Pergamon

Tetrahedron Letters 39 (1998) 7575–7578

TETRAHEDRON LETTERS

Stabilisation of pyrimidine nucleoside triflates by *N*-nitro groups

Carme Serra, Carme Aragonès, Jordi Bessa, Jaume Farràs,* and Jaume Vilarrasa

Departament de Química Orgànica, Universitat de Barcelona, Martí i Franquès 1, 08028 Barcelona, Catalonia (Spain)

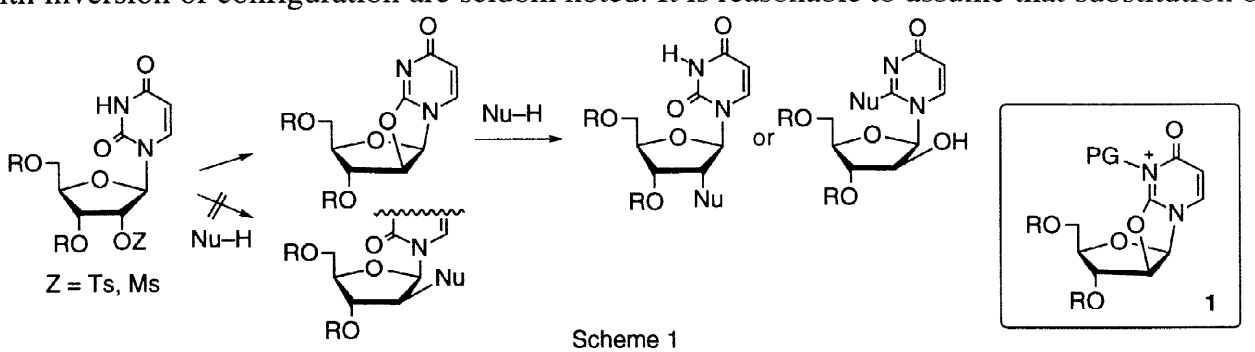
Received 2 July 1998; accepted 27 July 1998

Abstract

Triflation of N^3-protected uridines (*N*-COPh, *N*-CH=CH-COOMe, *N*-NO_2) has been investigated. A stable 2'-*O*-triflyl derivative, that of *N*-nitro-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)uridine, has been isolated for the first time; by contrast to its congeners, it does not give cyclonucleoside-like intermediates. Nucleophilic attacks on this substrate lead to 2'ß-substituted nucleosides rather than the usual 2'α epimers. 3'-*O*-Triflyl *N*-nitro derivatives behave similarly. Several novel nucleosides (*lyxo* dihalo derivatives, 2',3'-α-epoxy derivatives) are accessible by means of this approach.

Keywords: Nucleosides; Uridines; Nitro compounds; Sulfonic acids and derivatives.

Activation of sugar hydroxy groups as triflates (OSO_2CF_3), tosylates, or mesylates has been widely used in nucleoside chemistry. The corresponding pyrimidine derivatives tend to undergo intramolecular cyclisations to *O*-anhydronucleosides (cyclonucleosides); e.g., 2'-*O*-triflyl-uridines are so prone to this reaction that they have never been isolated. In less extreme cases, reaction of these substrates with nucleophiles generally provides cyclonucleosides and/or α-substituted or base-modified nucleosides (Scheme 1) [1]. Anyway, direct S_N2-type reactions with inversion of configuration are seldom noted. It is reasonable to assume that substitution of



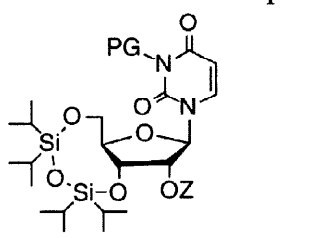
Scheme 1

the imide-like proton by a suitable protecting group (PG) would lead to an unstable, charged intermediate of type **1** and, therefore, it would increase the chance of S_N2 reactions or even of preparing uridine triflates.

