AN EFFICIENT ONE-POT SYNTHESIS OF CYCLOVIROBUXINE A FROM BUXOZINE C

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UDC 547.945

For many years, alkylation of 1,2-aminoalcohols was usually performed in high yield by catalytic hydrogenation of oxazolidine. Cope et al. reported that the ring opening of oxazolidine under catalytic hydrogenation with platinum oxide afforded 2-alkylaminoethanols as the only detectable product. The yield is nearly quantitive [1].

The ring opening of tetrahydro-1, 3-oxazine is previously performed with nucleophilic agents such as lithium aluminum hydride [2] and bromozincioacetate [3, 4], which is a useful synthetic method to obtain 3-aminopropanol derivatives.

Buxozine-C (**1**), the first *Buxus* alkaloid possessing a tetrahydro-oxazine ring joined to position 16a, 17b of the androstane skeleton, was first isolated from *Buxus sempervirens* L. Its structure elucidation was reported by Voticky [5] in 1977, and it was obtained by semisynthesis from cyclovirobuxine D [6].

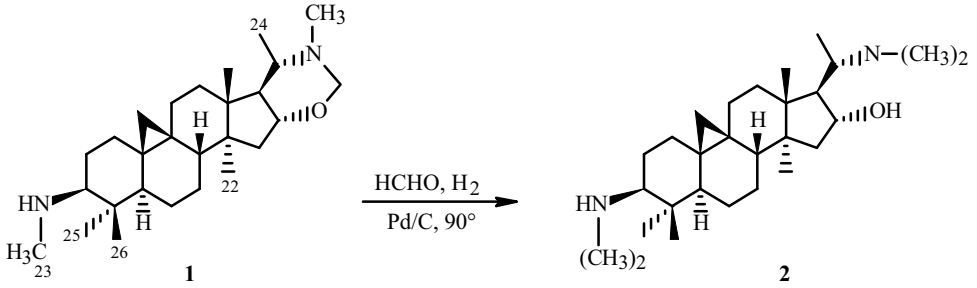
Cyclovirobuxine A (**2**), a *Buxus* alkaloid, was first isolated by Khuong-Huu-Laine [7] in 1966. It has potential application for the treatment of cardiovascular and cerebrovascular diseases [8].

Similar to platinum oxide, palladized carbon is an important hydrogenation catalyst. Meanwhile palladized carbon is also an effective catalyst for reductive amination.

In the current attempt at the semisynthesis of cyclovirobuxine A from buxozine C, the real issue is to choose an efficient catalyst reacting both on reductive ring cleavage and amination.

The above-mentioned data on platinum oxide led to speculation that palladized carbon may be an effective catalyst for both direct ring opening of tetrahydro-1,3-oxazine and reductive amination of buxozine C.

Results showed that reductive amination and ring cleavage of compound **1** with 10% palladized carbon as catalyst afforded alkaloid **2** in nearly quantitive yield (Scheme 1).



Scheme 1. Synthesis of cyclovirobuxine A (**2**) from buxozine C (**1**).

The postulated formulation of compound **2** is in accordance with the number of acid hydrogen found in the molecule. Characteristically, The TOF-MS displayed a peak of the $[M+H]^+$ at 431.7($C_{28}H_{50}N_2OH^+$, requires 431.71). The ^1H NMR showed the presence of the hydroxy group at 4.49 ppm. The IR spectrum exhibited the vibration of the O-H bond (3414 cm^{-1}) and the *tert*-amino group (1175 cm^{-1}).

Melting point was determined on an RY-1 melting point apparatus and is uncorrected. Infrared spectra were recorded in KBr on a Nicolet Impact 410 spectrophotometer. NMR spectra were taken on Bruker AV-500 spectrometers (300 MHz for

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0009-3130/08/4406-0829

^{1}H and 125 MHz for ^{13}C). Deuteriochloroform was used as the solvent. Chemical shifts are given in the δ-scale (ppm), and coupling constants J in Hz. Assignment of C atoms in the ^{13}C NMR spectra was based on previous studies with *Buxus* alkaloids [9, 10]. API-MS was recorded on an Agilent 1100 LC-MS mass spectrometer.

Cyclovirobuxine A (2). In a high-pressure autoclave (1000 mL) containing 10% Pd/C (1g) and absolute ethanol (300 mL) was added 37% aqueous formaldehyde (2.25 mL, 0.03 mol) and buxozine C (10.35 g, 0.025 mol). Stirring led to the ring opening reaction with H_2 at 2 atm pressure at 90°C. After 6 h, the mixture was filtered, the solvent evaporated, and the residue recrystallized with acetone to afford 10.46 g (97%) of cyclovirobuxine A, mp 241–242°C (acetone, decomposed), lit. [7] 244°C.

IR spectrum (KBr, ν_{max}, cm^{-1}): 3414, 2965, 2926, 2861, 2824, 2783, 2765, 1640, 1648, 1455, 1384, 1376, 1369, 1354, 1336, 1398,1255, 1175, 1151, 1100, 1029, 1003, 987, 897.

^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.49 (1H, s, OH), 4.18 (1H, m, H-16), 2.76 (1H, m, H-20), 2.40 (3H, s, H-23), 2.40 (3H, s, H-23′), 2.28 (3H, s, H-24), 2.28 (3H, s, H-24′), 1.09 (3H, s, H-22), 1.08 (3H, s, H-18), 0.99 (3H, s, H-26), 0.91 (3H, s, H-25), 0.64 (1H, d, J = 3.8, H-19), 0.39 (1H, d, J = 4.1, H-19′)

^{13}C NMR (125 MHz, $CDCl_3$): 79.1 (C-16), 71.9 (C-3), 62.4 (C-20), 57.1 (C-17), 49.5 (C-14), 48.2 (C-8), 47.3 (C-24, C-24′), 44.9 (C-13), 44.7 (C-4), 44.3 (C-5), 41.9 (C-10), 33.4 (C-12), 31.6 (C-15), 30.3 (C-1), 26.9 (C-19), 26.3 (C-25, C-26), 26.2 (C-23, C-23′), 26.0 (C-6, C-7), 21.4 (C-2), 21.1 (C-9), 20.4 (C-11), 19.5 (C-22), 19.0 (C-18), 16.0 (C-21).

API-MS (*m/z*): 431.7 $[M+H]^+$.

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