# Synthesis of Substituted 1,8-Naphthyridine-3-carboxylates from *Baylis–Hillman* Adducts of Substituted 2-Chloronicotinaldehydes

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A series of substituted 1,8-naphthyridine-3-carboxylates were synthesized for the first time from the *Baylis–Hillman* adducts obtained from 2-chloronicotinaldehyde derivatives. Three methods were adopted to synthesize 1,8-naphthyridine-3-carboxylates, of which the azide-reduction route (*Scheme 5*) gave the best yields compared to the other attempted methods (*Schemes 2* and *3*).

**1. Introduction.** – Naphthyridines are an important class of pharmaceutically active compounds, and their chemistry has been reviewed since their evaluation [1]. A large number of 1,8-naphthyridines were reported to exhibit antimicrobial [2a], antitumor [2b–d], anti-inflammatory [2e], and diuretic activities [2f]. Many other 1,8-naphthyridines have been found to be active as antiallergics [3a], local anaesthetics [3b], antiplatelet agents [3c], anticonvulsants [3d], and antihypertensives [3e]. The 1,8-naphthyridine derivatives were also reported to be associated with the property of inhibiting secretion of acid in stomach known as a gastric antisecretary [4], and also used for the treatment of memory disorders, in particular *Alzheimer*'s disease [5]. Some new 1,8-naphthyridine derivatives have recently been patented as plant-growth regulators, fungicides, bactericides, herbicides, insecticides, and nematicides [6]. Arylnaphthyridines have been reported as potent mGlu5-receptor antagonists [7]. In addition to medicinal applications, 1,8-naphthyridines have been employed in the study of bioorganic and bioorganometallic processes (for a recent example, see [8]) and in organometallic [9] applications.

A survey of the literature shows that there are two general methods available for the preparation of 1,8-naphthyridines, namely the *Skraup* and the *Friedländer* reaction. The former is a powerful method for the synthesis of quinolines and many naphthyridines [10]. However, it is very much substrate-dependent and not suitable for the preparation of 2-substituted 1,8-naphthyridines [11]. On the other hand, the *Friedländer* reaction is one of the most important methods for synthesizing pyridines, quinolines, and naphthyridines [12], but one of its major drawbacks is that unsymmetrical ketones give both regioisomeric products, generally with little or no selectivity.

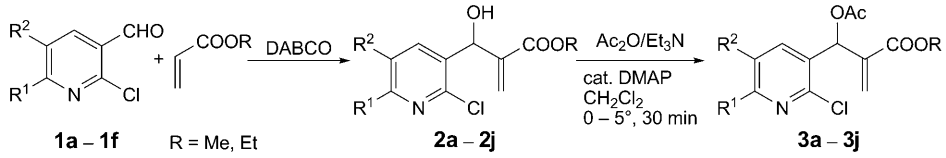
Moreover, both methods for the synthesis of 1,8-naphthyridines require high reaction temperatures and prolonged reaction times, and suffer from low product yields. Thus, in view of their immense biological importance, the development of a simple, convenient, and environmentally compatible synthesis of 1,8-naphthyridines is very much desirable.

In continuation of our work on the study of N-containing heterocyclic compounds [13], we report herein a novel, simple, and efficient route for the synthesis of substituted 1,8-naphthyridine-3-carboxylates from *Baylis–Hillman* adducts, which are often difficult to obtain by other routes.

**2. Results and Discussion.** – 2.1. Baylis–Hillman *Actates*. The *Baylis–Hillman* reaction is a useful method for C–C bond-formation from activated vinyl and CO substrates [14]. Chemical transformation of the *Baylis–Hillman* adducts or their derivatives into useful heterocyclic compounds have been studied recently by us and other groups [13][15]. Thus, we have reported new *Baylis–Hillman* adducts derived from 2-chloronicotinaldehydes (=2-chloropyridine-3-carboxaldehydes) [13b,d], and the transformation of these adducts into the quinoline skeleton [13c] is a useful entry to quinoline chemistry.

The *Baylis–Hillman* adducts **2a–2j** were now synthesized similarly [13b,d] from the substituted 2-chloronicotinaldehydes **1a–1f** with ethyl or methyl acrylate (=ethyl or methyl prop-2-enoate) in very good yields (*Scheme 1*). The allyl acetate derivatives **3a–3j** of these adducts were then efficiently obtained by treatment with either AcCl/pyridine or $Ac_2O/Et_3N$ (cat. DMAP (=*N*,*N*-dimethylpyridin-4-amine)) [16]. All the new compounds were well characterized by spectral data.

