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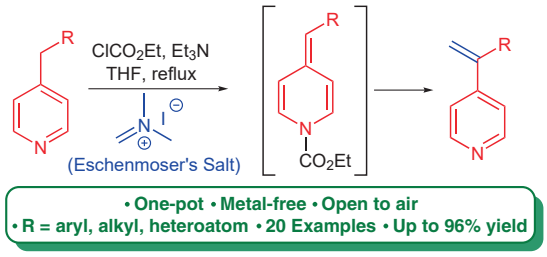
Direct Methenylation of 4-Alkylpyridines Using Eschenmoser's Salt

Grant N. Shivers
Soe L. Tun
Shay L. McLean
F. Christopher Pigge*

Department of Chemistry, University of Iowa, Iowa City, Iowa, 52242-1294, USA
chris-pigge@uiowa.edu



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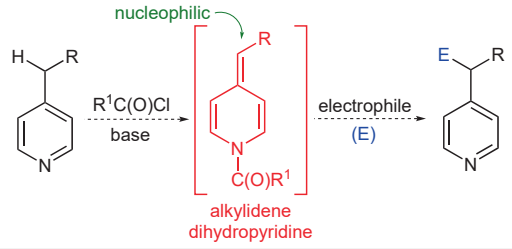
Abstract 4-Alkylpyridines are converted into conjugated 1,1-disubstituted alkenyl pyridines (vinyl pyridines) upon treatment with excess ethyl chloroformate, triethylamine, and Eschenmoser's salt. The reaction proceeds under mild conditions via alkylidene dihydropyridine intermediates.

Key words pyridine, alkylidene dihydropyridine, anhydrobase, alkylation, Eschenmoser's salt, dearomatization

Pyridine rings are often encountered as structural components in natural products, active pharmaceutical ingredients (APIs), and organic materials.[1] Accordingly, access to functionalized and synthetically versatile pyridine derivatives is crucial to advances in these fields. The range of commercially available pyridine building blocks, however, is limited by the costs associated with their synthesis.[2] Consequently, uncovering new synthetic methods to directly manipulate known and/or relatively simple pyridines is of high value.[3] An attractive strategy to manipulate 4-alkylpyridines entails in situ activation of the pyridine ring by N-acylation. Under mildly basic conditions N-acylated alkylpyridinium salts can be converted into the corresponding pyridine anhydrobases (alkylidene dihydropyridines) which are susceptible to reaction with suitable electrophiles at the exocyclic alkylidene carbon (Scheme 1).[4] We and others have employed this tactic to functionalize alkylpyridines via aldol-type condensations, Heck-type reactions, Pd-catalyzed allylations, and conjugate additions.[5,6] We now report an extension of this method to include methenylation of 4-alkylpyridines upon condensation of 4-alkylidene dihydropyridine intermediates with Eschenmoser's salt (*N*,*N*-dimethylmethyleneiminium iodide). The 1,1-disubstituted vinyl pyridine products obtained from this transformation represent versatile synthetic building blocks.[7]



Scheme 1 Pyridine functionalization using alkylidene dihydropyridines

Conjugated vinyl and alkenyl pyridines are particularly useful synthetic intermediates that have been employed as substrates in numerous complexity-generating transformations, such as hydrogenation, cyclopropanation, and Michael/conjugate addition (Scheme 2).[8] Most existing syntheses of 4-alkenyl pyridines have targeted the preparation of 4-vinyl pyridine itself, as well as 1,2-disubstituted and tri-/tetrasubstituted alkenyl pyridines.[9] In contrast, synthetic strategies for accessing geminal 1,1-disubstituted 4-alkenyl pyridines are less common and generally involve reactions of 4-acyl pyridines (Wittig reaction, organometallic addition–dehydration).[10] Additionally, a Cu-promoted methenylation between 4-benzylpyridines and *N*,*N*-dimethylacetamide has been reported.[11] While these strategies rely on well-established chemistry, they often require use of strongly basic reaction conditions or organometallic reagents and are limited to use of 4-pyridine carboxaldehydes, 4-pyridyl ketones, or 4-benzylpyridines as substrates.

