A New Thermal Study of The Reaction of 6-Azidopyridones With Different Amines and Hydrazines

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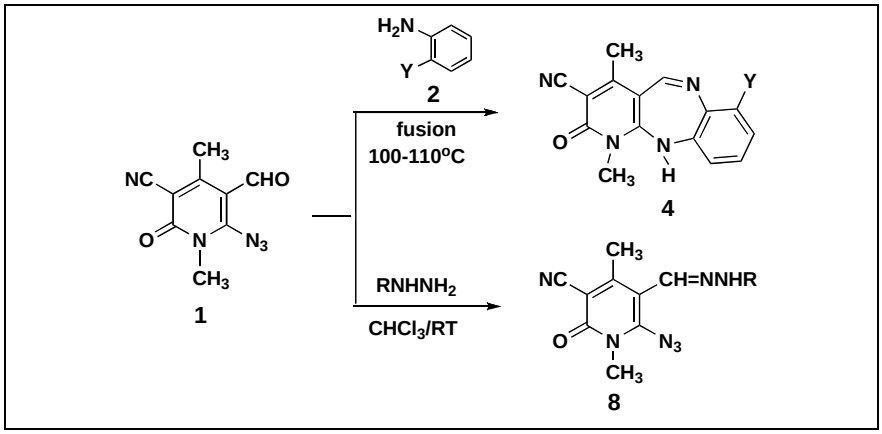

Reacting of 6-azidopyridone derivatives **1** with *o*-phenylenediamine (**2a**) in chloroform at room temperature afforded the new azidopyridones **3**. However, its fusion with **2a**,**b** at 100-110°C gave the interesting pyrido[2,3-*b*][1,5]diazepines **4a**,**b**. Alternatively, compound **4a** could also be obtained by heating azidopyridones **3** at 100-110°C. When compound **1** was allowed to react with hydrazines **7a-d** at room temperature it gave the corresponding azido compounds **8a-d**. Fusion of **1** with phenylhydrazine (**7d**) at 140-160°C afforded the new aminopyridones **10**. The 6-azidopyridones **1** could also be converted to the corresponding 6-alkylaminopyridones **15a-d** by reaction with an excess of alkylamines at room temperature.

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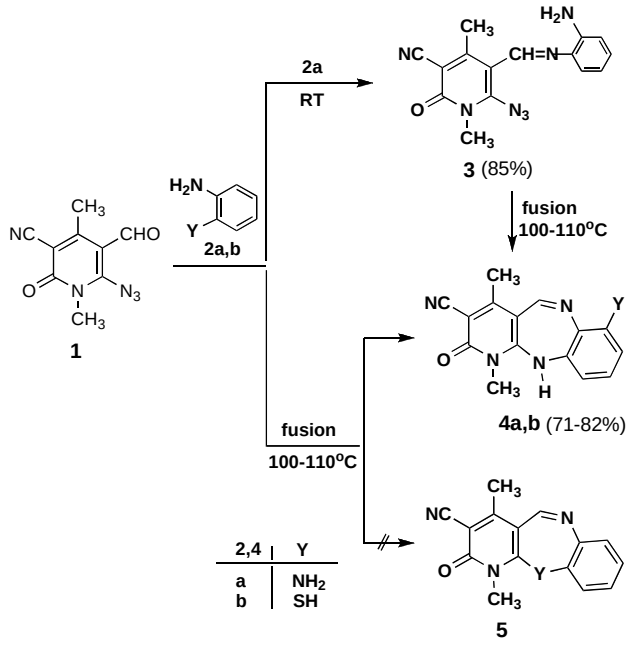
INTRODUCTION