*Scheme 1*




| | $R^1$ | $R^2$ |
|---|---|---|
| **1a** | H | Me |
| **1b** | H | Et |
| **1c** | H | 4-$MeOC_6H_4$ |
| **1d** | Ph | Me |
| **1e** | COOMe | H |
| **1f** | H | Ph |

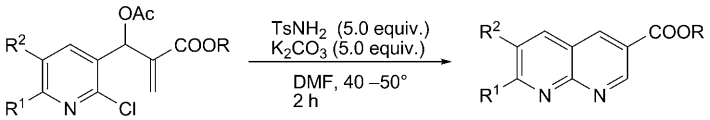
| | $R^1$ | $R^2$ | R |
|---|---|---|---|
| **2a**,**3a** | H | Me | Me |
| **2b**,**3b** | H | Et | Me |
| **2c**,**3c** | H | 4-$MeOC_6H_4$ | Me |
| **2d**,**3d** | Ph | Me | Me |
| **2e**,**3e** | COOMe | H | Me |
| **2f**,**3f** | H | Me | Et |
| **2g**,**3g** | H | Et | Et |
| **2h**,**3h** | H | Ph | Et |
| **2i**,**3i** | Ph | Me | Et |
| **2j**,**3j** | COOMe | H | Et |

It was anticipated that the acetate derivatives **3** are convertible into primary-allylamine derivatives, which could easily lead to the formation of substituted 1,8-naphthyridines *via* an $S_NAr$ reaction, the allylamine moiety acting as a nucleophile and substituting the Cl-atom at the pyridine ring even under moderate conditions. This

assumption prompted us to look for an efficient synthesis of allylamine derivatives from the *Baylis–Hillman* acetates **3**. Thus the primary-allylamines were generated from **3** by using different nucleophiles such as *i*) *p*-toluenesulfonamide (=4-methylbenzenesulfonamide), *ii*) ammonium acetate, and *iii*) sodium azide followed by reduction.

2.2. *Reaction of Acetate Derivatives* **3** *with* p-*Toluenesulfonamide:* The reaction of the *Baylis–Hillman* acetates **3a–3j** with *p*-toluenesulfonamide ($TsNH_2$) [15a][17] in the presence of $K_2CO_3$ in dimethylformamide as solvent at 40–50° gave the substituted 1,8-naphthyridine-3-carboxylates **4a–4j** in 55–64% yield (*Scheme 2*). With the aid of $K_2CO_3$, $TsNH_2$ generates the nucleophile that undergoes *Michael* addition to the exocyclic C=C bond of acetates **3** and subsequent migration of the C=C bond with the simultaneous ejection of the AcO group to give the rearranged sulfonamide derivatives $TsNHOH_2C(COOR)=CHPy$. This reaction is also known as tandem nucleophilic-addition–elimination reaction ($S_N2'$) [18][19]. The intermediates could not be isolated, and subsequently the TsNH moiety again generates a nucleophile with the aid of $K_2CO_3$, which can now attack in an $S_NAr$ reaction at C(2) of the pyridine ring followed by elimination of $Cl^-$ to give the 1,2-dihydro-1-tosyl-1,8-naphthyridine-3-carboxylates. The latter are then converted into the 1,8-naphthyridine-3-carboxylates **4** by the elimination of *p*-toluenesulfonic acid under normal elimination-reaction conditions.

*Scheme 2*

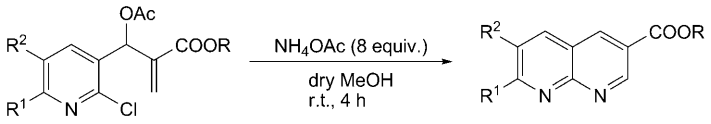



**3a – 3j** **4a – 4j**

| | $R^1$ | $R^2$ | R |
|---|---|---|---|
| **4a** | H | Me | Me |
| **4b** | H | Et | Me |
| **4c** | H | 4-$MeOC_6H_4$ | Me |
| **4d** | Ph | Me | Me |
| **4e** | COOMe | H | Me |
| **4f** | H | Me | Et |
| **4g** | H | Et | Et |
| **4h** | H | Ph | Et |
| **4i** | Ph | Me | Et |
| **4j** | COOMe | H | Et |

2.3. *Reaction of Acetate Derivatives* **3** *with Ammonium Acetate.* The *Baylis–Hillman* acetates **3a–3j** were treated with $NH_4OAc$ in anhydrous MeOH at room temperature for 1–2 h to obtain the substituted 1,8-naphthyridine-3-carboxylates **4a–4j** in 20–26% yield (*Scheme 3*). The primary-allylamine derivatives were not isolated as they underwent the aromatic nucleophilic substitution reaction ($S_NAr$) as soon as they were formed, yielding the 1,2-dihydro-1,8-naphthyridine-3-carboxylates in low yields due to the formation of by-products [20]. Presumably, the formed 1,2-dihydro-1,8-naphthyri-

*Scheme 3*

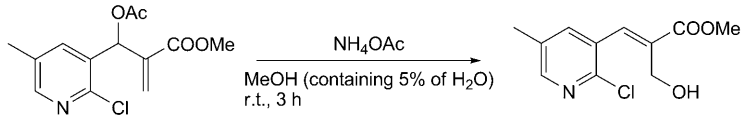



**3a – 3j** **4a – 4j**

dine-3-carboxylates underwent an auto-oxidation during the workup procedure to yield the 1,8-naphthyridine-3-carboxylates **4**.

