22 (d, J = 16.0 Hz, 1H, C8-H), 2.43-2.53 (m, 2H, CH_2), 4.74 (s, 2H, NH_2), 5.24 (s, 1H, CH), 7.24 (d, J = 2.4 Hz, 1H, phenyl), 7.32 (dd, J = 2.4, 8.4 Hz, 1H, phenyl), 7.80 (d, J = 8.4 Hz, 1H, phenyl); ir (potassium bromide): 3457, 3346, 2961, 2196, 1684, 1597, 1522, 1468, 834,752 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}ClN_3O_4$: C, 57.84; H, 4.31; N, 11.24; Found: C, 58.03; H, 4.22; N, 11.17 %.

2-Amino-3-cyano-4-(3-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4c**).

4c: mp 213-215° (lit. 10 213-214°); ^{1}H nmr ($CDCl_3$): δ 1.08 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.23 (d, J = 16 Hz, 1H, C8-H), 2.29 (d, J = 16 Hz, 1H, C8-H), 2.43-2.53 (m, 2H, CH_2), 4.56 (s, 1H, CH), 4.71 (s, 2H, NH_2),; 7.51 (dd, J = 7.6, 8.0 Hz, 1H, phenyl), 7.70 (d, J = 7.6 Hz, 1H, phenyl), 8.06 (t, J = 2.0 Hz, 1H, phenyl), 8.10 (dd, J = 2.0, 8.0 Hz, 1H, phenyl); ir (potassium bromide): 3324, 3212, 2968, 2192, 1684, 1654, 1604, 1521, 1472, 786, 692 cm^{-1}.

2-Amino-3-cyano-4-(3,4-dimethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4d**).

4d: mp 235-236°; ^{1}H nmr ($CDCl_3$): δ 1.07 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 2.24 (s, 2H, CH_2), 2.46-2.55 (m, 2H, CH_2), 4.34 (s, 1H, CH), 4.49 (s, 2H, NH_2), 6.93 (dd, J = 2.0, 8.0 Hz, 1H, phenyl), 6.98 (d, J = 2.0 Hz, 1H, phenyl), 7.04 (d, J = 8.0 Hz, 1H, phenyl); ir (potassium bromide): 3330, 3216, 2964, 2193, 1683, 1637, 1600, 1507, 830, 774 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69; Found: C, 74.70; H, 6.65; N, 8.56 %.

2-Amino-3-cyano-4-(2-thienyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4e**).

4e: mp 224-226° (lit. 16 214-216°); ^{1}H nmr ($CDCl_3$): δ 1.08 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.28 (s, 2H, CH_2), 2.44 (s, 2H, CH_2), 4.61 (s, 2H, NH_2), 4.79 (s, 1H, CH), 6.92 (dd, dd, J = 0.8, 5.2, 6.4 Hz, 1H, thiophene-H), 7.00 (dd, J = 0.8, 6.4 Hz, 1H, thiophene-H), 7.14 (dd, J = 0.8, 5.2 Hz, 1H, thiophene-H); ir (potassium bromide): 3322, 3208, 2964, 2199, 1679, 1603, 1541, 1466, 758, 700 cm^{-1}.

2-Amino-3-cyano-4-(3,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4f**).

4f: mp 223-225°; ^{1}H nmr ($CDCl_3$): δ 1.05 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 2.22 (d, J = 16 Hz, 1H, C8-H), 2.27 (d, J = 16 Hz, 1H, C8-H), 2.42-2.52 (m, 2H, CH_2), 4.38 (s, 1H, CH), 4.63 (s, 2H, NH_2), 7.13 (dd, J = 2.0, 8.4 Hz, 1H, phenyl), 7.29 (d, J = 2.0 Hz, 1H, phenyl), 7.37 (d, J = 8.4 Hz, 1H, phenyl); ir (potassium bromide): 3330, 3215, 2961, 2196, 1684, 1663, 1471 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}Cl_2N_2O_2$: C, 59.52; H, 4.44; N, 7.71; Found: C, 59.70; H, 4.51; N, 7.58 %.

2-Amino-3-cyano-4-(3,4-dimethoxylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4g**).

4g: mp 178-180° (lit. 17 173-174°); ^{1}H nmr ($CDCl_3$): δ 1.08 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.23 (d, J = 16 Hz, 1H, C8-H), 2.28 (d, J = 16 Hz, 1H, C8-H), 2.47 (s, 2H, CH_2), 3.86 (s, 3H, CH_3), 3.89 (s, 3H, CH_3), 4.38 (s, 1H, CH), 4.54 (s, 2H, NH_2), 6.77 (dd, J = 1.6, 8.0 Hz, 1H, phenyl), 6.81 (s, 1H, phenyl), 6.83 (d, J = 8.0 Hz, 1H, phenyl); ir (potassium bromide): 3328, 3215, 2957, 2194, 1681, 1657, 1606, 1513, 863, 844, 651 cm^{-1}.

