Pergamon

Tetrahedron Letters 41 (2000) 8741–8745

TETRAHEDRON LETTERS

Synthesis of 5,6-bis(alkyn-1-yl)pyrimidines and related nucleosides

E. Sathyajith Kumarasinghe, Matt A. Peterson* and Morris J. Robins*

Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602-5700, USA

Received 10 August 2000; accepted 28 August 2000

Abstract

Sonogashira coupling of 5-iodo-1-methyluracil or 5′-*O*-TBDMS-5-iodo-2′,3′-*O*-isopropylideneuridine with alkynes gave 5-(alkyn-1-yl) derivatives that underwent 6-lithiation/iodination to give 5-(alkyn-1-yl)-6-iodo-(1-methyluracil or uridine) intermediates (57–80%). Coupling of the 5-(alkyn-1-yl)-6-iodo intermediates gave 5,6-bis(alkyn-1-yl)pyrimidines and protected nucleosides (51–79%). Two of the 5,6-bis(ethynyl)-1,3-dimethyluracil derivatives underwent Bergman cycloaromatization at 130°C with half-lives of 2–8 h. © 2000 Published by Elsevier Science Ltd.

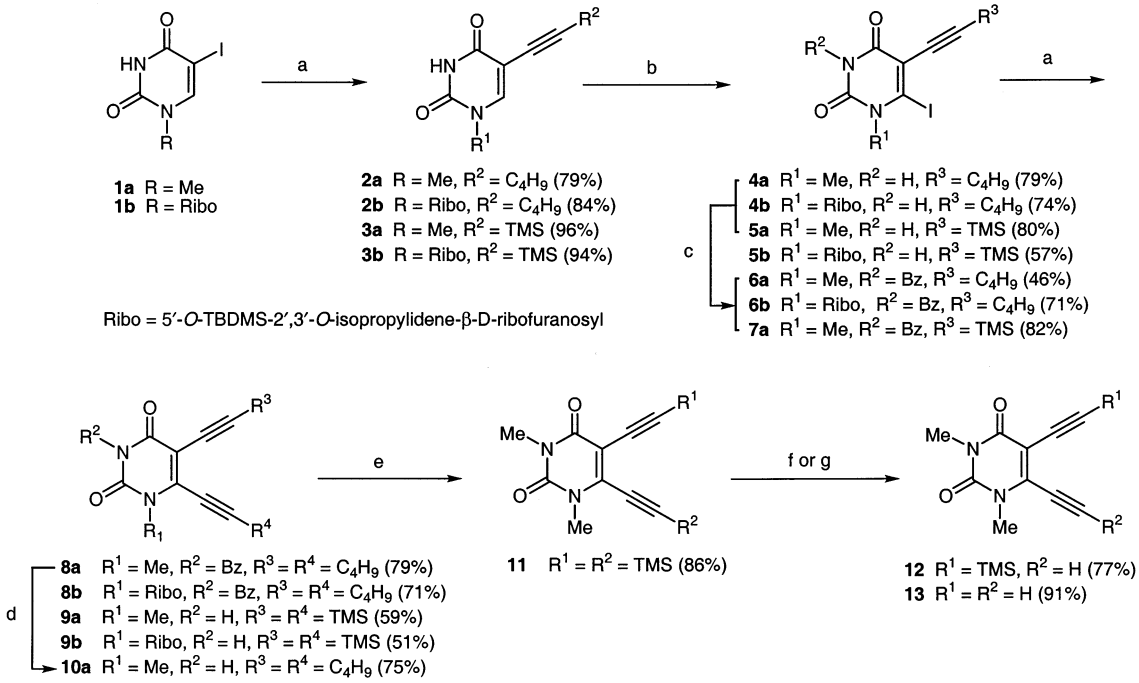
The Bergman[1] cycloaromatization reaction is of interest both from a mechanistic point of view and because of its relevance to the mode of action of enediyne antibiotics including the esperamicins, calicheamicins, dynemicins, and kedarcidin. These DNA-cleaving molecules are among the most cytotoxic compounds known,[2] and considerable efforts have been focused on the synthesis of analogs with enhanced properties for chemotherapeutic applications.[3] Unfortunately, most cytotoxic enediynes exhibit limited selectivity for tumor cells, and this has been a major obstacle to their development as anticancer drugs.[2] We reasoned that enediyne moieties elaborated at the 5,6-bond of pyrimidines might provide a scaffold for directed delivery of aryl diradical precursors for the cleavage of nucleic acids. The enhanced uptake of base and nucleoside analogs by certain rapidly dividing tumor cells might provide some selectivity. Progression from bases to nucleosides to oligonucleotides containing strategically incorporated pyrimidine-based enediynes should generate enhanced selectivity for nucleic acid target structures.

