# Convenient Synthesis of 3,5-Biscarbamoyl-pyridine Derivatives

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An efficient and convenient method for synthesis of 3,5-bis-carbamoyl-2,6-dimethylpyridine derivatives was achieved in good to excellent yields by reaction of anilines with 3,5-bis(3',5'-dimethyl-1'-pyrazolyl-carbonyl)-2,6-dimethylpyridine, in which pyrazoles served as leaving groups. The structures of products were confirmed by spectra data and microanalysis.

**Keywords** heterocycles, amide, aromatic amine, synthesis

## Introduction

Since the discovery of nifedipine, which is a clinically important antihypertensive and antiangina drug, much attention has been paid to the transformations and modifications of substituted 1,4-dihydropyridines.[1] However, to the best of our knowledge, published data on the transformations and modifications of Hantzsch pyridines are lacking due to the difficulty of modification of 3,5-dialkoxycarbonyl groups simultaneously.[2] Furthermore, the compounds bearing carboxamide moieties have attracted the attention of organic chemists for quite a long time. For example, nicotinamide,[3] Linomide,[4] *etc*., all of them contain the carboxamide fragment. In terms of formation of carboxamides promoted by organometallic, recent elegant work by Buchwald[5] and Shakespeare[6] has demonstrated the palladium catalyzed *N*-arylation of amides with aryl halides, meanwhile, Hartwig[7] has also reported an analogous *N*-arylation of carbamates. However, there has been few report on the preparation of 3,5-bis[(arylamino)-carbonyl]-2,6-dimethylpyridine. Generally, the common access to the product consists of two methods. One involves oxidation of the corresponding 1,4-dihydropyridine derivatives, obtained form one-pot cyclization reaction of the corresponding acetoacetic acid amides with hexamethylenetetramine in the presence of ammonium acetate,[8] however, the present method poses the first problem due to the moderate yields of the prerequisite intermediates. The alternative way involves the modifications of alkoxycarbonyl groups at 3,5-position of pyridine,[2] however, no present work has been reported concerning the modification reaction of 3,5-dialkoxylcarbonyl simultaneously. Considering the importance of several pyridines bearing carboxamide fragment in medical chemistry, we are interested in developing synthetic methods for targeted compounds. In this work, we report a simple and convenient synthesis of these compounds involving the reaction of anilines with 1-acylated pyrazoles, in which the pyrazoles acted as leaving groups.

## Results and discussion

To begin with our studies, we firstly investigated the direct methods for preparation of target products. For example, we have carried out the reaction of 2,6-dimethyl-pyridine-3,5-dicarboxylic acid diethyl ester (**1**) with an excess of aniline[9] in ethanol under refluxing conditions by aminolysis, however, the expected product was not formed. Alternatively, the reaction of aniline with 2,6-dimethyl-pyridine-3,5-dicarbonyl dichloride, obtained form the reaction of 2,6-dimethyl-pyridine-3,5-dicarboxylic acid with $SOCl_2$,[10] was also investigated, unfortunately, the reaction afforded the desired product in lower yields.

It has been reported previously that 1-acylated pyrazoles were sensitive to nucleophilic reagent. Reaction of 1-acylated pyrazole derivatives with anilines gave the corresponding amide products in good to excellent yields, in which pyrazole rings acted as leaving groups.[11,12]

Inspired by the above-mentioned work, we shifted our attention to the reaction of aniline with 1-acylated

