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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 483–486

Efficient coupling of low boiling point alkynes and 5-iodonucleosides

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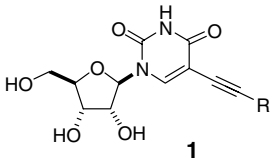
Received 21 August 2006; revised 1 November 2006; accepted 8 November 2006
Available online 4 December 2006

Abstract—The coupling of unprotected 5-iodonucleosides and low boiling point alkynes has been achieved in a high yield for the first time. The coupling is highly dependent on concentration and can be carried out at low temperature and pressure conditions.

In recent years, there has been remarkable interest in nucleosides in which the base unit has been modified to provide new and unique biological and chemical properties. Of particular interest has been a generation of C5 substituted uridine derivatives, particularly 5-alkynyl uridines **1** as they have been shown to be potent antiviral and anti-cancer agents.[1]

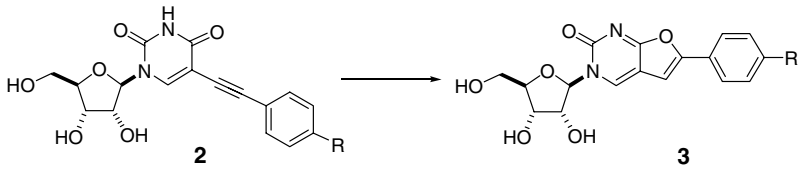


1

5-Alkynyl substituted uridine derivatives are also crucial intermediates in the syntheses of bicyclic furano- and bicyclopyrrolopyrimidine units, which have been shown to have remarkable biological properties of their own.[2] In particular, furanopyrimidines of the general form **3** have been shown to inhibit the replication of the varicella-zoster virus (VZV).[3]

Therefore, it is not surprising that a great deal of effort has been dedicated to both the synthesis of the 5-alkynyl uridine derivatives and their cyclisation to the bicyclofurano and bicyclopyrrolopyrimidine nucleosides using a number of conditions.[4] Thus, there are now a number of recently reported procedures for the synthesis of 5-alkynyl uridines from both protected and unprotected nucleosides.[5]

However, despite extensive interest, the current methods for the synthesis of 5-alkynyl uridines using low molecular weight and low boiling point alkynes are less than optimal; with the exception of TMS acetylide.[6] Currently, the highest yielding methods available involve the use of pressure vessels and high temperatures. Unfortunately, these conditions often afford the desired alkyne coupling product **5** as a mixture with the copper(I) catalysed cyclisation product **6**.[7]



2 **3**

Keywords: Sonogashira; Alkynes; 5-Iodonucleosides.
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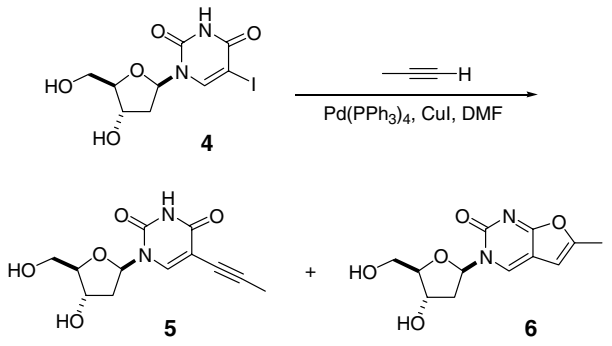
0040-4039/$ - see front matter
doi:10.1016/j.tetlet.2006.11.047

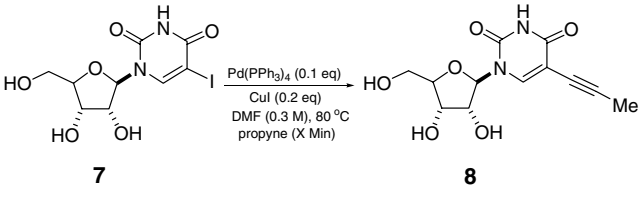


Needless to say, an efficient method for the coupling of low boiling point alkynes to the corresponding nucleosides would also greatly simplify the synthesis of the corresponding methyl, ethyl and propyl bicyclic furano and pyrrolopyrimidine nucleosides.

