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Reaction of Uridines and Thymidines with Methyl Propynoate. A New N-3 Protecting Group

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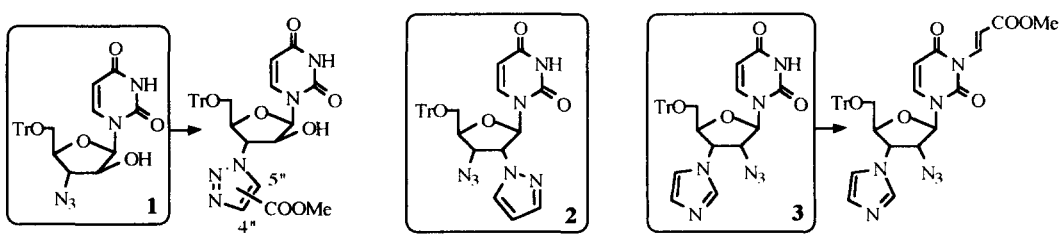
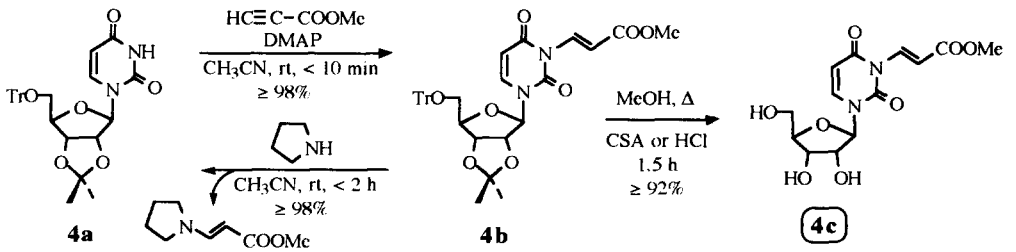
Abstract: *A fast conjugated addition takes place when uridines and thymidines are treated with HC≡C-COOMe in the presence of suitable bases such as DMAP. As the resulting N-CH=CH-COOMe moiety appears to be very stable under acidic conditions, but it is readily cleaved by nucleophiles such as pyrrolidine or methylamine, a new protection protocol for N-3 of uridines and thymidines is disclosed.*

In connection with a project on synthesis of bioisosters of 3'-azido-3'-deoxythymidine (AZT) and related deoxynucleosides,[1] we tried to convert azido uridines such as **1–3** into 1,2,3-triazolyl derivatives through [3+2]-cycloadditions.[2] Our goal was to prepare a series of hitherto unknown 2',3'-bis(azolyl) derivatives.

While treatment of 1-(3-azido-3-deoxy-5-*O*-trityl-β-D-arabinofuranosyl)uracil (**1**) with methyl propynoate (or methyl propiolate, HC≡C-COOMe, 3 equiv.) in refluxing CH_3CN afforded a mixture of the expected triazolyl nucleosides (4"-COOMe/5"-COOMe, 5:1), 3'-azido-2',3'-dideoxy-2'-(pyrazol-1-yl)-5'-*O*-trityluridine (**2**) did not react under the same conditions (probably due to the steric hindrance around the azide group). Surprinsingly, 2'-azido-2',3'-dideoxy-3'-(imidazol-1-yl)-5'-*O*-trityluridine (**3**), when heated in CH_3CN with HC≡C-COOMe as in the preceding cases, gave exclusively a N-3-substituted product (a metoxycarbonylvinyl derivative); in other words, addition of the NH of the pyrimidine ring to the triple bond predominated over [3+2]-cycloaddition.[3] This result, which we attributed to the higher basicity of the imidazole appendage of **3** in relation to that of the pyrazole ring of **2**, prompted us to investigate the reactivity of standard nucleosides with activated alkynes. We wish to report here the behaviour of several uridines and thymidines in this regard, as well as to advance some possible applications of the methoxycarbonylvinyl as a N-3 protecting group for these nucleosides.

