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# SYNTHESIS OF SUBSTITUTED 1,3-DIMETHYL-1*H*-QUINOXALIN-2-ONES FROM ANILINE DERIVATIVES

**Xun Li, [a] Donghua Wang, [b] Jifeng Wu, [c] and Wenfang Xu*[a]**

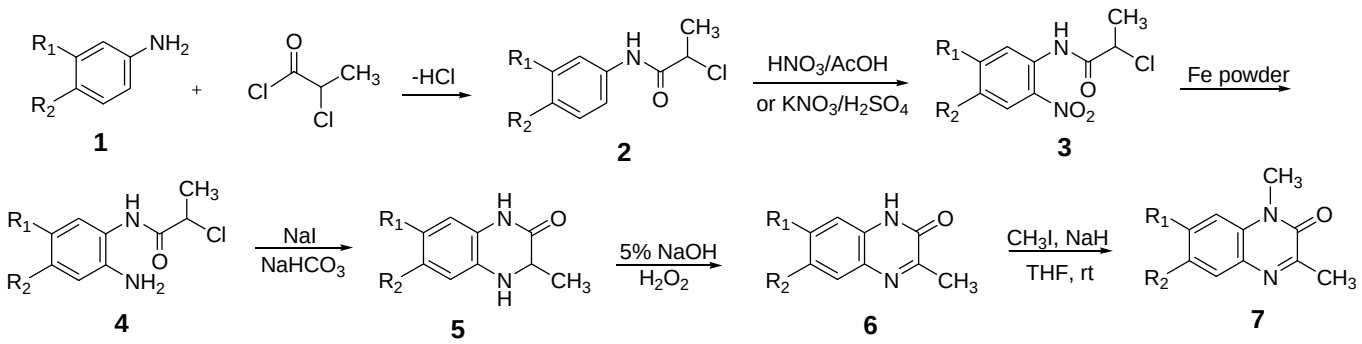
College of Pharmacy, Shandong University, Jinan, 250012, P. R. China [a], College of Pharmaceuticals and Biotechnology, Tianjin University, Tianjin, 300072, P. R. China[b] and Jinan Public Security Bureau, Jinan, 250002, P. R. China[c]
e-mail:tjulx2004@sdu.edu.cn

**Abstract** – Substituted 1,3-dimethyl-1*H*-quinoxalin-2-ones (**7**) have been synthesized through the procedures of acylation, nitration, reduction, intramolecular alkylation, oxidation, and *N*-methylation starting from 3,4-disubstituted aniline.

## INTRODUCTION

Substituted phenoxymethylquinoxalinones, which can selectively antagonize P-glycoprotein (Pgp) other than multidrug-resistance-related protein-1 (MRP-1), have been reported by Smith groups to be used as multiple drug resistance (MDR) antagonists to reverse tumor resistance to many chemotherapeutic agents.[1] A variety of substituted phenoxymethylquinoxalinones with different substituents on the phenol ring have been prepared to study their structure-activity relationships. During the process to develop a drug candidate, we required an efficient and practical method to obtain sufficient 1,3-dimethyl-1*H*-quinoxalin-2-ones as key intermediates.

The principal synthetic route for the substituted 1,3-dimethyl-1*H*-quinoxalin-2-ones comprised the condensation of *N*-methyl-1,2-phenylenediamines with pyruvic acid, but multiple by-products were obtained when unsymmetrical diamine were used, which leading to the target compounds in extremely low yields. Therefore, a highly regioselective method is urgently needed. However, there have been relatively few such methods available to produce substituted 1,3-dimethyl-1*H*-quinoxalin-2-ones.[2] In this paper, we reported a regioselective methodology for the synthesis of substituted 1,3-dimethyl-1*H*-quinoxalin-2-ones through a quite efficient sequence of acylation, nitration, reduction, intramolecular alkylation, oxidation, and *N*-methylation.(Scheme 1)




Scheme 1

## RESULTS AND DISCUSSION

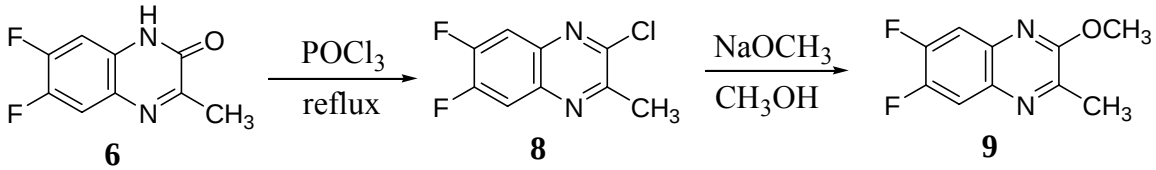
Reaction of substituted anilines with 2-chloropropionyl chloride in toluene under refluxing afforded acetamides (**2**) in excellent yield (>90%). Base was not used to prevent the hydrolysis of 2-chloropropionyl chloride and refluxing was needed to decompose the chloride generated in the reaction to force the reaction completely, thus hydrogen chloride could be released as gas.

Nitration of **2** with appropriate nitrating reagents led to the formation of a single product (**3**), isolated in 87~95% yields. The results illustrated that when $R_1$ or/and $R_2$ was electron-withdrawing group, $KNO_3/H_2SO_4$ could be used. Whereas $R_1$ or/and $R_2$ was electron-donating group, mild nitrating reagents such as $HNO_3$/AcOH should be selected to improve the reaction regioselectivity.

Reduction of nitro group with iron powders afforded *o*-aminoacetamides (**4**) in 83~97% yields. The reaction proceeded in DMF/$H_2O$ (1:9) at 50~60 °C with little or none dechlorinating by-products. The conjugative effect of amino group on the benzene ring led to the difficulty of intramolecular alkylation of **4**. The reaction proceeded rapidly in the presence of two equivalents of $NaHCO_3$ in $CH_3CN$ with sodium iodine as catalyst and the corresponding substituted 3-methyl-3,4-dihydro-1*H*-quinoxalin-2-ones (**5**) were obtained in 31~82% yields, and 10~15 h were still needed to make the reaction completely. The subsequent oxidation of **5** with $H_2O_2$ in 5% NaOH solution at 60 °C afforded **6** in 51~93% yields.

