

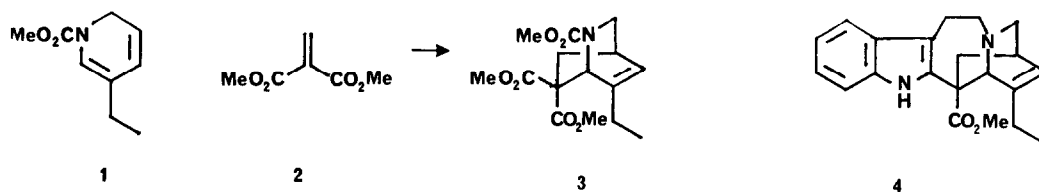
PREPARATION AND DIELS-ALDER REACTION OF N-CARBOMETHOXY-5-ETHYL-1,2-DIHYDROPYRIDINE:
AN APPROACH FOR THE SYNTHESIS OF CATHARANTHINE

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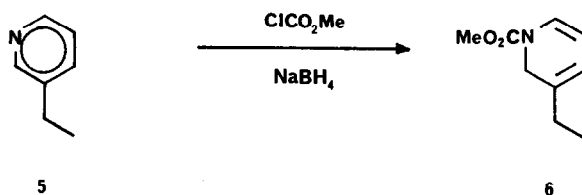
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Abstract: N-carbomethoxy-5-ethyl-1,2-dihydropyridine (1) may be prepared by the bromination of N-carbomethoxy-3-ethyl-1,2,5,6-tetrahydropyridine (10), and subsequent double dehydrobromination with EtAlCl₂/HMPA; this diene undergoes Diels-Alder reaction with dimethyl methylenemalonate (2) to give the isoquinuclidine (3), an intermediate in our planned approach to catharanthine.

The key step in our planned approach for the synthesis of the Iboga alkaloid catharanthine (4) involves the Diels-Alder reaction of N-carbomethoxy-5-ethyl-1,2-dihydropyridine (1) with an appropriate dieneophile such as 2. Since isoquinuclidines have been previously prepared by the reaction of N-carboalkoxy-1,2-dihydropyridines and various dienophiles,^{2,3,4} this approach is limited by the availability of the requisite dihydropyridine 1.

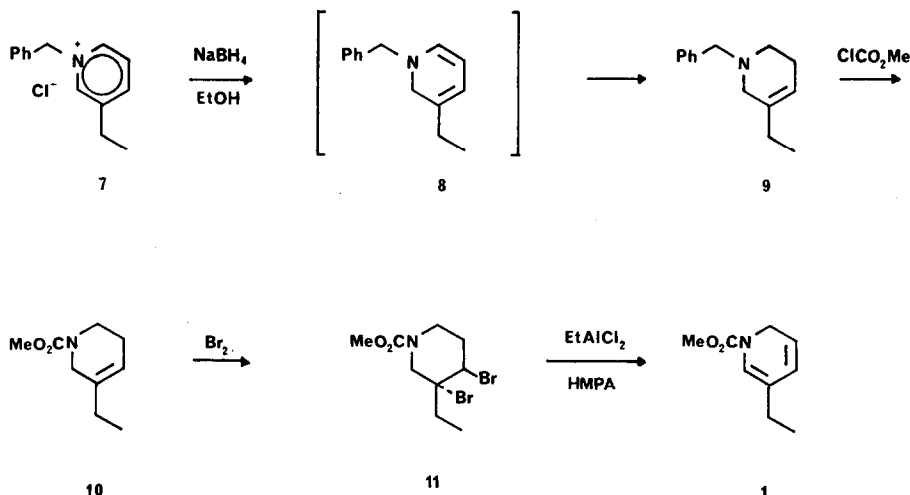


Fowler^{2a} has developed an excellent route to N-carbomethoxy-1,2-dihydropyridine by the reaction of pyridine, methyl chloroformate, and NaBH₄; unfortunately, use of this procedure with 3-ethylpyridine (5) affords N-carbomethoxy-3-ethyl-1,2-dihydropyridine (6),⁵ the incorrect regioisomer for a catharanthine synthesis. However, Fowler has converted 6 to 1 by a reduction, bromination, double dehydrobromination sequence.⁶

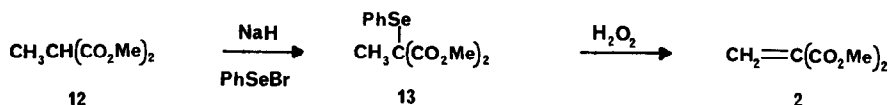


We have recently employed a bromination - double dehydrobromination sequence for the synthesis of an N-acyl-5-ethyl-1,2-dihydropyridine.⁷ Our observation that $\text{EtAlCl}_2/\text{HMPA}$ effects double dehydrobromination of a vicinal dibromide derived from an N-acyl-tetrahydropyridine under mild conditions was crucial to the success of this transformation.⁷ We now wish to report the application of this method for the regioselective synthesis of N-carbomethoxy-5-ethyl-1,2-dihydropyridine (1), and to describe the Diels-Alder reaction of 1 with 2.

