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A general and versatile synthesis of 2-alkyl-4-aminopyridines

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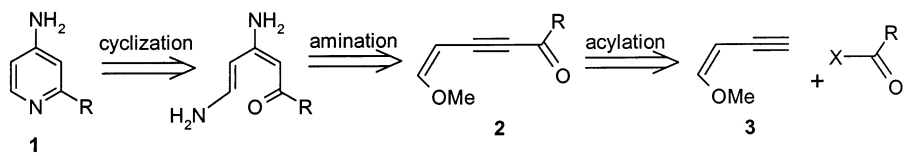
Abstract—A versatile two-step synthesis of 2-alkyl-4-aminopyridines from commercially available *cis*-1-methoxy-1-buten-3-yne is described. Acylation of the yne derivative followed by amination and cyclization in ammonia produced the desired substituted pyridines in high yield.

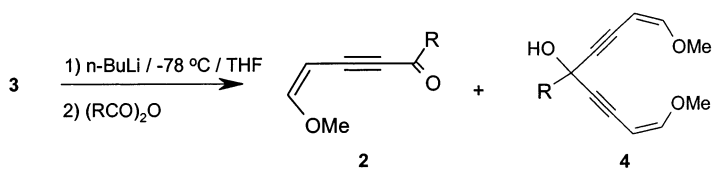
2-Alkyl-4-aminopyridines **1** are key intermediates for the preparation of *N*-(3-chloro-2-ethylpyridin-4-yl)-arylacetamides, potent inhibitors of mitochondrial electron transport which show broad spectrum control of insects, mites and nematodes.[1] Although numerous syntheses of 2,6-dialkyl-4-aminopyridines have been reported,[2] practical, scalable routes for the preparation of 2-alkyl-4-aminopyridines are lacking. For example, direct amination of haloalkylpyridines is reported,[3] but the relative inaccessibility of 4-halo-2-alkylpyridine makes this an unattractive approach.[4] Alternatively, the classical entry, and most commonly used method, into this structural type involves the reduction of the 4-nitro-2-alkylpyridine *N*-oxides. Aside from problems associated with the isolation of the product, the yield in our hands was poor and variable (5–33% yield).[5]

Although these methods have general applicability they are often difficult to perform on a large scale and, moreover, lack versatility to accommodate a variety of substituents. Accordingly, an efficient and scalable synthesis of a wide assortment of 2-substituted 4-aminopyridines was required for the analog synthesis and sample preparation for field studies.

Retrosynthetically, 2-alkyl-4-aminopyridine **1** arises from the cyclization of the enamino derivative, as depicted in Scheme 1. The enamino moiety presumably can be generated from the attack of ammonia on the ketoalkyne **2** in a Michael fashion. This ketoalkyne should be readily obtainable from *cis*-1-methoxy-1-buten-3-yne **3**[6] and an anhydride using known metalation chemistry, as illustrated in Scheme 2.[7]



Scheme 1.



Scheme 2.

Keywords: aminopyridines; *cis*-1-methoxy-1-butyn-3-yne; acetylenic ketones.
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Table 1. Acylation of *cis*-1-methoxy-1-buten-yne

	R	Substrate[a]	Yield[b]	Purity % GC
2a	Me	A	97	95
2b	CF_3	A	80	69
2b	CF_3	C	82	88
2c	Et	A	96	94
2d	C_2F_5	A	81	90
2e	*i*-Pr	A	98	91
2f	CycloPr	B	95	89
2g	*t*-Bu	A	80	90
2h	$(CH_2)_3OH$	D	45[c]	

[a] A = $(RCO)_2O$, B = RCOCl, C = $RCON(OCH_3)CH_3$, D = butyrolactone.

[b] Yields are crude oils of listed GC purities and were of sufficient purity to be converted to the corresponding alkyl aminopyridines. These oils were often distilled for analytical sample.

[c] Isolated yield, considerable decomposition occurred during Kugelrohr distillation.