The *N*-methylation reaction of **6** with $CH_3I$ in the presence of NaH in THF proceeded smoothly at room temperature to afford the desired product (**7**), isolated in 50~93% yields. Other methods such as $(CH_3)_2SO_4$/NaOH,[3] diazomethane[4] and so on were less efficient in our hand. The isolated overall yields of 1,3-dimethyl-1*H*-quinoxalin-2-ones from substituted anilines were 14~32%.

To confirm that the methyl group occurred at the 1-*N* position not *O*-position, 6,7-difluoro-2-methoxy-3-methylquinoxaline (**9**) was prepared (Scheme 2) in 42% total yields. Compared the $^1$H NMR spectra of **7e** with **9**, different chemical shift (δ=3.57 ppm for $CH_3$ group of **7e** while δ=4.03 ppm for $OCH_3$ group of **9**) supported the conclusion.[5]




**6** **8** **9**

Scheme 2

In summary, we have reported an approach for the synthesis of 1,3-methyl-1*H*-quinoxalin-2-ones using substituted anilines as readily available starting materials.

## EXPERIMENTAL

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Reaction courses and product mixtures were routinely monitored by thin-layer chromatography on silica gel (precoated $GF_{254}$ plates) and visualized with iodine. Flash chromatography was performed using 200~300 mesh silica gel and the solvent system indicated in the procedure. All commercially available solvents and reagents were used as received. Melting points were determined with capillary apparatus and are uncorrected. IR spectra were recorded in the range of 4000~600 $cm^{-1}$ using a Nicolet Nexus 470FT spectrophotometer, KBr disks were used as indicated. $^1$H NMR spectra were recorded on a Bruker AM-400 spectrometer. Chemical shift (δ) are given in ppm upfield from tetramethylsilane as internal standard, and the spectra were recorded in appropriate deuterated solvents indicated in the procedure. Coupling constants (*J*) are reported in Hz. Microanalyses were performed on a Perkin-Elmer C, H and N elemental analyzer.

**General procedures were as follows:**

**2:** To a stirred solution of substituted anilines (10 mmol) in 20 mL of toluene was added 2-chloropropionyl chloride (1.52 g, 12 mmol), the mixture was stirred at 120 °C for 1 h. Toluene was removed under vacuum and the residue was recrystallized from ethyl acetate/petroleum ether (1:2) to give crystalline products.

**2a:** 98%; mp 109-110 °C; $^1$H NMR (DMSO-$d_6$) δ 10.39 (s, 1H, NH), 7.61 (d, 2H, *J*=8.8, ArH), 7.38 (d, 2H, *J*=8.8, ArH), 4.54 (q, 1H, *J*=5.1, CH), 1.76 (d, 3H, *J*=1.6, $CH_3$). Anal. Calcd for $C_9H_9NOCl_2$: C, 49.54; H, 4.13; N, 6.42. Found: C, 49.79; H, 3.88; N, 6.57.

**2b:** 99%; mp123-124 °C; $^1$H NMR (DMSO-$d_6$) δ 10.33 (s, 1H, NH), 7.54 (d, 2H, *J*=8.8, ArH), 7.41 (d, 2H, *J*=8.8, ArH), 4.54 (q, 1H, *J*=8.0, CH), 1.76 (d, *J*=1.6, 3H, $CH_3$). Anal. Calcd for $C_9H_9NOBrCl$: C, 41.16; H, 3.43; N, 5.34. Found: C, 41.33; H, 3.50; N, 5.25.

**2c:** 98.5%; mp 83-84 °C; $^1$H NMR (DMSO-$d_6$) δ 10.33 (s, 1H, NH), 7.62 (q, 2H, *J*=8.0, ArH), 6.97 (q, 2H, *J*=8.4, ArH), 4.54 (q, 1H, *J*=6.0, CH), 1.76 (d, 3H, *J*=2.4, $CH_3$). Anal. Calcd for $C_9H_9NOClF$: C, 53.60; H, 4.47; N, 6.95. Found: C, 53.76; H, 4.50; N, 6.88.

**2d:** 95%; mp 113-114 °C; $^1$H NMR (DMSO-$d_6$) δ 10.34 (s, 1H, NH), 7.53 (d, 2H, *J*=8.4, ArH), 7.40 (q, 1H, *J*=8.0, ArH), 7.01 (m, 1H, ArH), 4.59 (q, 1H, *J*=9.0, CH), 2.35 (s, 3H, $CH_3$), 1.77 (d, 3H, *J*=3.2, $CH_3$). Anal. Calcd for $C_{10}H_{11}NOCl_2$: C, 51.72; H, 4.74; N, 6.03. Found: C, 51.77; H, 4.82; N, 5.90.

**2e:** 99%; mp 78-79 °C; $^1$H NMR (DMSO-$d_6$) δ 10.31 (s, 1H, NH), 7.39 (q, 1H, *J*=8.0, ArH), 7.33 (m, 1H, ArH), 6.93 (q, 1H, *J*=6.8, ArH), 4.57 (q, 1H, *J*=7.0, CH), 1.75 (d, *J*=4.8, 3H, $CH_3$). Anal. Calcd for $C_9H_8NOClF_2$: C, 49.20; H, 3.64; N, 6.38. Found: C, 49.12; H, 3.76; N, 6.33.

**2f:** 99%; mp 119-120 °C; $^1$H NMR (DMSO-$d_6$) δ 10.32 (s, 1H, NH), 7.52 (q, 2H, *J*=8.4, ArH), 7.04 (d, 2H, *J*=8.8, ArH), 4.54 (q, 1H, *J*=6.8, CH), 1.76 (d, *J*=1.6, 3H, $CH_3$). Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.08; N, 7.09. Found: C, 60.68; H, 6.13; N, 7.20.

