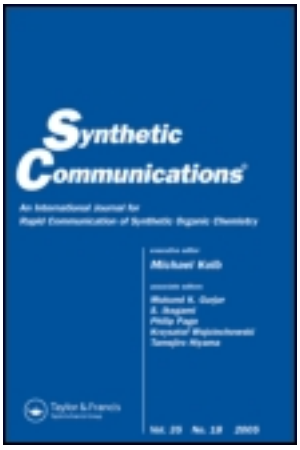

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PTC-Promoted Japp-Klingmann Reaction for the Synthesis of Indole Derivatives

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Abstract: Indole derivatives have been efficiently synthesized from ethyl 2-phenylhydrazono-5-phthalimido-pentanoate and its derivatives, which were obtained by Japp–Klingmann reaction under phase-transfer catalytic (PTC) conditions. Several different phase-transfer catalysts were investigated and dimethyldioctadecyl ammonium chloride (DMDOA) was found to promote this reaction efficiently. Using DMDOA as the PTC, aryl hydrazones were obtained in yields of 90%. The pure aryl hydrazones were then efficiently cyclized to indole derivatives in yields of more than 80%.

Keywords: Aryl hydrazones, Fischer indolization, Japp–Klingmann reaction, phase-transfer catalysts

INTRODUCTION

Indole is an important structural element in peptides and antibiotics as well as in indole alkaloids, which are frequently found in various classes of pharmacologically active compounds. Replacement of the indole by other heterocycles is often accompanied by loss of the desired biological

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activity.[1] The important biological activity of indoles in natural products has led to a continued strong interest in the practical synthesis of the indole nucleus. Numerous indole syntheses have been described in the literature.[2] Among the diverse and creative approaches that have been discovered, the Fischer indole synthesis via Japp–Klingmann reaction plays an important role as it provides a versatile and convergent route to a wide variety of indole derivatives.[3] Despite being quite versatile, the Fischer indole synthesis via Japp–Klingmann reaction often suffers from cumbersome manipulations and low to moderate yields.[4]

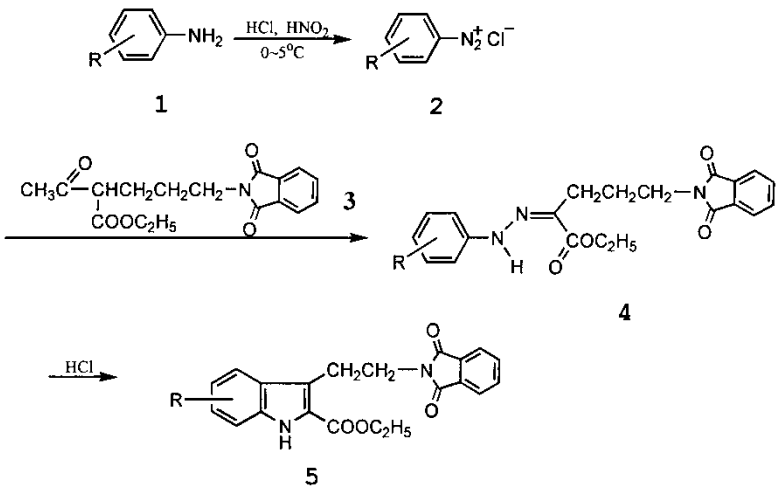
Phase-transfer catalysis (PTC) is one of the most important and useful methods in synthetic organic chemistry because of its preparative advantages, such as simple reaction procedures, mild conditions, inexpensive and environmentally friendly reagents, atom economy, and the ease in scaling the reaction.[5] As a general technique for catalyzing reactions, PTC has been quite successfully used in a wide range of reactions, such as S_N2 type alkylations using C-, O-, S- and N-nucleophiles,[6] dehydrohalogenations,[7] oxidations and epoxidations,[8] *O*-acylations,[9] etherification reactions,[10] aldol condensations,[11] and isomerizations.[12] To the best of our knowledge, no Japp–Klingmann reaction promoted by PTC has been reported previously.