Many pyridine compounds and their derivatives have recently occupied an important place in synthetic organic chemistry due to their pharmacological and therapeutic properities [1-5]. Moreover, 2-pyridones represent an important class of pyridine derivatives. A number of compounds with this substitution pattern are found in natural products with biological activity, such as *tenellin* [6] and *sambutoxin* [7]. In recent years, 2-pyridones have attracted considerable attention due to their promising features as an important core structure for the development of biologically active compounds [8]. In addition, pharmaceuticals with the 2-pyridone skeleton have emerged as antitumor, antifungal, antiviral, antithrombotic, antioxidant, antidiabetic and antimicrobial agents [9-14]. Owing to the importance of this class of heterocycle and also as part of our research program dealing with the synthesis of pharmacologically interesting new heterocycles, particulary those containing the pyridine moiety [15-19], herein we describe the first study on the reaction of 6-azidopyridones **1** [15] with aromatic and aliphatic amines and hydrazines in order to synthesize novel polyfunctionally substituted pyridines of expected significant biological activity, which are often difficult to obtain by alternative routes. Although a number of studies in the chemistry of azide compounds have been carried out [20-23], to the best of our knowledge, the title studies have not been reported so far.

RESULTS AND DISCUSSION

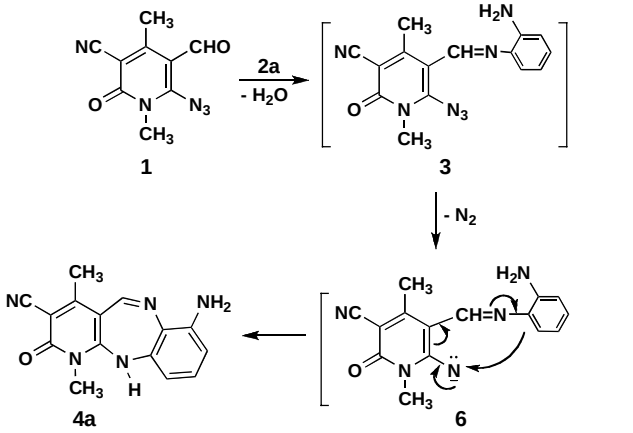
In our studies, we first investigated the reaction of 6-azidopyridones **1** with aromatic amines such as *o*-phenylenediamine (**2a**) and *o*-aminothiophenol (**2b**). Reaction of azidopyridones **1** with equimolar amount of *o*-phenylenediamine (**2a**), for example, in $CHCl_3$ for 1 h at room temperature gave the corresponding azidopyridones **3**. However, fusion of **1** with **2a,b** at 100-110°C for 10 min., did not give the expected tricycle **5**, but rather the previously unknown tricyclic system pyrido[2,3-*b*]-[1,5]benzodiazepines **4a,b**. Alternatively, compound **4a** could also be obtained by heating compound **3** at 100-110°C for 5 min. (Scheme 1). The structures of **4a,b** were confirmed as the reaction products from their IR, NMR and correct elemental analyses as well as mass spectra. Thus, for example, the IR spectrum of **4a** revealed the

Scheme 1



absence of the azido and aldehydic carbonyl groups and the presence of absorption bands at ν 3375 and 3200 cm^{-1} due to amino functions (NH, NH_2). The ^1H nmr spectrum of **4a** showed besides the signals due to aromatic and two methyl protons, three singlet signals at δ 7.54, 7.82 and 12.35 ppm attributable to NH_2, CH at C-5 and diazepine NH, respectively. Moreover, the structure of **4a** has been established by its ^{13}C nmr spectrum which showed signals at 164.70 (CO), 160.62 (C-4), 155.72 (C-5), 149.11 (C-7), 143.33 (C-11a), 140.04 (C-10a), 129.06 (C-9), 125.41(C-6a), 116.37 (C-4a), 115.42 (CN), 114.32 (C-3), 111.22 (C-10), 110.52 (C-8), 29.14 (N-CH_3), 20.19 (CH_3 at C-4). Furthermore, the mass spectrum this product shows the molecular ion m/z 279 (M^+, 100) and other peaks (see Experimental), confirming its presumed structure. Analytical data are in accordance with the proposed structure for compound **4a**. Formation of **4a** can be accounted for by condensation of **1** with **2a** to give the ring-opened intermediate **3**, with loss molecular nitrogen to give nitrene intermediate **6**. Subsequent intramolecular cyclization leads to the final product **4a** (Scheme 2).