**2g:** 97%; mp 76-77 °C; $^1$H NMR (DMSO-$d_6$) δ 10.36 (s, 1H, NH), 7.59 (d, 2H, *J*=1.6, ArH), 7.10 (d, 2H, *J*=8.4, ArH), 4.59 (q, 1H, *J*=7.0, CH), 2.51 (t, 2H, *J*=10.3, $CH_2$), 1.62 (m, 2H, $CH_2$), 1.34 (q, 2H, *J*=3.2, $CH_2$), 1.77 (d, *J*=8.8, 3H, $CH_3$), 0.96 (t, 3H, *J*=4.0, $CH_3$). Anal. Calcd for $C_{13}H_{18}NOCl$: C, 65.14; H, 7.52; N, 5.85. Found: C, 65.23; H, 7.48; N, 5.97.

**2h:** 98%; mp 105-106 °C; $^1$H NMR (DMSO-$d_6$) δ 10.34 (s, 1H, NH), 7.53 (d, 2H, *J*=8.8, ArH), 6.75 (d, 2H, *J*=8.8, ArH), 4.54 (q, 1H, *J*=7.2, CH), 1.76 (d, *J*=2.4, 3H, $CH_3$). Anal. Calcd for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.62; N, 6.56. Found: C, 56.33; H, 5.74; N, 6.48.

**2i:** 96%; mp 120-121 °C; $^1$H NMR (DMSO-$d_6$) δ 10.33 (s, 1H, NH), 7.53 (d, 2H, *J*=8.4, ArH), 6.77 (d, 2H, *J*=8.4, ArH), 4.59 (q, 1H, *J*=3.6, CH), 4.09 (q, 2H, *J*=10.5, $CH_2$), 1.76 (d, *J*=2.4, 3H, $CH_3$), 1.35 (t, 3H, *J*=7.7, $CH_3$). Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C, 58.02; H, 6.15; N, 6.15. Found: C, 57.99; H, 6.23; N, 6.20.

**2j:** 97%; mp 139-140 °C; $^1$H NMR (DMSO-$d_6$) δ 10.35 (s, 1H, NH), 7.35 (d, 2H, *J*=2.4, ArH), 7.33 (s, 1H, ArH), 6.92 (d, 2H, *J*=8.8, ArH), 4.57 (q, 1H, *J*=8.2, CH), 2.35 (s, 6H, 2$CH_3$); 1.76 (d, *J*=1.6, 3H, $CH_3$). Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.41; H, 6.62; N, 6.62. Found: C, 62.53; H, 6.58; N, 6.69.

**3:** To a stirred solution of **2** (4.20 mmol) in 10 mL of acetic acid was added 1 mL of 65% nitric acid at 0 °C, or to a stirred solution of **2** (4.20 mmol) in concentrated sulfuric acid (15 mL) was added potassium nitrate (509 mg, 5.04 mmol), the mixture was stirred at rt for 1 h. The resulting yellow-brown solution was poured into 50 g of crushed ice, and the yellow solid product was filtered off, washed with water (10 mL). The crude product obtained was purified by recrystallization from methanol and dried to give crystalline product (**3**) in 70~90% yield.

**3a:** 92%; mp 219-220 °C; $^1$H NMR (DMSO-$d_6$) δ 10.54 (s, 1H, NH), 8.18 (s, 1H, ArH), 7.83 (d, 1H, *J*=9.6, ArH), 7.36 (d, 1H, *J*=6.8, ArH), 4.59 (q, 1H, *J*=4.2, CH), 1.67 (d, 3H, *J*=8.4, $CH_3$). Anal. Calcd for $C_9H_8N_2O_3Cl_2$: C, 41.06; H, 3.04; N, 10.65. Found: C, 41.14; H, 3.11; N, 10.58.

**3b:** 94%; mp 106-107 °C; $^1$H NMR (DMSO-$d_6$) δ 10.54 (s, 1H, NH), 8.18 (s, 1H, ArH), 7.86 (d, 1H, *J*=9.6, ArH), 7.74 (d, 1H, *J*=6.8, ArH), 4.59 (q, 1H, *J*=8.1, CH), 1.67 (d, 3H, *J*=8.8, $CH_3$). Anal. Calcd for

$C_9H_8N_2O_3ClBr$: C, 35.13; H, 2.60; N, 9.11. Found: C, 35.20; H, 2.66; N, 9.03.

**3c:** 95%; mp 68-69 °C; $^1$H NMR (DMSO-$d_6$) δ 10.48 (s, 1H, NH), 7.88 (q, 2H, *J*=4.8, ArH), 7.34 (q, 1H, *J*=4.0, ArH), 4.59 (q, 1H, *J*=4.8, CH), 1.67 (d, 3H, *J*=8.4, $CH_3$). Anal. Calcd for $C_9H_8N_2O_3ClF$: C, 43.81; H, 3.25; N, 11.36. Found: C, 43.78; H, 3.20; N, 11.44.

**3d:** 91%; mp 94-95 °C; $^1$H NMR (DMSO-$d_6$) δ 10.54 (s, 1H, NH), 8.72 (s, 1H, ArH), 8.26 (s, 1H, ArH), 4.54 (q, 1H, *J*=2.2, CH), 2.35 (s, 3H, $CH_3$); 1.76 (d, *J*=8.4, 3H, $CH_3$). Anal. Calcd for $C_{10}H_{10}N_2O_3Cl_2$: C, 43.32; H, 3.61; N, 10.11. Found: C, 43.26; H, 3.59; N, 10.17.

**3e:** 92%; mp 111-112 °C; $^1$H NMR (DMSO-$d_6$) δ 10.53 (s, 1H, NH), 7.86 (q, 1H, *J*=11.5, ArH), 7.54 (q, 1H, *J*=8.6, ArH), 4.59 (q, 1H, *J*=9.0, CH), 1.67 (d, 3H, *J*=8.4, $CH_3$). Anal. Calcd for $C_9H_7N_2O_3ClF_2$: C, 40.83; H, 2.65; N, 10.59. Found: C, 40.86; H, 2.72; N, 10.50.

**3f:** 93%; mp 77-78 °C; $^1$H NMR (DMSO-$d_6$) δ 10.48 (s, 1H, NH), 7.97 (s, 1H, ArH), 7.62 (d, 1H, *J*=8.8, ArH), 7.43 (d, 1H, *J*=8.4, ArH), 4.57 (q, 1H, *J*=8.7, CH), 2.35 (s, 3H, $CH_3$), 1.74 (d, 3H, *J*=8.4, $CH_3$). Anal. Calcd for $C_{10}H_{11}N_2O_3Cl$: C, 49.48; H, 4.54; N, 11.55. Found: C, 49.41; H, 4.59; N, 11.60.