During the course of our studies, Russell and co-workers reported the synthesis and Bergman cycloaromatization of three 5,6-bis(alkyn-1-yl)pyrimidine derivatives.[4] Their synthesis started with 6-chloro-2,4-dimethoxypyrimidine and was not oriented to the preparation of nucleosides. We now report efficient syntheses of 5,6-bis(ethynyl)uracil derivatives *and related nucleosides* from uracil or uridine.[5a]

* Corresponding authors. Fax: (801) 378-5474; e-mail: matt_peterson@byu.edu; morris_robins@byu.edu

0040-4039/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4039(00)01566-5

The respective 5-iodo-1-methyluracil (**1a**) or 5′-*O*-(*tert*-butyldimethylsilyl)-5-iodo-2′,3′-*O*-isopropylideneuridine (**1b**) derivatives were readily obtained in 2–3 steps from uracil or uridine (Scheme 1).[5] Sonogashira coupling[5,6] of **1a**,**b** with TMS-ethyne or 1-hexyne proceeded smoothly to give 5-alkynyl derivatives **2a**–**3b** (79–96%). C6-lithiation,[7] followed by treatment with iodine gave 5-(alkyn-1-yl)-6-iodo analogs **4a**–**5b** in good yields. Coupling of **4a** with 1-hexyne afforded minor amounts of 5,6-bis(hexyn-1-yl) derivative **10a**, but the major product of this reaction was bicyclic compound **14** (Fig. 1). Furano[2,3-*d*]pyrimidin-2-ones related to **14** are known byproducts of Sonogashira couplings with 5-iodouracil substrates,[5,8] and variable amounts (10–15%) of the corresponding bicyclic pyrimidine-2-ones were observed when **2a**,**b** were prepared from **1a**,**b**. In the case of **2a**,**b**, cyclization was minimized with optimized reaction conditions, but coupling of the 6-iodo derivatives **4a**,**b** was considerably slower. The longer reaction times invariably gave furano[2,3-*d*]pyrimidin-2-ones as major products. This furan cyclization was circumvented by



Scheme 1. Reagents: (a) HC≡CR/Pd(0), Cu(I). (b) (i) LDA, –78°C; (ii) I_2. (c) BzCl/(iPr)$_2$NEt. (d) NH_3/MeOH. (e) CH_2N_2/Et_2O. (f) NH_4F/BTAC/THF. (g) NH_4F/MeOH[16]

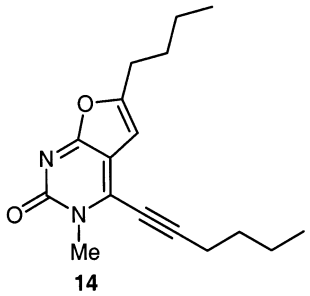
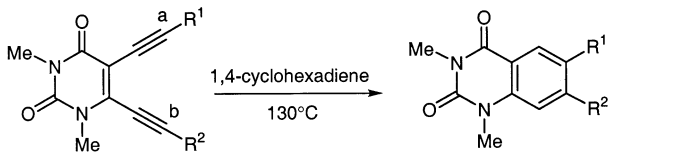


Figure 1.

N^3-benzoylation of **4a**,**b**. The resulting **6a**,**b** underwent coupling to give **8a**,**b** without accompanying addition of O4 to the C5-alkynyl triple bond. Compound **5a** was N^3-benzoylated to give **7a**, but **5a**,**b** underwent coupling without formation of furano[2,3-*d*]pyrimidin-2-one byproducts. Thus, **9a**,**b** were prepared from **5a** or **5b** by direct coupling with (trimethylsilyl)acetylene. The N^3-benzoyl group was removed under standard conditions, and treatment of **8a** with NH_3/MeOH gave **10a** (75%).

Attempts[9] to bis-desilylate **9a** gave intractable mixtures. Remarkably, N^3-methylation overcame this problem and **13** was obtained in 91% yield upon treatment of **11** with NH_4F/MeOH. The C6-ethynyl TMS group was selectively cleaved[10] to give **12** (77%) with NH_4F/benzyltriethylammonium chloride (BTAC)/THF.

Enediynes **12** and **13** underwent thermal Bergman cycloaromatization in 1,4-cyclohexadiene at 130°C with half-lives of 8 and 2 h, respectively (Scheme 2).[11] Compound **11** did not undergo Bergman cyclization under these conditions, and higher temperatures resulted in significant decomposition. Isolated yields of **15** and **16** were approximately 20%, and decomposition of starting material (prolonged reaction time with **12**, low solubility in 1,4-cyclohexadiene with **13**) contributed to the modest yields.