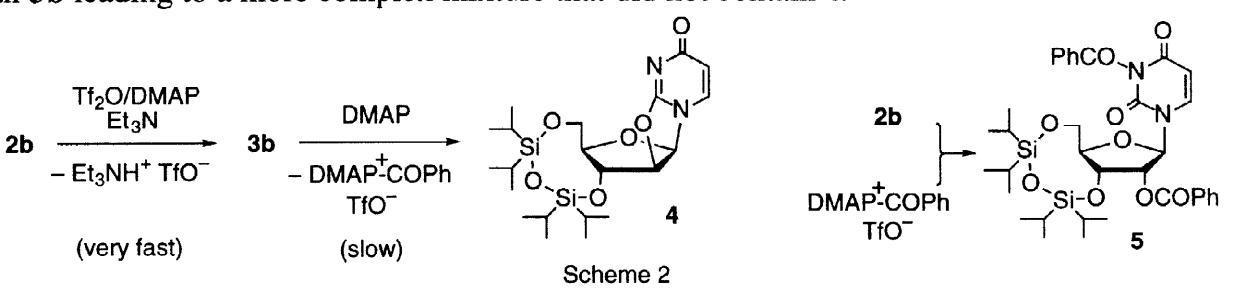
0040-4039/98/$ - see front matter
PII: S0040-4039(98)01616-5

Surprisingly, such a strategy has been hardly utilised. The most relevant, synthetically successful instance is due to Matsuda et al. [2], who prepared 1-(2'-azido-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)-ß-D-arabinofuranosyl)-*N*-benzoyluracil from the corresponding *N*-benzoyluridine (**2b**) by means of a Mitsunobu-type reaction; nevertheless, Fukukawa et al. [3] failed in preparing triflate **3b** and reported the formation of an anhydrouridine as the only isolable product. We report herein our studies on the triflation of nucleosides with electron-withdrawing groups on N^3, i.e. with PG = EWG like benzoyl [4], Mocvinyl [5], and nitro [6,7], as well as the stereochemical outcome of the reaction of *N*-nitro triflates with nucleophiles.

We started our study by monitoring the triflation of compounds **2a–d** in $CDCl_3$ by ^1H NMR at rt. Treatment of *N*-unprotected uridine **2a** with 1.35 eq. of Tf_2O, 1.5 eq. of DMAP and 1.0 eq. of Et_3N lead to a fast conversion to the anhydrouridine **4** (10 min, 71% isolated yield), as expected; triflate **3a** could not be detected in the reaction mixture. When DMAP and Et_3N were replaced by 2.5 eq. of pyridine, **2a** was almost quantitatively transformed to **3a** within 2 min, but this triflate was unstable and decomposed leading to **4** as the only isolable product (1 h, 48% yield). Triflates of uridines with *N*-EWG were more stable than **3a**. Thus, *N*-benzoyluridine **2b** could be quantitatively triflated in $CDCl_3$ by using 1.2 eq. of Tf_2O, 1.2 eq. of DMAP, and 1.0 eq. of Et_3N.[1] The product, **3b**, was moderately stable in the reaction mixture and *slowly* afforded **4** (4 h, 81% isolated yield) as well as, surprisingly, a minor amount of dibenzoyl uridine **5** (Scheme 2).[2] Triflate **3c** decomposed faster than **3b** leading to a more complex mixture that did not contain **4**.



2a: PG = H, Z = H
3a: PG = H, Z = Tf
2b: PG = COPh, Z = H
3b: PG = COPh, Z = Tf
2c: PG = CH=CHCO$_2$Me, Z = H
3c: PG = CH=CHCO$_2$Me, Z = Tf
2d: PG = NO_2, Z = H
3d: PG = NO_2, Z = Tf