**3g:** 87%; mp 76-77 °C; $^1$H NMR (DMSO-$d_6$) δ 10.52 (s, 1H, NH), 8.03 (s, 1H, ArH), 7.85 (d, 1H, *J*=2.0, ArH), 7.48 (d, 1H, *J*=8.4, ArH), 4.59 (q, 1H, *J*=8.5, CH), 2.55 (t, 2H, *J*=8.9, $CH_2$), 1.73 (d, 3H, *J*=2.4, $CH_3$), 1.63 (m, 2H, $CH_2$), 1.35 (m, 2H, $CH_2$), 0.95 (t, 3H, *J*=8.8, $CH_3$). Anal. Calcd for $C_{13}H_{17}N_2O_3Cl$: C, 54.83; H, 5.98; N, 9.84. Found: C, 54.79; H, 5.61; N, 9.84.

**3h:** 89%; mp 63-64 °C; $^1$H NMR (DMSO-$d_6$) δ 10.48 (s, 1H, NH), 7.79 (d, 1H, *J*=8.4, ArH), 7.68 (s, 1H, ArH), 7.14 (d, 1H, *J*=8.0, ArH), 4.61 (q, 1H, *J*=4.4, CH), 3.68 (s, 3H, $CH_3$), 1.75 (d, *J*=15.6, 3H, $CH_3$). Anal. Calcd for $C_{10}H_{11}N_2O_4Cl$: C, 46.42; H, 4.26; N, 10.83. Found: C, 46.39; H, 4.30; N, 10.89.

**3i:** 87%; mp 50-51 °C; $^1$H NMR (DMSO-$d_6$) δ 10.46 (s, 1H, NH), 7.79 (d, 1H, *J*=2.8, ArH), 7.68 (s, 1H, ArH), 7.14 (d, 1H, *J*=3.6, ArH), 4.60 (q, 1H, *J*=5.4, CH), 4.04 (q, 2H, *J*=5.1, $CH_2$), 1.76 (d, *J*=2.4, 3H, $CH_3$), 1.33 (t, 3H, *J*=8.7, $CH_3$). Anal. Calcd for $C_{11}H_{13}N_2O_4Cl$: C, 48.44; H, 4.77; N, 10.28. Found: C, 48.37; H, 4.81; N, 10.32.

**3j:** 90%; mp 114-115 °C; $^1$H NMR (DMSO-$d_6$) δ 10.56 (s, 1H, NH), 7.84 (s, 1H, ArH), 7.63 (s, 1H, ArH), 4.56 (q, 1H, *J*=6.5, CH), 2.29 (s, 3H, $CH_3$), 2.27 (s, 3H, $CH_3$), 1.76 (d, *J*=8.8, 3H, $CH_3$). Anal. Calcd for $C_{11}H_{13}N_2O_3Cl$: C, 51.46; H, 5.07; N, 10.92. Found: C, 51.49; H, 5.05; N, 11.05.

**4:** A mixture of reduction iron powder (2.00 g, 35.71 mmol), ammonium chloride (0.10 g, 1.85 mmol) and acetic acid (0.50 mL, 8.74 mmol) in water (30 mL) was vigorously stirred at 50 °C for 10~15 min. A solution of **3** (4 mmol) in DMF (10 mL) was then added. The reaction mixture was stirred at 50 °C until TLC showed the reaction was completed (about 15 min), the residual slurry was basified with 10% aqueous $Na_2CO_3$ solution to pH=8~9. The resulting suspension was filtered, washed with water (2×20 mL) and ethyl acetate (2×30 mL). The filtrate and washings were combined, and the organic phase was separated and the aqueous phase was further extracted with ethyl acetate (4×10 mL). The combined

organic extracts were washed with water (3×25 mL) and brine (25 mL), dried (sodium sulfate) and evaporated in vacuum yielded the reduction compound (**4**) as oil. The crude product was recrystallized from ethyl acetate/petroleum ether (4:1) to give the solid compound.

**4a:** 90%; mp 112-113 °C; $^1$H NMR (DMSO-$d_6$) δ 9.03 (s, 1H, NH), 7.53 (d, 1H, *J*=8.8, ArH), 6.87 (d, 1H, *J*=8.4, ArH), 6.45 (s, 1H, ArH), 5.29 (s, 2H, $NH_2$), 4.59 (q, 1H, *J*=7.3, CH), 1.76 (d, 3H, *J*=7.2, $CH_3$). Anal. Calcd for $C_9H_{10}N_2OCl_2$: C, 46.35; H, 4.29; N, 12.02. Found: C, 46.41; H, 4.20; N, 12.07.

**4b:** 93%; mp 69-100 °C; $^1$H NMR (DMSO-$d_6$) δ 9.13 (s, 1H, NH), 7.28 (d, 1H, *J*=8.8, ArH), 6.77 (d, 1H, *J*=8.4, ArH), 6.61 (s, 1H, ArH), 5.27 (s, 2H, $NH_2$), 4.59 (q, 1H, *J*=3.3, CH), 1.76 (d, 3H, *J*=7.2, $CH_3$). Anal. Calcd for $C_9H_{10}N_2OBrCl$: C, 38.93; H, 3.60; N, 10.09. Found: C, 39.01; H, 3.58; N, 10.00.

**4c:** 90%; mp 107-108 °C; $^1$H NMR (DMSO-$d_6$) δ 9.13 (s, 1H, NH), 7.68 (q, 1H, *J*=6.8, ArH), 6.66 (m, 1H, ArH), 6.25 (q, 1H, *J*=7.2, ArH), 5.23 (s, 2H, $NH_2$), 4.57 (q, 1H, *J*=6.3, CH), 1.83 (d, 3H, *J*=8.4, $CH_3$). Anal. Calcd for $C_9H_{10}N_2OClF$: C, 49.88; H, 4.62; N, 12.93. Found: C, 49.93; H, 4.74; N, 12.02.

