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Microwave-mediated reactions of 3-aminomethylpyridines with acetylenedicarboxylates. A novel synthetic route to dihydronaphthyridines and naphthyridine-1-ones

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Abstract—Reaction of 3-(1-alkylamino)pyridines with electron deficient acetylenes in the presence of acids yields 1,2-dihydro-[2,7]naphthyridine-3,4-dialkyldicarboxylates **4** in 35–72% yield. Compounds **4** unsubstituted in position 1 can be easily oxidized with potassium permanganate into the respective naphthyridine-1-ones derivatives **5** in good yields.

The 2,7-naphthyridine template is well represented both in nature (e.g., Sceavodimerine C,[1a] see Fig. 1) as well as in drug discovery programs of pharmaceutical companies (see characteristic compounds **A**,[1b] **B**,[1c] **C**,[1d] Fig. 1). Derivatives of [2,7]naphthyridine could be considered as rigidified analogs of nicotine.[1e] In the course of our medicinal chemistry efforts, a robust and reliable approach to this template was needed.

As part of our ongoing program of new 'drug-like' library templates development we decided to look closer onto the reaction of substituted pyridines, including *l*-anabasine **1a** (Scheme 1), with activated acetylenes. Reaction of acetylenes with amines has been studied in great details. It has been suggested that the outcome is dependent on (i) stoichiometry of reagents, (ii) nature of reagents, and (iii) reaction conditions.[2a–c] For example, it has been reported that the reaction of one equivalent of acetylenecarboxylates with amines yields the respective enamines.[1a] In our hands, slow addition of the stoichiometric amount of diethyl acetylenedicarboxylate to a solution of *l*-anabasine **1a** in EtOH or

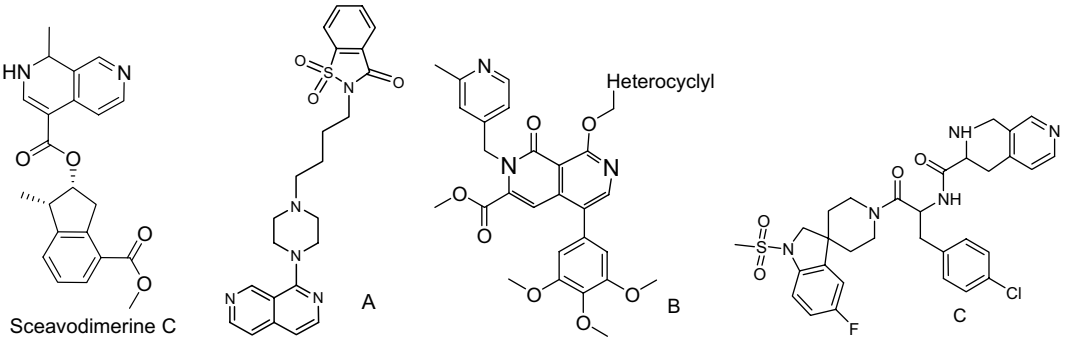

Figure 1.

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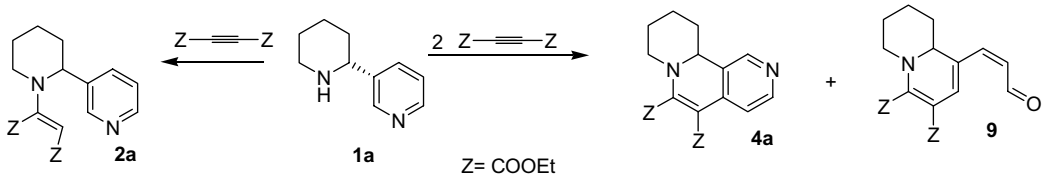


Scheme 1.