In our pursuit of an efficient synthesis of melatonin,[13] we found that the intermediate aryl hydrazone **4c** could be easily obtained as a fine solid rather than viscous oil in near quantitative yields when using a PTC in the reaction. These results encouraged us to investigate the scope and effect of PTC in the Japp–Klingmann reaction for Fischer indole synthesis. In this article, we report systematically a convenient and practical synthesis of aryl hydrazones and the corresponding indole derivatives in good to excellent yield under PTC conditions.

RESULTS AND DISCUSSION

The indole derivatives could be prepared as indicated in Scheme 1. At first, commercially available aryl amines **1** were diazotized and reacted under alkaline conditions with ethyl 2-acetyl-5-phthalimidopentanote **3** using PTC-promoted Japp–Klingmann reaction to form the ring-opened aryl hydrazones **4**. These aryl hydrazones were then cyclized and converted into the corresponding indole derivatives **5** by treatment with hydrochloric acid in ethanol.

In previously reported Japp–klingmann reactions,[4] the solvents are EtOH/H_2O (10:1) and it is often difficult to separate pure aryl hydrazones. Previous procedures required large volumes of CH_2Cl_2[4] or benzene[14] to extract the product after the reaction mixture was diluted with a large amount of water at the end of the reaction. Despite this, dark viscous reaction products were obtained, which were difficult to purify. In our experiment, the ratio of H_2O to EtOH was increased to 1:1 and the phase-transfer



Scheme 1. Synthesis of the indole derivatives.

catalysts were added to improve the reaction process. After considerable study of the effect of PTC, it was discovered that addition of a suitable PTC to the reaction could significantly improve the reaction profile, producing pure crystalline aryl hydrazones **4** rather than viscous oils in near quantitative yields. The effect of PTC is shown in Table 1. Of the PTCs investigated, quaternary ammonium salts were found to be superior to polyethylene glycol in this reaction, and the long chain quaternary ammonium salts were superior to the short ones. Dimethyldioctadecyl ammonium chloride (DMDOA) was optimal, affording aryl hydrazones **4c** as pure product in 98% yield by simple filtration process.

Table 1. Japp–Klingmann reaction under different phase-transfer catalysts

PTC	Aryl hydrazones 4c (R = *p*-OCH_3)	Yield (%)	Mp of crude product
no PTC	Dark red oil	—	—
PEG 400	Dark red oil and semisolid	82	<65°C
PEG 1000	Dark red oil and semisolid	86	<65°C
PEG 6000	Semisolid	87	<65°C
TEBA	Semisolid	90	<70°C
TMHA	Dark solid	96	74–76°C
TBAB	Dark solid	93	73–76°C
DMDOA	Light yellow crystal	99	76–77°C

PEG: polyethylene glycol; TEBA: triethyl benzyl ammonium chloride; TMHA: trimethylhexadecyl ammonium bromine; TBAB: tetrabutylammonium bromide; DMDOA: dimethyldioctadecyl ammonium chloride.

To expand the scope of the methodology, the reaction of aryl diazonium salts with other substituent groups were investigated. The generality of the process using DMDOA as PTC in the Japp–Klingmann reaction was demonstrated with a wide variety of aryl amines bearing *ortho*, *meta*, and *para* substituents. The results are shown in Table 2. Interestingly, aryl hydrazones bearing either electron-withdrawing or electron-donating substituent groups can be prepared from corresponding aryl amines and easily be isolated in excellent yields as fine solids, which then led to the efficient formation of substituted indoles. Here we should mentioned that the reaction mixture of **4f** should be kept overnight to get a crystalline product, whereas in other cases, the fine solid products can be derived directly from the reaction mixture. The aryl hydrazones **4a–h** and indole derivatives **5a–h** are known compounds, although some have only been partially characterized. Here we fully characterize all the hydrazones and indoles by melting point, IR, ^{1}H NMR, and elemental analysis. Compounds **4j** and **5j** are new compounds, which were also fully characterized.

