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Short Synthesis of (±)-Hirsutine: Direct Addition of Dimethyl Malonate Anion to a 1,4-Conjugate Iminium Salt of Appropriate 3-Ethylindolo[2,3-*a*]quinolizidine

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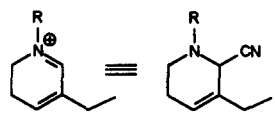
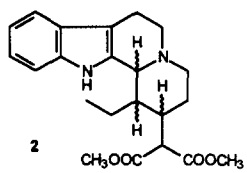
Abstract: Direct addition of dimethyl malonate anion to a 1,4-conjugate iminium salt of 3-ethylindolo[2,3-*a*]quinolizidine **4a** (regenerated from the corresponding α-aminonitrile **4b**) afforded enamine **5**. Catalytic hydrogenation of compound **5** led stereoselectively to compound **6** (*pseudo*), which is the highly desired intermediate for the preparation of several *Corynanthé* alkaloids, including (±)-hirsutine **7**.

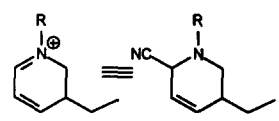
The reaction of β-dicarbonyl anions [*e.g.* $^{-}CH(COOCH_3)_2$] with 1,4-conjugated dihydropyridinium salts, or with their α-aminonitrile equivalents, prepared by the Polonovski-Potier reaction followed by cyano trapping from appropriate 1,2,5,6-tetrahydropyridine derivatives, has frequently been used in alkaloid syntheses.[1-4] However, application of the method to the preparation of *Corynanthé*-type indole alkaloids with an ethyl side chain at C-20 was less satisfactory. The exclusive formation of 3-ethyl-5,6-dihydropyridinium salt **1a** as intermediate, trapped under the form of its α-aminonitrile equivalent **1b**, led to the unnatural "inside" series, *e.g.* to compound **2**.[5,6] The presumably more useful intermediate 3-ethyl-2,3-dihydropyridinium salt **3a**, or its α-aminonitrile equivalent **3b**, was not formed.



1a R= tryptophyl **1b**

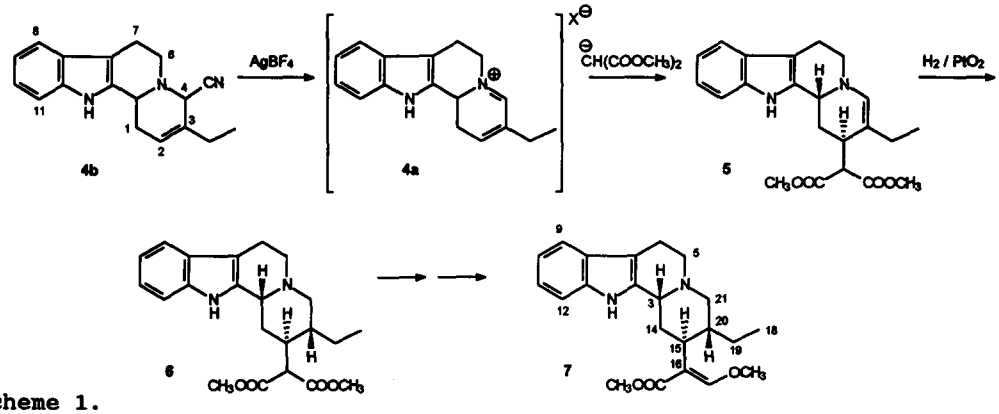


2



3a **3b**

We have now overcome this difficulty. Treatment of our recently described[7,8] 3-ethyl-4α-cyano-indolo[2,3-*a*]quinolizidine **4b** with sodium dimethylmalonate in the presence of $AgBF_4$ afforded, *via* iminium salt **4a**, compound **5**.[9] Catalytic hydrogenation of **5** yielded stereoselectively the highly desired compound **6** (*pseudo*).[10-13] Only two mundane reactions, partial reduction with $(i\text{-Bu})_2AlH$ and treatment with HCl_g/MeOH, remain to be done for completion of a total synthesis of (±)-hirsutine **7** (Scheme 1).[11,12]



Scheme 1.

