# A Rapid and Convenient Microwave-Promoted Synthesis of 3,5-Disubstituted 2-Chloropyridines and Their Conversion into Tetrazolo[1,5-*a*]pyridines

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**Abstract:** This work describes a rapid and convenient synthesis of 3,5-disubstituted 2-chloropyridines from various α,β-unsaturated ketoximes utilizing the Vilsmeier reaction under microwave irradiation. The 3,5-disubstituted 2-chloropyridines were further converted into tetrazolo[1,5-*a*]pyridines by a microwave-mediated solid-phase reaction. The products were isolated in good yields within a very short reaction time.

**Key words:** 2-chloropyridine, Vilsmeier reaction, tetrazolo[1,5-*a*]pyridine, microwave

The pyridine ring is ubiquitous in natural products having tremendous physiological properties.[1] In addition to naturally occurring pyridines, a large number of synthetic pyridines are known to possess numerous biological properties.[2] Among the substituted pyridines, 2-chloropyridine compounds find wide application both in pharmaceuticals[3] as well as in agrochemicals.[4] 2-Chloropyridine derivatives containing flavone, dihydropyrazole, or 1,3,4-oxadiazole units show potential telomerase inhibitors activity,[5] while some 2-chloropyridine derivatives exhibit antimalarial activity.[6] The presence of the chloro or bromo group at C2 of the pyridine ring opens up the possibility of a diverse range of functional group transformations, such as replacement with N-, O-, or S-containing nucleophiles[7a,b] or C–C bond formation by the Sonogashira coupling reaction[7c] or the Suzuki–Miyaura coupling reaction.[7d] 2-Chloropyridines are also used for nickel-mediated dimerization reactions for the synthesis of 2,2′-bipyridine ligands.[8] In addition, 2-chloropyridine derivatives are useful for the α-arylation of carbonyl compounds in the preparation of α-arylacetic acids, esters, and amides, and these are all common intermediates used in medicinal chemistry.[9]

On the other hand, tetrazolo[1,5-*a*]pyridines are an important class of aza heterocycle that have been utilized to synthesize a variety of heterocyclic compounds viz. cyanopyrroles, cyanopyrazoles, 2-aminopyridines, substituted 1,3-diazepines, and pyrido-2,3-furoxanes.[10] In addition, tetrazolo[1,5-*a*]pyridine derivatives act as sodium channel modulators and they may be used in the treatment of cardiovascular diseases and diabetes.[11] Fused tetrazolo[1,5-*a*]pyridine systems have been recently used as an azide surrogate in a click reaction for the efficient synthesis of 1,2,3-triazoles.[12]

Owing to their enormous biological potential, novel methods or modifications of existing synthetic methods for the synthesis of pyridines continue to be a subject of much attention for organic chemists. In one of our earlier attempts, we utilized benzylideneacetophenone oxime for the synthesis of 5-aryl-2-chloropyridine-3-carbaldehydes by Vilsmeier reaction under thermal conditions.[13] Although several methods are available for the synthesis of substituted pyridines,[14] the synthesis of 3,5-disubstituted 2-chloropyridines is obscure. To the best of our knowledge, no reports are available for the synthesis of 3-alkyl-2-chloropyridines by microwave-mediated Vilsmeier reaction; these compounds would find wide application in pharmaceuticals. For example, (2-chloro-5-phenylpyridin-3-yl)acetic acid derivatives (Figure 1) have antagonist properties on prostaglandin D2 receptors.[15] At the same time, despite the enormous potential of tetrazolo[1,5-*a*]pyridines, very few reports are available in the literature for their synthesis.[16] However, most conventional methods for the synthesis of tetrazolo[1,5-*a*]pyridines have disadvantages, such as longer reaction times and poor yields.

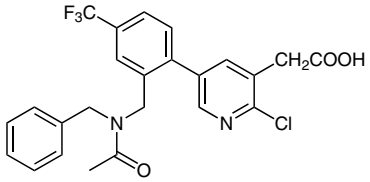


**Figure 1** Antagonists of prostaglandin D2 receptors

With these objectives and in continuation of our interest in the microwave-mediated synthesis of novel heterocycles,[17] herein, we report a new solvent-free, green strategy for the synthesis of 3-alkyl-5-aryl-2-chloropyridines utilizing the Vilsmeier reaction[18] with α,β-unsaturated ketoximes as the starting material under microwave irradiation. Furthermore, the 3-alkyl-5-aryl-2-chloropyridines were successfully converted into the corresponding tetrazolo[1,5-*a*]pyridines via a solid-phase reaction under microwave irradiation in moderate to good yields.