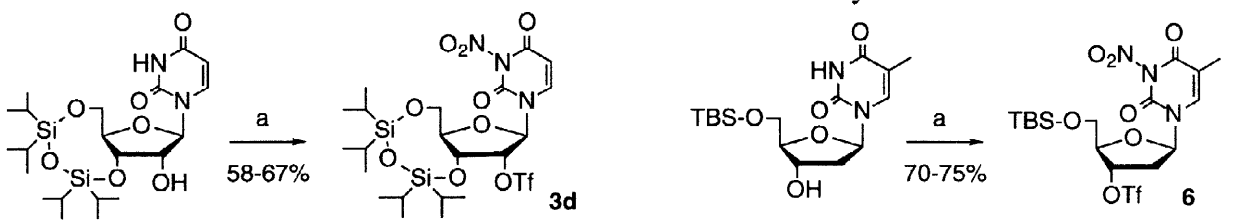


Scheme 2

On the other hand, triflation of **2d** under the conditions described above gives quantitatively **3d** in 5 min., which exhibits *remarkable stability* (it remains unchanged for several days in the reaction mixture). Whereas all attempts of purifying **3b** and **3c** were unsuccessful, **3d** can be purified by flash chromatography (80% isolated yield), handled without special care, and stored in the refrigerator for a long time without appreciable decomposition. To our knowledge, it is the most stable 2'-*O*-triflyluridine reported so far. We have taken advantage of the stability

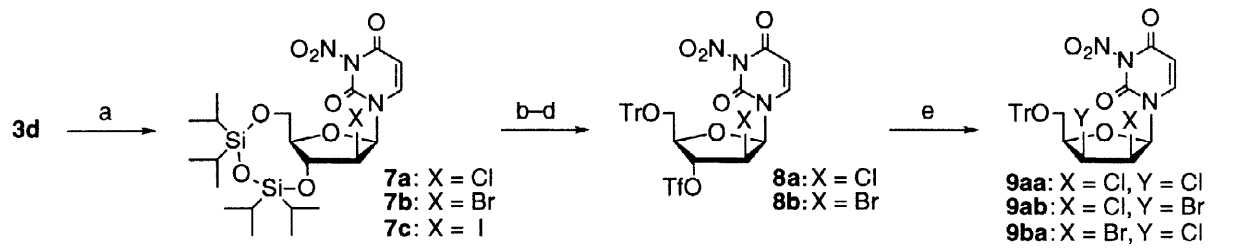
1. It is worth noting that 2 eq. of py, or 1 eq. of DMAP plus 1 eq. of Et_3N, are generally required. When only 1 eq. of base is used, triflates are hardly detected by NMR and the reactions lead to complex mixtures that contain significant amounts of starting material.
2. Although **1** cannot be completely ruled out as a reaction intermediate, we assume that formation of **4** is initiated by the attack of pyridine or DMAP to the benzoyl group of **3b**. The benzoylated pyridines generated in this process may react with remaining starting material to give the observed dibenzoyl uridine **5**. Additional support for this mechanism is provided by the fact that, when triflation is performed with a 2:1:2 molar ratio of **2b**/Tf_2O/base, similar amounts of **4** and **5** are obtained.

of **3d** under acid conditions to trap **3a** with CF_3COONO_2 [8], as shown in Scheme 3.[3] This procedure can also be applied to the thymidine series. It is a convenient, straightforward gram–scale route to *N*-nitro nucleoside triflates from uridine or thymidine.



Scheme 3. a) Tf_2O (1.5 eq.)/py (2.5 eq.), $CHCl_3$, rt, 1.5 min.; then, CF_3COONO_2 (8 eq.), CH_2Cl_2, 0 °C, 20 min.

Reaction of **3d**[4] with nucleophiles is summarised in Scheme 4. Halide ions (from $Bu_4N^+X^-$) in toluene lead to the corresponding *arabino* derivatives **7a–c**[4] in excellent yields while no anhydronucleosides or *ribo* derivatives could be detected as byproducts. Compounds **7a** and **7b** were transformed to the corresponding triflates **8a** and **8b**, which in turn yielded the unknown *lyxo* derivatives **9**[4] by nucleophilic substitution (again without participation of the upper ring, as *arabino* derivatives were not detected in the reaction mixture).