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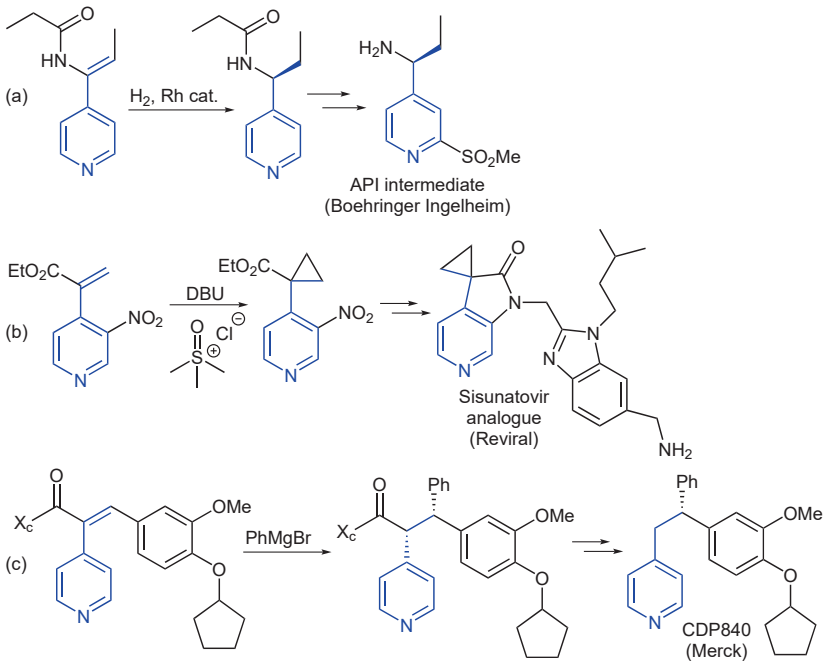
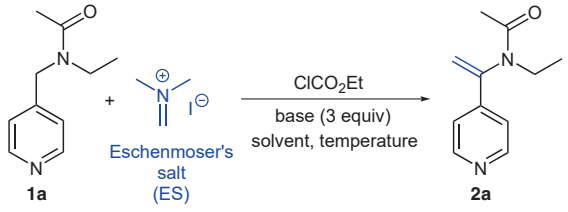


Scheme 2 Alkenyl pyridine substrates in API synthesis

Table 1 Reaction Conditions for 4-Alkylpyridine Methenylation[a]