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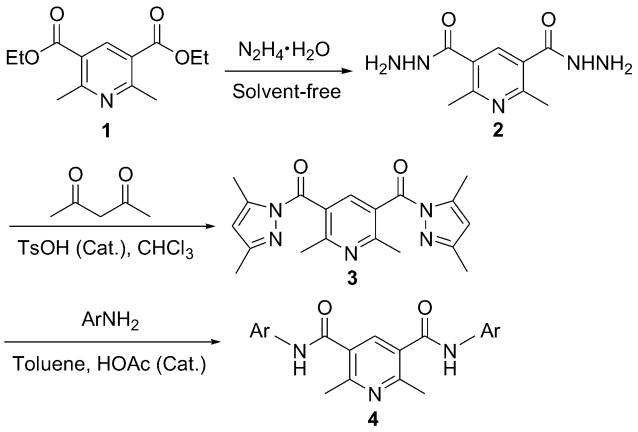
pyrazole derivatives. Thus, the compounds **3** were designed and synthesized in good to excellent yields by treatment of **1** with 85% hydrazine hydrate under the solvent-free conditions, followed by cyclization reaction of **2** with acetyl acetone in the presence of a catalytic amount of *p*-TsOH. Consequently, treatment of compounds **3** with anilines in refluxing toluene in the presence of a catalytic amount of acetic acid afforded the expected products **4** in good to excellent yields (Scheme 1).

**Scheme 1**




Investigation of the reaction scope revealed that various amines, both aliphatic and aromatic amines (bearing electron-withdrawing and electron-donating groups), can be utilized in this protocol. The reaction results were listed in Table 1. It has been observed that better yields were obtained with substrates having electron-donating groups. In the cases of *ortho*-substituted anilines the yields were slightly lower than *para*-substituted ones probably due to steric hindrance (Entries 3—5, 6—8, Table 1).

It was found that the catalyst played an important role in the reaction of **3** with the corresponding anilines. For example, in the absence of the catalyst, the completion of reaction needed 24 h in refluxing toluene as solvent. While using the catalyst such as *p*-TsOH or acetic acid, the reaction completed within 1 h under the same reaction conditions and afforded the corresponding products **4** in excellent yields. It was also observed that use of 10 mol% of HOAc was sufficient to push the reaction forward and 5 mol% of HOAc was not enough. Higher amounts of the catalyst did not further improve the yield of **4** significantly. Note that when the strong nucleophilic anilines such as 4-methoxyl-phenylamine was used as the substrates, the reaction proceeded smoothly and gave the corresponding product **4** within 1 h even though the reaction was carried out in the absence of catalyst. The similar results were observed

**Table 1** Reaction results of preparation of **4**[a]

| Entry | Ar | Reaction time/h | Product | Yield[b]/% |
|---|---|---|---|---|
| 1 | $C_6H_5$ | 1.5 | **4a** | 90 |
| 2 | 2-$NH_2C_6H_4$ | 1 | **4b** | 93 |
| 3 | 2-$CH_3C_6H_4$ | 1 | **4c** | 89 |
| 4 | 3-$CH_3C_6H_4$ | 1 | **4d** | 92 |
| 5 | 4-$CH_3C_6H_4$ | 1 | **4e** | 92 |
| 6 | 2-$ClC_6H_4$ | 1 | **4f** | 85 |
| 7 | 3-$ClC_6H_4$ | 1 | **4g** | 91 |
| 8 | 4-$ClC_6H_4$ | 1 | **4h** | 90 |
| 9 | 2-$BrC_6H_4$ | 1 | **4i** | 85 |
| 10 | 3-$BrC_6H_4$ | 1 | **4j** | 91 |
| 11 | 4-$BrC_6H_4$ | 1 | **4k** | 92 |
| 12 | 4-$FC_6H_4$ | 1 | **4l** | 89 |
| 13 | 2,4-$(F)_2C_6H_3$ | 1 | **4m** | 85 |
| 14 | 2-$CH_3OC_6H_4$ | 0.5 | **4n** | 86 |
| 15 | 4-$CH_3OC_6H_4$ | 0.5 | **4o** | 89 |
| 16 | 2-$C_2H_5OC_6H_4$ | 0.5 | **4p** | 92 |
| 17 | 2,4-$(CH_3)_2C_6H_3$ | 1 | **4q** | 91 |
| 18 | 1-Naphthyl | 2 | **4r** | 89 |
| 19 | Benzyl | 0.5 | **4s** | 95 |
| 20 | 3-$NO_2C_6H_4$ | 3 | **4t** | 59 |
| 21 | *n*-$C_4H_9$ | 0.5 | **4u** | 98 |

[a] Reaction conditions: **3** (1.0 mmol), amine (2.0 mmol), acetic acid (Cat. 0.1 mmol) in refluxing toluene (5.0 mL). [b] Isolated yields.