Conversion of 3-ethylpyridine (5) to N-benzyl-3-ethylpyridinium chloride (7), followed by reaction with NaBH_4 in EtOH gave N-benzyl-3-ethyl-1,2,5,6-tetrahydropyridine (9) in greater than 95% overall yield as a light yellow liquid: (bp 150°C at 0.1 mm).⁸ The first hydride addition to 7 occurs with the same regioselectivity as that observed in the conversion of 5 to 6; however, in the case of the N-alkyl-1,2-dihydropyridine 8 subsequent protonation at the 5-position, and reduction of the resulting iminium species occurs. Treatment of a 0.5 M solution of 9 in benzene with methyl chloroformate (2 equiv) at reflux for 5 hours, and purification by vacuum distillation gave an 83% yield of N-carbomethoxy-3-ethyl-1,2,5,6-tetrahydropyridine (10): (bp 77°C at 0.40 mm).^{8, 9} Reaction of 10 with Br_2 (1 equiv) in CH_2Cl_2 at 0°C and purification by flash chromatography¹⁰ and crystallization from hexane/ether gave the dibromide 11⁸ as colorless needles in 89% yield (mp $56-58^\circ\text{C}$, lit.⁶ $57-58^\circ\text{C}$). The desired dihydropyridine 1 was obtained in excellent yield under extremely mild conditions utilizing our $\text{EtAlCl}_2/\text{HMPA}$ double dehydrobromination procedure⁷ on the dibromide 11. Thus, addition of a 25% solution of EtAlCl_2 in hexane (5 ml, 2.5 equiv) to a solution of 11 (4.0 mmol) in HMPA (20 ml), followed by heating under an argon atmosphere at 60°C for 1.5 hours and aqueous workup gave a 90-95% yield of 1 as a colorless liquid of sufficient purity to be used in the Diels-Alder reaction.⁸ This compound is reasonably stable and may be stored for several weeks at -10°C . Although the exact role of the EtAlCl_2 in this process is not yet fully understood, it appears to be functioning as both a Lewis acid to assist in weakening the carbon-bromine bonds toward heterolytic cleavage and as an acid scavenger¹¹ to consume the liberated hydrogen bromide.



Dimethyl methylenemalonate (2) was selected as the dieneophile for initial studies of the Diels-Alder reaction. Although a number of procedures have been reported for the preparation of the corresponding diethyl ester,¹² the methyl ester polymerizes quite readily, hence we found it more convenient to generate 2 in situ by the two-phase oxidation of a CCl_4 solution of dimethyl (phenylseleno)methylmalonate (13) with excess 30% H_2O_2 (10 equiv) at 20°C for 2 hours, followed by separation of the organic layer and drying with Na_2SO_4 . The selenide 13⁸ was prepared by treatment of dimethyl methylmalonate (12) with NaH (1.5 equiv) in THF and then addition of PhSeBr (1.5 equiv). The Diels-Alder reaction was carried out by heating a solution of 1 (3.0 mmol) and 2, prepared from 6.6 mmol of 13, in CCl_4 (45 ml) at reflux under an atmosphere of argon for 6 hours. Evaporation of the CCl_4 and purification by flash chromatography (10% $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$) gave 3 as a colorless liquid in 68% yield.⁸



We are currently investigating the generality of the $\text{EtAlCl}_2/\text{HMPA}$ double dehydrobromination procedure, and pursuing the synthesis of catharanthine.

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- (8) All compounds gave spectra in accord with their proposed structures. NMR spectra were recorded on a Varian EM-360L (60 MHz) instrument; chemical shifts are reported in ppm downfield from TMS and coupling constants are reported in Hz: **1** NMR (CDCl_3) δ 1.0 (t, $J=7$, 3H), 1.7-2.2 (m, 2H), 3.75 (s, 3H), 4.3 (dd, $J=2$ and $J=3$, 2H), 5.3-5.8 (m, 2H), 6.4-6.7 (m, 1H); MS, m/e 167 (M^+), 166, 152, 122, 107, 93, 59. **2** NMR (CCl_4) δ 3.8 (s, 6H), 6.45 (s, 2H); MS, m/e 144 (M^+), 113, 59. **3** NMR (CDCl_3) δ 1.0 (t, $J=7$, 3H), 1.6-3.3 (m, 7H), 3.68 (overlapping singlets, 9H), 5.1 (m, 1H), 6.0 (m, 1H); IR (CH_2Cl_2) 1745, 1700, 1455, 1400, 910 cm^{-1} ; MS m/e (CI) 312 ($M+1^+$), 280, 237, 168, 167, 145; High Res MS Calcd. for $\text{C}_{15}\text{H}_{21}\text{NO}_6$: 311.1368; Found: 311.1324. **6** NMR (CCl_4) δ 1.0 (t, $J=7$, 3H), 1.7-2.2 (m, 2H), 3.7 (s, 3H), 4.1 (m, 2H), 4.8-5.2 (m, 1H), 5.4-5.7 (m, 1H), 6.4-6.7 (m, 1H). **9** NMR (CDCl_3) δ 0.97 (t, $J=7$, 3H), 1.6-2.3 (m, 4H), 2.3-2.6 (m, 2H), 2.84 (d, $J=2$, 2H), 3.55 (s, 2H), 5.4 (brs, 1H), 7.3 (s, 5H). **10** NMR (CDCl_3) δ 1.0 (t, $J=7$, 3H), 1.7-2.3 (m, 4H), 3.4 (t, $J=6$, 2H), 3.6 (s, 3H), 3.7 (d, $J=2$, 2H), 5.45 (brs, 1H); IR (neat) 1715, 1680, 1455, 1420, 1290, 1245, 1210, 1120, 970, 775 cm^{-1} . **11** NMR (CDCl_3) δ 1.1 (t, $J=7$, 3H), 1.7-3.5 (m, 6H), 3.7 (s, 3H), 3.8-4.3 (m, 2H), 4.6 (brt, 1H); IR (CH_2Cl_2) 1710, 1470, 1450, 1240, 1195, 1115, 1005 cm^{-1} . **13** NMR (CDCl_3) δ 1.67 (s, 3H), 3.68 (s, 6H), 7.2-7.8 (m, 5H); MS m/e 302 (M^+), 300, 166, 154.
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