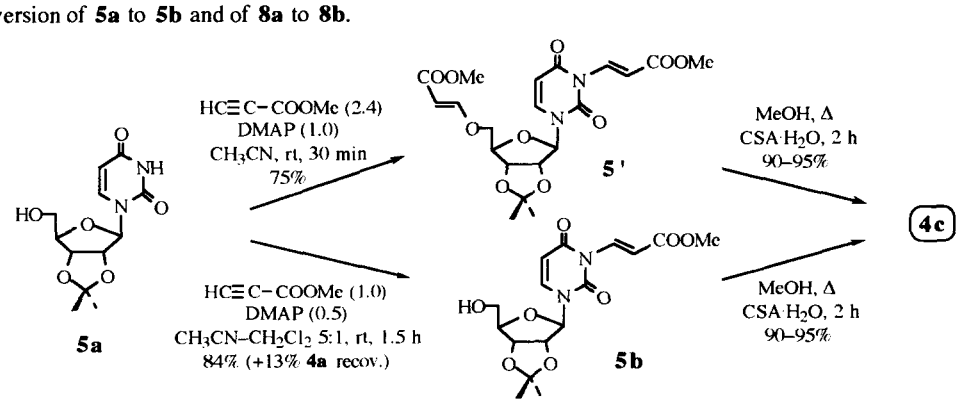


When 2',3'-*O*-isopropylidene-5'-*O*-trityluridine, **4a** (1.0 mmol), was treated with methyl propynoate (1.2 mmol) and 4-dimethylaminopyridine (DMAP, 1.2 mmol) in 5–10 mL of CH_3CN at room temperature (rt), a quick reaction occurred, so that within 10 min **4a** was quantitatively converted to N-protected derivative **4b**. Only one isomer, of *E* configuration, was obtained, in the light of the ^1H (olefinic protons at δ 7.03 and 8.22, with J = 14.8 Hz) and ^{13}C NMR spectra.[4,5]



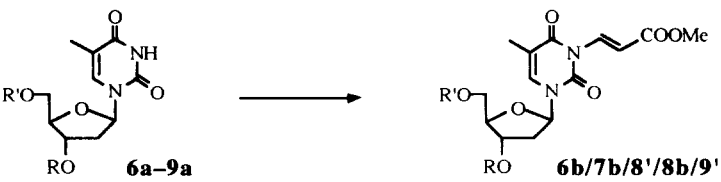
Even though reaction times were longer, Et_3N or 1-methylimidazole[6] could be utilised instead of DMAP; by contrast, with $EtPr^i_2N$ or 2,6-lutidine no reaction took place, whereas DBU 'reacted' with HC≡C-COOMe. For deprotection (**4b** → **4a**) a good nucleophile like pyrrolidine was added —at rt, with 3–4 equiv. the reaction was very rapid at 0.05–0.10 M substrate concentrations, while at higher concentrations the reaction was almost instantaneous—, which, probably through a conjugated addition–elimination mechanism, freed the imide-like anion; **4a** was easily separated from methyl *E*-3-(1-pyrrolidinyl)propenoate (see the preceding Scheme) by column chromatography. Instead of a moderate excess of pyrrolidine under dilute conditions, it can also be used a larger excess of CH_3NH_2/EtOH or a 1:1 mixture of aq. ammonia and CH_3NH_2/EtOH, which cleaved the N-3–CH bond in a few minutes. On the other hand, the hydroxy-protecting groups of **4b** could be removed quite readily, by heating with MeOH/camphor-10-sulfonic acid (CSA·H_2O, 2 equiv.) or MeOH/HCl, without touching the CH=CH-COOMe group, to give *N*-[*E*-2-(methoxycarbonyl)vinyl]uridine, **4c**, almost quantitatively (TLC and NMR; 92% yield after 'flash' column chromatography).

The reactivity of HC≡C-COOMe with other nucleosides is summarised below (next Scheme and Table). It can be observed that free hydroxy groups also react with methyl propynoate in the presence of DMAP, as could be expected,[4] since when an excess of the reagent was employed polysubstituted nucleosides were obtained (see **5'**, **8'**, and **9'**).[7] Cleavage of the O-CH=CH-COOMe moiety, leaving intact the N-CH=CH-COOMe one, was effected with MeOH/CSA, as shown for **5'**.[8] Nevertheless, it is wise to take advantage of the usually higher reactivity, in the presence of suitable bases, of the imide-like groups with regard to the hydroxy groups, in order to protect N-3 selectively. In fact, the chemoselective protection of NH vs. OH can be achieved by performing the reaction with only 1 equiv. of HC≡C-COOMe and smaller amounts of DMAP,[9] as indicated for the direct conversion of **5a** to **5b** and of **8a** to **8b**.