when the catalyst was shifted to *p*-TsOH. Meanwhile, the effect of solvent on the reaction efficiency and products was also screened. We observed that when the anilines with electron-donating groups were employed as the reaction substrates, the reaction could be carried out in refluxing ethanol instead of toluene as solvent. On the contrary, when the anilines with electron-withdrawing groups were used as substrates, the reaction must be carried out in refluxing toluene, otherwise, the major product obtained was the ethanolysis product along with a minor expected product **4**. This was attributed to the competition reaction between the ethanol and the aniline with weak nucleophilicity.

## Conclusions

In conclusion, we have developed an efficient and convenient method for synthesis of 3,5-bis-carbamoyl-pyridine derivatives in excellent yields. The key step in our synthetic sequence is the reaction of aniline with 1-acylated pyrazoles, in which pyrazoles served as the leaving groups. The shorter reaction time, easy work-up and high yields make this process attractive over the other available methods.

## Experimental

Melting points were uncorrected. IR spectra were recorded on AVATA 370 spectrometer (KBr). $^1$H NMR spectra were measured on a Bruker DM (500 MHz) spectrometer using TMS as internal standard. Mass spectra were determined on HP 5975-A instrument using the electron impact ionization technique (70 eV). Element analyses were measure on a Heraeus (CHNO, rapid) analyzer. 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethylester was synthesized according to the literature method.[13]

### Synthesis of 3.5-diethoxycarbonyl-2.6-dimethyl pyridine (1)

2,6-Dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethylester (0.01 mol) and sodium nitrite (0.02 mol) were dissolved in 35 mL of ethanol/water (5/2, *V*/*V*). To this solution was added dropwise acetic acid (0.02 mol). The reaction mixture was refluxed for 1 h. After removal of most of the ethanol solvent *in vacuo*, the precipitated solid material was filtered off, and washed with water for several times to give white solid **1** in 95% yield.

### Synthesis of 3,5-bis(hydrazino-carbonyl)-2,6-dimethylpyridine (2)

A mixture of **1** (0.01 mol) and hydrazine hydrate (0.04 mol) was refluxed for 6 h, then left to cool. The solid obtained was filtered off, dried and recrystallized from 80% ethanol to give **2** as white crystals in 85% yield.

### Synthesis of 3,5-bis(3',5'-dimethyl-1'-pyrazolyl-carbonyl)-2,6-dimethylpyridine (3)

A mixture of **2** (10.0 mmol), acetyl acetone (20.0 mmol) and a catalytic amount of TsOH (1.0 mmol) in $CHCl_3$ (12.0 mL) was refluxed for 2 h, the resultant solution was concentrated under reduced pressure, and the precipitate that formed was recrystallized from ethanol as a colorless solid in 90% yield.

### Typical procedure for synthesis of 3,5-bis[*N*-arylcarbamoyl]-2,6-dimethylpyridine (4)

To a mixture of **3** (1.0 mmol) and corresponding aniline (2.0 mmol) in 5.0 mL of toluene was added a catalytic amount of acetic acid (0.10 mmol). The resulting mixture was refluxed for 1 h, then left to cool. The solid obtained was filtered off, washed with ethanol and recrystallized from ethanol to afford pure products **4**.

**3,5-Bis[*N*-(phenyl)-carbamoyl]-2,6-dimethylpyridine (4a)** m.p. 290.5—290.8 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 7.13 (t, $J$=8 Hz, 2H), 7.36 (t, $J$=8 Hz, 4H), 7.72 (d, $J$=8 Hz, 4H), 8.03 (s, 1H), 10.45 (s, 2H); IR (KBr) $v$: 3283, 2966, 1654, 1545, 1497, 1321, 754, 690 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 345 ($M^+$, 18), 253 (100), 160 (46), 92 (54). Anal. calcd for $C_{21}H_{19}N_3O_2$: C 73.03, H 5.54, N 12.17; found C 73.09, H 5.50, N 12.17.

