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

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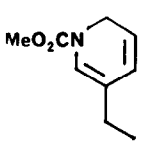
Abstract: *N-carbomethoxy-5-ethyl-1,2-dihydropyridine (1) may be prepared by the bromination of N-carbomethoxy-3-ethyl-1,2,5,6-tetrahydropyridine (10), and subsequent double dehydrobromination with $EtAlCl_2$/HMPA; this diene undergoes Diels-Alder reaction with dimethyl methylenemalonate (2) to give 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.



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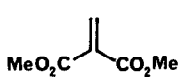

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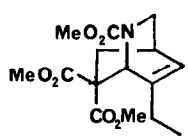

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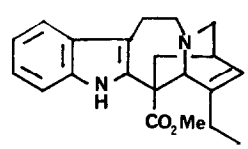

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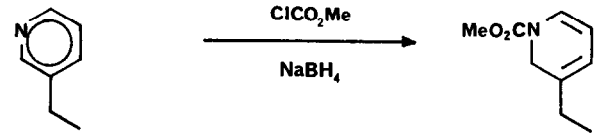
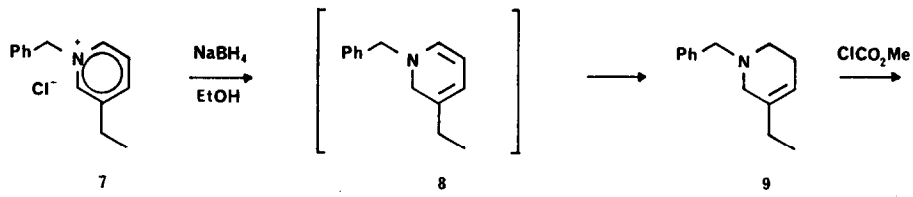
Fowler[2a] has developed an excellent route to N-carbomethoxy-1,2-dihydropyridine by the reaction of pyridine, methyl chloroformate, and $NaBH_4$; unfortunately, use of this procedure with 3-ethylpyridine (5) affords N-carbomethoxy-3-ethyl-1,2-dihydropyridine (6),[5] the incorrect regioisomer for a catharanthine synthesis. However, Fowler has converted 6 to 1 by a reduction, bromination, double dehydrobromination sequence.[6]



5 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 $EtAlCl_2$/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 chromatography[10] and crystallizaton from hexane/ether gave the dibromide 11[8] as colorless needles in 89% yield (mp 56-58°C, lit.[6] 57-58°C). The desired dihydropyridine 1 was obtained in excellent yield under extremely mild conditions utilizing our $EtAlCl_2$/HMPA double dehydrobromination procedure[7] 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 scavenger[11] to consume the liberated hydrogen bromide.



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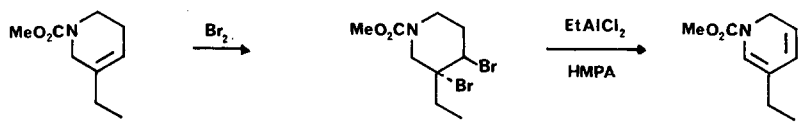
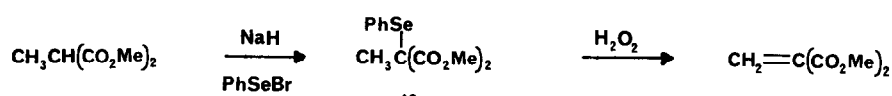


10 11 1

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 (phenyseleno)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 13[8] 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% Et_2O/CH_2Cl_2) gave 3 as a colorless liquid in 68% yield.[8]



12 13 2

We are currently investigating the generality of the $EtAlCl_2$/HMPA double dehydrobromination procedure, and pursuing the synthesis of catharanthine.

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(6) Reduction of 6 with $NaBH_4/CF_3CO_2H$ in benzene to give 10, bromination to 11, and double dehydrobromination with 1,4-diazabicyclo[2.2.2]octane in dimethylformamide at reflux gave 1. F. W. Fowler, personal communication, July 23, 1979.

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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 $C_{15}H_{21}NO_6$: 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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