The ^{13}C-nmr data (Figure 1) are in good agreement with the proposed structures.[14-16]

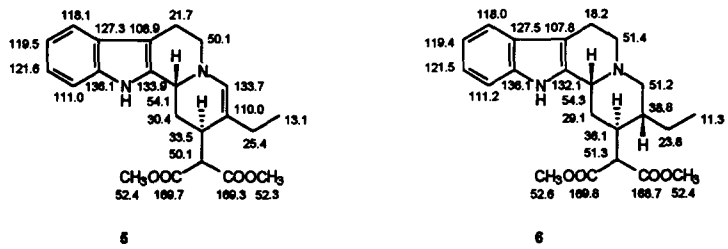


Figure 1. ^{13}C-nmr data of compounds **5** and **6**.

As far as we know, this is the first successful addition of a 1,3-dicarbonyl anion to a 1,4-conjugated iminium system of a 3-ethylindolo[2,3-*a*]quinolizidine skeleton. The reaction leads to the natural "outside" series (*vide supra*). The accessibility of the starting materials and the simplicity of the transformations add to the beauty of our method. Several applications of the method to the synthesis of other *Corynanthé* alkaloids can be expected.

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8. **Preparation of compound 4b:** The preparation of our starting material, compound **4b**, has been described earlier.[7]
9. **Preparation of compound 5:** Compound **4b** (70 mg, 0.25 mmol) was dissolved in 2 ml of dry THF. $AgBF_4$ (54 mg, 0.28 mmol) was added and the solution stirred at rt for 5 min. The sodium dimethyl malonate solution, prepared using NaH (9 mg, 0.38 mmol) in 0.5 ml of THF (Na dried and distilled) and dimethyl malonate (43 mg, 0.32 mmol), was added with syringe at rt during 20 min. Stirring was continued for 16 h. Aqueous Na_2CO_3 solution (10%) was added, and the mixture was extracted with CH_2Cl_2, dried with Na_2SO_4 and evaporated. The crude product was purified by flash chromatography (silica, CH_2Cl_2/MeOH, 99.8/0.2) to give compound **5**.

   Compound **5**. Yield 43 mg (45%). Amorphous material. IR ($CHCl_3$): 3360 (m, br, NH), 1725 (s, br, 2 x C=O). ^{1}H-nmr: 1.00 (3H, t, J=7.5 Hz, H-18), 2.00 (2H, q, J=7.5 Hz, H-19), 3.75 (3H, s, $-COOCH_3$), 3.79 (3H, s, $-COOCH_3$), 3.91 (1H, dd, $J_{3,14\alpha}$=10.5 Hz, $J_{3,14\beta}$=3 Hz, H-3), 5.95 (1H, s, H-21), 7.09 (1H, t-like, J=8 Hz, H-10), 7.15 (1H, t-like, J=8 Hz, H-11), 7.34 (1H, d, J=8 Hz, H-12), 7.47 (1H, d, J=8 Hz, H-9), 7.90 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. MS: 382 (M^+), 367, 353, 251 (100%), 221, 170, 169. HRms: Found 382.1912. Calcd for $C_{22}H_{26}N_2O_4$: 382.1893.

10. **Preparation of compound 6:** Compound **5** (39 mg, 0.102 mmol) in MeOH (5 ml) was hydrogenated [$PtO_2 \cdot H_2O$ (28 mg)]. After 1 h reaction time the mixture was filtered, the solvent evaporated, and the crude product **6** purified by PLC (silica, CH_2Cl_2/MeOH, 9/1).
Compound **6**. Yield 27.8 mg (71%). Mp. 175-176°C (toluene/n-hexane) (lit.[11] mp. 175-176°C). IR ($CHCl_3$): 3430 (m, br, NH), 1730 (s, br, 2 x C=O) cm^{-1}. ^{1}H-nmr ($CDCl_3$): 0.84 (3H, t, J=7 Hz, H-18), 3.77 (3H, s, $-COOCH_3$), 3.78 (3H, s, $-COOCH_3$), 4.22 (1H, br s, H-3), 7.10 (1H, t-like, J=7.5 Hz, H-11), 7.16 (1H, t-like, J=7.5 Hz, H-10), 7.39 (1H, d, J=7.5 Hz, H-12), 7.47 (1H, d, J=7.5 Hz, H-9), 8.18 (1H, br s, NH). For the ^{13}C-nmr data, see Figure 1. MS: 384 (M^+), 383, 369, 353, 325, 253 (100%), 225, 197, 184, 170, 169, 156. HRms: Found 384.2034. Calcd for $C_{22}H_{28}N_2O_4$: 384.2049.
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