Analogues of the aryl hydrazone **4** in Ishii et al.'s paper[15] have ***Z,E-***isomers via Japp–Klingmann reaction and the ratio of two isomers is about 1:1. In our case, each substance we used only got a single product via Japp–Klingmann reaction because there was only one spot on thin-layer chromatography (TLC). The geometrical structure of the aryl hydrazone **4** should be ***Z-***isomer, established by the infrared spectrum (IR) and the nuclear magnetic resonance spectrum (^{1}H NMR).

In conclusion, a general, efficient method for the synthesis of indole derivatives through PTC-promoted Japp–Klingmann reaction has been demonstrated. The procedure is general with respect to both the electron-withdrawing and electron-donating substituted aryl amines and the method is superior to other previously reported methods with regard to its simplicity

Table 2. Fischer indole synthesis via Japp–Klingmann reaction promoted by DMDOA

Entry	Substrate (R=)	Aryl hydrazone **4**	Yield (%)	Indole **5**	Yield (%)
1	H	**4a**	97	**5a**[4a]	82
2	*p*-CH_3	**4b**	98	**5b**[4a]	87
3	*p*-OCH_3	**4c**	98	**5c**[4c]	86
4	*p*-OCH_2Ph	**4d**	98	**5d**[14]	88
5	*m*-OCH_2Ph	**4e**	94	**5e**[4e]	85
6	*p*-NO_2	**4f**	99	**5f**[4a]	83
7	*o*-NO_2	**4g**	95	**5g**[4f]	80
8	*p*-Cl	**4h**	99	**5h**[4a]	85
9	*p*-Br	**4i**	99	**5i**	83
10	*p*-$COCH_3$	**4j**	98	**5j**	86

and efficiency, and avoidance of toxic solvents and complicated work up procedures. It is therefore an environmentally friendly methodology amenable for scaling.

EXPERIMENTAL

Melting points were measured on a XRC-1 melting apparatus and are uncorrected. Infrared spectra were recorded with KBr disks on a PE-938G Spectrometer. NMR spectra were recorded on a Varian INOVA 400 MHz spectrometer in $CDCl_3$ solutions and tetramethylsilane was used as the internal standard (d1/4 0 ppm). Element analyses were obtained using a Foss-Heraeus Vario EL instrument.

Ethyl 2-acetyl-5-phthalimidopentanote **3** was synthesized using phase-transfer catalysis as we have previously reported.[13] All other solvents and chemicals were obtained from commercial sources and were used without further purification unless otherwise stated.

Typical Procedure

Preparation of Aryl Diazonium Salts **2**

The substituted aryl amine **1** (0.01 mol) was added to a mixture of water (6 mL) and ethanol (4 mL). A solution of $NaNO_2$ (0.69 g, 0.01 mol) in concentrated HCl (37%, 2 mL, 0.05 mol) was added dropwise to the mixture and temperature was maintained at 0–5°C for 0.5 h. This produced the solution of aryl diazonium salts **2**.

Preparation of 2-Phenylhydrazono-5-Phthalimido-Pentanoic Acid Ethyl Ester and Its Derivatives **4a–j**

Ethyl 2-acetyl-5-phthalimidopentanote **3** (3.17 g, 0.01 mol) was dissolved in ethanol (20 mL). The phase-transfer catalysts (0.05 g) were added to the solution. A solution of $NaOAc \cdot 3H_2O$ (6.24 g, 0.048 mol) in water (20 mL) was added and the mixture was cooled down to 0°C. The aforementioned alcohol–water solution of aryl diazonium salts **2** was added to the mixture and stirred at a temperature of 0°C for 1 h. The temperature was then gradually raised to 25°C and the reaction mixture was stirred for 3 h. The resulting solid was filtered and then washed with a small amount of ethanol to yield pure yellow crystals of compounds **4a–j**.

4a (R=H): yield 97%; mp 67.5–68.5°C; IR (KBr) ν (cm^{-1}): 3470 (m, N–H); 1770, 1710 (s, C=O); 1605 (w, C=N); ^1H NMR δ: 12.06 (s, 1H, N–H); 8.20–7.80 (m, 4H, Ar–H); 7.30–7.13 (m, 5H, Ar′–H); 4.30 (q, 2H, $CH_3C^*H_2O$–); 3.80 (t, 2H, $-NC^*H_2CH_2CH_2-$); 2.61 (t, 2H,

–N=C–C*$H_2$$CH_2$–); 2.04 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.22 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found C, 66.51; H, 5.60; N, 11.11.