2-Amino-3-cyano-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyran (**4h**).

4h: mp 132-133°; ^{1}H nmr ($CDCl_3$): δ 1.09 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.20 (d, J = 16 Hz, 1H, C8-H), 2.27 (d, J = 16 Hz, 1H, C8-H), 2.47 (s, 2H, CH_2), 4.62 (s, 2H, NH_2), 4.83 (s, 1H, CH), 7.17-7.22 (m, 2H, phenyl), 7.37 (s, 1H, phenyl); ir (potassium bromide): 3363, 3156, 2966, 2192, 1686, 1654, 1607, 1560, 1473, 862, 844 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}C_{l2}N_2O_2$: C, 59.52; H, 4.44; N, 7.71; Found: C, 59.63; H, 4.37; N, 7.79 %.

Ethyl 2-amino-4-(2,4-dichlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4i**).

4i: mp 187-188° (lit. 10 186-188°); ^{1}H nmr ($CDCl_3$): δ 1.02 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.17 (t, 3H, J = 7.2 Hz, CH_3), 2.17 (d, J = 16 Hz, 1H, C8-H), 2.25 (d, J = 16 Hz, 1H, C8-H), 2.40-2.50 (m, 2H, CH_2), 4.05 (q, 2H, J = 7.2 Hz, OCH_2), 4.99 (s, 1H, CH), 6.26 (br. s, 2H, NH_2), 7.14 (dd, J = 2.0, 8.0 Hz, 1H, phenyl), 7.23-7.29 (m, 2H, phenyl); ir (potassium bromide): 3426, 3313, 2959, 1696, 1650, 1614, 867, 847, 804, 758 cm^{-1}.

Methyl 2-amino-4-(4-methoxphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4j**).

4j: mp 200-202°; ^{1}H nmr ($CDCl_3$): δ 1.02 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.16 (d, J = 16 Hz, 1H, C8-H), 2.24 (d, J = 16 Hz, 1H, C8-H), 2.44 (s, 2H, CH_2), 3.59 (s, 3H, OCH_3), 3.74 (s, 3H, CH_3), 5.04 (s, 1H, CH), 6.22 (br. s, 2H, NH_2), 7.06 (d, J = 8.4 Hz, 2H, phenyl), 7.23 (d, J = 8.4 Hz, 2H, phenyl); ir (potassium bromide): 3422, 3313, 2968, 1694, 1652, 1613, 1517, 829, 762, 743, 644 cm^{-1}.

Anal. Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92; Found: C, 67.44; H, 6.63; N, 3.81 %.

Methyl 2-amino-4-(3-chlorophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4k**).

4k: mp 178-179°; ^{1}H nmr ($CDCl_3$): δ 0.98 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.17 (d, J = 16 Hz, 1H, C8-H), 2.26 (d, J = 16 Hz, 1H, C8-H), 2.44 (s, 2H, CH_2), 3.61 (s, 3H, OCH_3), 4.70 (s,1H, CH), 6.24 (br. s, 2H, NH_2), 7.18-7.23 (m, 4H, phenyl); ir (potassium bromide): 3477, 3317, 2961, 1693, 1660, 1619, 1522, 1488, 798 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}ClNO_4$: C, 63.07; H, 5.57; N, 3.87; Found: C, 63.29; H, 5.42; N, 3.75 %.

Methyl 2-amino-4-(2-nitrophenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4l**).

4l: mp 188-189°; ^{1}H nmr ($CDCl_3$): δ 1.00 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.17 (d, J = 16 Hz, 1H, C8-H), 2.26 (d, J = 16 Hz,

1H, C8-H), 2.47 (s, 2H, CH_2), 3.56 (s, 3H, OCH_3), 5.57 (s, 1H, CH), 6.28 (br. s, 2H, NH_2), 7.24-7.33 (m, 2H, phenyl), 7.43-7.47 (m, 1H, phenyl), 7.77 (dd, J = 0.8, 8.0 Hz, 1H, phenyl); ir (potassium bromide): 3417, 3308, 2947, 1697, 1642, 1524, 1438, 763 cm^{-1}.

Anal. Calcd. for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52; Found: C, 61.42; H, 5.54; N, 7.46 %.

Ethyl 2-amino-4-(2-nitro-3,4-methylenedioxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4m**).

4m: mp 190-192°; ^{1}H nmr ($CDCl_3$): δ 1.01 (s, 3H, CH_3), 1.09-1.12 (m, 6H, 2×CH_3), 2.17 (d, J = 16 Hz, 1H, C8-H), 2.25 (d, J = 16 Hz, 1H, C8-H), 2.44 (s, 2H, CH_2), 4.04 (q, 2H, J = 7.2 Hz, OCH_2), 5.74 (s, 1H, CH), 6.04 (s, 2H, OCH_2O), 6.32 (br. s, 2H, NH_2), 6.72 (s, 1H, phenyl), 7.36 (s, 1H, phenyl); ir (potassium bromide): 3413, 3308, 2964, 1695, 1656, 1531, 1483, 822, 804 cm^{-1};

Anal. Calcd. for $C_{21}H_{22}N_2O_8$: C, 58.60; H, 5.15; N, 6.51; Found: C, 58.43; H, 5.22; N, 6.54 %.