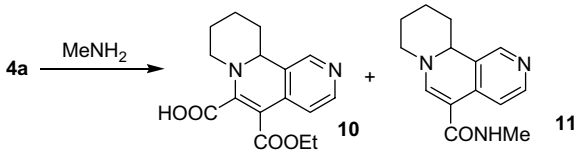
DMF at RT led to the exclusive formation of enamine **2a** (isolated yield 87%), as expected (Scheme 1). However, rapid addition of two equivalents of acetylenecarboxylate to a vigorously stirred mixture of anabasine **1a**, and K_2CO_3 in dry DMF at RT afforded complex mixture of products and ca. 50% of unreacted anabasine. Preparative TLC separation of this mixture (silica gel, 5% MeOH in $CHCl_3$) allowed us to identify two unexpected products: 1,2-dihydro[2,7]naphthyridine **4a**[3] (yield 10%) and acroleine derivative **9** (yield 4.5%)[4] (Scheme 1).

In order to further investigate this conversion, we varied the reaction conditions as well as the amine input. In this paper, we report an optimized general route to 1,2- and 2-substituted 1,2-dihydro[2,7]naphthyridine dialkyl-3,4-dicarboxylates **4** and their derivatives.

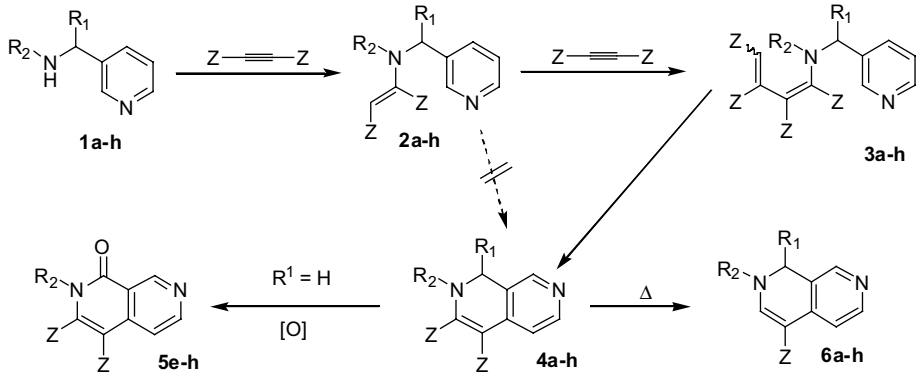
Slow addition of dialkyl acetylene dicarboxylate (2 equiv, 30 min) to the EtOH solution of amine **1a**–**h** in the presence of TFA or HCl at 0 °C led to the formation of the respective enamine **2a**–**h** (LCMS analysis). These species gradually reacted with the second equivalent of the acetylene to yield dienes **3a**–**h** (Scheme 2, LCMS detection).[2a–c] Attempted isolations of intermediates **3a**–**h** by flash chromatography were not successful, probably due to their instability on silica gel. Microwave irradiation of dienes **3a**–**h** without isolation (150 °C, 20 min) followed by flash chromatography or HPLC purification yielded naphthyridines **4a**–**h** in 35–76% isolated yields.[5] In contrast, the conventional heating of the mixtures at 150 °C in stainless steel autoclave required 3–5 h for complete conversion of dienes **3**, and the yields of **4a**–**h** were ca. 10–15% lower. In addition, under conventional heating we observed decarboxylated products **6a**–**h** (yield 10–12% vs 1–2% at microwave heating).[6] Microwave heating (up to 170 °C) of enamines **2** did not result in formation of naphthyridines **4** (Scheme 2). Mechanistically, the formation of compounds **4** is explained as intramolecular electrophilic attack of sp^2 carbon at β-position of dienamine **3** at the position 4 of its pyridine ring. Formally, this process should be accompanied with diethyl maleinate or fumarate formation. However, appropriate molecular ions were not detected on LC–MS spectra.

During the course of this study, we found that compounds **4a**–**d** substituted at position 1 of naphthyridine cycle are stable upon storage. In contrast, 1-unsubstituted compounds (R_1 = H, **4e**–**h**) are prone to a gradual oxidation by air into the respective naphthyridine-1-ones **5e**–**h**. This conversion is facilitated by $KMnO_4$ in CH_2Cl_2 (cat. 18-crown-6, Scheme 2)[7] to yield **5e**–**h** in good yields (61–92%). Attempts to synthesize **5e**–**h** directly from *N*-benzylnicotinamides and diethyl acetylenedicarboxylate under a variety of experimental conditions described in the literature[8] were unsuccessful.