4b (*p*-CH_3): yield 98%; mp 91.0–92.0°C; IR (KBr) ν (cm^{-1}): 3465 (m, N–H); 1769, 1745, 1711 (s, C=O); 1604(w, –C=N–); ^{1}H NMRδ: 7.89–7.69 (m, 4H, Ar–H); 7.20–7.45 (m, 4H, Ar′–H); 4.21 (q, 2H, CH_3C*H_2O–); 3.57 (t, 2H, –NC*$H_2$$CH_2$$CH_2$–); 2.08 (t, 2H, –N=C–C*$H_2$$CH_2$$CH_2$–); 1.79 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.29 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{22}H_{23}N_3O_4$: C, 67.16; H, 5.89; N, 10.68. Found C, 67.21; H, 5.90; N, 10.63.

4c (*p*-OCH_3): yield 98%; mp 76.0–77.0°C; IR (KBr) ν (cm^{-1}): 3463 (m, N–H); 1769, 1745, 1711 (s, C=O); 1604 (w, –C=N–); ^{1}H NMR δ: 7.83–7.63 (m, 4H, Ar–H); 7.09 (m, 4H, Ar′–H); 4.16 (q, 2H, CH_3C*H_2O–); 3.82 (s, 3H, –OCH_3); 3.57 (t, 2H, –NC*$H_2$$CH_2$$CH_2$–); 2.08 (t, 2H, –N=C–C*$H_2$$CH_2$$CH_2$–); 1.27 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.10 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{22}H_{23}N_3O_5$: C, 64.54; H, 5.66; N, 10.26. Found C, 64.51; H, 5.64; N, 10.21.

4d (R=*p*-OCH_2Ph): yield 98%; mp 86.0–87.0°C; IR (KBr) ν (cm^{-1}): 3463 (m, N–H); 1769, 1745, 1711 (s, C=O); 1604 (w, –C=N–); ^{1}H NMR δ: 12.04 (s, 1H, N–H); 7.82–7.68 (m, 4H, Ar–H); 7.50–7.11 (m, 9H, Ar′–H); 5.00 (s, 2H, phCH_2O); 4.43 (q, 2H, CH_3C*H_2O–); 4.01 (t, 2H, –NC*$H_2$$CH_2$$CH_2$–); 3.44 (t, 2H, –N$CH_2$$CH_2$$CH_2$*–); 1.57 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.43 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{28}H_{27}N_3O_5$: C, 68.26; H, 5.61; N, 8.65. Found C, 68.21; H, 5.67; N, 8.61.

4e (R=*m*-OCH_2Ph): yield 94%; mp 135.0–136.0°C; ν (cm^{-1}): 3451 (m, N–H); 1769, 1745, 1711 (s, C=O); 1610 (w, –C=N–); ^{1}H NMR δ:11.35 (s, 1H, N–H); 7.78–7.68 (m, 4H, Ar–H); 7.50–7.01 (m, 9H, Ar′–H); 5.11 (s, 2H, phCH_2O); 4.37(q, 2H, CH_3C*H_2O–); 3.95 (t, 2H, –NC*$H_2$$CH_2$$CH_2$–); 3.38 (t, 2H, –N$CH_2$$CH_2$$CH_2$*–); 1.61 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.32 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{28}H_{27}N_3O_5$: C, 68.26; H, 5.61; N, 8.65. Found C, 68.23; H, 5.57; N, 8.71.

4f (R = *p*-NO_2): yield 99%; mp 176.0–177.0°C; IR (KBr) ν: 3442 (m, N–H); 1768, 1750, 1700 (s, C=O); 1604 (w, –C=N–); ^{1}H NMR δ: 8.20–7.80 (m, 4H, Ar–H); 7.65–7.20 (m, 4H, Ar′–H); 4.2 (q, 2H, CH_3C*H_2O–); 3.8 (t, 2H, –NC*$H_2$$CH_2$$CH_2$–); 2.08 (t, 2H, –N=C–C*$H_2$$CH_2$$CH_2$-); 1.6 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.32 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{21}H_{20}N_4O_6$: C, 59.43; H, 4.75; N, 13.20. Found C, 59.40; H, 4.70; N, 13.21.