**4d:** 92%; mp 155-156 °C; $^1$H NMR (DMSO-$d_6$) δ 9.13 (s, 1H, NH), 7.28 (s, 1H, ArH), 6.18 (s, 1H, ArH), 5.27 (s, 2H, $NH_2$), 4.59 (q, 1H, *J*=7.7, CH), 2.35 (s, 3H, $CH_3$), 1.76 (d, 3H, *J*=8.0, $CH_3$). Anal. Calcd for $C_{10}H_{12}N_2OCl_2$: C, 48.58; H, 4.86; N, 11.34. Found: C, 48.66; H, 4.89; N, 11.27.

**4e:** 83%; mp 131-132 °C; $^1$H NMR (DMSO-$d_6$) δ 9.09 (s, 1H, NH), 7.08 (q, 1H, *J*=5.4, ArH), 6.17 (q, 1H, *J*=5.1, ArH), 5.27 (s, 2H, $NH_2$), 4.59 (q, 1H, *J*=7.5, CH), 1.76 (d, 3H, *J*=9.6, $CH_3$). Anal. Calcd for $C_9H_9N_2OClF_2$: C, 46.06; H, 3.84; N, 11.94. Found: C, 46.13; H, 3.76; N, 11.92.

**4f:** 89%; mp 145-146 °C; $^1$H NMR (DMSO-$d_6$) δ 9.19 (s, 1H, NH), 7.27 (d, 1H, *J*=8.4, ArH), 6.40 (q, 1H, *J*=7.5, ArH), 6.24 (s, 1H, ArH), 5.26 (s, 2H, $NH_2$), 4.54 (q, 1H, *J*=6.3, CH), 2.35 (s, 3H, $CH_3$), 1.76 (d, 3H, *J*=8.8, $CH_3$). Anal. Calcd for $C_{10}H_{13}N_2OCl$: C, 56.47; H, 6.12; N, 13.18. Found: C, 56.55; H, 6.08; N, 13.27.

**4g:** 83%; mp 96-97 °C; $^1$H NMR (DMSO-$d_6$) δ 9.35 (s, 1H, NH), 7.47 (d, 1H, *J*=1.2, ArH), 7.26 (s, 1H, ArH), 6.87 (d, 1H, *J*=8.4, ArH), 5.41 (s, 2H, $NH_2$), 4.58 (q, 1H, *J*=8.7, CH), 2.57 (t, 2H, *J*=6.5, $CH_2$), 1.78 (d, 3H, *J*=9.2, $CH_3$), 1.59 (m, 2H, $CH_2$), 1.29 (m, 2H, $CH_2$), 0.89 (t, 3H, *J*=5.3, $CH_3$). Anal. Calcd for $C_{13}H_{19}N_2OCl$: C, 61.30; H, 7.47; N, 11.00. Found: C, 61.38; H, 7.40; N, 10.95.

**4h:** 85%; mp 137-138 °C; $^1$H NMR (DMSO-$d_6$) δ 9.50 (s, 1H, NH), 7.28 (d, 1H, *J*=2.0, ArH), 6.71 (q, 1H, *J*=5.1, ArH), 6.04 (d, 1H, *J*=8.8, ArH), 5.17 (s, 2H, $NH_2$), 4.58 (q, 1H, *J*=7.7, CH), 3.75 (s, 3H, $CH_3$), 1.75 (d, 3H, *J*=7.2, $CH_3$). Anal. Calcd for $C_{10}H_{13}N_2O_2Cl$: C, 52.52; H, 5.69; N, 12.25. Found: C, 52.48; H, 5.76; N, 12.29.

**4i:** 90%; mp 164-165 °C; $^1$H NMR (DMSO-$d_6$) δ 9.68 (s, 1H, NH), 7.29 (d, 1H, *J*=2.8, ArH), 7.06 (d, 1H, *J*=3.6, ArH), 6.98 (q, 1H, *J*=7.1, ArH), 5.26 (s, 2H, $NH_2$), 4.58 (q, 1H, *J*=6.3, CH), 4.04 (q, 2H, *J*=3.4, $CH_2$), 1.69 (d, 3H, *J*=7.2, $CH_3$), 1.33 (t, 3H, *J*=8.9, $CH_3$). Anal. Calcd for $C_{11}H_{15}N_2O_2Cl$: C, 54.43; H, 6.19; N, 11.55. Found: C, 54.38; H, 6.25; N, 11.64.

**4j:** 86%; mp 140-141 °C; $^1$H NMR (DMSO-$d_6$) δ 9.56 (s, 1H, NH), 7.07 (s, 1H, ArH), 6.12 (s, 1H, ArH), 5.28 (s, 2H, $NH_2$), 4.54 (q, 1H, *J*=7.5, CH), 2.39 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 1.76 (d, 3H, *J*=8.4, $CH_3$). Anal. Calcd for $C_{11}H_{15}N_2OCl$: C, 58.28; H, 6.62; N, 12.36. Found: C, 58.27; H, 6.70; N, 12.41.

**5:** A mixture of **4** (3.88 mmol), NaI·$2H_2O$ (301 mg, 1.62 mmol) and $NaHCO_3$ (546 mg, 6.50 mmol) in 50 mL of acetonitrile was refluxed for about 15 h. After cooling to rt, the solvent was removed under reduced pressure and the residue was stirred in water (100 mL) for 10 min. The resulting suspension was acidified with 2*N* HCl to pH=5~6. The pale gray solid was collected by filtration then washed successively with water (2×20 mL), dried in *vacuo* to give the crude product which was purified by flash column chromatography (ethyl acetate: petroleum ether = 2:3, v/v) as pale yellow solid. The solid was recrystallized from ethyl acetate to give the target compound (**5**).

**5a:** 55%; mp 243-244 °C; $^1$H NMR (DMSO-$d_6$) δ 10.33 (s, 1H, NH), 6.67 (d, 1H, *J*=8.4, ArH), 6.65 (d, 1H, *J*=2.0, ArH), 6.57 (q, 1H, *J*=7.6, ArH), 6.21 (s, 1H, NH), 3.74 (m, 1H, CH), 1.43 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_9N_2OCl$: C, 54.96; H, 4.58; N, 14.25. Found: C, 54.88; H, 4.60; N, 14.33.