Finally, it deserves comment that desilylation of **6b** ($Bu_4N^+F^-$/AcOH, THF, 0 °C, 2 h) afforded *N*-[*E*-2-(methoxycarbonyl)vinyl]thymidine (**6c**) in 92% yield. Treatment of either **7b**, **8'**, **8b**, or **9'** with MeOH/CSA also deprotected the oxygen functions to give **6c**. Removal of CH=CH-COOMe of **6c** and **8b** by means of pyrrolidine (0.2 M in CH_3CN) or CH_3NH_2 (10% in EtOH) was accomplished at rt in quantitative yield.

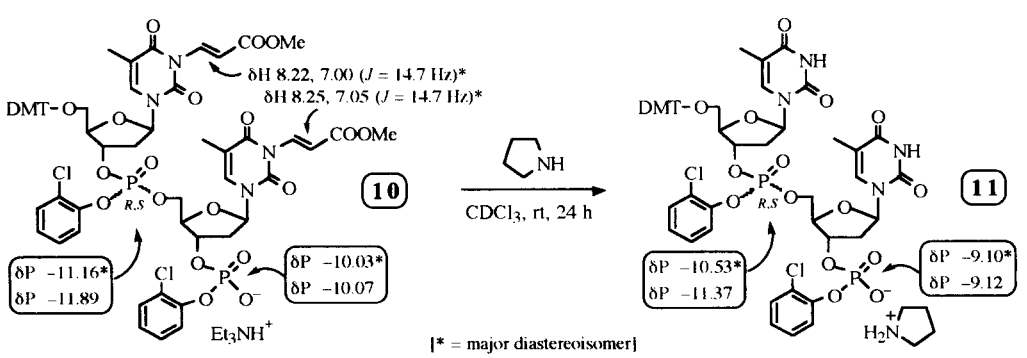
Table. Reaction of Thymidines with Methyl Propynoate in CH_3CN at rt



substrate	HC≡C-COOMe (no. equiv.)	DMAP (no. equiv.)	react. time	product	yield
6a (R,R' = $Pr^i_2SiOSiPr^i_2$)	1.2	1.2	10 min	**6b** (R,R' = $Pr^i_2SiOSiPr^i_2$)	93%
7a (R = R' = Ac)	1.2	1.2	10 min	**7b** (R = R' = Ac)	98%
8a (R = H, R' = Tr)	2.4	1.2	90 min	**8'** (R = OCHCHCOOMe, R' = Tr)	91%
8a (R = H, R' = Tr)[a]	1.0	0.3	40 min	**8b** (R = H, R' = Tr)	75%[b]
9a (R = R' = H)	3.1	1.2	30 min	**9'** (R = R' = OCHCHCOOMe)	94%

[a] In CH_3CN–CH_2Cl_2 4:1. [b] 15% of **8a** was recovered.

Although our main interest is focussed on the application of CH=CH-COOMe as a deactivating group of the pyrimidine ring regarding cyclonucleoside formation,[10] and even though the conditions for the removal of this protecting group are much milder than those generally utilised for the elimination of standard protecting groups (of the bases) in oligonucleotide synthesis,[11] we have investigated the stability of the internucleotide bonds in the presence of pyrrolidine.[12] We wish to advance here that both N-3 of TpTp derivative **10** are selectively deprotected to give the expected product (**11**) when treated with pyrrolidine (18 mmol per mmol) for 24 h at rt, as monitored by ^{31}P and ^1H NMR.[13] In fact, **11** appeared to be stable under the reaction conditions, since no additional cleavage was noted by mixing **11** with a further amount of pyrrolidine for 48 h.