4g (R = *o*-NO_2): yield 95%; mp: 106–107°C; IR (KBr) ν: 3442 (m, N–H); 1768, 1750, 1700 (s, C=O); 1604 (w, –C=N–); ^{1}H NMR δ: 11.19 (s, 1H, N–H); 7.8–7.72 (m, 4H, Ar–H); 7.68–7.30 (m, 4H, Ar′–H); 4.26 (q, 2H, CH_3C*H_2O–); 3.72 (t, 2H, –NC*$H_2$$CH_2$$CH_2$–); 2.28 (t, 2H, –N=C–C*$H_2$$CH_2$$CH_2$–); 1.87 (m, 2H, –$CH_2$C*$H_2$$CH_2$–); 1.28 (t, 3H, –$OCH_2$C*$H_3$); Anal. calcd. for $C_{21}H_{20}N_4O_6$:C, 59.43; H, 4.75; N, 13.20. Found C, 59.39; H, 4.77; N, 13.17.

4h (R = *p* -Cl):yield 99%; mp 147.0–148.0°C; IR (KBr) ν (cm^{-1}): 3452 (m, N–H); 1747, 1710 (s, C═O); 1604 (w, C═N); ^{1}H NMR δ: 8.00–7.8 (m, 4H, Ar–H); 7.66–7.20 (m, 4H, Ar′–H); 4.2 (q, 2H, $CH_3C^*H_2O$–); 3.70 (t, 2H, –$NC^*H_2CH_2CH_2$–); 2.2 (t, 2H, –N═C–$C^*H_2CH_2$–); 1.8 (m, 2H, –$CH_2C^*H_2CH_2$–); 1.25 (t, 3H, –$OCH_2C^*H_3$); Anal. calcd. for $C_{21}H_{20}ClN_3O_4$:C, 60.95; H, 4.87; N, 10.15. Found C, 60.91; H, 4.90; N, 10.12.

4i (R = *p*-Br): yield 99%; mp 90.0–91.0°C; IR (KBr)ν(cm^{-1}): 3457 (m, N–H); 1751, 1710 (s, C═O); 1604 (w, –C═N–); ^{1}H NMRδ:12.06 (s, 1H, N–H); 7.81–7.70 (m, 4H, Ar–H); 7.61–7.50 (m, 4H, Ar′–H); 4.26 (q, 2H, $CH_3C^*H_2O$–); 3.67 (t, 2H, –$NC^*H_2CH_2CH_2$–); 2.26 (t, 2H, –N═C–$C^*H_2CH_2$–); 1.80 (m, 2H, –$CH_2C^*H_2CH_2$–); 1.26 (t, 3H, –$OCH_2C^*H_3$); Anal. calcd. for $C_{21}H_{20}BrN_3O_4$: C, 55.03; H, 4.40; N, 9.17. Found C, 55.01; H, 4.40; N, 9.12.

4j (R = *p* -$COCH_3$): yield 98%; mp 101.0–102.0°C; IR (KBr) ν (cm^{-1}): 3463 (m, N–H); 1769, 1745, 1711 (s, C═O); 1604 (w, –C═N–); ^{1}H NMR δ: 12.23 (s, 1H, N–H); 8.08–7.71 (m, 4H, Ar–H); 7.82–7.70 (m, 4H, Ar′–H); 4. 27 (q, 2H, $CH_3C^*H_2O$–); 3.69 (t, 2H, –$NC^*H_2CH_2CH_2$–); 2.66 (s, 3H, CH_3CO); 2.21 (t, 2H, –N═C–$C^*H_2CH_2CH_2$–); 1.80 (m, 2H, –$CH_2C^*H_2CH_2$–); 1.27 (t, 3H, –$OCH_2C^*H_3$); Anal. calcd. for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found C, 65.51; H, 5.47; N, 10.01.