However, we observed the formation of allylic-alcohol derivative **5a** [21] when the *Baylis–Hillman* acetate **3a** reacted with ammonium acetate in the presence of aqueous MeOH (containing 5% of $H_2O$) (*Scheme 4*). OH Ions may attack the exocyclic C=C bond instead of ammonium ions when MeOH containing $H_2O$ was used.

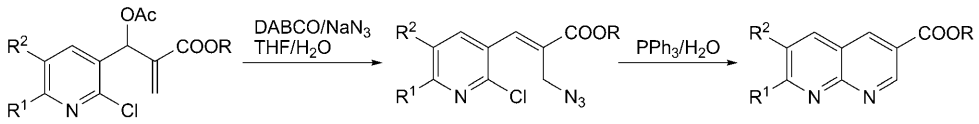
*Scheme 4*




**3a** **5a**

2.4. *Reaction of Acetate Derivatives* **3** *with* $NaN_3$. We have also developed another method to synthesize the substituted 1,8-naphthyridine-3-carboxylates **4a–4j** by converting first the *Baylis–Hillman* acetates **3a–3j** to the primary allyl azide derivatives **6a–6j**. Thus, after formation of the corresponding salts in the presence of DABCO (=1,4-diazabicyclo[2.2.2]octane) in aqueous THF at room temperature, $NaN_3$ was added to give **6a–6j** in 80–92% yield within 5 min, which were identified by spectroscopic analysis (*Scheme 5*). Reduction of **6a–6j** with triphenylphosphine in the presence of water for 14–16 h by the *Staudinger* reaction [22] gave the 1,8-naphthyridine-3-carboxylates **4a–4j** in 72–88% yield *via* the corresponding primary-allylamine derivatives which underwent immediately $S_NAr$ reaction (→1,2-dihydro-1,8-naphthyridine-3-carboxylates) followed by auto-oxidation.

*Scheme 5*




**3a – 3j** **6a – 6j** **4a – 4j**

**3. Conclusion.** – We developed for the first time an efficient route for the synthesis of substituted 1,8-naphthyridine-3-carboxylates under mild conditions in high yields *via* the *Baylis–Hillman* adducts. Three methods were adopted to synthesize the 1,8-

naphthyridine-3-carboxylates **4a**–**4j**, of which the azide/triphenylphosphine method was the best when compared to the *p*-toluenesulfonamide or ammonium acetate procedure.

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## Experimental Part

1. *General.* The chemicals $NaN_3$, DABCO, $Ph_3P$, *p*-toluenesulfonamide, and all the solvents were obtained commercially. The *Baylis–Hillman* adducts were synthesized according to our earlier-reported method [13c]. Column chromatography (CC): silica gel ($SiO_2$; 60–120 mesh). M.p.: *Mettler-Temp* apparatus; uncorrected. IR Spectra: *Perkin-Elmer-1600* FT-IR spectrometer; $\tilde{\nu}$ in $cm^{-1}$. $^1$H- and $^{13}$C-NMR Spectra: *Gemini-200* and *Bruker-Avance-300* spectrometers; chemical shifts $\delta$ in ppm rel. to $Me_4Si$ as an internal standard, *J* in Hz. EI-MS: *7070 H* spectrometers with a direct inlet system; at 70 eV; in *m*/*z* (rel. %).

2. *1,8-Naphthyridine-3-carboxylates* **4a**–**4j** *by the* p-*Toluenesulfonamide Method: General Procedure.* To a stirred soln. of the *Baylis–Hillman* acetate, **3a** (0.566 g, 2 mmol) in DMF were added *p*-toluenesulfonamide (1.71 g, 10 mmol) and $K_2CO_3$ (1 g, 10 mmol), and the mixture was stirred at 40–50° for 4 h (TLC monitoring). Then the mixture was poured into cold 10% HCl soln. and extracted with $Et_2O$ ($3 \times 50$ ml), the combined $Et_2O$ layer dried ($Na_2SO_4$) and concentrated, and the obtained residue subjected to CC (silica gel, hexane/AcOEt 6:4): **4a** as solid in 64% yield.

3. *1,8-Naphthyridine-3-carboxylates* **4a**–**4j** *by the Ammonium Acetate Method: General Procedure.* To a soln. of **3a** (0.283 g, 1 mmol) in anh. MeOH (10 ml) was added $NH_4OAc$ (0.616 g, 8 mmol) in one portion under $N_2$. The mixture was stirred at r.t. (TLC monitoring). After completion of the reaction, the mixture was diluted with $CHCl_3$ (30 ml) and filtered to remove excess of $NH_4OAc$. The filtrate was concentrated and the residue subjected to CC ($SiO_2$, hexane/AcOEt 5:5): pure **4a** as solid in 26% yield.