**3,5-Bis[*N*-(2-aminophenyl)-carbamoyl]-2,6-dimethylpyridine (4b)** m.p. >330 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.62 (s, 6H), 4.99 (s, 4H), 6.52 (t, $J$=8 Hz, 2H), 6.77 (d, $J$=8 Hz, 2H ), 6.97 (t, $J$=8 Hz, 2H), 7.26 (d, $J$=8 Hz, 2H), 8.20 (s, 1H), 9.66 (s, 2H); IR (KBr) $v$: 3435, 3245, 2968, 1643, 1603, 1497, 1456, 1306, 744 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 375 ($M^+$, 20), 239 (30), 160 (100), 107 (97). Anal. calcd for $C_{21}H_{21}N_5O_2$: C 67.18, H 5.64, N 18.65; found C 66.69, H 5.60, N 18.32.

**3,5-Bis[*N*-(2-methylphenyl)-carbamoyl-]2,6-dimethylpyridine (4c)** m.p. 179.8—179.9 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.29 (s, 6H), 2.64 (s, 6H), 7.15—7.29 (m, 6H), 7.43 (d, $J$=7.5 Hz, 2H), 8.08 (s, 1H), 9.96 (s, 2H); IR (KBr) $v$: 3242, 3035, 1684, 1640, 1554, 1309, 742 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 373 ($M^+$, 32), 267 (100), 160 (12), 106 (25). Anal. calcd for $C_{23}H_{23}N_3O_2$: C 73.97, H 6.21, N 11.25; found C 73.92, H 6.43, N 11.59.

**3,5-Bis[*N*-(3-methylphenyl)-carbamoyl]-2,6-dimethylpyridine (4d)** m.p. 252.7—253.2 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.30 (s, 6H), 2.59 (s ,6H), 6.92 (d, $J$=8 Hz, 4H), 7.23 (t, $J$=8 Hz, 2H), 7.51 (d, $J$=8 Hz, 2H), 7.99 (s, 1H), 10.36 (s, 2H); IR (KBr) $v$: 3249, 2920, 1645, 1564, 1322, 782, 689 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 373 ($M^+$, 50), 267 (100), 106 (25), 91 (18). Anal. calcd for $C_{23}H_{23}N_3O_2$: C 73.97, H 6.21, N 11.25; found C 74.24, H 6.16, N 11.34.

**3,5-Bis[*N*-(4-methylphenyl)-carbamoyl]-2,6-dimethylpyridine (4e)** m.p. 278.7—278.9 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.28 (s, 6H), 2.60 (s, 6H), 7.15 (d, $J$=8 Hz, 4H), 7.60 (d, $J$=8 Hz, 4H), 7.99 (s, 1H), 10.35 (s, 2H); IR (KBr) $v$: 3232, 2921, 1643, 1600, 1515, 1325, 815 cm$^{-1}$; MS (70 eV) *m*/*z* (%): 373 ($M^+$, 15), 267 (36), 149 (32), 105 (100). Anal. calcd for $C_{23}H_{23}N_3O_2$: C 73.97, H 6.21, N 11.25; found C 74.04, H 6.10, N 11.33.

**3,5-Bis[*N*-(2-chlorophenyl)-carbamoyl]-2,6-dimethylpyridine (4f)** m.p. 243.1—243.6 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.66 (s, 6H), 7.29 (t, $J$=8 Hz, 2H), 7.41 (t, $J$=8 Hz, 2H), 7.57 (d, $J$=8 Hz, 2H), 7.66 (d, $J$=8 Hz, 2H), 8.09 (s, 1H), 10.24 (s, 2H); IR (KBr) $v$: 3293, 1649, 1588, 1528, 1305, 764, 632 cm$^{-1}$; MS (70 eV) $m/z$ (%): 413 ($M^+$, 18), 378 (21), 287 (100), 91 (38). Anal. calcd for $C_{21}H_{17}Cl_2N_3O_2$: C 60.88, H 4.14, N 10.14; found C 61.08, H 4.10, N 10.10.