Scheme 2

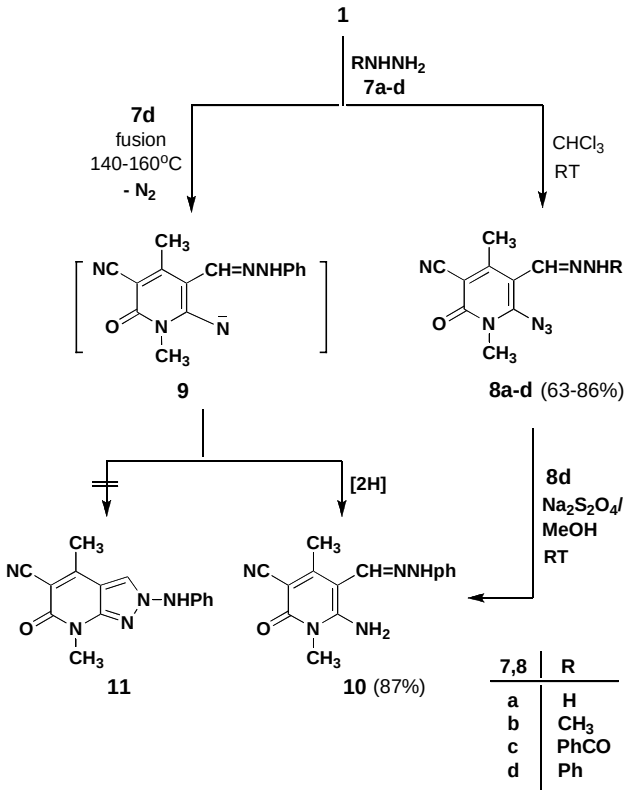


Attention was next turned to investigate the reactivity of azidopyridones **1** with some hydrazines at different temperature. At room temperature, the reaction of azidopyridones **1** with equimolar amounts of hydrazines **7a-d** in $CHCl_3$ for 2 h provided the corresponding new azido compounds **8a-d** in high yields (63-86%). However, when the reaction conditions were changed and azidopyridones **1** was treated with the same hydrazines under heating, we found that all trials to heat compound **1** with hydrazines **7a**,**b** were failed because a strong explosion happened at the beginning of heating. Moreover, our efforts to react **1** with **7c** at high temperature, whether in the absence or presence of solvent, were unsuccessful and gave a number of products which could not be isolated. Interestingly, heating equimolar amounts of **1** and phenylhydrazine (**7d**) at 140-160°C for 10 min. did not give the expected fused pyrazolopyridones **11**, instead the novel 6-aminopyridones **10** was formed as evidenced from spectral data. To obtain unequivocal evidence for the structure of compound **10**, it was alternatively synthesized from the azide **8d** by reduction of the azide moiety at C-6 in **8d** with sodium dithionite at room temperature. The mechanism of the formation of **10** from the reaction of **1** with **7d** is assumed to proceed *via* the formation of the azidopyridones **8d**, with loss one molecule of nitrogen to form the nitrene intermediate **9**, which then abstracts hydrogen, possibly from the hydrogen donor phenylhydrazine, to give the final product **10**, as depicted in Scheme 3.