4. *Allyl Azide Derivatives* **6a**–**6j**: *General Procedure.* To the stirred soln. of **3a** (0.283 g, 1 mmol) in THF/$H_2O$ 1:1 (4 ml) was added DABCO (0.112 g, 1 mmol). After 10 min, $NaN_3$ (0.1 g, 1.5 mmol) was added under stirring, and after 5 min, the mixture was extracted with AcOEt ($2 \times 20$ ml), the org. layer dried ($NaSO_4$) and concentrated, and the residue subjected to CC ($SiO_2$, hexane/AcOEt 98:2): **6a** (0.23 g, 92%).

5. *Reduction of Azide Derivatives* **6a**–**6j** *to 1,8-Naphthyridine-3-carboxylates* **4a**–**4j**: *General Procedure.* To a stirred soln. of **6a** (0.23 g, 0.9 mmol) in THF (5 ml) was added $Ph_3P$ (0.365 g, 1.4 mmol) and allowed to stir at r.t. for 1 h (→dark yellow mixture). Thereafter, $H_2O$ (50 ml) was added and the reaction allowed to proceed for further 14 h (TLC monitoring). Then the solvent was evaporated, the residue extracted with AcOEt, the AcOEt soln. washed with $H_2O$ ($2 \times 20$ ml), dried ($Na_2SO_4$), and concentrated and the obtained residue subjected to CC ($SiO_2$, hexane/AcOEt 4:6): **4a** in 88% yield.

6. *Data of* **4a**–**4j**, **6a**, **6d**–**6f**, **6j**, *and* **5a**. *Methyl 6-Methyl-1,8-naphthyridine-3-carboxylate* (**4a**). Yield 88%[1]). M.p. 274–276°. IR (KBr): 3396, 2922, 1663, 1426, 1375, 1028, 762, 697. $^1$H-NMR (200 MHz, ($D_6$)DMSO): 9.42 (*s*, 1 H); 8.99 (*s*, 1 H); 8.79 (*s*, 1 H); 8.09 (*s*, 1 H); 3.98 (*s*, 3 H); 2.57 (*s*, 3 H). EI-MS: 202 (100, $M^+$), 171 (92), 143 (45), 116 (60), 89 (40). Anal. calc. for $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85; found: C 65.35, H 4.99, N 13.89.

*Methyl 6-Ethyl-1,8-naphthyridine-3-carboxylate* (**4b**). Yield 78%[1]). M.p. 282–284°. $^1$H-NMR (200 MHz, $CDCl_3$): 9.57 (*s*, 1 H); 9.08 (*s*, 1 H); 8.8 (*s*, 1 H); 8.02 (*s*, 1 H); 4.01 (*s*, 3 H); 2.94 (*q*, $J$ = 7.17, 2 H); 1.42 (*t*, $J$ = 7.17, 3 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 165.2; 157.2; 152.3; 139.3; 138.9; 135.1; 124.0; 121.3; 52.5; 29.6; 25.9; 14.8. EI-MS: 216 (100, $M^+$), 201 (60), 185 (80), 174 (15), 157 (20), 130 (45). Anal. calc. for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.95; found: C 66.68, H 5.68, N 12.88.

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[1]) Yields of **4a**–**4j** from **3a**–**3j** according to the method of *Scheme 5*.

*Methyl 6-(4-Methoxyphenyl)-1,8-naphthyridine-3-carboxylate* (**4c**). Yield 72%[1]). M.p. 296–298°. $^1$H-NMR (200 MHz, $CDCl_3$): 9.57 (*s*, 1 H); 9.00 (*s*, 1 H); 8.61 (*s*, 1 H); 8.34 (*s*, 1 H); 7.60 (br. *s*, 4 H); 4.02 (*s*, 3 H); 3.86 (*s*, 3 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 166.7; 160.1; 150.3; 137.2; 134.2; 133.9; 129.0; 128.7; 128.4; 128.2; 128.1; 127.4; 114.8; 55.3; 52.3. EI-MS: 294 ($M^+$). Anal. calc. for $C_{17}H_{14}N_2O_3$: C 69.38, H 4.79, N 9.52; found: C 69.32, H 4.74, N 9.32.

*Methyl 6-Methyl-7-phenyl-1,8-naphthyridine-3-carboxylate* (**4d**). Yield 74%[1]). M.p. 285–287°. IR (KBr): 3060, 2924, 1721, 1611, 1429, 1254, 1103, 699. $^1$H-NMR (200 MHz, $CDCl_3$): 9.55 (*s*, 1 H); 8.78 (*s*, 1 H); 8.10 (*s*, 1 H); 7.48–7.67 (*m*, 5 H); 3.98 (*s*, 3 H); 2.53 (*s*, 3 H). EI-MS: 278 (23, $M^+$), 277 (100), 247 (8), 218 (10), 190 (7). Anal. calc. for $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; found: C 73.22, H 5.12, N 10.19.