**5b:** 52%; mp 211-212 °C; $^1$H NMR (DMSO-$d_6$) δ 10.35 (s, 1H, NH), 7.95 (s, 1H, ArH), 7.70 (d, 1H, *J*=8.4, ArH), 7.25 (d, 1H, *J*=8.8, ArH), 6.27 (s, 1H, NH), 3.74 (m, 1H, CH), 1.44 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_9N_2OBr$: C, 44.83; H, 3.74; N, 11.62. Found: C, 44.91; H, 3.76; N, 11.59.

**5c:** 48%; mp 252-253 °C; $^1$H NMR (DMSO-$d_6$) δ 10.30 (s, 1H, NH), 7.40 (q, 1H, *J*=7.7, ArH), 6.25 (m, 1H, ArH), 6.17 (q, 1H, *J*=7.6, ArH), 6.08 (s, 1H, NH), 3.71 (m, 1H, CH), 1.48 (s, 3H, $CH_3$). Anal. Calcd for $C_{11}H_{14}N_2OClF$: C, 60.00; H, 5.00; N, 15.56. Found: C, 60.03; H, 4.91; N, 15.60.

**5d:** 36%; mp 273-274 °C; $^1$H NMR (DMSO-$d_6$) δ 10.23 (s, 1H, NH), 7.31 (s, 1H, ArH), 6.52 (s, 1H, ArH), 6.12 (s, 1H, NH), 3.74 (m, 1H, CH), 2.38 (d, 3H, *J*=4.8, $CH_3$), 1.23 (d, 3H, *J*=4.8, $CH_3$). Anal. Calcd for $C_{10}H_{11}N_2OCl$: C, 57.01; H, 5.23; N, 13.30. Found: C, 57.02; H, 5.27; N, 13.19.

**5e:** 47%; mp 221-222 °C; $^1$H NMR (DMSO-$d_6$) δ 10.28 (s, 1H, NH), 6.68 (q, 1H, *J*=7.6, ArH), 6.62 (q, 1H, *J*=7.8, ArH), 6.23 (s, 1H, NH), 3.73 (m, 1H, CH), 1.42 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_8N_2OF_2$: C, 54.55; H, 4.04; N, 14.14. Found: C, 54.62; H, 3.96; N, 14.10.

**5f:** 45%; mp 182-183 °C; $^1$H NMR (DMSO-$d_6$) δ 10.34 (s, 1H, NH), 7.57 (s, 1H, ArH), 7.36 (q, 1H, *J*=7.2, ArH), 7.19 (d, 1H, *J*=8.0, ArH), 6.23 (s, 1H, NH), 3.72 (m, 1H, CH), 2.37 (s, 3H, $CH_3$), 1.42 (t, 3H, *J*=5.8, $CH_3$). Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.18; H, 6.82; N, 15.91. Found: C, 68.11; H, 6.85; N, 15.82.

**5g:** 82%; mp 157-158 °C; $^1$H NMR (DMSO-$d_6$) δ 10.28 (s, 1H, NH), 7.58 (d, 1H, *J*=1.6, ArH), 7.40 (q, 1H, *J*=7.4, ArH), 7.23 (d, 1H, *J*=8.4, ArH), 6.22 (s, 1H, NH), 3.74 (m, 1H, CH), 2.66 (t, 2H, *J*=6.4, $CH_2$), 1.59 (m, 2H, $CH_2$), 1.43 (s, 3H, $CH_3$), 1.31 (q, 2H, *J*=4.8, $CH_2$), 0.90 (t, 3H, *J*=6.1, $CH_3$). Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.56; H, 8.26; N, 12.84. Found: C, 71.48; H, 8.33; N, 12.92.

**5h:** 50%; mp 260-261 °C; $^1$H NMR (DMSO-$d_6$) δ 10.30 (s, 1H, NH), 7.28 (d, 1H, *J*=8.8, ArH), 7.25 (s, 1H, ArH), 7.21 (d, 1H, *J*=8.8, ArH), 6.24 (s, 1H, NH), 3.83 (s, 3H, $CH_3$), 3.71 (m, 1H, CH), 1.44 (s, 3H,

$CH_3$). Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.50; H, 6.25; N, 14.58. Found: C, 62.47; H, 6.32; N, 14.66.

**5i:** 56%; mp 275-276 °C; $^1$H NMR (DMSO-$d_6$) δ 10.32 (s, 1H, NH), 7.27 (s, 1H, ArH), 7.23 (s, 1H, ArH), 7.20 (d, 1H, *J*=8.4, ArH), 6.22 (s, 1H, NH), 4.09 (q, 2H, *J*=7.7, $CH_2$), 3.72 (m, 1H, CH), 1.43 (s, 3H, $CH_3$), 1.29 (t, 3H, *J*=6.4, $CH_3$). Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 64.11; H, 6.71; N, 13.59.

**5j:** 53%; mp 294-295 °C; $^1$H NMR (DMSO-$d_6$) δ 10.22 (s, 1H, NH), 6.48 (s, 1H, ArH), 6.43 (s, 1H, ArH), 6.24 (s, 1H, NH), 2.03 (s, 6H, $2CH_3$), 1.41 (s, 3H, $CH_3$). Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.47; H, 7.37; N, 14.74. Found: C, 69.52; H, 7.44; N, 14.62.

**6:** To a stirred solution of **5** (1 mmol) in 5% aqueous NaOH solution (10 mL) were added 30% $H_2O_2$ (1 mL, 32.6 mmol) and $H_2O$ (2 mL). The solution was stirred at 60 °C for 6 h. After the reaction mixture was cooled to rt, the solid was collected by filtration then washed with water (5 mL), dried in *vacuo* to afford the crude product which was purified by flash column chromatography (ethyl acetate: petroleum ether = 2:3, v/v) as white solid. The solid was recrystallized from acetone/petroleum ether (4:1) to give the target compound (**6**).