Metalation of **3** at −78°C, followed by treatment with propionic anhydride, produced the acetylenic ketone **2c** (R = Et) in 76% isolated yield after Kugelrohr distillation.[8] The major contaminant was identified as the bisacetylene **4**, formed by the attack of the lithium acetylide on the acetylenic ketone **2c**. The inverse addition of the lithium acetylide of **3** to the anhydride at −78°C gave essentially quantitative yield of **2c**, totally eliminating the formation of **4**. Although the substitution of ethyl propionate for propionic anhydride gave only 5% of **2c**, the lithium acetylide of **3** could be added to more reactive acylation reagents to prepare a variety of substituted acetylenic ketones (**2a**–**h**), as listed in Table 1.

Table 2. Aminolysis of **2c**

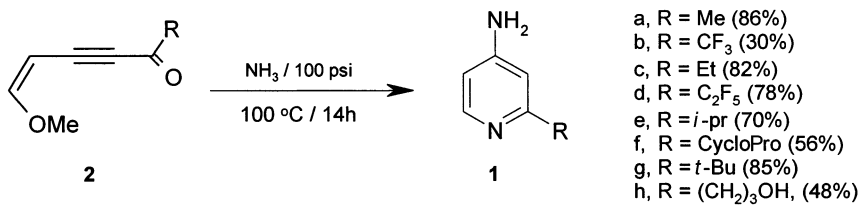
Conditions	Yields (isolated)[a]	
	1c	**5**
40–100°C	88% (68%)	12%
20–30°C	79% (55%)	15%
75–80°C, 50% EtOH	37%	19%
50–55°C, 10% THF	76%	19%
50–55°C, 50% $HCONH_2$	90%	6%

[a] Performed at 0.1 mol scale.

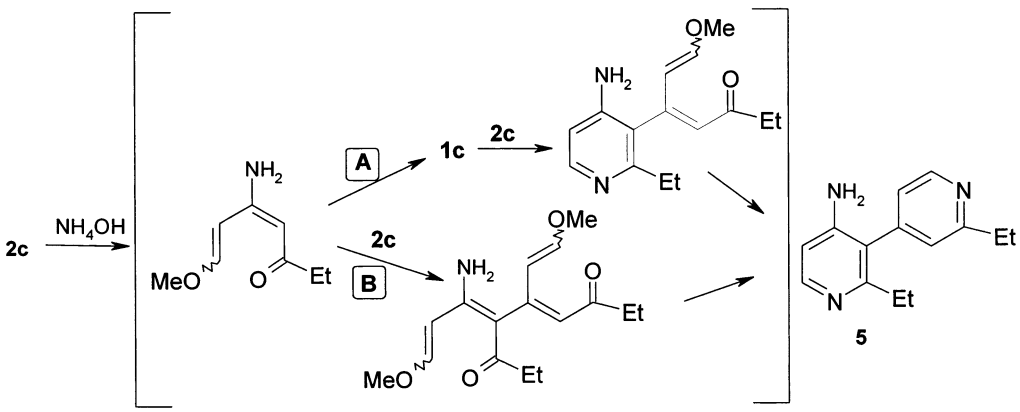
With the acetylenic ketone **2c** in hand, focus was directed toward the transformation of **2c** into **1c** (Scheme 3). High pressure aminolysis of ketone **2c** in methanol at 100–130°C for 14 h (100 psi) gave an 82% isolated yield of 4-amino-2-ethylpyridine **1c**.[9] When the reaction was run in ethanol at 130°C, a slow conversion (40 h) occurred and a poor yield (45%) resulted, suggesting that the choice of solvent is critical. It was also observed during scale-up that higher temperatures were not tolerated, resulting in lower yields. Consequently, the optimal yield was obtained when aminolysis was performed at 100°C (100 psi) for 14 h.

To further simplify the process, the aminolysis was performed in aqueous ammonia at atmospheric pressure under a variety of conditions (Table 2). Although the desired compound **1c**[10] was obtained in good yield, it was contaminated with a dimer product **5**.