*Dimethyl 1,8-Naphthyridine-2,6-dicarboxylate* (**4e**). Yield 88%[1]). M.p. 312–315°. IR (KBr): 2958, 1720, 1441, 1341, 1228, 1141, 1099, 775. $^1$H-NMR (200 MHz, $CDCl_3$): 9.69 (*s*, 1 H); 9.0 (*s*, 1 H); 8.8 (*d*, $J$ = 7.95, 1 H); 8.34 (*d*, $J$ = 7.95, 1 H); 4.08 (*s*, 3 H); 4.05 (*s*, 3 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 166.4; 165.8; 148.8; 148.4; 139.3; 138.6; 129.3; 128.3; 123.0; 121.3; 52.9; 52.3. EI-MS: 246 (100, $M^+$). Anal. calc. for $C_{12}H_{10}N_2O_4$: C 58.54, H 4.09, N 11.38; found: C 58.23, H 4.46, N 10.98.

*Ethyl 6-Methyl-1,8-naphthyridine-3-carboxylate* (**4f**). Yield 82%[1]). M.p. 282–285°. IR (KBr): 3396, 2922, 1663, 1426, 1375, 1028, 762, 697. $^1$H-NMR (200 MHz, $CDCl_3$): 9.52 (*s*, 1 H); 9.0 (*s*, 1 H); 8.78 (*s*, 1 H); 8.0 (*s*, 1 H); 4.42 (*q*, $J$ = 7.17, 2 H); 2.51 (*s*, 3 H); 1.39 (*t*, $J$ = 7.17, 3 H). EI-MS: 216 (100, $M^+$), 199 (33), 183 (33), 152 (8), 77 (10). Anal. calc. for $C_{12}H_{12}N_2O_2$: C 66.65, H 5.59, N 12.95; found: C 66.62, H 5.68, N 12.81.

*Ethyl 6-Ethyl-1,8-naphthyridine-3-carboxylate* (**4g**). Yield 80%[1]). M.p. 286–289°. IR (KBr): 3390, 2982, 1690, 1490, 1390, 1028, 762, 697. $^1$H-NMR (200 MHz, $CDCl_3$): 9.52 (*s*, 1 H); 8.83 (*s*, 1 H); 8.36 (*s*, 1 H); 8.13 (*s*, 1 H); 4.42 (*q*, $J$ = 7.21, 2 H); 2.92 (*q*, $J$ = 7.21, 2 H); 1.41 (*t*, $J$ = 7.21, 3 H); 1.31 (*t*, $J$ = 7.21, 3 H). EI-MS: 230 (100, $M^+$). Anal. calc. for $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found: C 67.78, H 6.08, N 12.14.

*Ethyl 6-Phenyl-1,8-naphthyridine-3-carboxylate* (**4h**). Yield 84%[1]). M.p. 240–242°. IR (KBr): 3060, 2924, 1721, 1611, 1426, 1254, 1103, 699. $^1$H-NMR (200 MHz, $CDCl_3$): 9.55 (*s*, 1 H); 8.78 (*s*, 1 H); 8.46 (*s*, 1 H); 8.10 (*s*, 1 H); 7.42–7.67 (*m*, 5 H); 4.38 (*q*, $J$ = 7.17, 2 H); 1.43 (*t*, $J$ = 7.17, 3 H). $^{13}$C-NMR (75 MHz, $CDCl_3$): 166.2; 150.5; 137.4; 137.3; 134.4; 134.0; 129.1; 128.9; 128.7; 128.4; 128.2; 127.2; 127.1; 61.1; 14.3. EI-MS: 278 (100, $M^+$), 249 (64), 183 (65), 137 (10), 128 (10). Anal. calc. for $C_{17}H_{14}N_2O_2$: C 73.36, H 5.07, N 10.07; found: C 73.42, H 5.09, N 10.45.

*Ethyl 6-Methyl-7-phenyl-1,8-naphthyridine-3-carboxylate* (**4i**). Yield 82%[1]). M.p. 282–285°. IR (KBr): 2927, 1706, 1613, 1407, 1257, 1106, 783. $^1$H-NMR (200 MHz, $CDCl_3$): 9.6 (*s*, 1 H); 8.8 (*s*, 1 H); 8.12 (*s*, 1 H); 7.75–7.45 (*m*, 5 H); 4.51 (*q*, $J$ = 7.21, 2 H); 2.60 (*s*, 3 H); 1.50 (*t*, $J$ = 7.21, 3 H). $^{13}$C-NMR (50 MHz, $CDCl_3$): 165.6; 156.0; 152.7; 139.6; 138.7; 133.2; 131.7; 129.4; 129.2; 129.0; 128.2; 124.1; 120.5; 61.7; 20.6; 14.3. EI-MS: 292 (40, $M^+$), 291 (100), 263 (75), 247 (10), 218 (11). Anal. calc. for $C_{18}H_{16}N_2O_2$: C 73.95, H 5.51, N 9.58; found: C 73.99, H 5.66, N 9.64.