**6a:** 62%; mp 264-265 °C; $^1$H NMR (DMSO-$d_6$) δ 12.33 (s, 1H, NH), 7.65 (d, 1H, *J*=2.4, ArH), 7.45 (q, 1H, *J*=9.0, ArH), 7.23 (d, 1H, *J*=8.8, ArH), 2.37 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_7N_2OCl$: C, 55.53; H, 3.60; N, 14.40. Found: C, 55.48; H, 3.69; N, 14.33.

**6b:** 76%; mp 256-257 °C; $^1$H NMR (DMSO-$d_6$) δ 12.37 (s, 1H, NH), 7.86 (d, 1H, *J*=2.4, ArH), 7.61 (q, 1H, *J*=8.1, ArH), 7.21 (d, 1H, *J*=8.8, ArH), 2.40 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_7N_2OBr$: C, 45.21; H, 2.93; N, 11.72. Found: C, 45.28; H, 2.85; N, 11.81.

**6c:** 88%; mp 274~275 °C; $^1$H NMR (DMSO-$d_6$) δ 12.34 (s, 1H, NH), 7.48 (d, 1H, *J*=9.2, ArH), 7.35 (t, 1H, *J*=8.4, ArH), 7.26 (d, 1H, *J*=4.4, ArH), 2.38 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_7N_2OF$: C, 60.67; H, 3.93; N, 15.73. Found: C, 60.59; H, 4.00; N, 15.80.

**6d:** 75%; mp 293 °C (decomp); $^1$H NMR (DMSO-$d_6$) δ 12.19 (s, 1H, NH), 7.63 (s, 1H, ArH), 7.24 (s, 1H, ArH), 2.37 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$). Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.55; H, 4.32; N, 13.43. Found: C, 57.63; H, 4.39; N, 13.31.

**6e:** 60%; mp 318 °C (decomp); $^1$H NMR (DMSO-$d_6$) δ 12.34 (s, 1H, NH), 7.74 (q, 1H, *J*=8.7, ArH), 7.14 (q, 1H, *J*=5.4, ArH), 2.34 (s, 3H, $CH_3$). Anal. Calcd for $C_9H_6N_2OF_2$: C, 55.10; H, 3.06; N, 14.29. Found: C, 55.06; H, 3.13; N, 14.37.

**6f:** 93%; mp 258-259 °C; $^1$H NMR (DMSO-$d_6$) δ 12.19 (s, 1H, NH), 7.48 (s, 1H, ArH), 7.28 (q, 1H, *J*=8.8, ArH), 7.16 (d, 1H, *J*=8.4, ArH), 2.38 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.97; H, 5.75; N, 16.09. Found: C, 69.03; H, 5.81; N, 15.98.

**6g:** 73%; mp 163-164 °C; $^1$H NMR (DMSO-$d_6$) δ 12.20 (s, 1H, NH), 7.47 (d, 1H, *J*=1.2, ArH), 7.29 (q, 1H, *J*=9.0, ArH), 7.17 (d, 1H, *J*=8.4, ArH), 2.49 (m, 2H, $CH_2$), 2.37 (s, 3H, $CH_3$), 1.56 (m, 2H, $CH_2$),

1.28 (m, 2H, $CH_2$), 0.88 (t, 3H, *J*=7.0, $CH_3$). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.22; H, 7.41; N, 12.96. Found: C, 72.30; H, 7.35; N, 13.04.

**6h:** 83%; mp 254-255 °C; $^1$H NMR (DMSO-$d_6$) δ 12.17 (s, 1H, NH), 7.21 (d, 1H, *J*=3.2, ArH), 7.18 (s, 1H, ArH), 7.10 (q, 1H, *J*=8.7, ArH), 3.79 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.16; H, 5.26; N, 14.74. Found: C, 63.22; H, 5.18; N, 14.81.

**6i:** 78%; mp 238-239 °C; $^1$H NMR (DMSO-$d_6$) δ 12.16 (s, 1H, NH), 7.19 (d, 1H, *J*=2.8, ArH), 7.17 (d, 1H, *J*=3.6, ArH), 7.09 (q, 1H, *J*=8.3, ArH), 4.05 (q, 2H, *J*=6.3, $CH_2$), 2.38 (m, 3H, $CH_3$), 1.33 (m, 3H, $CH_3$). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.71; H, 5.88; N, 13.73. Found: C, 64.80; H, 5.96; N, 13.69.

**6j:** 76%; mp 276-277 °C; $^1$H NMR (DMSO-$d_6$) δ 12.13 (s, 1H, NH), 7.45 (s, 1H, ArH), 7.01 (s, 1H, ArH), 2.35 (s, 3H, $CH_3$), 2.29 (m, 3H, $CH_3$), 2.26 (m, 3H, $CH_3$). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.17; H, 6.43; N, 14.95.

**7:** To a stirred solution of **6** (1 mmol) in tetrahydrofuran (15 mL) were added 50% NaH (96 mg, 2 mmol) and $CH_3I$ (283.8 mg, 2 mmol) successively, the resulting solution was stirred at rt for 10~12 h. Evaporation of solvents and the crude product was purified by flash column chromatography (ethyl acetate:petroleum ether =2:3, v/v) as pale gray solid. The solid was recrystallized from ethyl acetate/petroleum ether (3:1) to afford the final compound (**7**).

**7a:** 65%; mp 147-148 °C; $^1$H NMR ($CDCl_3$) δ 2.58 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 7.19~7.24 (m, 1H, ArH), 7.45~7.48 (m, 1H, ArH), 7.79 (d, 1H, *J*=2.4, ArH); IR: 1647.8(C=O), 1589.3 (C=N). Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.55; H, 4.32; N, 13.43. Found: C, 57.66; H, 4.29; N, 13.50.

**7b:** 64%; mp 171-172 °C; $^1$H NMR ($CDCl_3$) δ 2.62 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 7.16 (d, 1H, *J*=8.8, ArH), 7.60~7.63 (m, 1H, ArH), 8.02 (d, 1H, *J*=2.4, ArH); IR: 1660.1 (C=O), 1597.4 (C=N). Anal. Calcd for $C_{10}H_9N_2OBr$: C, 47.43; H, 3.56; N, 11.07. Found: C, 47.49; H, 3.40; N, 11.19.