12 R^1 = TMS, R^2 = H
13 R^1 = R^2 = H

15 R^1 = TMS, R^2 = H ($t_{1/2}$ = 8h)
16 R^1 = R^2 = H ($t_{1/2}$ = 2h)

Scheme 2.

Activation energies for Bergman cycloaromatizations have been correlated with the a,b-distance between the two terminal alkynyl carbon atoms.[12] Acyclic enediynes with a,b-distances >3.5 Å were unreactive at 25°C and required heating to effect cyclization. In compounds **11**–**13**, the a,b-distance is calculated to be approximately 4.1 Å.[13] Terminally substituted acyclic enediynes exhibit increased activation barriers due to unfavorable steric interactions and entropic effects,[14] and the relative reactivities of **11**–**13** are consistent with these observations.

In summary, we have prepared 5,6-bis(alkyn-1-yl)-1-methyluracil derivatives and protected nucleosides via successive Sonogashira couplings of 5- and 6-iodo(uracil or uridine) analogs **1a**,**b** and **5a**–**6b**. Coupling of the 6-iodo derivatives was sluggish and required longer reaction times or higher temperatures than couplings with the 5-iodo compounds. Extended reaction times resulted in increased formation of furano[2,3-*d*]pyrimidin-2-one byproducts from 5-(hexyn-1-yl) derivatives **4a**,**b**, but they were not observed with 5-(TMS-ethyn-1-yl) intermediates **3a**,**b** or **5a**,**b**. The 5,6-bis(ethynyl) derivatives underwent Bergman cycloaromatization at elevated temperatures to give quinazoline-2,4-dione derivatives **15** and **16**.[15] Connection of the two ethynyl substituents to form fused bicyclic uracil-based enediynes should significantly lower activation barriers to Bergman cycloaromatization. We are actively pursuing such studies and biological testing of nucleoside enediynes.

Acknowledgements

We thank the BYU Cancer Center and BYU for partial support of this work.