We began our study by investigating the reaction of 1-(*p*-tolyl)pent-1-en-3-one oxime (**1a**) with phosphoryl chloride and *N*,*N*-dimethylformamide under microwave irradiation without the use of chloroform as a solvent (Scheme 1). The typical reaction involved irradiating a

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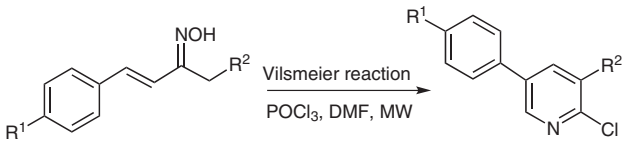


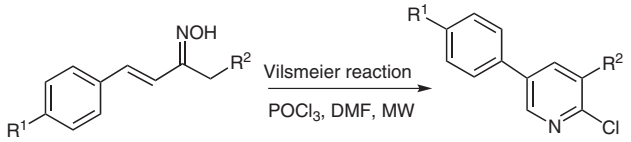

1a–k 2a–k

$R^1$ = H, Me, Cl
$R^2$ = H, Me, Et, *i*-Pr, $Me(CH_2)_4$, $Me(CH_2)_6$, CHO

**Scheme 1** Synthesis of 3,5-disubstituted 2-chloropyridines

mixture of phosphoryl chloride, *N*,*N*-dimethylformamide, and ketoxime **1** in the sealed vessel of a Synthos 3000 (Anton Paar) microwave reactor while maintaining the temperature and pressure (110 °C, 10 bar). Initially, the reaction was performed under conventional thermal conditions (110 °C) in order to compare the reaction rate and efficiency of the microwave-mediated reaction. We observed that the thermal reaction afforded poor yield of the product **2a** (41%) and took longer (2 h) compared to that obtained under microwave heating (96%, 3 min). Increasing the reaction time beyond two hours for the thermal reaction did not improve the yield of **2a**. This study showed that 3-alkyl-5-aryl-2-chloropyridines were best obtained under microwave irradiation within a few minutes.

**Table 1** Synthesis of 3-Alkyl-5-aryl-2-chloropyridines from α,β-Unsaturated Ketoximes via Microwave-Mediated Vilsmeier Reaction



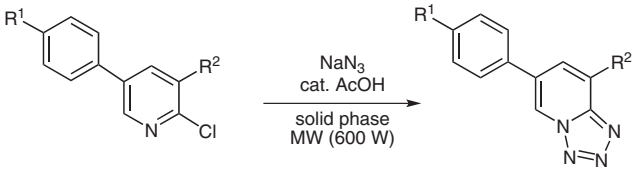

1a–k 2a–k

| Entry | $R^1$ | $R^2$ | Time (min) | Product | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | Me | Me | 3 | **2a** | 96 |
| 2 | Me | Et | 3 | **2b** | 95 |
| 3 | Me | *i*-Pr | 3 | **2c** | 92 |
| 4 | Me | $(CH_2)_4Me$ | 3 | **2d** | 91 |
| 5 | H | Me | 4 | **2e** | 88 |
| 6 | H | Et | 4 | **2f** | 88 |
| 7 | H | *i*-Pr | 4 | **2g** | 87 |
| 8 | H | $(CH_2)_4Me$ | 5 | **2h** | 81 |
| 9 | H | $(CH_2)_6Me$ | 5 | **2i** | 90 |
| 10 | Cl | Me | 8 | **2j** | 72 |
| 11 | Me | CHO[b] | 3 | **2k** | 72[c] |

[a] Referring to the amount of product isolated by chromatography.
[b] For **1k**, $R^2$ = H.
[c] For a previous synthesis of **2k**, see ref. 13.