In summary, the CH=CH-COOR group may be selectively introduced at N-3 (via a conjugate addition), is very stable towards acids in non-aqueous media, and is readily cleaved at rt by standard nitrogen nucleophiles (via an addition–elimination process). Other applications[10] will be reported soon.

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2. For previous works on the reaction of the azide group of AZT with triple bonds, see: (a) Wigerinck, P.; Aerschot, A. V.; Claes, P.; Balzarini, J.; De Clercq, E.; Herdewijn, P. *J. Heterocycl. Chem.* **1989**, 26, 1635. (b) Häbich, D.; Barth, W.; Rösner, M. *Heterocycles* **1989**, 29, 2083. (c) Hirota, K.; Hosono, H.; Kitade, Y.; Maki, Y.; Chu, C. K.; Schinazi, R. F.; Nakane, H.; Ono, K. *Chem. Pharm. Bull.* **1990**, 38, 2597. (d) Ariza, X. *Synthesis of 3'-Azolyl Nucleosides* (Graduation Thesis); University of Barcelona, 1990.
3. In principle, other acetylene derivatives (HC≡C-EWG) could work similarly. Regarding previous reports on this kind of addition reactions, it is known that propynal reacts with thymidine and 2'-deoxyuridines also through N-3 to afford cytotoxic 3-oxo-1-propenyl derivatives: Johnson, F.; Pillai, K. M. R.; Grollman, A. P.; Tseng, L.; Takeshita, M. *J. Med. Chem.* **1984**, *27*, 954. Yields between 9% and 28% have been reported: Lin, T.-S.; Guo, J.-Y.; Zhang, X.-H. *Nucleosides Nucleotides* **1990**, *9*, 923. Kalman, T. I.; Marinelli, E. R.; Xu, B.; Reddy, A. R. V.; Johnson, F.; Grollman, A. P. *Biochem. Pharmac.* **1991**, *42*, 431. For a review on conjugated addition reactions to triple bonds, see: Perlmutter, K. "Conjugate Addition Reactions in Organic Synthesis", Pergamon Press, Oxford, 1992, Ch. 7. Also see: Lee, E.; Tae, J. S.; Lee, C.; Park, C. M. *Tetrahedron Lett.* **1993**, *34*, 4831.
4. For the stereochemistry of the addition products of amines and alcohols to HC≡C-COOMe and dimethyl acetylenedicarboxylate, see: Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450. Huisgen, R.; Herbig, K.; Siegl, A.; Huber, H. *Chem. Ber.* **1966**, *99*, 2526.
5. Spectral data of **4b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.37 (s, Me), 1.58 (s, Me), 3.43 (m, H-5' & H-5"), 3.79 (s, 3 H, COOMe), 4.43 (m, H-4'), 4.80 (dd, *J*=6.2, *J*=3.0, H-3'), 4.86 (dd, *J*=6.2, *J*=2.2, H-2'), 5.46 (d, *J*=8.2, H-5), 5.91 (d, *J*=2.2, H-1'), 7.03 (d, *J*=14.8, N-CH=CH), 7.26–7.40 (m, Ph_3C), 7.59 (d, *J*=8.2, H-6), 8.22 (d, *J*=14.8, N-CH=CH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.9 (Me), 27.7 (Me), 52.2 (COOMe), 64.1 (C-5'), 81.2, 85.9 & 87.0 (C-2', C-3' & C-4'), 88.0 (Ph_3C), 94.4 (C-1'), 101.8 (C-5), 114.2 (N-CH=CH), 114.8 (CMe_2), 128.0, 128.5 & 129.1 (Ph), 134.5 (N-CH=CH) 139.8 (C-6), 143.6 (C_i), 150.0 (C-2) 161.4 (C-4), 168.0 (COO). Spectral data of **4c**: ^{1}H NMR ($CDCl_3$, 200 MHz), δ 3.79 (s, Me), 3.84–3.91 (m, H-5' & H-5"), 4.10 (m, H-4'), 4.25 (br s, H-2' & H-3'), 5.78 (br s, H-1'), 5.81 (d, *J*=8.3, H-5), 7.03 (d, *J*=14.8, N-CH=CH), 7.93 (d, *J*=8.3, H-6), 8.23 (d, *J*=14.8, N-CH=CH); ^{13}C NMR ($CDCl_3$+CD_3OD drop, 50.3 MHz), δ 52.0 (Me), 60.8 (C-5'), 69.4, 74.8 & 84.9 (C-2', C-3' & C-4'), 91.2 (C-1'), 101.3 (C-5), 113.5 (N-CH=CH), 134.5 (N-CH=CH), 139.6 (C-6), 150.0 (C-2), 161.7 (C-4), 168.2 (COO).