**3,5-Bis[*N*-(3-chlorophenyl)-carbamoyl]-2,6-dimethylpyridine (4g)** m.p. 268.7—269.5 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 7.17—7.20 (m, 2H), 7.41 (t, $J$=8 Hz, 2H), 7.61 (d, $J$=8 Hz, 2H), 7.94 (t, $J$=8 Hz, 2H), 8.08 (s, 1H,), 10.63 (s, 2H); IR (KBr) $v$: 3263, 1647, 1593, 1478, 1318, 783, 681 cm$^{-1}$; MS (70 eV) $m/z$ (%): 413 ($M^+$, 28), 287 (100), 106 (28). Anal. calcd for $C_{21}H_{17}Cl_2N_3O_2$: C 60.88, H 4.14, N 10.14; found C 61.22, H 4.12, N 10.17.

**3,5-Bis[*N*-(4-chlorophenyl)-carbamoyl]-2,6-dimethylpyridine (4h)** m.p. 286.1—287.9 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 7.43 (d, $J$=8 Hz, 4H), 7.77 (d, $J$=8 Hz, 4H), 8.07 (s, 1H), 10.58 (s, 2H); IR (KBr) $v$: 3231, 3041, 1644, 1596, 1551, 1319, 1090, 823 cm$^{-1}$; MS (70 eV) $m/z$ (%): 413 ($M^+$, 20), 378 (22), 287 (100), 91 (37). Anal. calcd for $C_{21}H_{17}Cl_2N_3O_2$: C 60.88, H 4.14, N 10.14; found C 60.75, H 4.09, N 10.09.

**3,5-Bis[*N*-(2-bromophenyl)-carbamoyl]-2,6-dimethylpyridine (4i)** m.p. 257.9—258.4 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 7.32—7.33 (m, 4H), 7.65 (d, $J$=7 Hz, 2H), 8.08 (d, $J$=7 Hz, 2H), 8.10 (s, 1H), 10.62 (s, 2H); IR (KBr) $v$: 3266, 1677, 1650, 1579, 1520, 1299, 744, 635 cm$^{-1}$; MS (70 eV) $m/z$ (%): 503 ($M^+$, 8), 422 (32), 331 (100), 106 (59). Anal. calcd for $C_{21}H_{17}Br_2N_3O_2$: C 50.13, H 3.41, N 8.35; found C 50.02, H 3.59, N 8.64.

**3,5-Bis[*N*-(3-bromophenyl)-carbamoyl]-2,6-dimethylpyridine (4j)** m.p. 302.0—302.1 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 7.30—7.35 (m, 4H), 7.65—7.66 (m, 2H), 8.08 (s, 2H), 8.09 (s, 1H), 10.62 (s, 2H); IR (KBr) $v$: 3231, 3074, 1647, 1589, 1674, 1317, 782, 681 cm$^{-1}$; MS (70 eV) $m/z$ (%): 503 ($M^+$, 8), 331 (100), 160 (23), 106 (45). Anal. calcd for $C_{21}H_{17}Br_2N_3O_2$: C 50.13, H 3.41, N 8.35; found C 50.35, H 3.39, N 8.37.

**3,5-Bis[*N*-(4-bromophenyl)-carbamoyl]-2,6-dimethylpyridine (4k)** m.p. 302.0—302.1 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.60 (s, 6H), 7.55 (d, $J$=9 Hz, 4H), 7.71 (d, $J$=9 Hz, 4H), 8.06 (s, 1H), 10.58 (s, 2H); IR (KBr) $v$: 3227, 1645, 1598, 1529, 1487, 1312, 1071, 821, 502 cm$^{-1}$; MS (70 eV) $m/z$ (%): 503 ($M^+$, 30), 331 (100), 160 (25), 106 (39). Anal. calcd for $C_{21}H_{17}Br_2N_3O_2$: C 50.35, H 3.41, N 8.35; found C 50.38, H 3.35, N 8.46.

