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Tetrahedron Letters 45 (2004) 6461–6463
Tetrahedron Letters

A benzyloxy group migration under Mitsunobu reaction conditions

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Received 10 May 2004; revised 25 June 2004; accepted 29 June 2004
Available online 20 July 2004

Abstract—When compounds **3a** and **3b** were subjected to a Mitsunobu reaction with benzoylthymine, the expected substitution products were formed together with the regioisomers corresponding to benzyloxy group migrations.

A recent paper of Saksena et al.[1] shows that an unusual acetonide group migration occurs in the reaction of a nucleic base with a mesylate. We report here our results on a benzyloxy group migration during the introduction of a pyrimidine base.

In the course of our research programme on carbocyclic nucleoside analogues,[2] we intended to synthesize the dihydroxylated cyclobutane compounds **1a** and **1b** (Fig. 1).

In our laboratory, good results were previously obtained by introducing purine and pyrimidine bases under Mitsunobu reaction conditions from hydroxymethyl cyclobutenic[2a] and dienic[3] compounds. We then envisaged to use this method to prepare **1a** and **1b** from benzoylthymine and compounds **3a** and **3b** (Scheme 1).

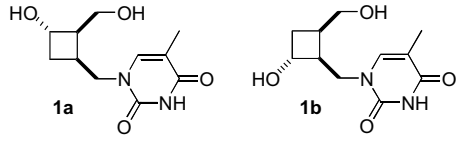

Figure 1.

Precursors **3a** and **3b** were obtained in four steps, starting from alcohol **4**[4] (Scheme 2). The hydroboration/oxidation step of protected cyclobutene **5** provided four regioisomers. As it was expected, the *trans* regioisomers were predominant in the mixture and can be separated by column chromatography.

Surprisingly, when each isolated precursor **3a** and **3b** was subjected to reaction with a protected thymine under Mitsunobu conditions, a mixture of two regioisomers **2a**[5] and **2b**[6] was formed. They were separable by column chromatography. In both cases the product of direct substitution was predominant. However the amount of the other product was not negligible (Scheme 3).

Regiochemistry was deduced from the HMBC experiment for the compound **2b**. The long range correlations between H-7′/C-6′, H-3′/C-1′ and H-1′/C-6 showed that thymine was fixed on the methylene group close to the acetoxy group (Fig. 2).

Unexpectedly under similar Mitsunobu conditions with other nucleophiles such as adenine, thiophenol and benzoic acid, precursor **3b** yielded only one regioisomer **7b**, **8b** and **9b** in 70%, 40% and 95% yield, respectively (Scheme 4). No benzyloxy group migrations were observed in these cases.

Benzyloxy group migrations have already been observed via an intermediate oxonium ion.[7] In the case of

Keywords: Nucleoside; Mitsunobu; Protecting group.
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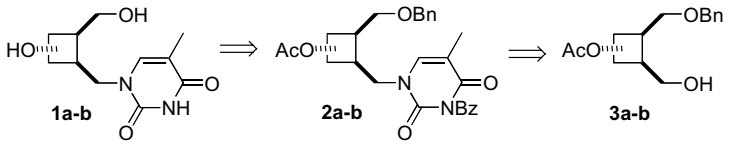
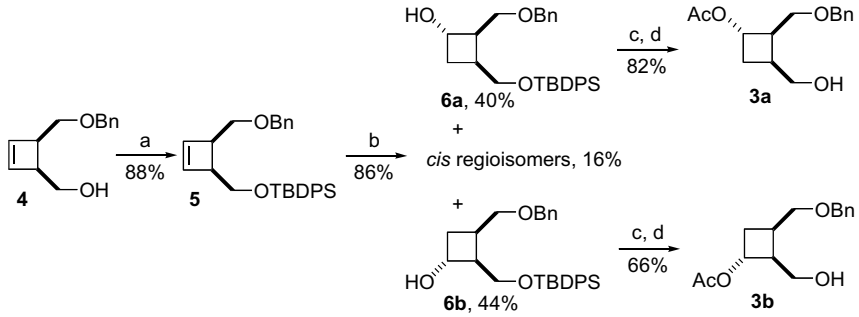
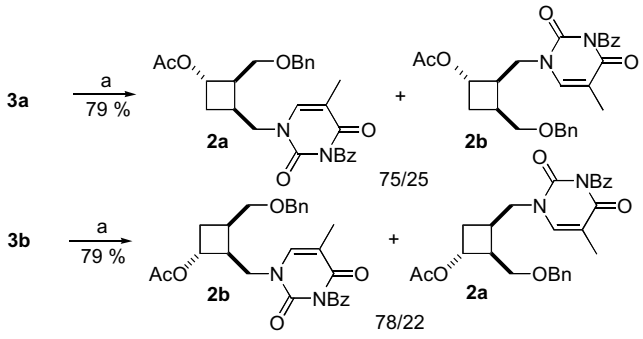
doi:10.1016/j.tetlet.2004.06.123



Scheme 1.



