UNEXPECTED REDUCTION OF INDOLE DOUBLE BOND IN MITRAGYNINE USING $n$-BUTYLSILANE AND CATALYTIC TRIS(PENTAFLOROPHENYL)BORANE

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GRAPHICAL ABSTRACT

Abstract An unexpected reduction of indolic double bond of mitragynine was described by using $n$-butyl silane and tris(pentafluorophenyl)triborane.

Keywords Mitragynine; $n$-butylsilane; reduction; tris(pentafluorophenyl)triborane

INTRODUCTION

It was previously suggested that the 9-methoxy group of mitragynine is compulsory for the opioid activity of the mitragynine-related analog.\cite{1,2} However, mitragynine was reported to exhibit hepatotoxicity effects in animal models\cite{3} and human beings under prolonged consumption.\cite{4,5,6} The carbonyl functional group on mitragynine might be responsible for the hepatotoxicity.\cite{7} Hence, this prompted us to find a semisynthetic approach to selectively reduce the carboxylate group of mitragynine. Currently, several methods are available for the reduction of carbonyl group to methyl using silane and Lewis base.\cite{8–14} Silanes are mild reducing agents that have been commonly used in selective reductions.\cite{8,9} However, silane reagents require either strong acid or Lewis acid catalysts to become a hydride source. Tris(pentafluorophenyl)borane [B(C6F5)$_3$] is a convenient Lewis acid that has previously been used in conjunction with triethylsilane for the selective reduction of carbonyl and carboxylic functions to methylene/methyl groups.\cite{8–11} Our main objective is to reduce the carbonyl group to methyl group by using $n$-butylsilane and tris(pentafluorophenyl)borane.

Received June 6, 2013.
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Unexpectedly we have observed the reduction of indolic double bond instead of carbonyl group.

RESULTS AND DISCUSSION

Reduction of carbonyl group is an important step in synthesis chemistry. In our study we use silane coupled with Lewis base as catalyst to reduced mitragynine. Previously, the common conventional method of sodium borohydride and lithium aluminium hydride was used for simple carboxylic reduction.\[9\] We investigate the effects of various silane reducing agents on the carbonyl and the indole group of mitragynine in comparison to sodium borohydride. It was evident from Table 1 that the silane has no reduction effects on the carboxylic group of mitragynine. This was unexpected because a published paper has reported that silane can be utilized to reduce the carboxylic group.\[9–11\] The failure of the carbonyl functional group reduction on mitragynine may be due to the steric hindrance or the structure or reactivity of mitragynine. However, linear silane such as \(n\)-butylsilane reduced the indolic double bond on mitragynine unexpectedly with almost 100% conversion (Table 1). Approximately 1.0–1.5 equivalents of \(n\)-butylsilane was used to reduce mitragynine. We performed the experiments under various reactive conditions: different temperatures (25, 40 °C) and times (30, 60, 180 min) as shown in Tables 1 and 2. As outlined in Table 3, the product was obtained in good yields (>80%) and nearly 100% of conversion with negligible percentage of impurities in 3h. The end point was determined by thin-layer chromatography (TLC) and confirmed by gas chromatography–mass spectrometry (GC-MS). The yield was quantitative. The spectral data, mass profile, and thorough \textit{nmr} structure assignment and elucidation of the compound was accomplished. This results served as an alternative to the hydrogenation reduction using Pd/C approach as reported in the literature.\[15,16\]

The postulated reaction mechanism is depicted in Scheme 2.\[17\] Initially, hydride ion transferred from \(n\)-butylsilane to tris(pentafloro)borane to give the complex 3. This complex, on reacting with mitragynine, provides the intermediate 4, which undergoes hydride ion transfer to give the intermediate 5. An additional equivalent of silane or hydridoborate delivers the hydride to consummate hydrosilation to give the product 6.

CONCLUSION

In summary, we have described a new and novel method for the reduction indolic double bond of mitragynine by employing \(n\)-butylsilane and tris(pentafloro)borane. The product may exhibit interesting biological activity, and studies are under progress.

| Types of reagent       | Dosage     | Indole group | Conversion (%) | Carbonyl group |
|------------------------|------------|--------------|----------------|----------------|
| Triethylsilane         | 10 mol %  | No reaction  | 24 pt          |                |
| \(n\)-Butylsilane      | 10 mol %  | Reduced      | 100            | No reaction    |
| Polydimethylsilane     | 10 mol %  | No reaction  | No reaction    |                |
| Sodium borohydride     | 10 mol %  | No reaction  | No reaction    |                |
EXPERIMENTAL

Chemicals and Solvents

Triethylsilane, n-butyllsilane, polydimethylsilane, sodium borohydride, and tris(pentaphenyl)triborane were obtained from Sigma-Aldrich, St. Louis, USA, and used as received. Pure mitragynine was obtained from ketum leaves using the published purification protocol. Solvents (anhydrous dichloromethane, hexane, and ethyl acetate) were of analytical grade and purchased from Fischer Scientific, Loughborough, UK.