**3,5-Bis[*N*-(4-fluorophenyl)-carbamoyl]-2,6-dimethylpyridine (4l)** m.p. 308.1—309.1 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.62 (s, 6H), 7.21 (t, $J$=9 Hz, 4H), 7.74—7.77 (m, 4H), 8.05 (s, 1H), 10.51 (s, 2H); IR (KBr) $v$: 3248, 3061, 1649, 1556, 1508, 1406, 1220, 833, 515 cm$^{-1}$; MS (70 eV) $m/z$ (%): 381 ($M^+$, 37), 271 (100), 106 (28). Anal. calcd for $C_{21}H_{17}F_2N_3O_2$: C 66.14, H 4.49, N 11.02; found C 66.10, H 4.46, N 10.98.

**3,5-Bis[*N*-(3,4-diflourophenyl)-carbamoyl]-2,6-dimethylpyridine (4m)** m.p. 274.2—274.8 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 7.43—7.46 (m, 4H), 7.88—7.93 (m, 2H,), 8.07 (s, 1H), 10.68 (s, 2H); IR (KBr) $v$: 3260, 1652, 1518, 1415, 1288, 856, 757 cm$^{-1}$; EI-MS $m/z$: 417 ($M^+$, 26), 289 (100), 106 (28). Anal. calcd for $C_{21}H_{15}F_4N_3O_2$: C 60.43, H 3.62, N 10.07; found C 60.60, H 3.59, N 9.92.

**3,5-Bis[*N*-(2-methoxyphenyl)-carbamoyl]-2,6-dimethylpyridine (4n)** m.p. 314.7—315.0 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.61 (s, 6H), 3.82 (s, 6H), 6.96—6.99 (m, 2H), 7.10 (d, $J$=8 Hz, 2H), 7.17—7.20 (m, 2H) 7.84 (d, $J$=8 Hz, 2H), 7.98 (s, 1H), 9.63 (s, 2H); IR (KBr) $v$: 3248, 2932, 1640, 1531, 1494, 1035, 741 cm$^{-1}$; MS (70 eV) $m/z$ (%): 405 ($M^+$, 51), 283 (100), 160 (26). Anal. calcd for $C_{23}H_{23}N_3O_4$: C 68.13, H 5.72, N 10.36; found C 67.72, H 5.65, N 10.20.

**3,5-Bis[*N*-(4-methoxyphenyl)-carbamoyl]-2,6-dimethylpyridine (4o)** m.p. 265.2—265.6 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.58 (s, 6H), 3.73 (s, 6H), 6.92 (dd, $J$=7, 2 Hz, 4H), 7.63 (dd, $J$=7, 2 Hz, 4H), 7.79 (s, 1H), 10.29 (s, 2H); IR (KBr) $v$: 3219, 2963, 1638, 1551, 1445, 1245, 1034, 829 cm$^{-1}$; MS (70 eV) $m/z$ (%): 405 ($M^+$, 49), 283 (100), 160 (21), 83 (33). Anal. calcd for $C_{23}H_{23}N_3O_4$: C 68.13, H 5.72, N 10.36; found C 68.08, H 5.66, N 10.44.

**3,5-Bis[*N*-(4-ethoxyphenyl)-carbamoyl]-2,6-dimethylpyridine (4p)** m.p. 248.8—249.5 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 1.33 (t, $J$=7 Hz, 6H), 2.60 (s, 6H), 4.01 (q, $J$=7 Hz, 4H), 6.91 (d, $J$=8 Hz, 4H), 7.62 (d, $J$=8 Hz, 4H), 7.99 (s, 1H), 10.29 (s, 2H); IR (KBr) $v$: 3220, 2928, 1638, 1596, 1512, 1477, 1243, 1115, 835 cm$^{-1}$; MS (70 eV) $m/z$ (%): 433 ($M^+$, 63), 297 (100), 160 (16). Anal. calcd for $C_{25}H_{27}N_3O_4$: C 69.27, H 6.28, N 9.69; found C 68.94, H 6.31, N 9.65.