Preparation of Ethyl 3-(2-phthalimidoethyl) Indole-2-carboxylate and its Derivatives **5a–i**

Aryl hydrazone **4** (0.01 mol) was placed in a three-necked flask. A solution of 10% HCl-EtOH (24 mL) was added dropwise over a period of 0.5 h. The solution was then heated at reflux for a period of 2 h, accompanied with stirring throughout the whole process. After cooling, the solution was filtered under reduced pressure. The solid residue was washed with methanol, water, and methanol and then dried, producing the light yellow solids **5a–i**.

5a (R=H): yield 82%; mp 190.0–191.0°C; IR (KBr) ν (cm^{-1}): 3500 (m, ν_{N-H}); 2941 (w, ν_{C-H}); 1772, 1740, 1722 (s, $\nu_{C=O}$); ^{1}H NMR δ: 8.89 (s, N–H); 7.90–7.70 (m, 4H, Ar–H); 7.30–6.80 (m, 4H, Ar–H); 4.21 (q, 2H, –$O^*CH_2CH_3$); 3.87 (t, 2H, –$CH_2{}^*CH_2N$–); 2.16 (t, 2H, –$^*CH_2CH_2CH_2N$–); 1.30 (t, 3H, –$OCH_2{}^*CH_3$). Anal. calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found C, 69.61; H, 5.00; N, 7.75.

5b (R=5-CH_3): yield 87%; mp 223.0–224.0°; IR (KBr) ν (cm^{-1}): IR: 3330 (NH), 1775, 1715, 1690 (s, $\nu_{C=O}$); ^{1}H NMR δ: 8.73 (s, N–H); 7.98–7.66 (m, 4H, Ar–H); 7.20–6.45 (m, 3H, Ar–H); 4.40 (q, 2H, –$O^*CH_2CH_3$); 4.00 (t, 2H, –$CH_2{}^*CH_2N$–); 3.43 (t, 2H, –$^*CH_2CH_2N$–); 2.33 (s, 3H, Ar–CH_3); 1.46 (t, 3H, –$OCH_2{}^*CH_3$). Anal. calcd. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found C, 70.28; H, 5.40; N, 7.39.

5c (R=5-OCH_3): yield 86%; mp 238.0–240.0°C; IR (KBr)ν(cm^{-1}): IR: 3330 (NH), 1775, 1715, 1690 (s, $\nu_{C=O}$); ^{1}H NMR δ:10.1 (s, N–H); 8.10–7.70

(m, 3H, Ar–H); 7.20–6.80 (m, 4H, Ar–H); 4.20 (q, 2H, $-O^*CH_2CH_3$); 3.90 (t, 2H, $-CH_2{}^*CH_2N-$); 3.20 (t, 2H, $-{}^*CH_2CH_2N-$); 1.30 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.14; N, 7.14. Found C, 67.31; H, 5.16; N, 7.17.

5d (R=5-OCH_2Ph): yield 88%; mp 188.0–190.0°C; IR (KBr) ν (cm^{-1}): 3330 (NH), 1775, 1715, 1690 (s, $\nu_{C=O}$); ^1H NMR δ: 8.07 (s, N–H); 7.80–7.68 (m, 4H, Ar–H); 7.55–7.02 (m, 8H, Ar–H); 5.03 (s, 2H, $PhCH_2O$); 4.26 (q, 2H, $-O^*CH_2CH_3$); 3.78 (t, 2H, $-CH_2{}^*CH_2N-$); 2.59 (t, 2H, $-{}^*CH_2CH_2N-$); 1.32 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98. Found C, 71.76; H, 5.14; N, 5.89.

5e (R=6-OCH_2Ph): yield 85%; mp 199–201°C; IR (KBr) ν (cm^{-1}): 3330 (NH), 1780, 1720, 1680 (s, $\nu_{C=O}$); ^1H NMR δ: 8.90 (s, N–H); 7.79–7.68 (m, 4H, Ar–H); 7.47–7.12 (m, 8H, Ar–H); 5.10 (s, 2H, $PhCH_2O$); 4.18 (q, 2H, $-O^*CH_2CH_3$); 3.84 (t, 2H, $-CH_2{}^*CH_2N-$); 2.79 (t, 2H, $-{}^*CH_2CH_2N-$); 1.28 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98. Found C, 71.80; H, 5.14; N, 5.90.

