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Chemo-, regio- and stereoselective Mitsunobu reaction of unprotected pyrimidine bases with hydroxypyrrolidines

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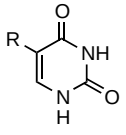
Abstract—Unprotected pyrimidine bases were used in Mitsunobu reaction to afford in high yield new substituted pyrrolidines. The reaction is chemo-, regio- and stereoselective affording exclusively *N*-1 alkylated derivatives of (3*S*)-*N*-benzyl-3-hydroxypyrrolidine and (3*S*,4*S*)-*N*-benzyl-3,4-dihydroxypyrrolidine.

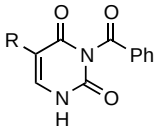
In the course of our ongoing research aimed at the exploitation of hydroxypyrrolidines[1] in organic synthesis we envisaged their use as possible scaffolds to produce, after proper substitution, nucleoside analogues.[2] The introduction of a nucleobase on the hydroxypyrrolidine ring and the optimisation of this process was then considered as the crucial step. Various syntheses of pyrrolidine derivatives[3] bearing a nucleobase have been published, which used as a key step both a nucleosidation reaction[4] or the final closure of the pyrimidine ring.[5]

Mitsunobu reaction[6] represents a useful alternative for the stereoselective synthesis of nucleosides. This reaction has been previously used to insert both purine and pyrimidine bases onto complex molecular structures.[7] The Mitsunobu reaction conditions require the use of suitably protected form of the nucleobases: purine derivatives are obtained from 6-chloro purine, while the insertion of uracil (**1**) or thymine (**2**) is commonly obtained through the use of *N*-3-benzoylated reagents **3** and **4**.[8]



1 R = H

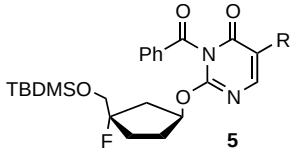
2 R = Me



3 R = H

4 R = Me

N-3-Benzoyl thymine was recently used to introduce thymine on 4-hydroxyproline under standard Mitsunobu conditions (Ph_3P and DIAD at rt).[9] A major drawback of this reaction is its low chemoselectivity. Actually, the high reactivity of the C-2 carbonyl group is responsible for the formation of relevant amounts of *O*-alkylated products, which decreases the overall yield of the reaction. With a judicious choice of the solvent, switching from THF to a mixture of dioxane and DMF, Chu et al.[10] reduced the amount of the *O*-alkylated byproducts **5**. Unprotected bases were used, occasionally affording a mixture of *O*-alkylated and *N*,*N*′-dialkylated compounds and low yield of the products.[11]



5

R = H, Me, F

We can now demonstrate that the synthesis of pyrrolidine derivatives **7**–**8** and **10**–**11** (Scheme 1) can be achieved with high regio- and chemoselectivity by using unprotected pyrimidine bases.

In our experiments, when *N*-benzoylated pyrimidine bases were used with pyrrolidine **6**,[12] no reaction took place at room temperature, although the starting mate-

Keywords: Mitsunobu reaction; pyrrolidine; pyrimidine bases.

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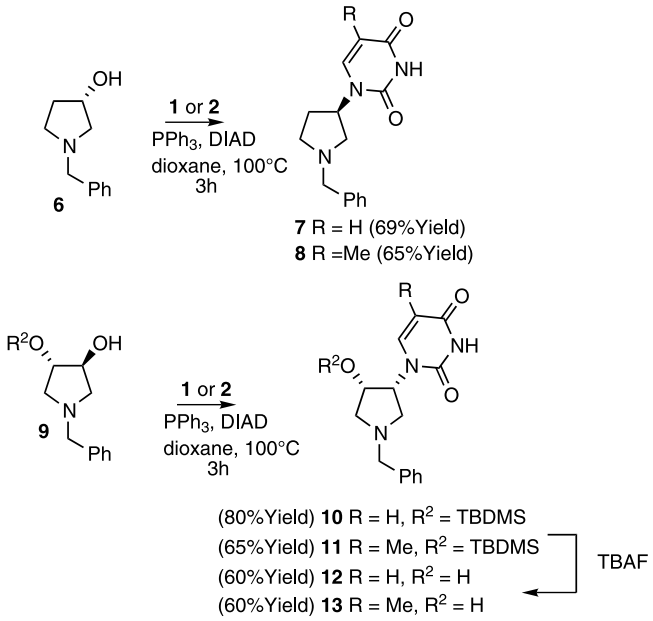

Scheme 1.

rial could not be recovered from the reaction mixture. By switching to refluxing dioxane[13,10] (100°C), eventually compound **7** was obtained in moderate yield (30%). The purification of the crude reaction was troublesome due to impurities of triphenylphosphine oxide, difficult to remove from the products with simple column chromatography. The use of solid-phase supported Ph_3P made the purification easier although it did not alter the final yield. We were not surprised to find as the product the pyrrolidine **7** without the *N*-3 protecting group, as a similar observation was found by Benner et al.,[8b] who observed the loss of the protecting group along with the purification process. However, a comparison of the ^1H NMR spectrum of the crude reaction mixture and of pure **7** demonstrated that the removal of the benzoyl group took place during the reaction, and not in the work up. Very likely, the higher reaction temperature together with the presence of the reduced form of DIAD, can probably account for the loss of the benzoyl group, also for unreacted **3**. We then decided to use for the reaction unprotected uracil and we found that the ^1H NMR of the crude reaction mixture was much cleaner and the purification afforded compound **7** in a higher yield (69%).