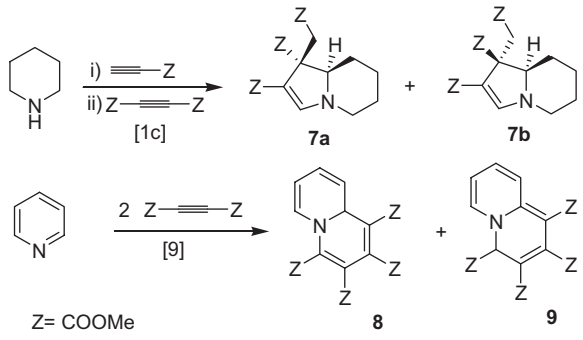
We further investigated the reaction of compound **4a** with aqueous methylamine (Scheme 3). Under the reaction conditions (0.2 M solution of **4a** in 40% aq $MeNH_2$, microwave heating, 30 min, 150 °C) the isolated products of the reaction were acid **10** (major component, 85% isolated yield) along with 4-substituted mono-methylamide **11** (minor component, yield 10%). Thus, the



Scheme 3.



Scheme 2.



Scheme 4.

Table 1. Yields of naphthyridines **4a–h** and naphthyridine-2-ones **5e–h**

Compound	Z	R_2	R_1	Yield (%)
4a	COOEt	$(CH_2)_4$		34[a]
				49
4a′	COOMe	$(CH_2)_4$		70
4b	COOEt	$(CH_2)_3$		35
4c	COOEt	$(CH_2)_3OMe$	Me	43
4d	COOEt	$(CH_2)_2NMe_2$	Me	45
4e	COOEt	$PhCH_2$	H	67
4f	COOEt	2-F-$PhCH_2$	H	75
4g	COOEt	3-F-$PhCH_2$	H	73
4h	COOEt	4-F-$PhCH_2$	H	76
5e	COOEt	$PhCH_2$	H	62[b]
5f	COOEt	2-F-$PhCH_2$	H	92
5g	COOEt	3-F-$PhCH_2$	H	89
5h	COOEt	4-F-$PhCH_2$	H	61

[a] Conventional heating in stainless steel autoclave.
[b] Spontaneous oxidation by air.

reported protocol could be used for desymmetrization of COOEt moieties in 4.

In a conclusion, we found a facile one-pot approach to 1,2-dihydro[2,7]naphthyridine-4-alkoxycarboxylates **4** from 3-alkylaminopyridines and electron deficient acetylenes. The reaction was mediated by a microwave irradiation. Upon oxidation of compounds **4e–h** with $KMnO_4$, respective naphthyridine-1-ones **5** were isolated in good yields (61–92%). The protocol for dysymmetrization of carboxylic moieties in **4** was developed and respective monosubstituted derivatives **6** and **10** were obtained.