Representative Procedure for the Synthesis of (Z)-Methyl 2-((2S,3S,12bS)-3-ethyl-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacrylate

Mitragynine (1 mmol) was weighed into a flask, which was then closed with a septum and purged with nitrogen. The catalyst (B(C₆F₅)₃, 5–10 mol%) was introduced via syringe in 5 mL of anhydrous dichloromethane. Stirring was continued for 10 min at rt and then 2 equiv. of triethylsilane, polydimethylsilane, or n-butyllsilane was added. The reaction mixture was stirred for about 3 h at rt and the reaction progress was monitored by GC-MS. After complete conversion of the starting material, the reaction mixture was quenched with 0.1 mL of triethylamine. The solvent was evaporated, and the crude was purified by column chromatography to get the pure product as yellow amorphous solid (yield: 82%). Mp (DSC): 155–157°C. UV/Vis λmax (MeOH) nm (log ε): 225 (4.76), 290 (3.94). IR (KBr): 3352.8, 2947.7, 2793.2, 1682.8, 1620.9, 1433.9 1237.3, 1102.9 cm⁻¹. CD (MeOH): Δε₂₁₀ −16.2, Δε₂₃₀ +90.1, Δε₂₅₀ +16.5, Δε₂₇₀ +25.8, Δε₂₉₀ +11.1, Δε₃₁₀ +63.8, Δε₃₃₀ +40.6, Δε₃₅₀ +44.7. hRf: 0.52
Scheme 1. Synthesis of (Z)-methyl 2-(2S,3S,12bS)-3-ethyl-8-methoxy-1,2,3,4,6,7,7a,12,12a,12b-decahydroindolo[2,3-a]quinolizin-2-yl)-3-methoxyacylate.

(C₆H₁₄: EtOOCMe, 92:8). GC-MS m/z = 400 [M+]. CHN: Calcd for C₂₃H₃₀N₂O₄: C, 69.00; H, 8.00; N, 7.00. Found C, 69.02; H, 8.01; N, 6.98. ¹H NMR (400 MHz, MeOD): δ 7.43 (1H, s, H-14), 7.26 (1H, s, CDCl₃), 7.00 (1H, t, J = 7.2 Hz, H-7), 6.91 (1H, d, J = 8.1 Hz, H-6), 6.46 (1H, d, J = 7.7, H-8), 5.23 (1H, br-s, N-H [H-9]), 3.87 (3H, s, 12-OCH₃), 3.73 (3H, s, 19-OCH₃), 3.70 (3H, s, 17-OCH₃), 3.08 (1H, m, H-5), 3.01 (1H, m, H-1), 2.54 (1H, m, H-3β), 2.52 (1H, m, H-3α), 2.04 (1H, m, H-19β), 2.40 (1H, m, H-12), 1.97 (1H, m, H-19α), 1.87 (1H, m, H-4β), 1.86 (1H, m, H-4α), 1.77 (2H, m, H-11β), 1.67 (1H, m, H-11α), 1.29 (1H, m, H-17β), 1.26 (1H, m, H-17α), 1.19 (1H, m, H-16), 0.87 (3H, m, H-18); ¹³C NMR (100 MHz, MeOD): 169.14 (C-16), 160.60 (C-18), 154.53 (C-7), 137.34 (C-11), 122.03 (C-9), 117.55 (C-6), 111.25 (C-15), 104.25 (C-8), 99.78 (C-10), 64.22 (C-2) 61.59 (19-OCH₃), 66.82 (C-1), 57.33 (C-21), 53.55 (C-3), 51.36 (17-COOCH₃), 55.30 (12-OCH₃), 40.36 (C-20), 34.32 (C-5), 31.98 (C-14), 29.74 (C-13), 23.55 (C-4), 19.25 (C-22), 12.81 (C-23).

**Sodium Borohydride**

Sodium borohydride powder (27.0 mmol) was added to a stirred solution of mitragynine (27.0 mmol) in tetrahydrofuran (THF) (16 mL) at 50 °C and refluxed for 4 h. The reaction mixture was quenched with 2 N HCl (10 mL). The crude product was purified by column chromatography to obtained unconverted mitragynine.

Scheme 2. Postulated mechanism.
FUNDING

This work was supported by the Research University Grant Scheme (RUT), Universiti Sains Malaysia.

SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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