Scheme 2. Reagents and conditions: (a) *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 12 h; (b) (1) BH_3·THF, 20 °C, THF, 1 day; (2) NaOH, H_2O_2, 50 °C, 2 h; (c) Ac_2O, pyridine, 20 °C, 1 day; (d) TBAF, AcOH, THF, 20 °C, 12 h.



Scheme 3. Reagents and conditions: (a) *N*-3-benzoylthymine, DIAD, PPh_3, THF, 2 days, 20 °C.

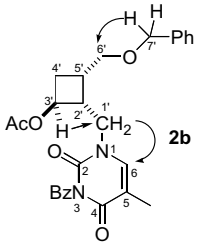


Figure 2.

reactions between compounds **3a** and **3b** and benzoylthymine, the mechanism probably involves a competitive formation of such an intermediate **A** (Fig. 3) besides the normal Mitsunobu displacement. As this intermediate may be attacked on both sides, the partial [1,4]-benzyloxy group migration is thus explained. Involvement of five-membered ring intermediate cations has already been postulated to explain unusual results in the conditions of Mitsunobu reaction.[8] A partial contribution of the transition state **B** is another possibility equally coherent with our results.

Finally, the desired nucleoside precursor **12b** was obtained under the same experimental conditions but using a silylated precursor **11b**. In this case, no migration was observed (Scheme 5).

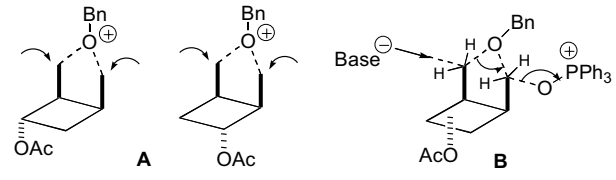
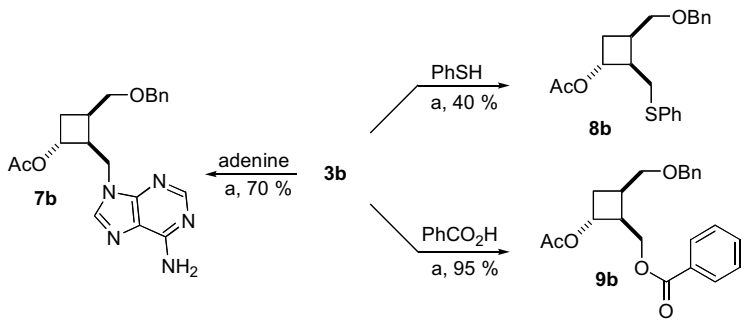
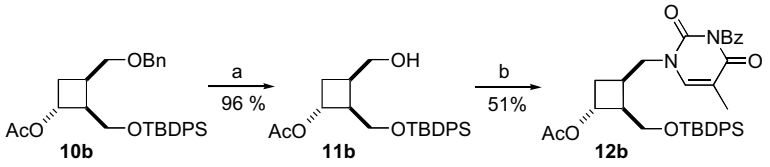


Figure 3.



Scheme 4. Reagents and conditions: (a) DIAD, PPh_3, THF, 20 °C.



Scheme 5. Reagents and conditions: (a) $Pd(OH)_2/C$ 20%, cyclohexene, EtOH, reflux, 38 h; (b) *N*-3-benzoylthymine, DIAD, PPh_3, THF, 2 days, 20 °C.

These results show that the choice of the protecting group in these experiments may be important.

Acknowledgements

We thank the local section of Sarthe of the Ligue Nationale contre le Cancer for a fellowship to Y.M. and the referee for interesting suggestions.