We would now like to report our results into the coupling of low boiling point alkynes with completely unprotected 5-iodo-uridine. In the first instance, we decided to focus on the palladium catalysed Sonogashira coupling of propyne with 5-iodo-uridine. 5-Propynyl nucleosides have been shown to be significant building blocks in the synthesis of fluorescent oligonucleotides, and as such, their syntheses have been reported a number of times in a wide range of yields from 20–50%.[8]

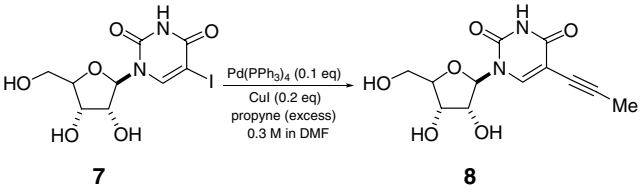
Our initial attempts to improve the yield and the reproducibility of the couplings, focused on the amount of volatile propyne present in the reaction mixture. Our thoughts being, that once the reaction vessel became pressurised, any further alkyne addition would be impractical.

Unfortunately, despite extensive experimentation with regards to flow rate and time of addition through the reaction mixture, all attempted conditions failed to improve the yield above 15–20%. Furthermore, the exact equivalents of propyne added into the reaction system were difficult to determine accurately.



Propyne addn time (min)	Yield (%)
2	15
5	15
10	20
15	17
20	20

Faced with this lack of improvement, we decided to focus our attention on the effect of temperature and reaction time on the coupling outcome. After attempting a wide range of temperatures (20–100 °C) and reaction times (6–72 h), the isolated yield of 5-propynyl-uridine was still never above 20%.



Temp (°C)	Time (h)	Yield (%)
20	6	10
40	6	10
40	12	15
40	24	15
60	48	15–18
80	72	20
100	72	20

At this point, we switched our efforts to the evaluation of the effect of the nature of the catalyst and its loading on the reaction outcome. Initially, a number of palladium(II) and palladium(0) sources were investigated under the same high pressure conditions, however, in all cases the yield remained low.

This lack of improvement on the yield despite modification of the reaction temperature, time and catalyst prompted us to consider the effect of concentration on the reaction outcome. We were particularly interested in decreasing the reaction concentration, which we believed would slow the reaction down and possibly increase the coupling efficiency.

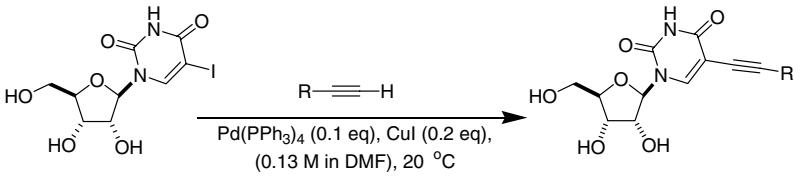
Hence, we were extremely pleased when by significantly decreasing the reaction concentration; the coupling between unprotected 5-iodo-uridine and propyne proceeded in a high yield, and perhaps more importantly, at room temperature overnight.[9]

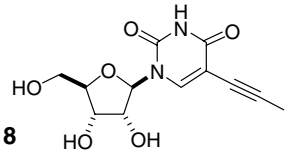
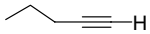
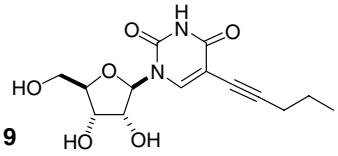
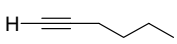
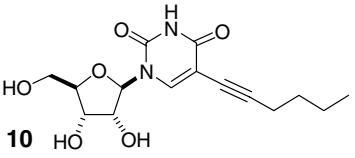
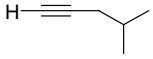
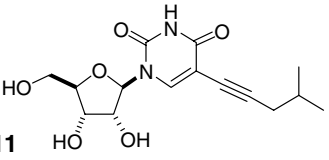
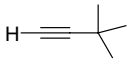
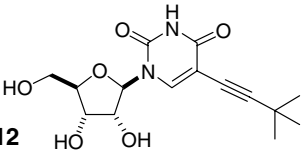
This significant improvement in the reaction efficiency, prompted us to apply the same reaction conditions to the coupling of our unprotected nucleoside to volatile, low molecular weight alkynes. A successful coupling at low concentrations with low temperatures and pressures would minimise the risk of explosion, and conversely, the need for high pressure reaction flasks. Furthermore, through the use of this efficient, non-pressurised system, extra amounts of volatile alkyne could still be added to the reaction mixture with minimal effort and without having to stop and re-start the reaction.

We are now also pleased to report that our low concentration, temperature and pressure conditions can also be successfully exported to the coupling of volatile alkynes (both liquids and gases) with unprotected 5-iodonucleosides to generate the desired 5-alkynyl nucleosides in high yields (Table 1).