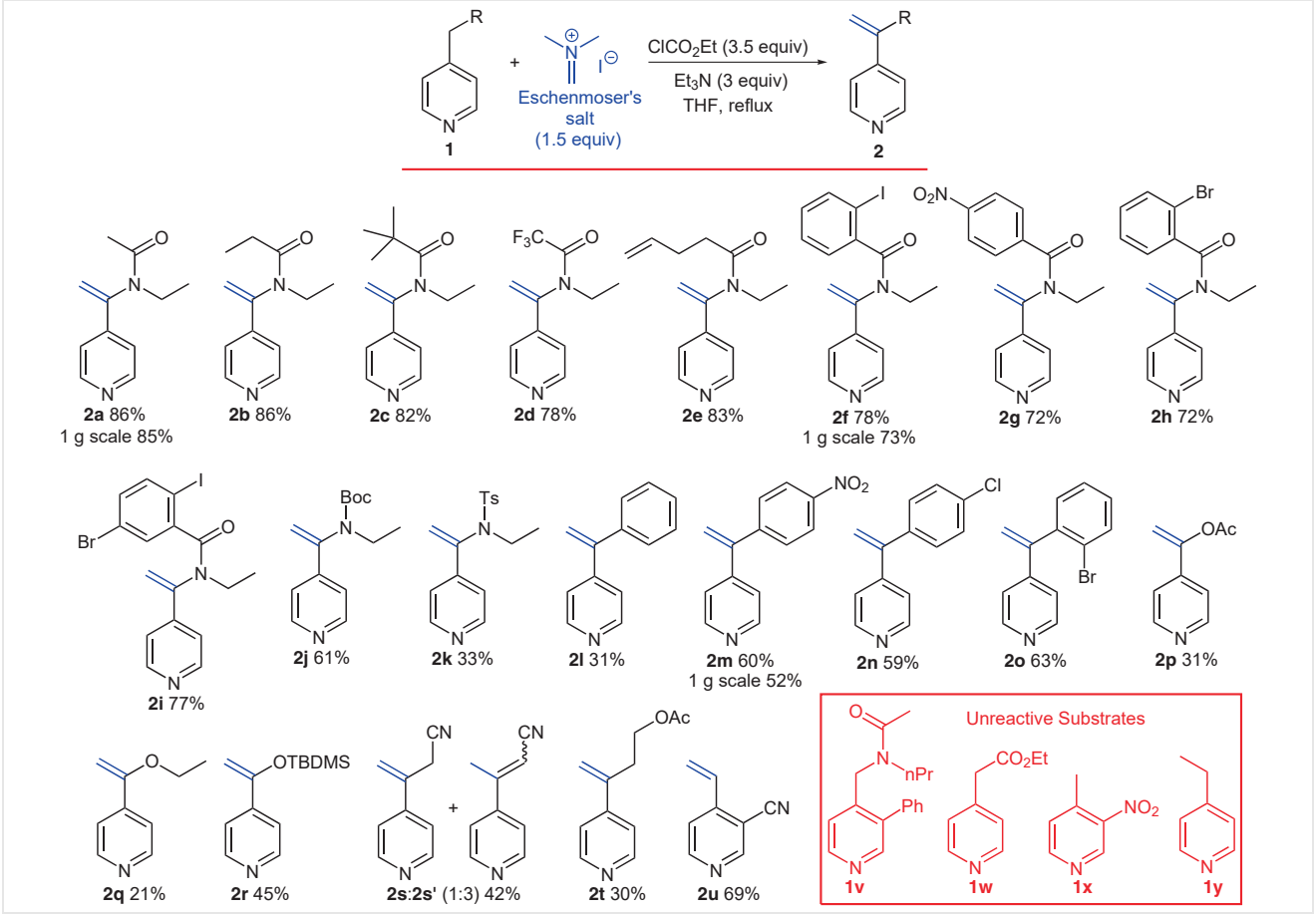
Entry	Base (3 equiv)	Solvent[b]	Temp	$ClCO_2Et$ (equiv)	ES (equiv)	Yield (%)[c]
1	Et_3N	THF	reflux	2.5	2	47
2	DBU	THF	reflux	2.5	2	np
3	PS	THF	reflux	2.5	2	np
4	Cs_2CO_3	THF	reflux	2.5	2	23
5	Et_3N	DCE	reflux	2.5	2	np
6	Et_3N	CH_3CN	reflux	2.5	2	np
7	Et_3N	dioxane	reflux	2.5	2	np
8	Et_3N	THF	0 °C	2.5	2	np
9	Et_3N	THF	rt	2.5	2	np
10	Et_3N	THF	reflux	3.5	2	89
11	Et_3N	THF	reflux	3.5	1.5	89
12	Et_3N	THF	reflux	3.5	1.1	96

[a] Reactions performed using 50 mg **1a**.
[b] [**1a**] = 0.1 M.
[c] Isolated yield.

We envisioned that a convenient and experimentally straightforward preparation of 1,1-disubstituted alkenyl pyridines may be available from reaction of 4-alkylidene dihydropyridines and a suitable methenylating agent. In turn, 4-alkylidene dihydropyridine reactants may be generated from a range of simple 4-alkylpyridines. Eschenmoser's salt was selected as a methenylating agent due to its higher reactivity and superior ease of handling and use compared to aqueous formaldehyde or paraformaldehyde.[12] Initial screenings of methenylating conditions were conducted using substrate **1a**, a compound known to be conducive to anhydrobase formation.[5d,e] Encouragingly, our first methenylation attempt gave the desired 1,1-disubstituted alkenyl pyridine **2a** in 47% isolated yield (Table 1, entry 1). Ethyl chloroformate was used as a pyridine activating agent in combination with Et_3N to mediate anhydrobase formation in refluxing THF. Replacing Et_3N with stronger organic bases (DBU, Proton Sponge) resulted in no product formation (Table 1, entries 2, 3), while use of Cs_2CO_3 delivered **2a** in reduced yield (Table 1, entry 4). A limited solvent screen revealed THF to be the solvent of choice as no product was obtained when reactions were performed in refluxing DCE, CH_3CN, and 1,4-dioxane (Table 1, entries 5–7). Reducing reaction temperature also resulted in no product formation (Table 1, entries 8, 9). Increasing the equivalents of $ClCO_2Et$ to 3.5 (relative to **1a**), however, led to significantly improved yield of **2a** (Table 1, entry 10). We attribute this result to the ability of excess $ClCO_2Et$ to assist in olefin formation by facilitating elimination of the dimethylamino group originating from Eschenmoser's salt (*vide infra*). Reducing the

amount of Eschenmoser's salt was also found to be beneficial (Table 1, entries 11, 12). While methenylation of **1a** using 1.1 equivalents of Eschenmoser's salt returned the highest yield of **2a** (96%, Table 1, entry 12), reactions of other substrates subsequently examined performed best with slightly more iminium ion electrophile. Thus, the conditions outlined in Table 1, entry 11 were selected for probing the scope of the reaction.[13,14]