*6-Ethyl 2-Methyl-1,8-naphthyridine-2,6-dicarboxylate* (**4j**). Yield 88%[1]). M.p. 314–316°. IR (KBr): 3023, 2954, 1742, 1712, 1324, 1280, 1173, 1093, 783. $^1$H-NMR (200 MHz, $CDCl_3$): 9.78 (*d*, $J$ = 2.93, 1 H); 8.91 (*d*, $J$ = 2.93, 1 H); 8.48 (*d*, $J$ = 8.08, 1 H); 8.38 (*d*, $J$ = 8.08, 1 H); 4.50 (*q*, $J$ = 7.34, 2 H); 4.09 (*s*, 3 H); 1.50 (*t*, $J$ = 7.34, 3 H). $^{13}$C-NMR (50 MHz, $CDCl_3$): 165.3; 164.2; 156.4; 154.4; 152.7; 139.8; 139.4; 125.7; 122.9; 122.7; 62.1; 53.2; 14.3. EI-MS: 260 (3, $M^+$), 230 (17), 215 (10), 202 (100), 174 (42), 160 (10), 128 (8), 101 (6). Anal. calc. for $C_{13}H_{12}N_2O_4$: C 60.40, H 4.65, N 10.76; found: C 60.35, H 4.68, N 10.68.

*Methyl (2*E*)-2-(Azidomethyl)-3-(2-chloro-5-methylpyridin-3-yl)prop-2-enoate* (**6a**). Yield 92%. M.p. 82–84°. $^1$H-NMR (200 MHz, $CDCl_3$): 8.22 (*s*, 1 H); 7.90 (*s*, 1 H); 7.58 (*s*, 1 H); 4.02 (*s*, 2 H); 3.92 (*s*, 3 H); 2.39 (*s*, 3 H). EI-MS: 266 (100, $M^+$), 224 (76), 210 (23).

*Methyl (2*E*)-2-(Azidomethyl)-3-(2-chloro-5-methyl-6-phenylpyridin-3-yl)prop-2-enoate* (**6d**). Yield 91%. M.p. 110–112°. $^1$H-NMR (200 MHz, $CDCl_3$): 7.95 (*s*, 1 H); 7.68 (*s*, 1 H); 7.60–7.42 (*m*, 5 H); 4.08 (*s*, 2 H); 3.93 (*s*, 3 H); 2.43 (*s*, 3 H). EI-MS: 342 (100, $M^+$), 300 (66), 286 (45), 258 (12).

*Methyl 5-[(1*E*)-2-(Azidomethyl)-3-methoxy-3-oxoprop-1-en-1-yl]-6-chloropyridine-2-carboxylate* (**6e**). Yield 92%. M.p. 119–121°. $^1$H-NMR (200 MHz, $CDCl_3$): 8.09 (*d*, $J$ = 8.08, 1 H); 7.91 (*d*, $J$ = 8.08, 1 H); 7.90 (*s*, 1 H); 3.99 (*s*, 3 H); 3.97 (*s*, 2 H). EI-MS: 310 (100, $M^+$), 295 (76), 253 (65), 225 (36).

*Ethyl (2*E*)-2-(Azidomethyl)-3-(2-chloro-5-methylpyridin-3-yl)prop-2-enoate* (**6f**). Yield 84%. M.p. 95–96°. $^1$H-NMR (200 MHz, $CDCl_3$): 8.21 (*s*, 1 H); 7.89 (*s*, 1 H); 7.58 (*s*, 1 H); 4.36 (*q*, *J* = 7.43, 2 H); 4.02 (*s*, 2 H); 2.39 (*s*, 3 H); 1.41 (*t*, *J* = 7.43, 3 H). EI-MS: 280 (100, $M^+$), 238 (76), 224 (23).

*Methyl 5-[(1*E*)-2-(Azidomethyl)-3-ethoxy-3-oxoprop-1-en-1-yl]-6-chloropyridine-2-carboxylate* (**6j**). Yield 90%. $^1$H-NMR (200 MHz, $CDCl_3$): 8.09 (*d*, *J* = 8.08, 1 H); 7.93 (*d*, *J* = 8.08, 1 H); 7.90 (*s*, 1 H); 4.35 (*q*, *J* = 7.34, 2 H); 3.98 (*s*, 3 H); 3.97 (*s*, 2 H); 1.39 (*t*, *J* = 7.34, 3 H).

*Methyl (2*E*)-3-(2-Chloro-5-methylpyridin-3-yl)-2-(hydroxymethyl)prop-2-enoate* (**5a**). Yield 75%. M.p. 152–155°. IR (KBr): 3314, 2956, 1708, 1021. $^1$H-NMR (200 MHz, $CDCl_3$): 8.16 (*s*, 1 H); 7.74 (*s*, 1 H); 7.52 (*s*, 1 H); 4.28 (*s*, 2 H); 3.81 (*s*, 2 H); 2.30 (*s*, 3 H); 1.60 (br. *s*, OH). EI-MS: 241 (100, $M^+$). Anal. calc. for $C_{11}H_{12}NClO_3$: C 54.67, H 5.00, N 5.79; found: C 54.69, H 5.12, N 5.82.