In conclusion, we have demonstrated that volatile alkynes can be successfully coupled to unprotected 5-iodo-

Table 1. Low temperature and pressure Sonogashira coupling of 5-iodo-uridine with low boiling point alkynes[9]



Alkyne	Bp (°C)	Product	Yield (%)
	−23.2	 **8**	98
	40	 **9**	88
	71–72	 **10**	96
	61–62	 **11**	80
	37–38	 **12**	86

uridine in high yields and without any side products through the accurate control of the palladium(0) to copper(I) molar ratios at low temperatures and pressures. This modified procedure removes the need to determine accurately the amounts of alkyne added in the first instance, as it allows for further alkyne additions without the need to stop and re-start the reaction.

This method provides a fast, safe and efficient approach for the synthesis of short chain 5-alkynyl nucleosides,[10] which are pivotal intermediates in the generation of biologically relevant substrates.

Acknowledgements

We would like to thank Scottish Enterprise for supporting this work. R.M. would like to thank Dr. Ian Sword and the University of Glasgow for the financial support.

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9. *Representative procedure*. A 0.13 M solution of unprotected 5-iodonucleoside (1 mmol, 1 equiv) in anhydrous DMF was treated with tetrakis(triphenylphosphine)palladium(0) (0.1 mmol, 0.1 equiv), copper(I) iodide (0.2 mmol, 0.2 equiv) and triethylamine (2.0 equiv). The alkyne was then added to the reaction mixture (10 min bubbling in the case of the gaseous alkynes (ca. 15 equiv), and 5.0 equiv in the case of liquid alkynes) at room temperature. The resulting reaction mixture was then stirred at room temperature until completion by TLC analysis (72 h). The solvents were evaporated and the residue was purified by column chromatography eluting with 10% methanol in dichloromethane.
10. *1-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-5-prop-1-ynyl-1H-pyrimidine-2,4-dione*, **8**. R_f [DCM/MeOH (9:1)] 0.18; $[\alpha]_D^{20}$ −48 (*c* 0.14, DMSO); δ_H (500 MHz, DMSO) 11.63 (1H, s, NH), 8.15 (1H, s, CH), 5.76 (1H, d, *J* 5.2, OH), 5.41 (1H, d, *J* 5.6, OH), 5.21 (1H, t, *J* 4.9, OH), 5.09 (1H, d, *J* 5.2, CH), 4.06–4.02 (1H, q, *J* 5.2, CH), 4.00–3.96 (1H, m, CH), 3.86–3.85 (1H, m, CH), 3.68–3.64 (1H, ddd, *J* 12.1, 4.7 and 3.1, CH_AH_B), 3.59–3.55 (1H, ddd, *J* 12.0, 4.6 and 3.0, CH_AH_B) and 1.95 (3H, s, CH_3); δ_C (125 MHz, DMSO) 161.8, 149.7, 142.8, 99.1, 89.15, 88.2, 87.9, 73.8, 71.9, 69.6, 60.5 and 4.1 (Found MNa^+, 305.0661. $C_{12}H_{14}NaN_2O_6$ requires 305.0742).