In order to explore the scope and limitations of this methodology, the reaction was carried out with different ketoximes, **1b–j** by subjecting them to Vilsmeier reaction under identical conditions (Table 1). The α,β-unsaturated ketoximes **1a–j**, were readily obtained from the oximation of the condensation products of different aromatic aldehydes with aliphatic ketones. It was observed that 1-(*p*-tolyl)pent-1-en-3-one oximes **1a–d**, containing an electron-releasing substituent in the *para*-position of the aromatic ring, gave **2a–d** in enhanced 91–96% yields (entries 1–4), compared with 1-phenylpent-1-en-3-one oximes **1e–i** which gave **2e–i** in 81–90% yields (entries 5–9). 1-(3-Chlorophenyl)pent-1-en-3-one oxime (**1j**), with an electron-withdrawing substituent in the *para*-position of the aromatic ring, gave **2j** with a significantly lower 72% yield (entry 10).

**Table 2** Synthesis of Tetrazolo[1,5-*a*]pyridines




chloropyridines **2** tetrazolo[1,5-*a*] pyridines **3**

| Entry | Substrate | $R^1$ | $R^2$ | Time (min) | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|
| 1 | **2a** | Me | Me | 5 | **3a** | 88 |
| 2 | **2b** | Me | Et | 5 | **3b** | 87 |
| 3 | **2c** | Me | *i*-Pr | 7 | **3c** | 79 |
| 4 | **2d** | Me | $(CH_2)_4Me$ | 8 | **3d** | 62 |
| 5 | **2e** | H | Me | 5 | **3e** | 84 |
| 6 | **2f** | H | Et | 5 | **3f** | 80 |
| 7 | **2g** | H | *i*-Pr | 8 | **3g** | 78 |
| 8 | **2h** | H | $(CH_2)_4Me$ | 8 | **3h** | 72 |
| 9 | **2j** | Cl | Me | 8 | **3j** | 88 |
| 10 | **2k** | Me | CHO | 8 | **3k** | 88 |

[a] Referring to the amount of product isolated by chromatography.

With a variety of 3,5-disubstituted 2-chloropyridines **2a–k** in hand, we further explored the possible transformation of this chloro functionality to afford new tetrazolo[1,5-*a*]pyridines (Table 2). Thus, it was noteworthy to observe that finely ground equimolar amounts of 2-chloro-3-methyl-5-(*p*-tolyl)pyridine (**2a**), a catalytic amount of acetic acid, and sodium azide under microwave irradiation (80%) for five minutes afforded **3a** in 88% yield (entry 1). Interestingly, when the same reaction was performed initially under solvent-free conditions, with thermal heating (140 °C) for eight hours, the product **3a** was obtained in 29% yield. Similarly, the reaction of 2-chloropyridines **2b–h**,**j**,**k**[13] with sodium azide under microwave irradia-



tion afforded tetrazolo[1,5-*a*]pyridine derivatives **3b**–**h**,**j**,**k** in moderate to good yields (entries 2–10). As can be observed from Table 2, the bulky 3-substituted 2-chloropyridines **2d**,**h** gave the product tetrazolo[1,5-*a*]pyridines **3d**,**h** with a lower yields (entries 4 and 8). All of the 3-alkyl-5-aryl-2-chloropyridines and tetrazolo[1,5-*a*]pyridines were fully characterized using $^1$H NMR, $^{13}$C NMR, IR, and MS (EI) spectroscopic techniques.

A plausible mechanism has been proposed for the microwave-assisted synthesis of 3-alkyl-5-aryl-2-chloropyridines from different α,β-unsaturated ketoximes, utilizing the Vilsmeier reaction (Scheme 2).

In the presence of phosphoryl chloride, the α,β-unsaturated ketoxime initially undergoes Beckmann rearrangement to generate the enamide **A**. The enamide **A** reacts with the in situ generated chloromethyleneiminium salt (the Vilsmeier reagent), which then eliminates one molecule of HCl to afford presumably the intermediate **B**. The intermediate **B**, undergoes tautomerization followed by chlorination in presence of phosphoryl chloride to form the intermediate **C**. The in situ generated base $PO_2Cl_2^-$ then abstracts one of the methylene protons and on cyclization affords intermediate **D**. Finally, elimination of a molecule of dimethylamine provides 3-alkyl-5-aryl-2-chloropyridines **2** as the desired product.