**3,5-Bis[*N*-(2,4-dimethylphenyl)-carbamoyl]-2,6-dimethylpyridine (4q)** m.p. 301.6—301.8 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.23 (s, 6H), 2.29 (s, 6H), 2.64 (s, 6H), 6.98 (d, $J$=7.5 Hz, 2H), 7.14 (d, $J$=7.5 Hz, 2H), 7.26 (s, 2H), 8.04 (s, 1H) , 9.90 (s, 2H); IR (KBr) $v$: 3254, 1642, 1593, 1473, 1315, 786, 681 cm$^{-1}$; MS (70 eV) $m/z$ (%): 401 ($M^+$, 46), 281 (100), 160 (17), 120 (36). Anal. calcd for $C_{25}H_{27}N_3O_2$: C 74.49, H 6.78, N 10.47; found C 74.45, H 6.68, N 10.25.

**3,5-Bis[*N*-(1-naphthyl)-carbamoyl]-2,6-dimethylpyridine (4r)** m.p. >330 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.73 (s, 6H), 7.75—7.60 (m, 6H), 7.77 (d, $J$=7 Hz, 2H), 7.87 (d, $J$=8 Hz, 2H), 7.98—8.00 (m, 2H), 8.16 (d, $J$=8 Hz, 2H), 8.39 (s, 1H), 10.57 (s, 2H); IR (KBr) $v$: 3278, 2966, 1650, 1542, 1495, 1325, 758, 690 cm$^{-1}$; MS (70 eV) $m/z$ (%): 445 ($M^+$, 37), 303 (57), 142 (28). Anal. calcd for $C_{29}H_{23}N_3O_2$: C 78.78, H 5.20, N 9.43; found C 78.26, H 5.10, N 9.36.

**3,5-Bis[*N*-(benzoy)l-carbamoyl]-2,6-dimethylpyridine (4s)** m.p. 195.0 — 195.3 ℃; $^1$H NMR

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(DMSO-$d_6$, 500 MHz) $\delta$: 2.39 (s, 6H), 4.41 (d, $J$=5.5 Hz, 4H), 7.23—7.33 (m, 12H), 7.38 (s, 1H); IR (KBr) $v$: 3259, 2872, 1635, 1565, 1449, 1287, 1159, 724, 696 $cm^{-1}$; MS (70 eV) $m/z$ (%): 373 ($M^+$, 82), 267 (32), 240 (41), 91(100). Anal. calcd for $C_{23}H_{23}N_3O_2$: C 73.97, H 6.21, N 11.25; found C 73.84, H 6.19, N 10.97.

**3,5-Bis[*N*-(3-nitrophenyl)-carbamoyl]-2,6-dimethylpyridine (4t)** m.p. 284.5—284.6 ℃; $^1$H NMR (DMSO-$d_6$, 500 MHz) $\delta$: 2.64 (s, 6H), 7.67 (t, $J$=8 Hz, 2H), 7.98 (dd, $J$=8, 1 Hz, 2H), 8.07 (dd, $J$=8, 1 Hz, 2H), 8.19 (s, 1H), 8.78 (s, 2H), 10.95 (s, 2H); IR (KBr) $v$: 3283, 2966, 1654, 1545, 1497, 1321, 754, 690 $cm^{-1}$; MS (70 eV) $m/z$ (%): 435 ($M^+$, 26), 298 (100), 137 (29), 122 (56). Anal. calcd for $C_{21}H_{17}N_5O_6$: C 57.93, H 3.94, N 16.09; found C 58.06, H 3.98, N 15.84.

**3,5-Bis[*N*-(*n*-butyl)-carbamoyl]-2,6-dimethylpyridine (4u)** m.p. 182.6—183.6 ℃; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 0.96 (t, $J$=7.5 Hz, 6H), 1.37—1.45 (m, 4H), 1.56—1.62 (m, 4H), 2.56 (s, 6H), 3.40 (t, $J$=7.0 Hz, 4H), 6.44 (s, 2H), 7.5 (s, 1H); IR (KBr) $v$: 3268, 2961, 1634, 1569, 1440, 1296, 1164, 746, 646 $cm^{-1}$; MS (70 eV) $m/z$ (%): 305 ($M^+$, 35), 248 (17), 233 (100), 106 (30). Anal. calcd for $C_{17}H_{27}N_3O_2$: C 66.85, H 8.91, N 13.76; found C 67.39, H 8.92, N 13.59.

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