In addition to **1a**, various other 4-(aminomethyl)pyridine derivatives were found to undergo methenylation in good to excellent yield under the conditions shown in Table 1, entry 11. Specifically, *N*-ethyl propionamide, pivalamide, trifluoroacetamide, and pentenyl amide substrates all gave the reaction, and alkenyl pyridines **2b–e** were isolated in good yield (Scheme 3). Likewise, benzamide substrates underwent smooth methenylation to afford pyridyl enamides **2f–i**, also in good yield. In addition to aminomethyl amides, a Boc-protected substrate was viable, giving **2j** in reasonable yield, but a sulfonamide-protected derivative **2k** was obtained in more modest 33% yield. A selection of 4-benzylpyridines was also successfully methenylated. While 4-benzylpyridine itself reacted with modest efficiency, giving **2l** in 31% isolated yield, nitro- and halo-substituted benzylpyridines were converted into the corresponding 1,1-diaryl ethylenes **2m–o** in ca. 60% yield. Notably, the reaction could be performed on a larger scale for these substrate types (1 g) to afford alkenyl pyridines in yields comparable to smaller-scale reactions, as indicated for products **2a**, **2f**, and **2m**. Interestingly, subjection of pyridyl methanol derivatives to anhydrobase-mediated methenylation returned 4-pyridyl enol ethers **2p–r** in 21–45% isolated yield. Pyridine-substituted propionitrile featuring a relatively unactivated 4-picolyl position gave the expected methenylated product **2s** along with isomerized product **2s′** (1:3 ratio) in 42% yield. Similarly, an acetoxy-substituted 4-alkylpyridine was converted into **2t**, albeit in modest yield. Finally, 3-cyano-4-methylpyridine was transformed into the vinyl pyridine **2u** in good yield. Several substrates were found to be unreactive toward methenylation under the conditions used in this study. Disubstituted 4-(aminomethyl)pyridine **1v** failed to re-

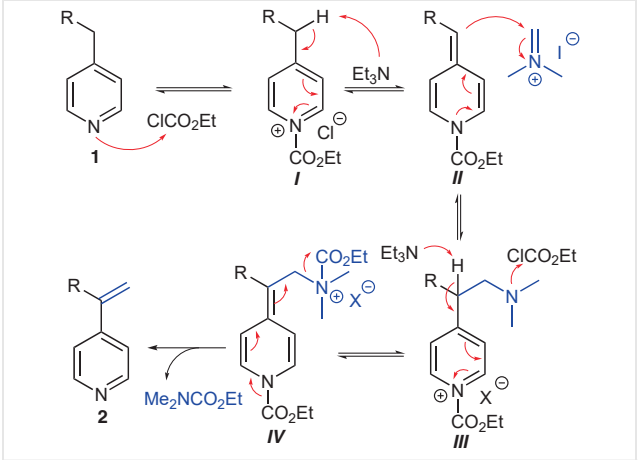


Scheme 3 Scope of 4-alkylpyridine methenylation. Reactions performed using 50 mg pyridine substrate **1** unless otherwise noted.

act, presumably due to steric congestion provided by the 3-phenyl substituent. Pyridine acetic acid ester **1w** was also unreactive, and we speculate that the corresponding alkylidene dihydropyridine intermediate is not sufficiently nucleophilic for reaction with Eschenmoser's salt.