In conclusion, we have developed a fast, convenient and high-yielding method for the synthesis of new 3,5-disubstituted 2-chloropyridines **2a**–**j** via the Vilsmeier reaction of various α,β-unsaturated ketoximes under microwave irradiation. Due to the hazardous/toxic solvent-free conditions and the use of microwave energy, this method can be considered as an green and environmentally benign protocol for the synthesis of 3,5-disubstituted 2-chloropyridines. Moreover, this method is significantly advantageous over a previously reported Vilsmeier reaction, where maintaining the reaction temperature at –5 °C to 0 °C was not necessary for the in situ generation of the chloromethyleneiminium salt (the Vilsmeier reagent), which is a prerequisite in all classical Vilsmeier reactions.[19] In addition, these newly synthesized compounds were converted into the corresponding tetrazolo[1,5-*a*]pyridines by microwave-mediated solid-phase reaction in presence of an acid catalyst in moderate to good yields.

Melting points were measured with a Buchi B-540 melting point apparatus and are uncorrected. IR spectra were recorded on Elmer FT-IR-2000 spectrophotometer using KBr pellets or on a thin film using $CHCl_3$. NMR spectra were recorded on Avance DPX 300 MHz FT-NMR spectrometer using TMS as an internal standard. Mass spectra were recorded on Trace DSQ GCMS instrument. All the commercially available regents were used as received. All experiments were monitored by TLC performed on pre-coated silica gel plates (Merck). Column chromatography was performed on silica gel (100–200 mesh, Merck). All microwave reactions were carried out in a Synthos 3000 (Anton Paar) microwave reactor.

**2-Chloro-Substituted 3-Alkyl-5-arylpyridines 2a–k; General Procedure**

$POCl_3$ (0.18 mL, 2.0 mmol), DMF (0.15 mL, 2.0 mmol), and the ketoxime (100 mg) were added to the sealed reaction vessel of a Synthos 3000 (Anton Paar) microwave reactor and microwave irradiated for 3–8 min, while maintaining the temperature at 110 °C and pressure at 10 bar. On completion of the reaction, the mixture was poured into ice-cold $H_2O$, neutralized with $NaHCO_3$, and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed several times with $H_2O$ and dried (anhyd $Na_2SO_4$); the solvent was removed in a rotavapor to obtain the crude product. The crude product was purified by column chromatography (EtOAc–hexane) to afford 3-alkyl-5-aryl-2-chloropyridines **2**.

**2-Chloro-3-methyl-5-(*p*-tolyl)pyridine (2a)**

Yellow crystalline solid; yield: 110 mg (96%); mp 115–118 °C.

IR (KBr): 2996, 1577, 1554, 1456, 1080, 823 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 2.4 Hz, 1 H), 7.72 (d, *J* = 2.5 Hz, 1 H), 7.47 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.1 Hz, 2 H), 2.43 (s, 3 H), 2.41 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 150.1, 145.0, 138.3, 137.6, 135.8, 133.7, 129.9, 129.3, 126.9, 21.2, 19.7.

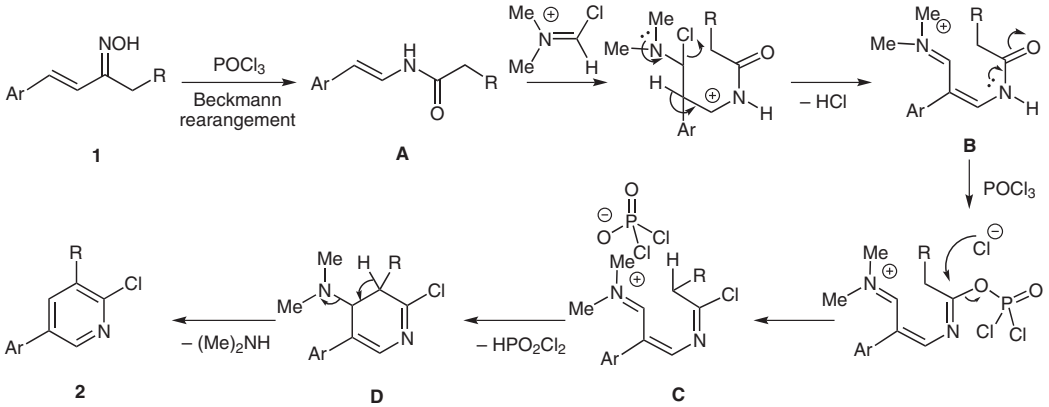
MS (EI): *m*/*z* = 217 $[M]^+$, 219 $[M^+ + 2]$.

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43. Found: C, 71.63; H, 5.45; N, 6.42.