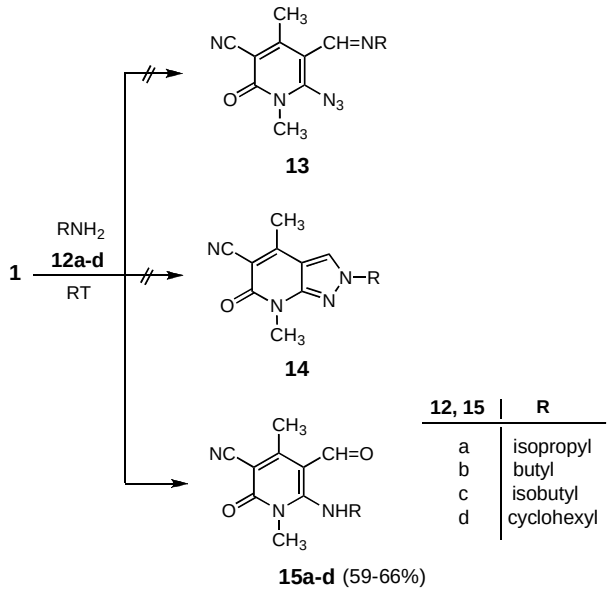
In conjunction with this study, we investigated the behavior of the reaction of azidopyridones **1** with primary alkyl amines. Treatment of compound **1** with an excess of alkylamines **12a-d** in EtOH at room temperature for 3 h afforded the hitherto unknown 6-alkylamino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitriles **15a-d**, which formed *via* the nucleophilic substitution of the azido group at pyridinic C-6 in **1** with amino group, in moderate and good yields (59-66%) (Scheme 4). Alternative uncyclized structure **13** could be eliminated on the basis of the disappearance of the azido signal and the presence of CHO and NH signals in the ir spectra, while ^1H nmr spectra, elemental analyses as well as mass spectra eliminated the linearly fused system **14**. The data used to characterize these prepared compounds **15a-d** are given in experimental.

In summary, we have presented for the first time, a novel, simple and one-pot synthetic method for the

Scheme 3



Scheme 4



construction of different multiple substituted pyridone derivatives, which might be used in many different areas. Furthermore, the above route is very convenient for its simplicity, the affordability of the starting materials and good yields obtained and opens the way for synthesis of new examples of pyridone compounds, which are scarcely represented in the literature. Further studies in our laboratory aimed at the synthesis of a wide variety of novel heterocycles containing the pyridine moiety, utilizing 6-azidopyridones as the starting material, are in progress.

EXPERIMENTAL

All melting points are uncorrected. ir spectra were recorded in KBr disks using a Schimadzu 470 spectrophotometer. Nmr spectra were recorded on Bruker AM 400 spectrometer at 400 MHz with DMSO-d_6 and $CDCl_3$ as solvents and tetramethylsilane (TMS) as an internal standards. Chemical shifts (δ) are reported in ppm downfield of TMS. Mass spectra were measured on a GCMS-QP1000EX mass spectrometer. Microanalyses were performed at the Microanalytical Data Unit, Cairo University.

5-[(2-Aminophenylimino)methyl]-6-azido-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (3). A mixture of **1** (0.217 g, 1 mmol) and *o*-phenylenediamine (**2a**) (0.108 g, 1 mmol) in $CHCl_3$ (5 ml) was stirred for 1 h at room temperature (25˚C). The resulting solid product was filtered off, dried and recrystallized from $CHCl_3$ to afford 0.260 g (85%) of **3** as reddish crystals, mp: 204-206˚C; ir (KBr): ν 3450, 3350 (NH_2), 2900 (aliph. CH), 2220 (CN), 2150 (N_3), 1645 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ 2.75 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 6.56 (s, 2H, NH_2), 6.62-7.01 (m, $4H_{arom}$), 8.81 (s, 1H, CH); ms: *m/z* 280 (M^{+1}-N_2, 100), 279 (M^+, 86), 265 (92), 250 (15), 119 (17), 105 (18), 92 (30), 76 (31). *Anal.* Calcd. for $C_{15}H_{13}N_7O$ (307.29): C, 58.63; H, 4.26; N, 31.90. Found: C, 58.47; H, 4.43; N, 31.79.