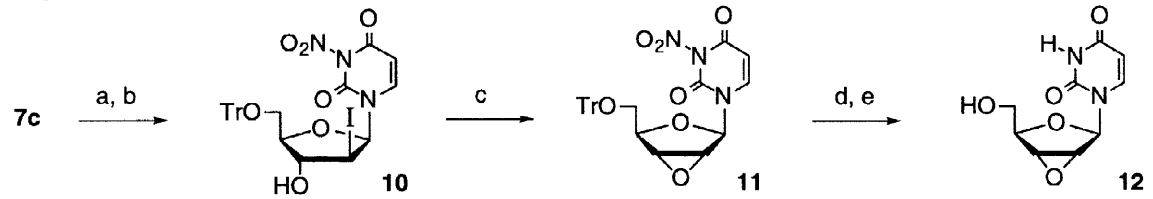
Scheme 4. a) Bu_4NX, toluene (X = Cl or Br, 40 °C, 30 min., 99%; X = I, reflux, 5 min., 70%); b) TBAF/AcOH, THF,–20 °C (X = Cl or Br, 95%; X = I, 80%); c) TrCl, py, Δ (94–99%); d) Tf_2O/DMAP/Et_3N, CH_2Cl_2, 0 °C, 15 min. (X = Cl, 77%; X = Br, 84%); e) Bu_4NY, toluene, 60 °C, 1 h (X = Y = Cl, 58%; X = Cl, Y = Br, 60%; X = Br, Y = Cl, 36%).

N-Nitro iodide **10** provided another example of the ability of the NO_2 group to avoid the formation of cyclonucleosides (see Scheme 5). Treatment with 1.1 eq. of t-BuOK in DMF at 40 °C for 16 h gave α-epoxide **11** in 71% yield. Detritylation of **11** followed by hydrogenolysis of the NO_2 group gave the fully deprotected α-epoxide (**12**). We should stress that, although such kind of oxiranes have been postulated as intermediates in several reactions, **12** could not be isolated until very recently, by Reese et al. [9]. The reason for the elusive preparation of **12**

3. **Preparation of the nitrating solution:** 0.93 mL (6.58 mmol) of $(CF_3CO)_2O$ are added to 263 mg (3.29 mmol) of powdered NH_4NO_3 in 7.6 mL of CH_2Cl_2 under N_2 and stirred at rt for 1 h until most of the solid is solubilised. The resulting solution cannot be stored and must be used immediately. **Preparation of triflate 3a:** 92 µL (0.56 mmol, 1.35 eq.) of Tf_2O are added to a solution of 82 µL (1.03 mmol, 2.5 eq.) of pyridine in 1.8 mL of $CHCl_3$ and stirred for 5 min. at rt under N_2. Then, a solution of 200 mg (0.41 mmol, 1 eq.) of **2a** in 1.5 mL of $CHCl_3$ under N_2 is cannulated into the reaction mixture (15 s) and the remaining nucleoside is transferred by means of other additional 1.5 mL of $CHCl_3$ (15 s). Finally, the solution is stirred for 60 s at rt and *immediately* cooled to 0 °C. **Preparation of nitro triflate 3d:** 8 eq. of a freshly prepared solution of CF_3COONO_2 in 7.6 mL of CH_2Cl_2 is cannulated *immediately* into the reaction mixture and stirred at 0 °C for 20 min. This mixture is added dropwise to a pH 7 buffer solution, extracted with CH_2Cl_2, dried with anh. Na_2SO_4, and the solvent is removed. The crude product is purified by 'flash' chromatography over silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to yield **3d** (58–67%). This procedure can be carried out at gram scale in similar yield (53–57%) provided that the addition time is reasonably short (< 60 s), the temperature is kept below 20 °C and the triflate solution is *rapidly* poured into the nitrating mixture to quench the formation of **4**.