**2-Chloro-3-ethyl-5-(*p*-tolyl)pyridine (2b)**

Yellow solid; yield: 108 mg (95%); mp 117–120 °C.

IR (KBr): 2994, 1575, 1553, 1454, 1080, 825 cm$^{-1}$.




**Scheme 2** Proposed mechanism for the synthesis of 3-alkyl-5-aryl-2-chloropyridines

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.43 (d, *J* = 2.4 Hz, 1 H), 7.72 (d, *J* = 2.3 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 2 H), 7.25 (d, *J* = 8.3 Hz, 2 H), 2.82 (q, *J* = 7.5 Hz, 2 H), 2.41 (s, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 149.7, 144.9, 138.3, 137.6, 136.2, 135.9, 133.8, 129.9, 129.5, 126.9, 126.6, 26.4, 21.2, 13.5.

MS (EI): *m*/*z* = 231 $[M]^+$, 233 $[M^+ + 2]$.

Anal. Calcd for $C_{14}H_{14}ClN$: C, 72.57; H, 6.09; N, 6.04. Found: C, 72.53; H, 5.99; N, 6.01.

**2-Chloro-3-isopropyl-5-(*p*-tolyl)pyridine (2c)**
Yellow solid; yield: 104 mg (92%); mp 123–126 °C.

IR (KBr): 2989, 1576, 1550, 1450, 1086, 825 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 2.5 Hz, 1 H), 7.75 (d, *J* = 2.4 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.24 (d, *J* = 8.2 Hz, 2 H), 3.39 (heptet, *J* = 6.9 Hz, 1 H), 2.41 (s, 3 H), 1.32 (d, *J* = 6.9 Hz, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 149.4, 144.9, 141.7, 138.3, 136.2, 134.1, 133.8, 129.9, 126.9, 30.1, 22.3, 21.2.

MS (EI): *m*/*z* = 245 $[M]^+$, 247 $[M^+ + 2]$.

Anal. Calcd for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.15; H, 6.32; N, 5.55.

**2-Chloro-3-pentyl-5-(*p*-tolyl)pyridine (2d)**
Orange gum; yield: 101 mg (91%).

IR ($CHCl_3$): 2997, 1571, 1554, 1455, 1082, 821 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 1.8 Hz, 1 H), 7.68 (d, *J* = 1.8 Hz, 1 H), 7.44 (d, *J* = 7.9 Hz, 2 H), 7.24 (d, *J* = 7.7 Hz, 2 H), 2.75 (t, *J* = 7.5 Hz, 2 H), 2.40 (s, 3 H), 1.74–1.60 (m, 2 H), 1.59–1.24 (m, 4 H), 0.92 (t, *J* = 6.5 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 149.8, 145.0, 143.7, 139.9, 138.8, 136.9, 133.8, 129.9, 126.9, 33.2, 31.5, 28.9, 22.5, 21.4, 14.2.

MS (EI): *m*/*z* = 273 $[M]^+$, 275 $[M^+ + 2]$.

**2-Chloro-3-methyl-5-phenylpyridine (2e)**
Pale yellow solid; yield: 102 mg (88%); mp 122–125 °C.

IR (KBr): 2997, 1577, 1553, 1453, 1082, 823 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 2.1 Hz, 1 H), 7.73 (d, *J* = 2.0 Hz, 1 H), 7.57–7.23 (m, 5 H), 2.44 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 150.4, 145.2, 138.6, 137.8, 136.6, 132.3, 129.1, 128.8, 126.6, 19.7.

MS (EI): *m*/*z* = 203 $[M]^+$, 205 $[M^+ + 2]$.

Anal. Calcd for $C_{12}H_{10}ClN$: C, 70.77; H, 4.95; N, 6.88. Found: C, 70.45; H, 4.89; N, 6.70.

**2-Chloro-3-ethyl-5-phenylpyridine (2f)**
Orange solid; yield: 101 mg (88%); mp 128–130 °C.

IR (KBr): 2997, 1575, 1554, 1453, 1084, 825 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.45 (d, *J* = 2.3 Hz, 1 H), 7.74 (d, *J* = 2.2 Hz, 1 H), 7.56–7.26 (m, 5 H), 2.81 (q, *J* = 7.5 Hz, 2 H), 1.30 (t, *J* = 7.5 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 150.0, 145.1, 137.6, 136.7, 136.4, 129.8, 129.7, 128.5, 127.3, 26.4, 13.7.