General procedure for the synthesis of 3-cyano-1,4-dimethyl-7-substituted-pyrido[2,3-*b*][1,5]benzodiazepin-2,6(1*H*,11*H*)-ones (4a,b). Route (A) for 4a,b: A mixture of **1** (0.217 g, 1 mmol) and **2a,b** (1 mmol) in $CHCl_3$ (5 ml) was heated for 10 min. at 100-110˚C. After cooling to room temperature, the resulting solid product was collected by filtration, washed with EtOH, dried and recrystallized from EtOH to afford **4a,b.**

Route (B) for compound 4a: Compound **3** (0.20 g, 0.65 mmol) was heated at 100-110˚C for 5 min. After cooling to room temperature, the mixture was treated with MeOH. The resulting solid product was collected by filtration and dried to afford **4a.**

7-Amino-3-cyano-1,4-dimethyl-pyrido[2,3-*b*][1,5]benzodiazepin-2,6(1*H*,11*H*)-ones (4a). This compound was obtained as brownish crystals, yield: [0.200 g (72%) (route A) and 0.150 g (82%) (route B)]; mp: 276-278˚C; ir (KBr): ν 3375, 3200 (NH, NH_2), 2200 (CN), 1640 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 3.43 (s, 3H, CH_3), 7.10-7.13 (m, $3H_{arom}$), 7.54 (br s, 2H, NH_2) 7.82 (s, 1H, CH), 12.35 (br s, 1H, NH); ms: *m/z* 281 (M^{+2}, 19), 280 (M^{+1}, 97), 279 (M^+, 100), 264 (57), 249 (5), 234 (9), 208 (4), 133 (2), 118 (9), 105 (5), 91 (6), 75 (3). *Anal.* Calcd. for $C_{15}H_{13}N_5O$ (279.28): C, 64.50; H, 4.69; N, 25.08. Found: C, 64.62; H, 4.87; N, 25.19.

3-Cyano-7-mercapto-1,4-dimethyl-pyrido[2,3-*b*][1,5]-benzodiazepin-2,6(1*H*,11*H*)-ones (4b). This compound was obtained as reddish crystals, yield: 0.210 g (71%); mp: 298-

300°C; ir (KBr): ν 3350 (NH), 2220 (CN), 1640 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.90 (s, 3H, CH_3), 3.47 (s, 3H, CH_3), 7.36-7.46 (m, $2H_{arom}$), 7.93 (d, $1H_{arom}$, J = 8 Hz), 8.02 (s, 1H, CH), 12.39 (br s, 1H, NH); ms: *m/z* 297 (M^{+1}, 29), 296 (M^+, 99), 281 (100), 264 (30), 238 (7), 148 (15), 136 (10), 135 (8), 121 (5), 108 (14), 76 (10), 57 (41). *Anal.* Calcd. for $C_{15}H_{12}N_4OS$ (296.33): C, 60.79; H, 4.08; N, 18.90; S, 10.82. Found: C, 60.72; H, 4.19; N, 18.79; S, 10.69.

General procedure for the synthesis of 5-arylhydrazonomethyl-6-azido-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitriles (8a-d). A mixture of **1** (0.217 g, 1 mmol) and hydrazines **7a-d** (1 mmol) in $CHCl_3$ (5ml) was stirred for 2 h at room temperature (25°C). The resulting solid product was filtered off, dried and recrystallized from $CHCl_3$ to afford **8a-d**. It should be noticed that the reaction of compound **1** with hydrazines **7** under heating may be explosive.

6-Azido-5-hydrazonomethyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (8a). This compound was obtained as reddish crystals, yield: 0.150 g (65%); mp: 210-212°C (dec.); ir (KBr): ν 3350, 3200 (NH_2), 2200 (CN), 2150 (N_3), 1640 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 8.75 (s, 1H, CH), 10.00 (s, 2H, NH_2). *Anal.* Calcd. for $C_9H_9N_7O$ (231.20): C, 46.75; H, 3.92; N, 42.40. Found: C, 46.63; H, 3.78; N, 42.52.