4. **Selected spectroscopic data: 3d.** ^{1}H-NMR(200MHz,$CDCl_3$): 0.70-1.30(4x^{i}Pr), 4.03(dd,J=13.9,2.6;$H_{5'}$), 4.16(dd,J=9.5,2.6;$H_{4'}$), 4.30(d,J=13.9,$H_{5''}$), 4.44(dd,J=9.5,4.1;$H_{3'}$), 5.23(d,J=4.1;$H_{2'}$), 5.85(d,J=8.4;H_5), 5.91(s;$H_{1'}$), 7.81(d,J=8.4;H_6); ^{13}C-NMR(50.3 MHz, $CDCl_3$): 12.0-18.0(4x^{i}Pr), 58.7($C_{5'}$), 66.8($C_{3'}$), 82.3($C_{4'}$), 87.3, 88.2($C_{1'}$,$C_{2'}$), 101.4(C_5), 119.4(q,J=317.6;CF_3), 138.2(C_6), 144.8(C_2), 154.9(C_4). **7a.** ^{1}H-NMR(200MHz,$CDCl_3$): 0.70-1.30(4x^{i}Pr), 3.86(ddd,J=8.3,2.4,2.8;$H_{4'}$), 4.06(dd, J=13.3,2.8;$H_{5'}$), 4.14

must rely upon its tendency to cyclise to the corresponding 2,2'-*O*-anhydronucleoside, especially in the presence of base. Unlike **12**, *N*-nitro nucleoside **11** and its detrityl derivative are quite stable, as they can be stored for several months without significant decomposition. The reactivity of **11** with several nucleophiles is under study.



Scheme 5. a) TBAF/AcOH, THF, –20 °C (80%); b) TrCl, py, reflux (99%); c) 1.1 eq. t-BuOK, DMF, 40 °C,16 h (71%); d) TFA, CH_2Cl_2, rt, 30 min. (78%); e) H_2, Pd/C, MeOH, rt, 3 h (80%).

In summary, *N*-nitration of uridines can be used to prevent the formation of cyclonucleoside-like intermediates, in order to gain access to the otherwise unstable α-epoxides and 2'-*O*-triflyl derivatives as well as to invert the "normal" stereochemical outcome of the nucleophilic substitution at the 2' or 3' positions.

Acknowledgments

Thanks are due to the CIRIT and CICYT (Grant QFN93-4422, 1994–96), to the CIRIT for a doctorate studentship to C. S. (1995–98), to the Ministerio de Educación y Cultura (DGES, Grant PM96-0033, 1997–99), and to E. Llorens for preliminary experiments.

References

[1] Ueda T. Synthesis and reactions of pyrimidine nucleosides. In Townsend LB, editor. Chemistry of nucleosides and nucleotides. Vol I. New York: Plenum Press, 1988:1–112.

[2] Matsuda A, Yasuoka J, Sasaki T, Ueda T. J. Med. Chem. 1991;34:999–1002.

[3] Fukukawa K, Ueda T, Hirano T. Chem. Pharm. Bull. 1983; 31:1582–1592.

[4] Sekine M. J. Org. Chem. 1989; 54:2321–2326.

[5] Faja M, Ariza X, Gálvez C, Vilarrasa J. Tetrahedron Lett. 1995;36:3261–3264.

[6] Ariza X, Bou V, Vilarrasa J. J. Am. Chem. Soc. 1995;117:3665–3673.

[7] Ariza X, Farràs J, Serra C, Vilarrasa J. J. Org. Chem. 1997;62:1547–1549.

[8] Romea P, Aragonès M, Garcia J, Vilarrasa J. J. Org. Chem. 1991; 56:7038–7042.

[9] Miah A, Reese CB, Song QL. J. Chem. Soc:Chem. Commun. 1997; 407–408.