5f (R=5-NO_2): yield 83%; mp 316.0–317.0°C; IR (KBr) ν (cm^{-1}): 3330 (NH), 1775, 1715, 1690 (s, $\nu_{C=O}$); ^1H NMR δ: 12.3 (s, N–H); 8.53–7.14 (m, 3H, Ar–H); 8.1–7.7 (m, 4H, Ar–H); 4.23 (q, 2H, $-O^*CH_2CH_3$); 3.87 (t, 2H, $-CH_2{}^*CH_2N-$); 3.36 (t, 2H, $-{}^*CH_2CH_2N-$); 1.35 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{21}H_{17}N_3O_6$: C, 61.91; H, 4.21; N, 10.31. Found C, 61.89; H, 4.22; N, 10.30.

5g (R=7-NO_2): yield 80%; mp 194–195°C; IR (KBr) ν (cm^{-1}): IR: 3330 (NH), 1775, 1715, 1690 (s, $\nu_{C=O}$); ^1H NMR δ: 13.83 (s, N–H); 7.80–7.68 (m, 4H, Ar–H); 8.03–7.62 (m, 3H, Ar–H); 4.37 (q, 2H, $-O^*CH_2CH_3$); 3.85 (t, 2H, $-CH_2{}^*CH_2N-$); 2.71 (t, 2H, $-{}^*CH_2CH_2N-$); 1.38 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{21}H_{17}N_3O_6$:C, 61.91; H, 4.21; N, 10.31. Found C, 61.86; H, 4.27; N, 10.26.

5h (R=5–Cl); yield 85%; mp 265.0–266.0°C; IR (KBr) ν (cm^{-1}): 3330 (NH_2); 1760, 1700, 1675 (CO). ^1H NMR δ: 8.90 (s, N–H); 7.90–7.70 (m, 4H, Ar–H); 7.61–6.80 (m, 3H, Ar–H); 4.21 (q, 2H, $-O^*CH_2CH_3$); 3.85 (t, 2H, $-CH_2{}^*CH_2N-$); 3.30 (t, 2H, $-{}^*CH_2CH_2N-$); 1.30 (3t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{21}H_{17}ClN_2O_4$: C, 63.56; H, 4.32; N, 7.06. Found C, 63.57; H, 4.35; N, 7.08.

5i (R=5-Br); yield 83%; mp 229.0–230.0°C; IR (KBr) ν (cm^{-1}): 3330 (NH); 1765, 1710, 1670 (CO). ^1H NMR δ: 8.82 (s, N–H); 7.87–7.70 (m, 4H, Ar–H); 7.30–6.93 (m, 3H, Ar–H); 4.26 (q, 2H, $-O^*CH_2CH_3$); 3.80 (t, 2H, $-CH_2{}^*CH_2N-$); 2.61 (t, 2H, $-{}^*CH_2CH_2N-$); 1.32 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{21}H_{17}BrN_2O_4$: C, 57.16; H, 3.88; N, 6.35. Found C, 57.2; H, 3.92; N, 6.30.

5j (R=5-$COCH_3$): yield 86%; mp 184.0–185.0°C; IR (KBr) ν (cm^{-1}): IR: 3330 (NH), 1775, 1715, 1690 (s, $\nu_{C=O}$); ^1H NMR δ: 9.01 (s, N–H); 7.93–7.82 (m, 4H, Ar–H); 7.95–7.69 (m, 3H, Ar–H); 4.29 (q, 2H, $-O^*CH_2CH_3$); 4.04 (t, 2H, $-CH_2{}^*CH_2N-$); 3.53 (t, 2H, $-{}^*CH_2CH_2N-$);

2.56 (s, 3H, CH_3CO); 1.25 (t, 3H, $-OCH_2{}^*CH_3$). Anal. calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found C, 68.28; H, 4.94; N, 6.89.

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