MS (EI): *m*/*z* = 217 $[M]^+$, 219 $[M^+ + 2]$.

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43. Found: C, 71.57; H, 5.35; N, 6.28.

**2-Chloro-3-isopropyl-5-phenylpyridine (2g)**
Orange gum; yield: 99 mg (87%).

IR ($CHCl_3$): 2994, 1575, 1555, 1456, 1082, 822 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 0.8 Hz, 1 H), 7.76 (d, *J* = 0.5 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 2 H), 7.32–7.22 (m, 3 H), 3.39 (heptet, *J* = 6.9 Hz, 1 H), 1.35 (d, *J* = 6.4 Hz, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 149.4, 144.7, 141.7, 138.4, 136.2, 134.1, 132.8, 129.2, 127.6, 23.3, 22.2.

MS (EI): *m*/*z* = 231 $[M]^+$, 233 $[M^+ + 2]$.

**2-Chloro-3-pentyl-5-phenylpyridine (2h)**
Orange gum; yield: 91 mg (81%).

IR ($CHCl_3$): 2986, 1573, 1558, 1457, 1086, 821 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 2.3 Hz, 1 H), 7.72 (d, *J* = 2.3 Hz, 1 H), 7.57–7.25 (m, 5 H), 2.76 (t, *J* = 7.6 Hz, 2 H), 1.75–1.62 (m, 2 H), 1.44–1.28 (m, 4 H), 0.9 (t, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 149.9, 144.9, 136.7, 136.4, 136.3, 128.9, 128.7, 128.5, 126.8, 33.0, 31.8, 29.1, 22.6, 14.1.

MS (EI): *m*/*z* = 259 $[M]^+$, 261 $[M^+ + 2]$.

**2-Chloro-3-heptyl-5-phenylpyridine (2i)**
Orange gum; yield: 100 mg (90%).

IR ($CHCl_3$): 2987, 1576, 1553, 1453, 1082, 822 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 2.4 Hz, 1 H), 7.70 (d, *J* = 2.4 Hz, 1 H), 7.60–7.22 (m, 5 H), 2.75 (t, *J* = 7.7 Hz, 2 H), 1.72–1.58 (m, 2 H), 1.47–1.28 (m, 8 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 150.1, 145.2, 137.1, 136.8, 136.6, 135.9, 132.8, 132.1, 129.1, 128.3, 127.1, 33.2, 31.8, 29.4, 29.3, 29.1, 22.7, 14.1.

MS (EI): *m*/*z* = 287 $[M]^+$, 289 $[M^+ + 2]$.

**2-Chloro-5-(4-chlorophenyl)-3-methylpyridine (2j)**
Orange gum; yield: 81 mg (72%).

IR ($CHCl_3$): 2997, 1576, 1554, 1456, 1082, 824 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 2.2 Hz, 1 H), 7.71 (d, *J* = 2.1 Hz, 1 H), 7.50–7.41 (m, 4 H), 2.45 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 150.8, 145.0, 137.6, 135.1, 134.7, 134.6, 132.5, 129.4, 128.3, 19.8.

MS (EI): *m*/*z* = 237 $[M]^+$, 239 $[M^+ + 2]$

**2-Chloro-5-(*p*-tolyl)pyridine-3-carbaldehyde (2k)**
Yellow gum; yield: 88 mg (72%).

IR ($CHCl_3$): 2929, 2859, 1689, 1561, 1458, 1042, 817 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 10.5 (s, 1 H), 8.81 (d, *J* = 2.6 Hz, 1 H), 8.39 (d, *J* = 2.6 Hz, 1 H), 7.50 (d, *J* = 8.1 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 2.43 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 189.4, 152.1, 151.8, 139.3, 136.6, 135.7, 132.3, 130.1, 128.4, 126.9, 21.2.

MS (EI): *m*/*z* = 231 $[M]^+$, 233 $[M^+ + 2]$.