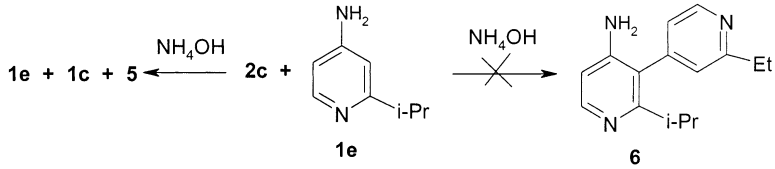
The formation of this dimer can proceed via pathway A or B, as illustrated in Scheme 4. To determine the



Scheme 3.



Scheme 4.



Scheme 5.

mechanism leading to the dimer formation, a crossover experiment was performed (Scheme 5). This involved the aminolysis of acetylenic ketone **2c** in the presence of **1e** in ammonium hydroxide. If pathway [A] were operative, attack of **1e** on **2c** in a Michael fashion followed by cyclization would give a dimer with an isopropyl group on the aminopyridine **6**. However, GC/MS analysis of the aminolysis reaction indicated dimer **5** and **1c** as the products formed with the recovery of the unreacted **1e**. This result supports the formation of **5** via pathway [B], with carbon–carbon bond formation occurring prior to pyridine ring formation.

In conclusion, we have described a direct and efficient preparation of 2-alkyl-4-aminopyridines **1**. This method was used for preparing analogs of pyridine carboxamides, samples in excess of 100 g for field studies and radiolabeled samples for biological studies.[11] The readily available anhydrides, acid chlorides and lactones and the versatility of the metalation and aminolysis make this method an attractive approach for the preparation of 2-alkyl-4-aminopyridines **1**.

References

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4. Unpublished results—Treatment of ethyl maltol with ammonia affords a 2:1 mixture of 2-ethyl-3,4-dihydroxypyridine and 4-amino-2-ethyl-3-hydroxypyridine, which was separated by recrystallization. Reaction of dihydroxypyridine with phenyl phosphonic dichloride at 200°C gave the dichloropyridine, which on treatment with ammonia at 200°C gave 4-amino-3-chloro-2-ethylpyridine in 20% overall yield.
5. Reduction was carried out using iron in acetic acid at 100°C.
6. Distilled before use from commercially available material supplied by Aldrich as a 50 wt% solution in methanol–water (4:1).
7. Crimmins, M. T.; O'Mahoney, R. *J. Org. Chem.* **1990**, *55*, 5894.
8. A solution of *n*-BuLi (1.6 or 2.5 M, 0.11 mol) was added to a freshly distilled **3** (bp 122–124°C, 8.2 g, 0.1 mol) in THF (200 mL) at −78°C over a 45 min period under nitrogen. After 1.0 h, the resulting suspension was added via cannula to a solution of an appropriate anhydride or acid chloride (0.1 mol) in THF and stirred for an additional 1.5 h. After quenching with aq. NH_4Cl, the reaction mixture was extracted with diethyl ether. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude oils were acceptable for conversion to the aminopyridines **1**, but they were often purified by Kugelrohr distillation or by chromatography for analytical sample. Data for **2c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (t, 3H, $J=2.4$ Hz), 2.55 (q, 2H, $J=2.5$ Hz), 3.83 (s, 3H), 4.62 (d, 1H, $J=2.1$ Hz), 6.55 (d, 1H, $J=2.1$ Hz); EI-MS m/z 138 (M^+), 109; anal. calcd for $C_8H_{10}O_2$: C, 69.53; H, 7.30. Found: C, 69.35; H, 7.33.
9. High-pressure aminolysis performed in a Hastelloy pressure reactor available from Parr apparatus.
10. Data for **1c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, 3H, $J=7.7$ Hz), 2.67 (q, 2H, $J=7.7$ Hz), 4.2 (bs, 2H), 6.34 (dd, 1H, $J=2.3$, 5.6 Hz), 6.38 (d, 1H, $J=2.3$ Hz), 8.11 (d, 1H, $J=5.6$ Hz); EI-MS m/z 121 (M^+), 94, 80; anal. calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.81; H, 8.43; N, 22.71.
11. Pearson, N. R. *J. Labeled Compd. Rad.* **1998**, *41*, 151.