Chinese Chemical Letters Vol. 15, No. 6, pp 649-651, 2004
http://www.imm.ac.cn/journal/ccl.html

A New Deoxygenation Method for Taxanes Using Hypophosphorous Acid

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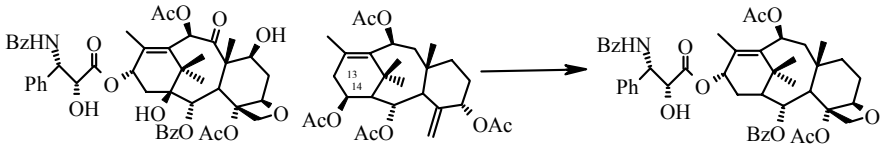
Abstract: An efficient and practical radical chain deoxygenation method by phosphorus centered radicals generated from hypophosphorous acid was developed in the synthesis of analogues of paclitaxel.

Keywords: Deoxygenation, taxanes, hypophosphorous acid.

The important anticancer agent paclitaxel and the semisynthetic analog, docetaxel, so far, continue to show impressive clinical efficiency againts ovarian, breast and lung cancer. It is also the subject of intense interest in the chemical, biological and medical communities today [1].

The chemistry of paclitaxel has been found to be particularly challenging. There are several oxygen functionalities in the taxane skeleton. But structure activity ralationship studies have showed that some of the groups were not necessary for anticancer activity. So the deoxygenation or removal of hydroxyl group are frequently encountered. Sinenxan A (SIA), which is readily available as a biosynthetic taxane, has the same taxane skeleton with that of paclitaxel. It has a 14β-OAc but without the oxetane ring and 13-oxygen which are the key moieties for anticancer activity. The development of a procedure using SIA as starting material for the preparation of bioactive paclitaxel analogues would be significant.



paclitaxel sinenxan(SIA) 1, 7, 9-trideoxypaclitaxel

An ongoing program in our laboratory is the synthesis of 1,7,9-trideoxypaclitaxel *via* SIA Yin D.L *et al.* has reported that 14β-OH and its derivatives were less important for antitumor activity [2]. So we decided to remove the 14β-OH in the first step.

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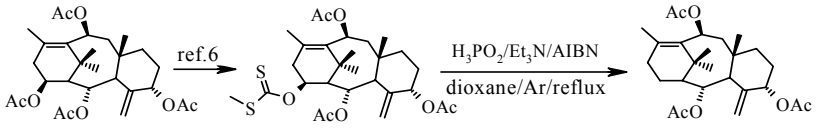
Based on the chemistry involved in the radical chain deoxygenation of alcohols by the Barton-McCombie reaction, numerous applications in the synthesis of taxanes were reported up to now [3]. In the original Barton-McCombie reaction, tributyltin hydride was the hydrogen atom source and tributyltin radical generated from the hydride serves as a chain carrier [4]. Although the method gave good yield and found many applications, the problems associated with the price, toxicity and removal of tin residues prompted the search for other hydrogen atom sources.

Radical chain deoxygenation of alcohols can be carried out with phosphorus centered radicals, generated from hypophosphorous acid or its salts. Barton *et al*. have reported that a series of alcohol thiocarbonyl derivatives were deoxygenated when treated with hypophosphorous acid and a tertiary nitrogen base (*e.g.* triethylamine) in boiling dioxane in high yields [5].

So we tried to remove 14β-OH of SIA and its derivatives by this method. Compound **1** was prepared from SIA by reference methods [6], then **1** was treated with triethylamine, 50% H_3PO_2 in dioxane under argon, and 2,2'-Azobisisobutyronitrile (AIBN) as an initiator. TLC showed that the reaction was complicated. The major product was isolated and comfirmed by NMR and MS as the target 14-deoxy –SIA [7], but the yield was as low as 42%(**Scheme 1**). We were wondering if the 4,20-terminal double bond was attacked by the reagent. H_3PO_2 was initiated to produce numerous H_2PO_2•radicals by AIBN. The excess H_2PO_2•was inclined to add to 4,20-double bond of SIA to lead to side-products. In order to confirm our suspicion of the involvement of 4,20-terminal double bond, we selected another compound **2**, which was also prepared in the synthesis of 1, 7, 9-trideoxypaclitaxel *via* SIA and without 4,20-terminal double bond. **2** was treated under the same conditions to give compound **3** [8] in about 82% yield (**Scheme 2**). So we tried to add olefin (*e.g.* cyclohexene or 1-dodecene) to the system as 'sacrificial olefin'. The presence of an excess of olefin protected **1** from attack by the phosphorus-centered reagent radical H_2PO_2•. So the result was better than that without sacrificial olefin . The yield was raised to 74% [9].

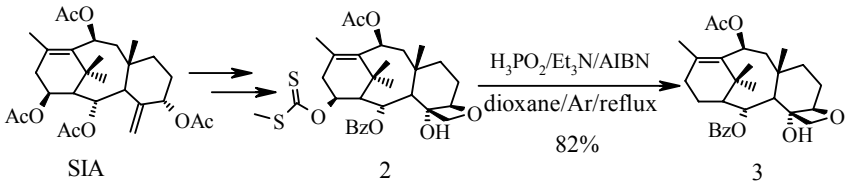


Scheme 1

In these reactions we succeeded to remove the 14β-OH of SIA and compound **2** by phosphorus centered radicals generated from hypophosphorous acid in satisfactory yield. The reagents used for the reaction are not expensive and less toxic. More important, this method is applicable for large scale preparation.