6-Azido-5-methylhydrazonomethyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (8b). This compound was obtained as reddish crystals, yield: 0.155 g (63%); mp: 230-232°C (dec.); ir (KBr): ν 3290 (NH), 2950, 2900 (aliph. CH), 2200 (CN), 2150 (N_3), 1660 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.32 (s, 3H, CH_3), 3.26 (d, 3H, J = 4 Hz, CH_3), 3.42 (s, 3H, CH_3), 8.56 (s, 1H, CH), 10.02 (br s, 1H, NH). *Anal.* Calcd. for $C_{10}H_{11}N_7O$ (245.23): C, 48.97; H, 4.52; N, 39.98. Found: C, 48.76; H, 4.65; N, 39.86.

6-Azido-5-benzoylhydrazonomethyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (8c). This compound was obtained as yellowish crystals; yield: 0.255 g (76%); mp: 250-252°C (dec.); ir (KBr): ν 3200 (NH), 3090 (arom. CH), 2200 (CN), 2150 (N_3), 1670 (CO), 1645 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.69 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 7.51-7.58 (m, $3H_{arom}$), 7.91 (d, $2H_{arom}$, J = 8 Hz), 8.68 (s, 1H, CH), 11.93 (s, 1H, NH). *Anal.* Calcd. for $C_{16}H_{13}N_7O_2$ (335.30): C, 57.31; H, 3.91; N, 29.24. Found: C, 57.26; H, 3.78; N, 29.34.

6-Azido-1,4-dimethyl-5-phenylhydrazonomethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (8d). This compound was obtained as yellow crystals, yield: 0.265 g (86%); mp: 190-192°C (dec.); ir (KBr): ν 3290 (NH), 2220 (CN), 2150 (N_3), 1635 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.60 (s, 3H, CH_3), 3.44 (s, 3H, CH_3), 6.63-7.98 (m, $5H_{arom}$), 8.29 (s, 1H, CH), 10.01 (s, 1H, NH); ms: *m/z* 281 (M^{+2} –N_2, 34), 267 (19), 190 (52), 119 (17), 106 (15), 105 (36), 93 (100), 92(56), 77 (63). *Anal.* Calcd. for $C_{15}H_{13}N_7O$ (307.29): C, 58.63; H, 4.26; N, 31.90. Found: C, 58.48; H, 4.39; N, 31.81.

6-Amino-1,4-dimethyl-5-phenylhydrazonomethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (10). Route (A): A mixture of **1** (0.217 g, 1 mmol) and **7d** (0.94 g, 1 mmol) was heated at 140-160°C for 10 min. After cooling to room temperature, the resulting solid product was collected by filtration, washed with EtOH, dried and recrystallized from EtOH to afford **10**.

Route (B): Sodium dithionite (0.40 g, 2.30 mmol) was added portionwise to a stirred solution of **8d** (0.20 g, 0.65 mmol) in MeOH (12 ml)-water (4 ml) mixture. Stirring was maintained at room temperature (25°C) for 5 h. Then, the reaction mixture was poured into water. The precipitated solid product was collected by filtration, washed well with water and dried to give [0.230 g (82%) (route A) and 0.160 (87%) (route B)] of **10** as yellow crystals, yield: mp: 278-280°C; ir (KBr): ν 3450, 3350, 3200 (NH, NH_2), 2220 (CN), 1640 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 3.35 (s, 3H, CH_3), 6.66 (t, $1H_{arom}$, J = 7 Hz), 6.90 (d, $2H_{arom}$, J = 8 Hz), 7.16 (t, $2H_{arom}$, J = 8 Hz), 7.57 (s, 2H, NH_2), 8.14 (s, 1H, CH), 10.07 (s, 1H, NH); ms: *m/z* 282 (M^{+1}, 92), 281 (M^+, 99), 265 (24), 190 (71), 189 (90), 146 (13), 135 (10), 119 (12), 93 (100), 92 (37), 77 (31). *Anal.* Calcd. for $C_{15}H_{15}N_5O$ (281.30): C, 64.04; H, 5.38; N, 24.89. Found: C, 64.18; H, 5.21; N, 24.76.