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3. This reported reactivity of 3-aminomethylpyridines **1a–h** towards activated acetylenes appears to be unique. Similar conversions of secondary amines and pyridines yield pyrrolizines **7a,b**[2a] or a mixture of 9a*H*-quinolizine **8** and its 4*H* isomer **9**, respectively[9a,b] (Scheme 4).
4. Similar pyridine ring openings were described, e.g. (a) Ferguson, G.; Fisher, K. J.; Ibrahim, B. E.; Ishag, C. Y.; Iskander, G. M.; Katritzky, A. R.; Parvez, M. *J. Chem. Soc., Chem. Comm.* **1983**, 1216–1217; (b) Ishag, C. Y.; Fisher, K. J.; Ibrahim, B. E.; Iskander, G. M.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 1* **1988**, 917–920.
5. General procedure for the synthesis of compounds **4a–h:** A solution of diethyl acetylenedicarboxylate (1 mmol) in 1 ml EtOH was added dropwise over 30 min at 0 °C to a mixture of amine **1** (0.5 mmol), 4 ml EtOH and TFA (0.5 mmol). The mixture was kept at 0 °C for 30 min and for additional 12 h at room temperature. After 12 h, the solution was heated for 20 min at 150 °C in microwave reactor (Personal Chemistry ™Optimizer, 300 W). The solvent were removed under reduced pressure and obtained crude mixtures were purified by preparative HPLC (Phenomenex Luna C18 column, mobile phase: water/acetonitrile with 0.05% TFA), or by flash chromatography on silica ($CHCl_3$/MeOH/Et_3N = 100:6:1). Yields: 34–76% (Table 1).
Diethyl 2-(4-fluorobenzyl)-1,2-dihydro[2,7]naphthyridine-3,4-dicarboxylate (**4h**). HRMS (ESI-TOF): *m/z* [M+H$^+$] calculated for $C_{21}H_{21}N_2O_4F$: 385.1558. Found: 385.1557. ^{1}H NMR (DMSO, TMS, ppm): d 8.51 (1H, *J* = 6.5 Hz), s 8.41 (1H), d 8.33 (1H, *J* = 6.5 Hz), m 7.43 (2H), m 7.27 (2H), s 4.66 (2H), s 4.62 (2H), q 4.36 (2H, *J* = 7.2 Hz), q 4.22 (2H, *J* = 7.2 Hz) t 1.26 (3H, *J* = 7.2 Hz), t 1.24 (3H *J* = 7.2 Hz). ^{13}C NMR (DMSO, TMS, ppm) 164.0, 162.6, 162.1 d (*J* = 250.2 Hz), 155.9, 150.4, 146.7, 140.2, 137.1, 132.4 d (*J* = 8.4 Hz), 130.3 d (*J* = 8.4 Hz), 117.5, 115.7 d (*J* = 21.4 Hz), 95.5 ppm.
6. Structure of compound **6b** was confirmed by NOESY experiment which showed cross-pick of N–C**H**= proton at position 3 (7.82 ppm) and equatorial proton of $CH_2C\mathbf{H}_2$–N group at 3.59 ppm.
7. The corresponding naphthyridine **4** (0.2 mmol) was added into suspension of $KMnO_4$ (158 mg, 1 mmol) in 20 ml of dichloromethane with catalytic amount of 18-crown-6 (3–4 drops of 10% solution in dichloromethane). The reaction mixture was stirred at room temperature until no starting naphthyridine was detected (~2 h, control by LC–MS). The final suspension was filtered through Celite and washed with concentrated solution of sodium metabisulfite in water (1 × 20 ml). The organic layer was separated and filtered through Celite to remove inorganic residue. The solvent was removed under reduced pressure and the oily residue was purified by flash chromatography (silica gel, hexane:ethyl acetate = 1:2). The corresponding naphthyridines **5e–h** were isolated as slightly yellow powders and the yields were 60–92%.
Diethyl 2-(4-fluorobenzyl)-1-oxo-1,2-dihydro[2,7]naphthyridine-3,4-dicarboxylate (**5h**). HRMS (ESI-TOF): *m/z* [M+H$^+$] calculated for $C_{21}H_{19}FN_2O_5$: 399.1351. Found: 399.1366. ^{1}H NMR ($CDCl_3$, TMS): d 9.65 (1H, *J* = 0.8 Hz), d 8.84 (1H, *J* = 5.8 Hz), dd 8.16 (1H, *J* = 5.8 Hz, *J* = 0.8 Hz), m 7.22–7.29 (1H), m 6.97–7.03 (3H), s 5.34 (2H), q 4.40 (2H, *J* = 7.0 Hz), q 4.24 (2H, *J* = 7.0 Hz), t 1.41 (3H, *J* = 7.0 Hz), t 1.74 (3H *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, TMS): 164.1, 163.6, 162.4 d (*J* = 247 Hz), 161.0, 152.3, 151.9, 144.2, 138.9, 131.2 d (*J* = 3.4 Hz), 129.3 d (*J* = 8.4 Hz), 119.7, 118.4, 115.6 d (*J* = 21.4 Hz), 106.8, 63.1, 62.2, 48.4, 14.1, 13.5 ppm.

8. Known examples of reaction of amides with substituted acetylenes: (a) Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.; Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett.* **2003**, *5*(13), 2287–2290; (b) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*(45), 8855–8865; (c) Noritaka, A.; Tarozaemon, N. *Bull. Soc. Chem. Jpn.* **1981**, *54*(4), 1277–1278.
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