**Tetrazolo[1,5-*a*]pyridines 3; General Procedure**
3,5-Disubstituted 2-chloropyridines **2** (0.30 mmol), $NaN_3$ (0.30 mmol), and AcOH (cat.) were intimately mixed with a pestle in a mortar and irradiated in a closed vessel in a Synthos 3000 microwave reactor at 600 W (140 °C and 21 bar) for 5–8 min. On completion of the reaction, the mixture was treated with $H_2O$ and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic extracts were washed several times with $H_2O$ and dried (anhyd $Na_2SO_4$); the solvent was removed on a rotavapor to obtain the crude product. This crude product on column chromatographic purification (silica gel, 100–200 mesh, Merck, EtOAc–hexane), afforded the tetrazolo[1,5-*a*]pyridines **3**.

**8-Methyl-6-(*p*-tolyl)tetrazolo[1,5-*a*]pyridine (3a)**
Yellow solid; yield: 59 mg (88%); mp 122–125 °C.

IR (KBr): 2958, 2849, 1628, 1545, 1489, 1049, 801 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.79 (d, *J* = 0.6 Hz, 1 H), 7.66 (s, 1 H), 7.51 (d, *J* = 8.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 2 H), 2.83 (s, 3 H), 2.46 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 139.4, 132.3, 131.5, 131.2, 130.2, 127.1, 126.7, 119.3, 21.2, 17.1.

MS (EI): *m*/*z* = 224 $[M]^+$, 196 $[M^+ - 28]$.

Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98. Found: C, 69.66; H, 5.44; N, 25.02

**8-Ethyl-6-(*p*-tolyl)tetrazolo[1,5-*a*]pyridine (3b)**
Yellow solid; yield: 62 mg (87%); mp 115–118 °C.

IR (KBr): 2962, 2857, 1627, 1560, 1483, 1081, 800 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.72 (s, 1 H), 7.58 (s, 1 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 3.17 (q, *J* = 7.5 Hz, 2 H), 2.37 (s, 3 H), 1.43 (t, *J* = 7.5 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 148.1, 135.4, 132.7, 131.6, 129.5, 129.3, 129.1, 127.3, 119.6, 24.6, 22.4, 13.2.

MS (EI): *m*/*z* = 238 $[M]^+$, 210 $[M^+ - 28]$.

Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.45; H, 5.88; N, 23.34

**8-Isopropyl-6-(*p*-tolyl)tetrazolo[1,5-*a*]pyridine (3c)**
Yellow solid; yield: 60 mg (79%); mp 127–132 °C.

IR ($CHCl_3$): 2961, 2876, 1625, 1564, 1487, 1079, 784 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.79 (s, 1 H), 7.64 (s, 1 H), 7.52 (d, *J* = 7.9 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 3.71 (heptet, *J* = 6.9 Hz, 1 H), 2.45 (s, 3 H), 1.53 (d, *J* = 6.9 Hz, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 147.6, 139.3, 137.1, 132.6, 131.5, 130.2, 127.4, 127.2, 119.2, 30.6, 21.9, 21.2.

MS (EI): *m*/*z* = 252 $[M]^+$, 224 $[M^+ - 28]$.

Anal. Calcd for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.21. Found: C, 70.68; H, 6.42; N, 21.98.

**8-Pentyl-6-(*p*-tolyl)tetrazolo[1,5-*a*]pyridine (3d)**
Orange gum; yield: 52 mg (62%).

IR ($CHCl_3$): 2966, 2874, 1624, 1560, 1481, 1069, 782 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.79 (s, 1 H), 7.63 (s, 1 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 3.17 (t, *J* = 7.8 Hz, 2 H), 2.44 (s, 3 H), 1.94–1.83 (m, 2 H), 1.47–1.39 (m, 4 H), 0.92 (t, *J* = 6.9 Hz, 3 H),

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 148.1, 139.3, 132.4, 131.4, 131.0, 130.1, 130.0, 127.1, 119.2, 31.5, 29.4, 22.7, 21.2, 14.1, 13.9.

MS (EI): *m*/*z* = 280 $[M]^+$, 252 $[M^+ - 28]$.

**8-Methyl-6-phenyltetrazolo[1,5-*a*]pyridine (3e)**
Yellow solid; yield: 53 mg (84%); mp 119–121 °C.

IR (KBr): 2969, 2876, 1628, 1565, 1480, 1086, 768 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 7.67 (s, 1 H), 7.66–7.34 (m, 5 H), 2.84 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 149.6, 135.3, 131.5, 131.2, 129.5, 129.2, 128.9, 127.3, 126.9, 119.6, 29.7.