References

1. (a) Bergman, R. G. *Acc. Chem. Res*. **1973**, *6*, 25–31. (b) Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc*. **1972**, *94*, 660–661.
2. *Cancer Therapeutics: Experimental and Clinical Agents*; Teicher, B. A., Ed.; Humana Press: Totowa, 1997.
3. (a) Maier, M. E. *Synlett* **1995**, 13–26. (b) Nicolaou, K. C.; Dai, W.-M.; Tsay, S.-C.; Estevez, V. A.; Wrasidlo, W. *Science* **1992**, *256*, 1172–1178.
4. (a) Kim, C.-S.; Russell, K. C. *J. Org. Chem*. **1998**, *63*, 8229–8234. (b) Kim, C.-S.; Diez, C.; Russell, K. C. *Chem. Eur. J*. **2000**, *6*, 1555–1558.
5. (a) Kumarasinghe, E. S. Masters Thesis, Brigham Young University, 2000. (b) Robins, M. J.; Barr, P. J. *Tetrahedron Lett*. **1981**, *22*, 421–424. (c) Robins, M. J.; Barr, P. J. *J. Org. Chem*. **1983**, *48*, 1854–1862. (d) De Clercq, E.; Descamps, J.; Balzarini, J.; Giziewicz, J.; Barr, P. J.; Robins, M. J. *J. Med. Chem*. **1983**, *26*, 661–666. (e) Robins, M. J.; Vinayak, R. S.; Wood, S. G. *Tetrahedron Lett*. **1990**, *31*, 3731–3734.
6. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, 4467–4470.
7. (a) Tanaka, H.; Hayakawa, H.; Shibata, S.; Haraguchi, K.; Miyasaka, T. *Nucleosides Nucleotides* **1992**, *11*, 319–328. (b) Tanaka, H.; Hayakawa, H.; Iijima, S.; Haraguchi, K.; Miyasaka, T. *Tetrahedron* **1985**, *41*, 861–866.
8. McGuigan, C.; Yarnold, C. J.; Jones, G.; Velázquez, S.; Barucki, H.; Brancale, A.; Andrei, G.; Snoeck, R.; De Clercq, E.; Balzarini, J. *J. Med. Chem*. **1999**, *42*, 4479–4484.
9. *Protective Groups in Organic Synthes*is, 3rd ed.; Greene, T. W.; Wuts, P. G. M., Eds.; John Wiley & Sons: New York, 1999; pp. 654–656.
10. Determined by HMBC NMR experiments.
11. Half-lives were determined by ^{1}H NMR.
12. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc*. **1988**, *110*, 4866–4868.
13. Determined by semi-empirical (AM-1) calculations.
14. (a) Chen, W.-C.; Chang, N.-Y.; Yu, C.-H. *J. Phys. Chem. A* **1998**, *102*, 2584–2593. (b) Schreiner, P. R. *J. Am. Chem. Soc*. **1998**, *120*, 4184–4190.
15. Compound **16** was identical to an authentic sample of 1,3-dimethyl-(1*H*,3*H*)-quinazoline-2,4-dione.[4b]
16. Yields shown are for isolated compounds. All new compounds were characterized by ^{1}H and ^{13}C NMR and had HRMS values within ±10 ppm of theory.[5a] Spectral data for representative compounds are: Compound **4a**: UV (MeOH) max 230, 309 nm, min 260 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.43 (s, 1H), 3.73 (s, 3H), 2.49 (t, $J=6.6$ Hz, 2H), 1.68–1.54 (m, 2H), 1.53–1.44 (m, 2H), 0.94 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.5, 148.7, 122.2, 111.8, 99.1, 42.7, 30.5, 22.2, 19.7, 13.8; MS (FAB) m/z 333.0092 (MH^+ [$C_{11}H_{14}IN_2O_2$]=333.0100). Compound **6a**: UV (MeOH) max 248, 316 nm, min 274 nm; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.93 (dd, $J=12.5$, 2.3 Hz, 2H), 7.64–7.60 (m, 1H), 7.53–7.50 (m, 2H), 3.78 (s, 3H), 2.48 (t, $J=6.8$ Hz, 2H), 1.62–1.40 (m, 4H), 0.93 (t, $J=7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 158.3, 147.4, 135.4, 131.2, 130.7, 129.3, 121.8, 111.8, 99.8, 77.3, 42.9, 30.4, 22.2, 19.7, 13.8; MS (CI) m/z 436.0294 (M^+ [$C_{18}H_{17}IN_2O_3$]=436.0284). Compound **8a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.91 (dd, $J=12.6$, 2.4 Hz, 2H), 7.63–7.55 (m, 1H), 7.51–7.47 (m, 2H), 3.54 (s, 3H), 2.61 (t, $J=7.0$ Hz, 2H), 2.46 (t, $J=6.8$ Hz, 2H), 1.62–1.40 (m, 8H), 0.98 (t, $J=7.2$ Hz, 3H), 0.91 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2, 149.3, 135.2, 131.6, 130.8, 129.4, 129.3, 100.2, 34.2, 30.8, 30.1, 29.9, 22.3, 22.1, 20.1, 19.9, 13.9, 13.8; MS (CI) m/z 391.2017 (MH^+ [$C_{24}H_{27}N_2O_3$]=391.2022). Compound **10a**: UV (MeOH) max 231, 333 nm, min 266 nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (s, 1H), 3.50 (s, 3H), 2.58 (t, $J=7.1$ Hz, 2H), 2.48 (t, $J=6.8$ Hz, 2H), 1.68–1.44 (m, 8H), 0.97 (t, $J=7.2$ Hz, 3H), 0.94 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.3, 149.9, 140.6, 109.9, 99.2, 73.1, 72.67, 34.0, 30.9, 30.2, 29.9, 22.25, 22.18, 19.92, 19.88, 13.9, 13.8; MS (CI) m/z 287.1742 (MH^+ [$C_{17}H_{23}N_2O_2$]=287.1760). Compound **11**: UV (MeOH) max 234, 340 nm, min 276 nm; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.57 (s, 3H), 3.36 (s, 3H), 0.32 (s, 9H), 0.26 (s, 9H); ^{13}C NMR

($CDCl_3$, 125 MHz) δ 161.1, 150.9, 138.8, 115.1, 104.0, 103.6, 96.7, 94.4, 34.9, 28.7, –0.1, –0.5; MS (EI) m/z 332.1370 (M^+ [$C_{16}H_{24}N_2O_2Si_2$] = 332.1376). Compound **13**: UV (MeOH) max 223, 325 nm, min 266 nm; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.05 (s, 1H), 3.61 (s, 3H), 3.46 (s, 1H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.9, 150.7, 138.9, 103.9, 94.5, 85.8, 75.7, 74.1, 35.1, 28.9; MS (CI) m/z 189.0653 (MH^+ [$C_{10}H_9N_2O_2$] = 189.0664).