6. When 1 equiv. of 1-methylimidazole was employed the reaction was completed in ca. 12 h, while in refluxing CH_3CN it required only 40 min. Thus, the behaviour of compound **3** vs. HC≡C-COOMe (self-catalysis) is understandable.
7. Relevant spectral data of **5'**: ^{1}H NMR δ 3.68 (s, COOMe), 3.77 (s, COOMe), 5.27 (d, *J*=12.6, O-CH=CH), 5.73 (d, *J*=1.8, H-1'), 5.81 (d, *J*=8.2, H-5), 7.05 (d, *J*=14.7, N-CH=CH), 7.33 (d, *J*=8.2, H-6), 7.57 (d, *J*=12.6, O-CH=CH), 8.22 (d, *J*=14.7, N-CH=CH); ^{13}C NMR δ 51.3 (COOMe), 51.8 (COOMe), 95.7 (C-1'), 97.6 (O-CH=CH), 101.7 (C-5), 113.9 (N-CH=CH), 133.9 (N-CH=CH), 140.1 (C-6), 149.4 (C-2), 160.8 (C-4), 161.4 (O-CH=CH), 167.4 (COO), 167.6 (COO). Assignments confirmed by 2D NMR (H/C COSY, Varian VXR-500). Relevant data of **8'**: ^{1}H NMR δ 5.15 (d, *J*=12.8, O-CH=CH), 6.38 (dd, *J*=8.6, *J*=5.4, H-1'), 7.06 (d, *J*=14.7, N-CH=CH), 7.3 (m, Ph_3C+OCH=CH), 7.62 (H-6), 8.30 (d, *J*=14.7, N-CH=CH); ^{13}C NMR δ 51.8 (COOMe), 52.2 (COOMe), 99.1 (O-CH=CH), 113.9 (N-CH=CH), 134.2 (N-CH=CH), 135.1 (C-6), 160.3 (O-CH=CH), 167.9 (COO), 168.2 (COO). And of **8b**: ^{1}H NMR δ 6.40 (t, *J*≈6.6, H-1'), 7.06 (d, *J*=14.7, N-CH=CH), 8.28 (d, *J*=14.7, N-CH=CH); ^{13}C NMR δ 52.9 (COOMe), 113.7 (N-CH=CH), 134.8 (N-CH=CH), 135.4 (C-6), 168.5 (COO).
8. With pyrrolidine both protecting groups are removed at a rather similar rate.
9. In the case of **5a**, an excess of DMAP and HC≡C-COOMe gave rise to the appearance, in addition to the product protected at N-3 and O-5' (**5'**), of its N^3,C^5-disubstituted isomer.
10. Work aimed at preparing modified pyrimidine nucleosides of the *xylo* and *lyxo* series (manuscript in preparation).
11. Heating for a few hours with conc. ammonia is often required. For reviews on oligonucleotide synthesis, see e.g.: Beaucage, S. L.; Iyer, R. P. *Tetrahedron* **1992**, *48*, 2223. Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543. Also see: Reddy, M. P.; Hanna, N. B.; Farooqui, F. *Tetrahedron Lett.* **1994**, *35*, 4311.
12. Thanks are due to a referee for suggesting an experiment of this kind.
13. δP values (see Scheme) are referred to 85% H_3PO_4 (ext. ref.); only the peaks indicated in **11** were observed at the end. Assignments of the ^{31}P signals were confirmed from undecoupled spectra and by selective proton-decoupling experiments. Also, the reaction can be easily followed by the disappearance of the signals at lower field in the ^{1}H NMR spectra, i.e. the doublets at δ 8.2–8.3 (N-CH=CH-COOMe).

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