MS (EI): *m*/*z* = 210 $[M]^+$, 182 $[M^+ - 28]$.

Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.80; H, 4.73; N, 26.60.

**8-Ethyl-6-phenyltetrazolo[1,5-*a*]pyridine (3f)**
Yellow solid; yield: 54 mg (80%); mp 115–118 °C.

IR (KBr): 2968, 2876, 1629, 1567, 1485, 1086, 767 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.82 (s, 1 H), 7.72–7.38 (m, 6 H), 3.24 (q, *J* = 7.8 Hz, 2 H), 1.50 (t, *J* = 7.3 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 148.1, 135.4, 132.7, 131.6, 129.5, 129.4, 129.2, 127.4, 119.6, 24.6, 13.2.

MS (EI): *m*/*z* = 224 $[M]^+$, 196 $[M^+ - 28]$.

Anal. Calcd for $C_{13}H_{12}N_4$: C, 69.62; H, 5.39; N, 24.98. Found: C, 69.64; H, 5.32; N, 25.03.

**8-Isopropyl-6-phenyltetrazolo[1,5-*a*]pyridine (3g)**
White solid; yield: 55 mg (78%); mp 127–130 °C.

IR (KBr): 2967, 2875, 1627, 1562, 1481, 1087, 762 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.82 (d, *J* = 1.1 Hz, 1 H), 7.69–7.49 (m, 6 H), 3.71 (heptet, *J* = 6.9 Hz, 1 H), 1.53 (d, *J* = 7.0 Hz, 6 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 147.7, 137.2, 135.5, 131.6, 129.5, 129.2, 127.5, 127.4, 119.5, 30.6, 21.9.

MS (EI): *m*/*z* = 238 $[M]^+$, 210 $[M^+ - 28]$.

Anal. Calcd for $C_{14}H_{14}N_4$: C, 70.57; H, 5.92; N, 23.51. Found: C, 70.65; H, 5.93; N, 23.56.

**8-Pentyl-6-phenyltetrazolo[1,5-*a*]pyridine (3h)**
Yellow gum; yield: 58 mg (72%).

IR ($CHCl_3$): 2970, 2877, 1627, 1563, 1482, 1082, 770 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.74 (s, 1 H), 7.59–7.29 (m, 6 H), 3.10 (t, *J* = 7.9 Hz, 2 H), 1.90–1.75 (m, 2 H), 1.36–1.20 (m, 4 H), 0.84 (t, *J* = 6.9 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 148.2, 135.3, 131.6, 131.5, 130.1, 129.5, 129.2, 127.3, 119.6, 31.5, 31.4, 28.6, 22.4, 13.9.

MS (EI): *m*/*z* = 266 $[M]^+$, 238 $[M^+ - 28]$.

**6-(4-Chlorophenyl)-8-methyltetrazolo[1,5-*a*]pyridine (3j)**
White solid; yield: 64 mg (88%); mp 162–165 °C.

IR (KBr): 2922, 2851, 1692, 1561, 1486, 1043, 819 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 8.80 (s, 1 H), 7.68–7.34 (m, 5 H), 2.82 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 148.6, 135.3, 131.5, 131.2, 129.5, 129.1, 128.9, 127.5, 126.5, 119.6, 29.7.

MS (EI): *m*/*z* = 244 $[M]^+$

Anal. Calcd for $C_{12}H_9N_4Cl$: C, 58.90; H, 3.71; N, 22.90. Found: C, 65.93; H, 3.77; N, 23.07.

**6-(*p*-Tolyl)tetrazolo[1,5-*a*]pyridine-8-carbaldehyde (3k)**
White solid; yield: 63 mg (88%); mp 162–165 °C.

IR (KBr): 2922, 2851, 1692, 1561, 1486, 1043, 819 $cm^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 10.79 (s, 1 H), 9.17 (d, *J* = 1.6 Hz, 1 H), 8.54 (d, *J* = 1.7 Hz, 1 H), 7.57 (d, *J* = 8.1 Hz, 2 H), 7.39 (d, *J* = 8.1 Hz, 2 H), 2.47 (s, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 190.1, 149.9, 137.4, 135.7, 132.6, 129.5, 129.4, 129.3, 127.4, 119.6, 21.4.

MS (EI): *m*/*z* = 238 $[M]^+$, 210 $[M^+ - 28]$.

Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.58; H, 4.34; N, 23.55

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