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Tandem Acylation - Cycloalkylation With Cyclohexene 1-Acetic Acid : A New Entry to Aporphine Alkaloids.

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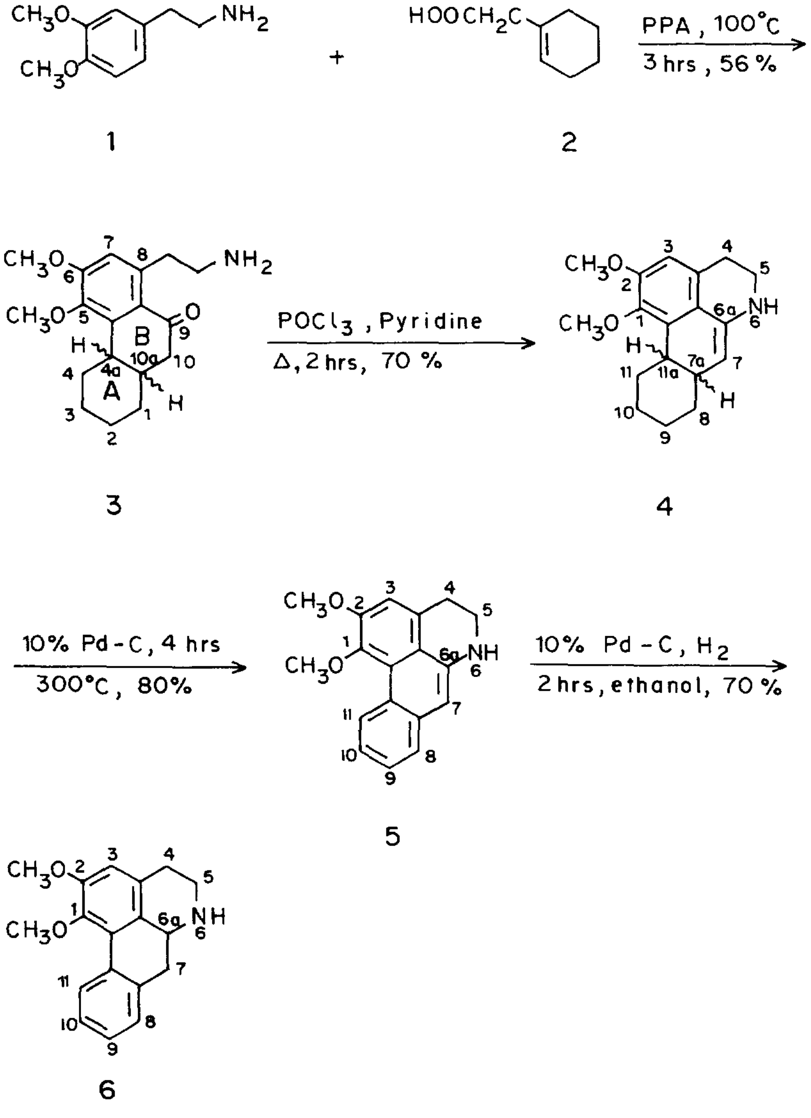
ABSTRACT : Tandem Acylation-Cycloalkylation of 3,4-dimethoxy phenylethylamine **(1)** with cyclohexene-1-acetic acid **(2)** in polyphosphoric acid (PPA) afforded 8-(2-aminoethyl)-1,2,3,4,4a,10a-hexahydro-9-oxo-phenanthrene **(3)** which on cyclisation followed by dehydrogenation with Pd-C afforded dehydronornuciferine **(5)**. Hydrogenation of 5 yielded (±) N-nornuciferine **(6)**.

Aporphine alkaloids[1] are a group of about three hundred alkaloids all of which possess tetracylic system. These aporphines are basically isoquinoline alkaloids and exhibit interesting pharmacological properties[2,3].

Previous syntheses of these pharmacologically important alkaloids are usually laborious and not always satisfactory[4-7].

In the present paper we report for the first time, tandem acylation-cycloalkylation of 3,4-dimethoxy phenylethylamine[8] **(1)** with cyclohexene -1-acetic acid[9] **(2)** for the synthesis of aporphine alkaloids namely dehydronornuciferine[10] **(5)** and (±) N-nornuciferine[11] **(6)**. As indicated in the scheme, tandem acylation-cycloalkylation of **1** with **2** in polyphosphoric acid (PPA) at 100°C for three hours afforded 8-(2-aminoethyl)-5,6-dimethoxy-1,2,3,4,4a,10a-hexahydro-9-oxo-phenanthrene **(3)**[12] in 56% yield. Compound **3** underwent cyclisation by heating with $POCl_3$-pyridine on water bath for two hours to give 1,2-dimethoxy-5,6,7a,8,9,10,11,11a-Octahydro-4H-dibenzo (de,g) quinoline[12] **(4)** in 70% yield. Dehydrogenation of **4** with 10% Pd-C for four hours at 300°C resulted in the formation of dehydronornuciferine **(5)** mp 150°C (Lit.[10] mp 149.5-150.5°C) . Hydrogenation of ethanolic solution of **5** with 10% Pd-C for two hours gave (±)-N-nornuciferine[11] **(6)** as brown oil. The physical, microanalytical and spectral data of the compounds **5** and **6** were found to be identical with the reported data.[10,11]

Scheme


PPA, 100°C
3 hrs, 56 %
1
2
3
4
POCl3, Pyridine
Δ, 2 hrs, 70 %
10% Pd-C, 4 hrs
300°C, 80%
5
10% Pd-C, H2
2 hrs, ethanol, 70 %
6

The method described is new, short, simple, utilises inexpensive chemicals and yields are also attractive.

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12. The Physical, microanalytical and spectral data for the compounds **3** and **4**.

    3 Brown Oil, IR (Oil film) 3500, 2950, 1680, 1600, 1265, ^{1}H-NMR (60 MHz, $CDCl_3$/TMS) 1.1-2.8 (m,15H, H-1,2,3,4,10a,10,CH_2, NH_2), 2.9-3.35(m,3H, H-4a, Ar-CH_2), 3.88 (s,3H,OCH_3), 3.90 (s,3H,OCH_3) 7.3 (s,1H, H$_{arom}$), UV (MeOH) λ_{max} (nm) (log ϵ) 232.0(0.953), 310.0 (2.683), 340.0 (4.826). Mass m/z (rel. intensity) = 303 (m$^+$,10), 260 (57), 259(87), 241(61), 183(42), 81(100). Anal. Calcd. (%) for $C_{18}H_{25}NO_3$: C,71.29, H,8.25; N, 4.62; found: C, 71.23; H 8.21; N 4.60.

    4 Red Oil, IR (Oil film) 3380, 3350, 3250, 2960, 1620, 1265,^{1}H-NMR (60 MHz, $CDCl_3$/TMS) 1.0-2.75 (m, 9H, H-7a,8,9,10,11), 3.0-3.35 (m,3H,H-11a, Ar-CH_2),3.45 (m,2H,CH_2), 3.89 (s, 3H, OCH_3), 4.0 (s,3H, OCH_3),6.15 (d, 1H, C_7-H), 6.80 (s,1H, H$_{arom}$), UV (MeOH)

λ_{max} (log ϵ), 249.0(0.554), 323.0 (0.968), 369.0 (5.826), Mass m/z (rel. intensity) = 285 (m^+,15), 227(100), 226 (50), 115(63), 69(75). Anal. Calcd (%) for $C_{18}H_{23}NO_2$; C, 75.78; H,8.07; N,4.91, found C, 75.70; H,8.0; N,4.88.

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