In conclusion, this method provides efficient, non-toxic and practical deoxygenation in the synthesis of taxanes. The structures of compounds in this paper were confirmed by ^{1}H NMR, ^{13}C NMR, FABMS. The synthesis of 1, 7, 9-trideoxypaclitaxel *via* SIA is in progress.

Scheme 2



Acknowledgment

This research work was financially supported by NNSFC (grant No.30100230) . We are grateful to Zhang Dayong for kindly providing SIA.

References and Notes

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7. Selected data of 14-deoxy-SIA: white solid, $[\alpha]_D^{20}$ +54 (c 0.83, $CHCl_3$); mp: 128.5-131.2℃; 1H NMR (500MHz, $CDCl_3$, δ ppm): 6.06 (dd,1H, J=5.3Hz,12.3Hz, H-10), 5.38 (dd,1H, J=2Hz, 6.3Hz, H-2), 5.27(t, 1H, J=3Hz, H-5), 5.25 (s, 1H, H-20), 4.89 (s, 1H, H-20), 3.08(d,1H, J=6Hz, H-3), 2.45 (m, 1H, H-13), 2.37 (dd, 1H, J=12Hz, 14.5Hz, H-9), 2.12 (s, 3H, OAc-CH_3-10), 2.06 (s, 3H, CH_3-18), 2.04 (s, 3H, OAc-CH_3-2), 2.03 (s, 3H, OAc-CH_3-4), 2.09-1.87 (m 3H, H-7, H-13, H-14), 1.80 (m, 3H, H-1, 2×H-6), 1.68 (m, 1H, H-14), 1.59 (s, 3H, CH_3-16), 1.58 (m, 1H, H-9), 1.22(m, 1H, H-7),1.05 (s, 3H, CH_3-17), 0.85 (s, 3H, CH_3-19); ^{13}CNMR (125MHz, $CDCl_3$, δ ppm): 170.18 (OAc-C=O), 169.63 (OAc-C=O), 169.62 (OAc-C=O), 144.35 (C-4), 136.96 (C-12), 133.90 (C-11), 116.36 (C-20), 78.73 (C-5), 72.25 (C-2), 70.49 (C-10), 52.01 (C-1), 43.78 (C-9), 41.19 (C-3), 39.68 (C-8), 37.09 (C-15), 33.65 (C-7), 31.67 (C-17), 30.10 (C-13), 28.96 (C-6), 25.33 (C-16), 22.50 (19-CH_3), 22.01 (OAc-CH_3), 21.66 (OAc-CH_3), 21.65 (OAc-CH_3), 21.22 (18-CH_3), 18.29 (C-14); FABMS: *m/z* 447.3(M+1).
8. Selected data of compound **3**: white solid, $[\alpha]_D^{20}$ +83 (c 0.54, $CHCl_3$); mp 198-200℃; ^{1}HNMR (500MHz, $CDCl_3$, δ ppm): 7.97(dt, 2H, J=7.7Hz, 1.5Hz, Bz), 7.58(t, 1H, J=7.5Hz, Bz), 7.46(t, 2H, J=7.5Hz, Bz), 6.00(dd, 1H, J=12.3Hz, 5.5Hz, H-10), 5.77(dd, 1H, J=5.7Hz, 2.5Hz, H-2), 4.75(dd, 1H, J=9.2Hz, 3.0Hz, H-5), 4.31(d, 1H, J=8.0Hz, H-20), 4.16(d, 1H, J=8.0Hz, H-20), 2.47(dd, 1H, J=14.5Hz, 12.5Hz, H-9), 2.42(m, 1H, H-13), 2.26(d, 1H, J=6Hz, H-3), 2.11(m, 2H, H-6, H-13), 2.06(s, 3H, OAc-CH_3-10), 1.97(m, 1H, H-6), 1.90(s, 3H,CH_3-18), 1.86(m, 1H, H-1), 1.67(s, 3H, CH_3-16), 1.63(m, 1H, H-7), 1.33(s, 3H, CH_3-19), 1.07(s, 3H, CH_3-17); ^{13}C NMR (125MHz, $CDCl_3$, δ ppm): 170.12(10-OAc-C=O), 165.34(2-Bz-C=O), 137.81(C-12), 134.43(C-11),133.34, 129.58, 129.48, 128.65(6xph), 87.56(C-5), 80.52(C-4), 76.24(C-20), 73.43(C-10), 70.50(C-2), 50.23(C-1), 46.01(C-9), 44.85(C-3), 37.21(C-8), 36.51(C-15), 35.03(C-17), 32.35(C-13), 29.60(C-7), 27.22(C-6), 25.12(C-16), 21.76(C-19), 21.51 (OAc-CH_3), 21.13(C-18), 18.18(C-14); FABMS: *m/z* 483.4(M+1).
9. Reaction procedure: The solution of compound **1** , triethyl amine(5eq), 50% hypophosphorous acid(5eq) and cyclohexene(5eq) in dioxane under argon was treated with AIBN(0.1eq) solution (0.1 mol/L in dioxane) for several times (at every 30 min) under reflux. The solution was washed with water and dried over anhydrous $NaSO_4$, concentrated and chromatographed to give 14-deoxy-SIA.

Received 29 July, 2003