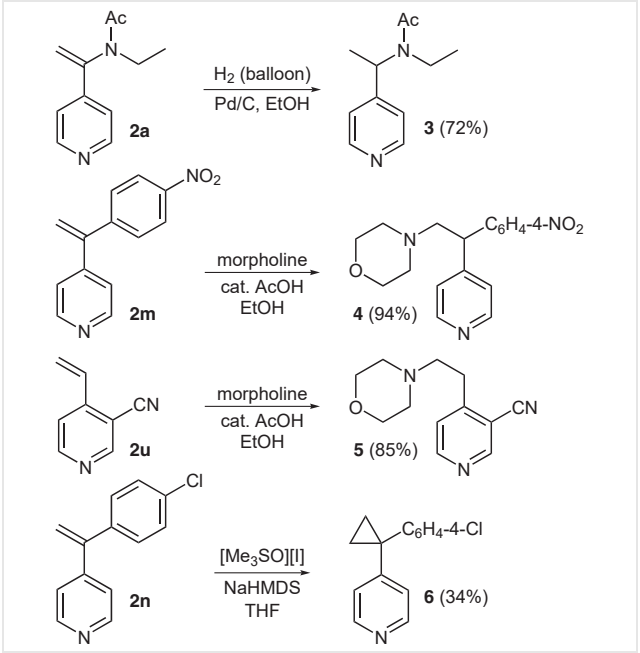
Pyridine **1x** suffers from steric congestion as well as attenuated nucleophilicity of the picolyl position due to the adjacent 3-nitro group. Simple 4-ethylpyridine was unreactive as the alkylidene dihydropyridine intermediate was not efficiently formed under these conditions.

A plausible mechanistic rationale for the methenylation sequence is outlined in Scheme 4. Pyridine substrate **1** is first acylated with $ClCO_2Et$ to give pyridinium salt intermediate ***I***. In the presence of Et_3N the 4-picolyl position is deprotonated, leading to alkylidene dihydropyridine ***II***. Alkylation of ***II*** by the iminium ion electrophile generates the pyridinium salt ***III***. Excess $ClCO_2Et$ and Et_3N can then react with ***III*** to afford anhydrobase ***IV*** which then undergoes rearomatization and elimination of the acylated dimethyl amino group to give alkenyl pyridine product **2**. Alternatively, direct elimination of the dimethyl amino group from ***III*** followed by cleavage of the *N*-acyl pyridinium linkage would also give **2**.



Scheme 4 Plausible mechanistic rationale for 4-alkylpyridine methenylation

To demonstrate the utility of this methenylation reaction for construction of functionalized pyridine building blocks, several alkenyl pyridine products were subjected to additional synthetic transformations (Scheme 5). Enamide **2a** was cleanly hydrogenated in the presence of Pd/C to alkylpyridine **3**. Both **2m** and **2u** underwent smooth hydroamination in the presence of morpholine and cat. AcOH to afford **4** and **5**, respectively, in high yield. Finally, alkenyl pyridine **2n** was successfully converted into cyclopropane derivative **6** (albeit in modest yield) upon treatment with a sulfoxonium ylide generated in situ.



Scheme 5 Further synthetic manipulation of 4-alkenyl pyridines

In summary, an efficient means of methenylating a range of 4-alkylpyridine derivatives using Eschenmoser's salt has been developed. The reaction proceeds via alkylidene dihydropyridine intermediates conveniently generated under mild conditions using ethyl chloroformate and triethyl amine. Moreover, reactions can be performed with no special precautions to exclude air and moisture. The 1,1-disubstituted alkenyl pyridine products available via this method are valuable preparative intermediates that are well-suited for additional synthetic manipulation.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1916-5335.

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(13) **Representative Procedure**
Reactions were performed in a 20 mL scintillation vial. To a solution of **1a** (50.0 mg, 0.28 mmol, 1 equiv) and Et_3N (3 equiv) in THF (2.8 mL) were added $ClCO_2Et$ (3.5 equiv) and Eschenmoser's salt (1.5 equiv). The vial was capped and placed in a J-KEM Lab benchtop shaker heating block set to 66 °C and agitated until the reaction was complete as indicated by TLC (ca. 16 h). After cooling to rt, the solvent was evaporated, and the residue purified by flash column chromatography using 25–100% EtOAc in hexanes as the eluent to afford **2a** as an orange oil (47. 4 mg, 89%).

(14) **Characterization Data for 2a**
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.65 (d, *J* = 5.9 Hz, 2 H), 7.31 (d, *J* = 5.9 Hz, 2 H), 6.00 (s, 1 H), 5.42 (s, 1 H), 3.52 (q, *J* = 7.1 Hz, 2 H), 2.01 (s, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 150.9, 145.2, 143.4, 120.0, 117.4, 41.6, 22.2, 13.1. HRMS (ESI$^+$): *m/z* calcd for $C_{11}H_{15}N_2O$ [M + H]$^+$: 191.1179; found: 191.1177.