The use of unprotected uracil can, of course, raise the question of regioselectivity, since the presence of two non-equivalent nitrogen atoms can lead to the formation of two regioisomeric products. The structure of compound **7**[14] and **8** was assigned on the basis of their ^1H and ^{13}C NMR spectra and of a NOESY spectrum. The NOESY spectrum evidenced the presence of NOE effects between hydrogen H-6 of the uracil ring (resonating at 7.8 ppm) and all the hydrogen atoms that lay on the same side of the five membered ring. The presence of these NOE effects allows the assignment of the regiochemistry, since in a *N*-3 alkylated product hydrogen H-6 would be too far from the five membered ring to show such effects. Furthermore, the presence of NOE effects, as observed in similar systems,[15] can be assumed as proof of the lack of *O*-alkylation products. A comparison between chemical shifts of C3 ($\delta = 53.1$ ppm for **7**, and $\delta = 53.5$ ppm for **8**) with literature data[10] confirmed this result, since the value is shifted highfield with respect to analogous *O*-alkylated products. The optical purity of product **8** was ascertained by its transformation into a Mosher amide, which attested the complete stereoselectivity of the Mitsunobu reaction.

The optimised reaction conditions were applied also to dihydroxylated pyrrolidine **9**[16] which, after monoprotection with TBDMSCl, afforded compounds **12** and **13** (Scheme 1) in 48 and 39% overall yields, respectively, after deprotection with TBAF. Again we could detect neither any *O*-alkylated derivatives nor the *N*-3 alkylated isomer in the reaction mixtures, once more indicating the good efficiency of the reaction without the need of any protection.

A straightforward approach made possible to synthesise pyrrolidine derivatives substituted with a uracil or thymine group in a chemo-, regio- and stereoselective process. The use of non-protected pyrimidine derivatives, besides obeying an 'atom economy'[17] and 'green chemistry' principle, makes the overall process more efficient. Study to generalise this approach towards the synthesis of other heterocyclic systems bearing a nucleobase is currently in progress in our laboratories

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14. Synthesis of **7**: To a solution of **6** (177 mg, 1 mmol), PPh_3 (786 mg, 3 mmol) and **1** (112 mg, 1 mmol) in 4 ml of refluxing dry dioxane, DIAD (606 mg, 3 mmol) was slowly added. The mixture was stirred at 100°C for 1 h, then concentrated under reduced pressure and purified by flash chromatography (95:5 CH_2Cl_2/MeOH; $R_f = 0.38$) to yield 187 mg of **7** as a yellow oil. $[\alpha]_D^{25} = -12.6$ (*c* 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$): $\delta = 8.57$ (bs, 1H, N-*H*), 7.83 (d, 1H, $J = 8$ Hz, C*H*-N), 7.25 (m, 5H, Ph), 5.66 (d, 1H, $J = 8$ Hz, C*H*-C=O), 5.11 (m, 1H, C*H*-uracil), 3.55 (AB, 2H, CH_2-Ph), 3.06 (t, 1H, $J = 8.2$ Hz, C*H*-N), 2.78 (d, 1H, $J = 11$ Hz, C*H*-N), 2.43 (dd, 1H, $J = 10.0$, 7.5 Hz, C*H*-N), 2.40 (m, 1H, C*H*-N), 2.15 (q, $J = 9$ Hz, C*H*-C), 1.68 (dtd, 1H, $J = 10.2$, 9.5, 4.4 Hz, C*H*-C). ^{13}C NMR: ($CDCl_3$) $\delta = 163.5$ (s, CH-*C*=O), 151.5 (s, NH-*C*=O), 142.2 (d, *C*H-C=O), 138.4 (s, 1C), 128.6 (d, 2C), 127.4 (d, 3C), 102.9 (d, *C*H-N), 59.8 (t, *C*H_2Ph), 59.5 (t, CH_2-N-*C*H_2-Ph), 53.5 (d, *C*H-uracil), 53.2 (t, *C*H_2-N-CH_2-Ph), 32.4 (t, *C*H_2-C). Anal Calcd for $C_{15}H_{17}N_3O_2$: C, 66.39; H, 6.32; N, 15.49. Found: C, 66.38; H, 6.60; N, 15.13.
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