## REFERENCES


[1] V. P. Litvinov, *Russ. Chem. Rev.* **2004**, *73*, 637; W. W. Paudler, R. R. Sheets, *Adv. Heterocycl. Chem.* **1983**, *33*, 147.

[2] a) G. R. Rao, K. Mogilaiah, B. Sreenivasulu, *Indian J. Chem., Sect. B* **1996**, *35*, 339; b) S. K. Srivastava, M. Jaggi, A. T. Singh, A. Madan, N. Rani, M. Vishnoi, S. K. Agarwal, R. Mukherjee, A. C. Burman, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6660; c) Y. Tsuzuki, K. Tomita, Y. Sato, S. Kashimoto, K. Chiba, *Bioorg. Med. Chem. Lett.* **2004**, *12*, 3189; d) S.-X. Zhang, K. F. Bastow, Y. Tachibana, S.-C. Kuo, E. Hamel, A. Mauger, V. L. Narayanan, K.-H. Lee, *J. Med. Chem.* **1999**, *42*, 4081; e) T. Kuroda, F. Suzuki, T. Tamura, K. Ohmori, H. Hosoe, *J. Med. Chem.* **1992**, *35*, 1130; f) D. K. J. Gorecki, E. M. Hawes, *J. Med. Chem.* **1977**, *20*, 124.

[3] a) S.-C. Kuo, S.-Y. Tsai, H.-T. Li, C.-H. Wu, K. Ishii, H. Nakamura, *Chem. Pharm. Bull.* **1988**, *36*, 4403; b) P. L. Ferrarini, C. Mori, N. Tellini, *Farmaco* **1990**, *45*, 385; c) P. L. Ferrarini, M. Badawneh, F. Franconi, C. Manera, M. Miceli, C. Mori, G. Saccomanni, *Farmaco* **2001**, *56*, 311; d) J. T. Leonard, R. Gangadhar, S. K. Gnanasam, S. Ramachandran, M. Sarvanan, S. K. Sridhar, *Biol. Pharm. Bull.* **2002**, *25*, 798; e) P. L. Ferrarini, C. Mori, M. Badawneh, V. Calderone, R. Greco, C. Manera, A. Martinelli, P. Nieri, G. Saccomanni, *Eur. J. Chem.* **2000**, *35*, 815.

[4] A. A. Santilli, A. C. Scotese, R. F. Bauer, S. C. Bell, *J. Med. Chem.* **1987**, *30*, 2270.

[5] V. P. Litvinov, *Adv. Heterocycl. Chem.* **2006**, *91*, 189.

[6] A. S. Noravyan, E. G. Paronikyan, S. A. Vartanyan, *Khim.-Farm. Zh.* **1985**, *19*, 790; V. P. Litvinov, S. V. Roman, V. D. Dyachenko, *Russ. Chem. Rev.* (*Engl. Transl.*) **2000**, *69*, 201; L. Chrzastek, B. Mianowska, W. Sliwa, *Aust. J. Chem.* **1994**, *47*, 2129; B. Bachowska, T. Zujewska, *Arkivoc* **2001**, *(vi)*, 77.

[7] P. Galatsis, K. Yamagata, J. A. Wendt, C. J. Connolly, J. W. Mickelson, B. J. Milbank, S. E. Bove, C. S. Knauer, R. M. Brooker, C. E. Augelli-Szafran, R. D. Schwarz, J. J. Kinsora, K. S. Kilgore, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6525.

[8] K. Nakatani, S. Sando, I. Saito, *Bioorg. Med. Chem.* **2001**, *9*, 2381; K. Nakatani, S. Sando, I. Saito, *J. Am. Chem. Soc.* **2001**, *122*, 2172; C. H. Nguyen, C. Marchand, S. Delage, J.-S. Sun, H. Garestier, C. Hélène, E. Bisagni, *J. Am. Chem. Soc.* **1998**, *120*, 2501; Y. Zhou, Y. Xiao, X. Qian, *Tetrahedron Lett.* **2008**, *49*, 3380.

[9] C. He, J. L. DuBois, B. Hedman, K. O. Hodgson, S. J. Lippard, *Angew. Chem., Int. Ed.* **2001**, *40*, 1484; C.-M. Che, C.-W. Wan, K.-Y. Ho, Z.-Y. Zhou, *New. J. Chem.* **2001**, *25*, 63; R. Ziessel, A. Harriman, A. El-ghayoury, L. Douce, E. Leize, H. Nierengarten, A. Van Dorsselaer, *New J. Chem.* **2000**, *24*, 729.

[10] Y. Hamada, I. Takeuchi, *Yakugaku Zasshi* **2000**, *120*, 206.

[11] Y. Hamada, I. Takeuchi, *Chem. Pharm. Bull.* **1971**, *19*, 1857.