**7c:** 70%; mp 152-153 °C; $^1$H NMR ($CDCl_3$) δ 2.58 (s, 3H, $CH_3$), 3.68 (s, 3H, $CH_3$), 7.23~7.26 (m, 2H, ArH), 7.47~7.50 (m, 1H, ArH); IR: 1644.3 (C=O), 1599.7 (C=N). Anal. Calcd for $C_{10}H_9N_2OF$: C, 62.47; H, 4.69; N, 14.58. Found: C, 62.59; H, 4.83; N, 14.39.

**7d:** 66%; mp 176-177 °C; $^1$H NMR ($CDCl_3$) δ 2.44 (s, 3H, $CH_3$), 2.63 (s, 3H, $CH_3$), 3.66 (s, 3H, $CH_3$), 7.24 (s, 1H, ArH), 7.78 (s, 1H, ArH); IR: 1661.4 (C=O), 1590.4 (C=N). Anal. Calcd for $C_{11}H_{11}N_2OCl$: C, 59.33; H, 4.94; N, 12.58. Found: C, 59.45; H, 4.83; N, 12.66.

**7e:** 90%; mp 213-214 °C; $^1$H NMR ($CDCl_3$) δ 2.41 (s, 3H, $CH_3$), 3.57 (s, 3H, $CH_3$), 7.69~7.74 (m, 1H, ArH), 7.81~7.86 (m, 1H, ArH); IR: 1656.3 (C=O), 1591.1 (C=N). Anal. Calcd for $C_{10}H_8N_2OF_2$: C, 57.14; H, 3.81; N, 13.33. Found: C, 57.30; H, 3.93; N, 13.19.

**7f:** 93%; mp 115-116 °C; $^1$H NMR ($CDCl_3$) δ 2.43 (s, 3H, $CH_3$), 2.56 (s, 3H, $CH_3$), 3.66 (s, 3H, $CH_3$), 7.16 (d, *J*=8.4, 1H, ArH), 7.30~7.33 (m, 1H, ArH), 7.58 (s, 1H, ArH); IR: 1666.2 (C=O), 1597.1 (C=N). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 70.33; H, 6.47; N, 14.72.

**7g:** 67%; mp 67-68 °C; $^1$H NMR ($CDCl_3$) δ 0.89~0.93 (m, 3H, $CH_3$), 1.31~1.37 (m, 2H, $CH_2$), 1.59~1.67 (m, 2H, $CH_2$), 2.57 (s, 3H, $CH_3$), 2.67~2.71 (m, 2H, $CH_2$), 3.66 (s, 3H, $CH_3$), 7.18 (d, *J*=8.4, 1H, ArH), 7.31~7.34 (m, 1H, ArH), 7.59 (d, *J*=2.0, 1H, ArH); IR: 1664.8 (C=O), 1589.1 (C=N). Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.04; H, 7.83; N, 12.17. Found: C, 73.06; H, 7.88; N, 12.09.

**7h:** 77.5%; mp 150-151 °C; $^1$H NMR ($CDCl_3$) δ 2.57 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 3.86 (s, 3H, $CH_3$), 7.11~7.14 (m, 1H, ArH), 7.19 (d, *J*=9.2, 1H, ArH), 7.27 (d, *J*= 2.8, 1H, ArH); IR: 1640.7 (C=O), 1594.3 (C=N). Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.71; H, 5.88; N, 13.73. Found: C, 64.72; H, 5.74; N, 13.79.

**7i:** 85%; mp 140-141 °C; $^1$H NMR ($CDCl_3$) δ 1.41~1.45 (m, 3H, $CH_3$), 2.57 (s, 3H, $CH_3$), 3.67 (s, 3H, $CH_3$), 4.05~4.11 (m, 2H, $CH_2$), 7.10~7.13 (m, 1H, ArH), 7.19 (d, *J*=9.2, 1H, ArH), 7.25 (d, *J*=2.8, 1H, ArH); IR: 1643.5 (C=O), 1590.6 (C=N). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.06; H, 6.42; N, 12.84. Found: C, 66.19; H, 6.53; N, 12.69.

**7j:** 69%; mp 165-166 °C; $^1$H NMR ($CDCl_3$) δ 2.32 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$), 2.55 (s, 3H, $CH_3$), 3.65 (s, 3H, $CH_3$), 7.03 (s, 1H, ArH), 7.53 (s, 1H, ArH); IR: 1663.7 (C=O), 1610.0 (C=N). Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: C, 71.34; H, 6.88; N, 13.92.

**8:** A solution of **6e** (19.6 mg, 100 mmol) in 5 mL of phosphoryl chloride was heated under reflux for 1.5 h. Then the reaction mixture was freed from phosphoryl chloride by distillation under reduced pressure. The residue was diluted with ice water, and the aqueous mixture was neutralized with saturated aqueous solution of $NaHCO_3$. It was extracted with ethyl acetate, and the extract was washed with water (10 mL) and brine (10 mL) respectively, dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure, the crude product was recrystallized from ethyl acetate/petroleum ether (4:1) to give the solid product (**8**) as gray solid (17.1 mg, 79.8%). mp 255 °C (decomp); $^1$H NMR ($CDCl_3$): δ 2.54 (s, 3H, $CH_3$), 7.86 (q, 1H, *J*=11.6, ArH), 8.04 (q, 1H, *J*=11.6, ArH). Anal. Calcd for $C_9H_5N_2ClF_2$: C, 50.35; H, 2.33; N, 13.05. Found: C, 50.22; H, 2.41; N, 13.12.

**9:** To a stirred solution of **8** (21.5 mg, 100 mmol) in $CH_3OH$ (10 mL) was added fresh prepared $NaOCH_3$ (5.4 mg, 200 mmol). The resulting solution was stirred at rt for 1 h, and the solvent was removed under reduced pressure to give the crude product which was recrystallized from ethyl acetate/petroleum ether (2:3) to give the solid product (**9**) as white solid (11.1 mg, 52.6%).[5] mp 276-277 °C; Anal. Calcd for $C_{10}H_8N_2OF_2$: C, 57.14; H, 3.81; N, 13.33. Found: C, 57.20; H, 3.73; N, 13.41.

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