Ethyl 2-amino-4-(4-methoxyphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4n**).

4n: mp 135-137° (lit. 10 137-139°); ^{1}H nmr ($CDCl_3$): δ 1.00 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.20 (t, 3H, J = 7.2 Hz, CH_3), 2.18 (d, J = 16 Hz, 1H, C8-H), 2.25 (d, J = 16 Hz, 1H, C8-H), 2.44 (s, 2H, CH_2), 3.77 (s, 3H, OCH_3), 4.06 (q, 2H, J = 7.2 Hz, CH_2), 4.67 (s, 1H, CH), 6.15 (br. s, 2H, NH_2), 6.77 (d, 2H, J = 8.4 Hz, phenyl), 7.19 (d, 2H, J = 8.4 Hz, phenyl); ir (potassium bromide): 3413, 3304, 3027, 2943, 1717, 1689, 1514, 1433, 820 cm^{-1}.

Ethyl 2-amino-4-(3,4-dimethylphenyl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-benzo[*b*]pyrano-3-carboxylate (**4o**).

4o: mp 188-190°; ^{1}H nmr ($CDCl_3$): δ 1.03 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.23 (t, 3H, J = 7.2 Hz, CH_3), 2.17-2.24 (m, 8H, 2×CH_3 +CH_2), 2.46 (s, 2H, CH_2), 4.08 (q, 2H, J = 7.2 Hz, CH_2), 4.67 (s, 1H, CH), 6.14 (br. s, 2H, NH_2), 6.98 (s, 2H, phenyl), 7.04 (s, 1H, phenyl); ir (potassium bromide): 3440, 3315, 2961, 1691, 1654, 1609, 1510, 1483, 809, 771 cm^{-1};

Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79; Found: C, 71.36; H, 7.43; N, 3.87 %.

Acknowledgement.

We are grateful to the Foundation of Natural Science Foundation (04XLB15 and 05XLB08) of Xuzhou Normal University for financial support.

REFERENCES AND NOTES

[1] K. P. Chitre, K. P. Jaywsal and H. D. Patel, *Orient. J. Chem.*, **20**, 377 (2004).

[2] J. Nawrot-Modranka, J. Ochocki and J. Graczyk, *Pharmazie*, **59**, 731 (2004).

[3] H. Takagaki, S. Tanabe, N. Kimura and Y. Aoki, European Patent 1273578 (2003); *Chem. Abstr.*, **138**, 73175 (2004).

[4] T. T. Wei, X. Y. Zhao, J. W. Hou, K. Ogata, T. Sakaue, A. Mori and W. J. Xin, *Biochemical Pharmacology*, **66**, 83 (2003).

[5] R. Thompson, S. Doggrell and J. O. Hoverg, *Bioorganic & Medicinal Chemistry*, **11**,1663 (2003).

[6] L. Tang, J. H. Yu, Y. Leng, Y. Feng, Y. S. Yang and R. Y. Ji, *Birorganic & Medicinal Chemistry Letters*, **13**, 3437 (2003).

[7] S. Hatakeyama, N. Ochi, H. Numata and S. Takano, *J . Chem. Soc., Chem. Commun.*, 1202 (1988).

[8] K. Singh, J. Singh and H. Singh, *Tetrahedron*, **52**, 14273 (1996).

[9] A. A. Hassanien, M. A. Zahran, M. S. A. El-Gaby and M. M. Ghorab, *J . Indian Chem. Soc.*, **76** , 350 (1999).

[10] D. Q. Shi, J. Mou, Q. Y. Zhuang and X. S. Wang, *J. Chem. Res.*, **23**, 821 (2004).

[11] S. J. Tu, C. B .Miao, Y. Gao, Y. J. Feng and J. C. Feng, *Chin. J. Chem.*, **20**, 703 (2002).

[12] P. Wasserscheid and W. Keim, *Angew. Chem., Int. Ed.*, **39**, 3772 (2000).

[13] S. Park and R. J. Kazlauskas, *J. Org. Chem.*, **66**, 8395 (2001).

[14] N. E. Leadbeater, H. M. Torenius and H. Tye, *Tetrahedron*, **59**, 2253 (2003).

[15] T. S. Jin, A. Q.Wang, X. Wang, J. S. Zhang and T. S. Li, *Synlett.* 871 (2004).

[16] F. F. Abdel-Latif, M. M. Masahaly and E. H. El-Gawish, *J. Chem. Res.*, 178 (1995).

[17] X. S. Wang, D. Q. Shi, S. J. Tu and C. S. Yao, *Synth. Commun.*, **33**, 119 (2003).