[12] C.-C. Cheng, S.-J. Yan, 'The Friedländer Synthesis of Quinolines', in 'Organic Reactions', Vol. 28, Ed. W. C. Dauben, J. Wiley & Sons, New York, 1982, p. 37; D.-Q. Yang, F. Lü, W. Guo, *Chin. J. Org. Chem.* **2004**, *24*, 366; P. G. Dormer, K. K. Eng, R. N. Farr, G. R. Humphrey, J. C. McWilliams, P. J. Reider, J. W. Sager, R. P. Volante, *J. Org. Chem.* **2003**, *68*, 467.

[13] a) B. Gangadasu, P. Narender, S. B. Kumar, M. Ravinder, B. Anada Rao, C. Ramesh, B. C. Raju, V. J. Rao, *Tetrahedron* **2006**, *62*, 8398; b) P. Narender, B. Gangadasu, M. Ravinder, U. Srinivas, G. Y. S. K. Swamy, K. Ravikumar, V. J. Rao, *Tetrahedron* **2006**, *62*, 954; c) P. Narender, U. Srinivas, M. Ravinder, B. Anand Rao, C. Ramesh, K. Harakishore, B. Gangadasu, U. S. N. Murthy, V. J. Rao, *Bioorg. Med. Chem.* **2006**, *14*, 4600; d) P. Narender, U. Srinivas, B. Gangadasu, S. Biswas, V. J. Rao, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 5378; e) P. Narendar, B. Gangadasu, C. Ramesh, B. C. Raju, V. J. Rao, *Synth. Commun*. **2004**, *34*, 1097; f) K. Srinivas, U. Srinivas, V. J. Rao, K. Bhanuprakash, K. H. Kishore, U. S. N. Murthy, *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1121.

[14] D. Basavaiah, K. V. Rao, R. J. Reddy, *Chem. Soc. Rev*. **2007**, *36*, 1581; V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511; D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001; E. Ciganek, 'Organic Reactions', Vol. 51, John Wiley & Sons, New York, 1997, pp. 201 – 350; S. E. Drewes, G. H. P. Roos, *Tetrahedron* **1988**, *44*, 4653; P. Langer, *Angew. Chem., Int. Ed*. **2000**, *39*, 3049.

[15] a) J. N. Kim, H. J. Lee, K. Y. Lee, H. S. Kim, *Tetrahedron Lett*. **2001**, *42*, 3737; b) J. N. Kim, K. Y. Lee, H. S. Kim, T. Y. Kim, *Org. Lett*. **2000**, *2*, 343; c) O. B. Familoni, P. T. Kaye, P. J. Klaas, *Chem. Commun*. **1998**, 2563; d) D. Basavaiah, R. M. Reddy, N. Kumaragurubaran, D. S. Sharada, *Tetrahedron* **2002**, *58*, 3693.

[16] D. Basavaiah, M. Krishnamacharyulu, R. S. Hyma, P. K. S. Sarma, N. Kumaragurubaran, *J. Org. Chem.* **1999**, *64*, 1197; P. L. H. Mason, N. D. Emslie, *Tetrahedron* **1994**, *50*, 12001.

[17] Y. M. Chung, H. J. Lee, S. S. Hwang, J. N. Kim, *Bull. Korean Chem. Soc.* **2001**, *22*, 799.

[18] M. Grignon-Dubois, F. Diaba, M.-C. Grellier-Marly, *Synthesis* **1994**, 800; F. Diaba, C. Le Houerou, M. Grignon-Dubois, P. Gerval, *J. Org. Chem*. **2000**, *65*, 907; F. Diaba, I. Lewis, M. Grignon-Dubois, S. Navarre, *J. Org. Chem*. **1996**, *61*, 4830.

[19] D. E. Minter, P. L. Stotter, *J. Org. Chem*. **1981**, *46*, 3965; F. W. Fowler, *J. Org. Chem*. **1972**, *37*, 1321; D. L. Comins, A. H. Abdullah, *J. Org. Chem.* **1982**, *47*, 4315.

[20] K. Tanemura, T. Suzuki, Y. Nishida, K. Satsumabayashi, T. Horagushi, *Chem. Commun*. **2004**, 470; V. Singh, R. Pathak, S. Kanojiya, S. Batra, *Synlett* **2005**, 2465.

[21] D. Basavaiah, K. Padmaja, T. Satyanarayana, *Synthesis* **2000**, 1662 and ref. cit. therein; D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; H. S. Kim, T. Y. Kim, K. Y. Lee, Y. M. Chung, H. J. Lee, J. N. Kim, *Tetrahedron Lett*. **2000**, *41*, 2613.

[22] H. Staudinger, E. Hauser, *Helv. Chim. Acta* **1921**, *4*, 861; A. Patra, A. K. Roy, S. Batra, A. P. Bhaduri, *Synlett* **2002**, 1819; Y. G. Gololobov, I. N. Zhumurova, L. F. Kashukin, *Tetrahedron* **1981**, *37*, 437.

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