(dd,J=13.3,2.4,$H_{5''}$), 4.37(t,J=8.4;$H_{3'}$), 4.59(dd,J=8.4,6.2;$H_{2'}$), 5.84(d,J=8.4;H_5), 6.30(d;J=6.2;$H_{1'}$), 7.71(d,J=8.4;H_6); ^{13}C-NMR(50.3 MHz,$CDCl_3$): 12.0-18.0(4x^{i}Pr), 60.1($C_{5'}$), 62.2($C_{2'}$), 74.6($C_{3'}$), 82.7($C_{4'}$), 84.0($C_{1'}$), 101.1(C_5), 139.1(C_6), 145.4(C_2), 155.0(C_4). **7b**. ^{1}H-NMR(200MHz, $CDCl_3$): 0.70-1.30(m,28H), 3.83(dt,J=8.0,2.7), 4.04(dd,J=13.4,2.7), 4.14(dd,J=13.4,2.7), 4.46 (t,J=8.8), 4.59(dd, J=8.8,6.2), 5.85(d,J=8.4), 6.27(d;J=6.2), 7.69(d,J=8.4); ^{13}C-NMR(50.3MHz,$CDCl_3$): 12.0-18.0(m), 52.8, 60.2, 75.0, 83.5, 84.0, 101.1, 139.0, 145.0, 155.0. **7c**. ^{1}H-NMR (200MHz,$CDCl_3$): 0.70-1.30(m,28H), 3.79(ddd,J=7.9,2.8,1.9), 4.05(dd,J=13.4, 2.8), 4.16(dd, J=13.4,1.9), 4.50(dd,J=9.6,7.9), 4.62(dd,J=9.6,6.4), 5.86(d,J=8.4), 6.14(d;J=6.4), 7.67(d,J=8.4); ^{13}C-NMR(50.3MHz, $CDCl_3$): 12.0-18.0(m), 29.3, 60.0, 75.8, 84.4, 84.9, 101.4, 138.7, 145.0,155.0. **9aa**. ^{1}H-NMR(300MHz,$CDCl_3$): 3.51(dd,J=10.4,4.8; $H_{5'}$), 3.67(dd, J=10.4,6.8;$H_{5''}$), 4.33(m,$H_{4'}$), 4.62(dd,J=5.4,3.6;$H_{3'}$), 4.85(dd,J=6.9,5.4;$H_{2'}$), 5.79(d,J=8.4;H_5), 6.32(d,J=6.9;$H_{1'}$), 7.22-7.46(m,Tr), 7.50(d,J=8.4;H_6); ^{13}C-NMR(75MHz,$CDCl_3$): 59.9, 60.3($C_{2'}$,$C_{3'}$), 63.0($C_{5'}$), 79.8($C_{4'}$),84.9($C_{1'}$), 87.4($Ph_3\underline{C}$), 100.6(C_5), 127.3 (Ph; C_p), 127.9,128.6(Ph;C_o,C_m), 139.6(C_6), 143.1(Ph;C_i), 146.8(C_2),154.8(C_4). **9ab**. ^{1}H-NMR(300MHz,$CDCl_3$): 3.50(dd,J= 10.5, 4.5), 3.66(dd,J=10.5,7.1), 4.29(m), 4.68(dd,J=5.9,4.4), 4.83(dd, J=6.9,5.9), 5.78(d,J=8.7), 6.28(d,J=6.9), 7.22-7.49(m), 7.55(d, J=8.7); ^{13}C-NMR(75MHz,$CDCl_3$): 51.7, 59.9, 65.0, 79.4, 85.1, 87.4, 100.4, 127.3, 127.9, 128.6, 139.8, 143.1, 146.8, 155.5. **9ba**. ^{1}H-NMR (300MHz,$CDCl_3$): 3.51(dd,J=10.5,5.0), 3.70(dd,J=10.5,6.6), 4.32(m), 4.61(dd, J=5.4,3.3), 4.92(dd,J=6.9,5.4), 5.81(d,J=8.4), 6.33(d, J=6.9), 7.26-7.46(m), 7.52(d,J=8.4); ^{13}C-NMR(75MHz,$CDCl_3$): 50.6, 60.6, 63.3, 77.2, 80.2, 84.9, 100.7, 127.4, 128.0, 128.6, 139.5, 143.1, 145.6, 154.0.