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5. Compound **2a**: ^{1}H NMR ($CDCl_3$) δ 7.90 (dd 2H, $H_{orthoC=O}$, $J_{HorthoC=O/HparaC=O} = 1.5$ Hz, $J_{HorthoC=O/HmetaC=O} = 8.4$ Hz), 7.66–7.61 (m, 1H, $H_{paraC=O}$), 7.50–7.46 (m, 2H, $H_{metaC=O}$), 7.38–7.28 (m, 5H, H arom), 7.07 (d, 1H, H-6, $J_{H6/CH_3thymine} = 1.1$ Hz), 5.05 (ddd, 1H, H-4′, $J_{H4'/H3'a} = J_{H4'/H3'b} = J_{H4'/H5'} = 6.9$ Hz), 4.54–4.47 (m, 2H, H-7′), 3.99–3.88 (m, 2H, H-1′), 3.64 (d, 2H, H-6′, $J_{H6'/H5'} = 5.6$ Hz), 2.89–2.75 (m, 2H, H-2′, H-5′), 2.26 (ddd, 1H, H-3′$_a$, $J_{H3'a/H2'} = 4.1$ Hz, $J_{H3'a/H4'} = 6.9$ Hz, $J_{H3'a/H3'b} = 12.0$ Hz), 2.16–2.11 (m, 1H, H-3′$_b$), 2.04 (s, 3H, CH_3), 1.88 (d, 3H, CH_3, $J_{CH_3thymine/H6} = 1.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 170.6 (C=O, Ac), 169.1 (C=O, Bz), 163.1 (C-2), 150.0 (C-4), 140.3 (C-6), 137.9–127.7 (C arom), 110.6 (C-5), 73.5 (C-7′), 68.6 (C-4′), 67.9 (C-6′), 49.7 (C-1′), 44.1 (C-5′), 30.4 (C-3′), 29.9 (C-2′), 20.9 (CH_3, Ac), 12.3 (CH_3, thymine); IR (neat, cm^{-1}) 3065, 2930–2857, 1744–1656, 1363, 1247, 1110–1054, 778–627; Anal. Calcd for $C_{27}H_{28}N_2O_6 \cdot 1.5H_2O$: C, 64.40; H, 6.21; N, 5.56. Found: C, 64.08; H, 5.81; N, 5.52; HMRS Calcd for $C_{27}H_{29}N_2O_6$ $[M+H]^+$: 477.2026. Found: 477.2085.
6. Compound **2b**:^{1}H NMR ($CDCl_3$) δ 7.92 (dd, 2H, $H_{orthoC=O}$, $J_{HorthoC=O/HparaC=O} = 0.8$ Hz, $J_{HorthoC=O/HmetaC=O} = 8.0$ Hz), 7.63 (m, 1H, $H_{paraC=O}$), 7.47 (m, 2H, $H_{metaC=O}$), 7.40–7.30 (m, 5H, H arom), 7.06 (d, 1H, H-6, $J_{H-6/CH_3thymine} = 1.2$ Hz), 5.05 (ddd, 1H, H-3′, $J_{H3'/H4'a} = J_{H3'/H4'b} = J_{H3'/H2'} = 8.0$ Hz), 4.54 (s, 2H, H-7′), 3.96 (dd, 1H, H-1′a, $J_{H1'a/H2'} = 7.4$ Hz, $J_{H1'a/H1'b} = 14.0$ Hz), 3.92 (dd, 1H, H-1′$_b$, $J_{H1'b/H2'} = 6.5$ Hz, $J_{H1'b/H1'a} = 14.0$ Hz), 3.63 (dd, 1H, H-6′$_a$, $J_{H6'a/H5'} = 4.4$ Hz, $J_{H6'a/H6'b} = 10.0$ Hz), 3.60 (dd, 1H, H-6′$_b$, $J_{H6'b/H5'} = 6.0$ Hz, $J_{H6'b/H6'a} = 10.0$ Hz), 2.90–2.82 (m, 1H, H-2′), 2.64–2.56 (m, 1H, H-5′), 2.21 (ddd, 1H, H-4′a, $J_{H4'a/H5'} = 2.8$ Hz, $J_{H4'a/H3'} = 8.0$ Hz, $J_{H4'a/H4'b} = 12.4$ Hz), 2.13 (ddd, 1H, H-4′$_b$, $J_{H4'b/H3'} = 8.0$ Hz, $J_{H4'b/H5'} = 10.0$ Hz, $J_{H4'b/H4'a} = 12.4$ Hz), 2.01 (s, 3H, CH_3), 1.80 (d, 3H, CH_3, $J_{CH_3thymine/H6} = 1.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 170.8 (C=O, Ac), 169.2 (C=O, Bz), 163.2 (C-2), 149.9 (C-4), 140.9 (C-6), 137.8–127.9 (C arom), 110.1 (C-5), 73.5 (C-7′), 70.6 (C-3′), 69.9 (C-6′), 48.0 (C-1′), 43.8 (C-2′), 30.5 (C-5′), 29.8 (C-4′), 20.9 (CH_3, Ac), 12.1 (CH_3, thymine); IR (neat, cm^{-1}) 3050, 2959, 1741–1650, 1363, 1240, 1105–1047, 726–699; HMRS Calcd for$C_{27}H_{29}N_2O_6$ $[M+H]^+$: 477.2026. Found: 477.1992.
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