1-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-5-pent-1-ynyl-1H-pyrimidine-2,4-dione, **9**. R_f [DCM/MeOH (9:1)] 0.22; $[\alpha]_D^{20}$ −51 (*c* 0.15, DMSO); δ_H (500 MHz, DMSO) 11.64 (1H, s, NH), 8.20 (1H, s, CH), 5.76 (1H, d, *J* 5.1, OH), 5.42 (1H, d, *J* 5.5, OH), 5.20 (1H, t, *J* 4.9, OH), 5.09 (1H, d, *J* 5.3, CH), 4.06–4.03 (1H, q, *J* 5.1, CH), 3.99–3.96 (1H, q, *J* 4.8, CH), 3.86–3.85 (1H, m, CH), 3.69–3.65 (1H, ddd, *J* 12.1, 4.8 and 3.1, CH_AH_B), 3.59–3.55 (1H, ddd, *J* 12.1, 4.7 and 3.0, CH_AH_B), 2.34 (2H, t, *J* 7.0, CH_2), 1.55–1.48 (2H, sextet, *J* 7.2, CH_2) and 0.97 (3H, t, *J* 7.4, CH_3); δ_C (125 MHz, DMSO) 161.7, 149.7, 142.8, 99.1, 93.1, 88.0, 84.5, 73.6, 72.9, 69.5, 60.4, 21.6, 20.7 and 13.2 (Found MNa^+, 333.1527. $C_{14}H_{18}NaN_2O_6$ requires 333.1055).
1-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-5-hex-1-ynyl-1H-pyrimidine-2,4-dione, **10**. R_f [DCM/MeOH (9:1)] 0.25; $[\alpha]_D^{20}$ −48 (*c* 0.12, DMSO); δ_H (500 MHz, DMSO) 11.65 (1H, s, NH), 8.19 (1H, s, CH), 5.76 (1H, d, *J* 5.0, OH), 5.41 (1H, d, *J* 5.6, OH), 5.19 (1H, t, *J* 4.9, OH), 5.09 (1H, d, *J* 5.3, CH), 4.06–4.03 (1H, q, *J* 5.2, CH), 4.00–3.96 (1H, q, *J* 4.9, CH), 3.86–3.84 (1H, m, CH), 3.68–3.64 (1H, ddd, *J* 12.1, 4.9 and 3.2, CH_AH_B), 3.59–3.55 (1H, ddd, *J* 12.1, 4.8 and 3.0, CH_AH_B), 2.37 (2H, t, *J* 6.9, CH_2), 1.51–1.44 (2H, m, CH_2), 1.43–1.37 (2H, m, CH_2) and 0.90 (3H, t, *J* 7.3, CH_3); δ_C (125 MHz, DMSO) 161.7, 149.7, 142.8, 99.1, 93.2, 88.0, 84.8, 73.7, 72.7, 69.5, 60.4, 30.2, 21.3, 18.5 and 13.5. (Found MNa^+ 347.2543. $C_{15}H_{20}NaN_2O_6$ requires347.3182).
1-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-5-(4-methyl-pent-1-ynyl)-1H-pyrimidine-2,4-dione, **11**. R_f [DCM/MeOH (9:1)] 0.22; $[\alpha]_D^{20}$ −47 (*c* 0.10, DMSO); δ_H (500 MHz, DMSO) 11.64 (1H, s, NH), 8.25 (1H, s, CH), 5.76 (1H, d, *J* 4.8, OH), 5.42 (1H, d, *J* 5.4, OH), 5.19 (1H, t, *J* 4.6, OH), 5.09 (1H, d, *J* 5.2, CH), 4.06–4.03 (1H, q, *J* 4.9, CH), 3.99–3.96 (1H, q, *J* 4.6, CH), 3.87–3.85 (1H, m, CH), 3.69–3.66 (1H, ddd, *J* 12.0, 4.8 and 3.0, CH_AH_B), 3.59–3.54 (1H, ddd, *J* 12.0, 4.7 and 3.0, CH_AH_B), 2.26 (2H, d, *J* 6.5, CH_2), 1.84–1.76 (1H, septet, *J* 6.5, CH_2) and 0.98 (6H, d, *J* 6.6, $2 \times CH_3$); δ_C (125 MHz, DMSO) 161.7, 149.7, 142.8, 99.1, 98.2, 88.1, 84.8, 73.8, 71.2, 69.6, 60.4, 27.8, 27.6 and 21.8 (Found MNa^+, 347.1132. $C_{15}H_{20}NaN_2O_6$ requires 347.3182).
1-(3,4-Dihydroxy-5-hydroxymethyl-tetrahydrofuran-2-yl)-5-(3,3-dimethyl-but-1-ynyl)-1H-pyrimidine-2,4-dione, **12**. R_f [DCM/MeOH (9:1)] 0.23; $[\alpha]_D^{20}$ −37 (*c* 0.16, DMSO); δ_H (500 MHz, DMSO) 11.62 (1H, s, NH), 8.19 (1H, s, CH), 5.74 (1H, d, *J* 4.9, OH), 5.41 (1H, d, *J* 5.5, OH), 5.21 (1H, t, *J* 4.8, OH), 5.09 (1H, d, *J* 5.3, CH), 4.06–4.02 (1H, q, *J* 5.1, CH), 4.00–3.96 (1H, q, *J* 4.9, CH), 3.86–3.84 (1H, m, CH), 3.70–3.66 (1H, ddd, *J* 12.0, 4.8 and 3.0, CH_AH_B), 3.59–3.55 (1H, ddd, *J* 12.1, 4.7 and 2.9, CH_AH_B) and 1.24 (9H, s, $3 \times CH_3$); δ_C (125 MHz, DMSO) 161.6, 149.7, 143.0, 100.9, 98.7, 88.1, 84.7, 73.7, 71.2, 69.3, 60.2, 30.7 and 27.6 (Found MNa^+, 347.3008. $C_{15}H_{20}NaN_2O_6$ requires 347.3182).