General procedure for the synthesis of 6-alkylamino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitriles (15a-d). Alkylamines **12a-d** (2 mmol) were added to a solution of compound 1 (0.217 g, 1 mmol) in dry EtOH and the mixture was stirred for 3 h at room temperature. The resulting solid product was collected by filtration, dried and recrystallized from EtOH to give compounds **15a-d.**

5-Formyl-6-isopropylamino-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (15a). This compound was obtained as yellow crystals; yield: 0.150 g (64%); mp: 202-204°C; ir (KBr): ν 3200 (NH), 2980, 2950 (aliph. CH), 2200 (CN), 1680 (CO), 1640 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.42 (d, 6H, J = 6 Hz, $2CH_3$), 2.44 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 3.75 (m, 1H, N-CH) 7.82 (d, 1H, J = 14 Hz, NH), 11.42 (s, 1H, CHO); ms: *m/z* 234 (M^{+1}, 70), 233 (M^+, 78), 218 (63), 190 (12), 175 (3), 146 (4), 58 (21), 57 (100). *Anal.* Calcd. for $C_{12}H_{15}N_3O_2$ (233.26): C, 61.79; H, 6.48; N, 18.01. Found: C, 61.87; H, 6.35; N, 18.23.

6-Butylamino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (15b). This compound was obtained as yellow crystals, yield: 0.155 g (63%); mp: 176-178°C. ir (KBr): ν 3200 (NH), 2950, 2900 (aliph. CH), 2200 (CN), 1670 (CO), 1640 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.95 (t, 3H, J = 7 Hz, CH_3), 1.45 (m, 2H, CH_2), 1.75 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.55 (q, 2H, J = 7 Hz, CH_2), 7.81 (dd, 1H, J = 13, 2 Hz, NH), 11.25 (s, 1H, CHO); ms: *m/z* 248 (M^{+1}, 55), 247 (M^+, 58), 218 (7), 205 (82), 204 (100), 190 (7), 176 (6), 146 (6), 71 (59), 57 (8), 56 (46). *Anal.* Calcd. for $C_{13}H_{17}N_3O_2$ (247.29): C, 63.14; H, 6.93; N, 16.99. Found: C, 63.30; H, 6.79; N, 16.84.

6-Isobutylamino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (15c). This compound was obtained as yellow crystals; yield: 0.145 g (59%); mp: 180-182°C; ir (KBr): ν 3300 (NH), 2970, 2900 (aliph. CH), 2200 (CN), 1670 (CO), 1640 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ 0.99 (d, 6H, J = 6 Hz, $2CH_3$), 1.95 (m, 1H, CH), 2.39 (s, 3H, CH_3), 3.30 (s, 3H, CH_3), 3.33 (t, 2H, J = 7 Hz, CH_2), 7.72 (t, 1H, J = 14 Hz, NH), 11.44 (s, 1H, CHO). *Anal.* Calcd. for $C_{13}H_{17}N_3O_2$ (247.29): C, 63.14; H, 6.93; N, 16.99. Found: C, 63.03; H, 7.02; N, 16.87.

6-Cyclohexylamino-5-formyl-1,4-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (15d). This compound was obtained as colorless crystals, yield: 0.180 g (66%); mp: 210-212°C; ir (KBr): ν 3400 (NH), 2950, 2850 (aliph. CH), 2200 (CN), 1680 (CO), 1640 (CO) cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.25-2.01 (m, $11H_{aliph}$), 2.44 (s, 3H, CH_3), 3.32 (s, 3H, CH_3), 7.82 (d, 1H, J = 13 Hz, NH,), 11.48 (s, 1H, CHO); ms: *m/z* 274 (M^{+1}, 47), 273 (M^+, 47), 230 (21), 191 (41), 190 (9), 175 (2), 160 (2), 146 (3), 120 (3), 97 (63), 83 (19), 55 (100). *Anal.* Calcd. for $C_{15}H_{19}N_3O_2$ (273.32): C, 65.91; H, 7.01; N, 15.37. Found: C, 65.82; H, 6.94; N, 15.48.

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