PERKIN 1 COMMUNICATION

Studies on uracils: an efficient method for the synthesis of novel 1-allyl-6-(1′,2′,3′-triazolyl) analogues of HEPT

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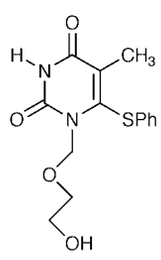
An efficient synthetic method for preparing novel 1-allyl-6-(1′,2′,3′-triazolyl) analogues of HEPT, an anti-HIV reverse transcriptase inhibitor, is reported. The key step is based upon selective intermolecular cycloaddition of azide to acetylenes.

The importance of uracil and its annulated substrates is well recognised by synthetic[1] as well as biological chemists.[2] With the development of clinically useful anticancer and antiviral drugs (AZT, DDI, DDC, BVDU) there has recently been remarkable interest in the synthetic manipulation of uracils. However until the emergence of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine[3] (HEPT) **1** as a potent and selective inhibitor of HIV-1, no attention was given to the synthetic manipulation at the 6-position of uracils. N^1-Allylated uracils are known to posses significant biological activity. ACURACIL[4] (1-allyl-3,5-diethyl-6-chlorouracil) **2** is a drug in use for the external treatment of herpes simplex and other viral infections of skin and mucous membranes.



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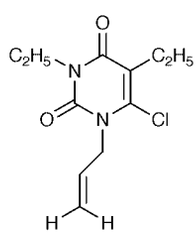

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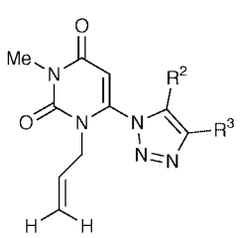

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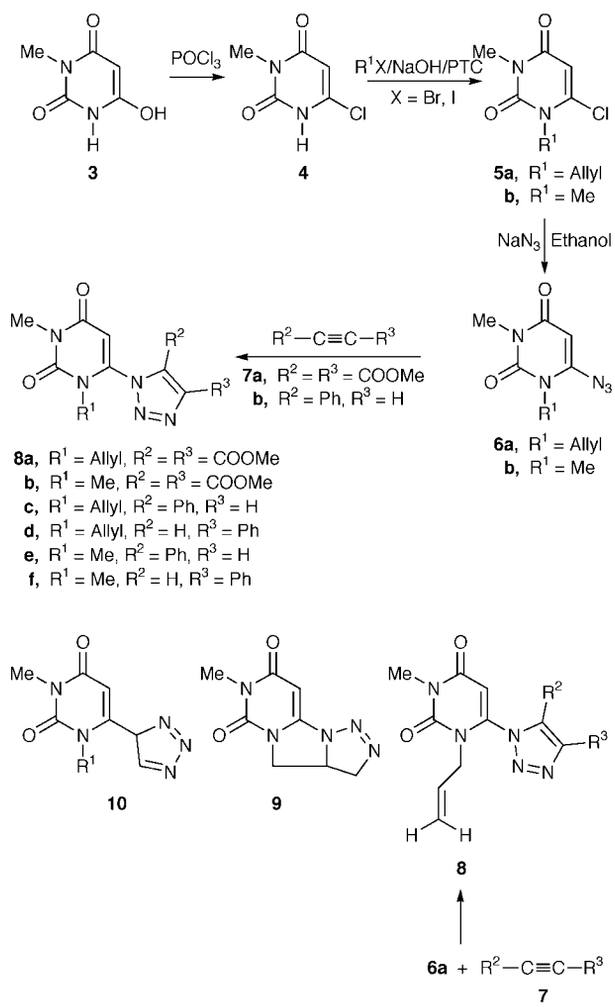
Triazoles, particularly 1,2,3-triazoles, continue to be of great interest due to their intriguing pharmacological properties.[5] Cefatrizin,[6] an antibiotic carrying a 1,2,3-triazole ring in its side chain belongs to the class of cephalosporins and is currently in clinical use, with activity against 342 different bacterial species. Another semisynthetic penicillin prepared from 2-phenyl-1,2,3-triazolecarboxylic acid has recently been reported.[7]

As a part of our research programme[8] in the area we report in this communication the synthesis of a novel class of 1-allyl-6-(1′,2′,3′-triazolyl)uracils **8** as novel candidates in the HEPT series (Scheme 1). The key step is based on selective intermolecular cycloaddition of 6-azidouracils to acetylenes, 1-alkyl-6-azidouracils **6**, the key intermediates are prepared from barbituric acid **3** in a three step synthesis. In a simple experimental pathway 6-chlorouracil **4** was first prepared from



Scheme 1

barbituric acid **3** following the standard method[9] and then alkylated under phase transfer catalytic (PTC) conditions[10] to obtain compound **5a**. It was then treated with a slight excess of sodium azide[11] in refluxing ethanol for 1 h to furnish the intermediate **6a**. The 6-azidouracil **6a** was refluxed with an equimolar amount of the acetylene **7a** in toluene for 1 h. A thick brownish precipitate appeared suddenly in the clear solution initially formed. The precipitate was filtered, washed with toluene and dried. A 95% yield of the compound was obtained and confirmed as **8a** from spectroscopic data and elemental analysis. The IR spectra showed the absence of azide functionality which confirmed its involvement in the cycloaddition. Compound **8b** was synthesised similarly and its structure confirmed from analytical data. In the reaction of **6a,b** with **7b** two isomers were isolated in each case. Thus the reaction of **6a** and **7b** yielded **8c** and **8d** (1:4 ratio from ^{1}H NMR data) in a 90% overall yield. The compounds were

separated by column chromatography using chloroform–methanol as eluent. Similarly the reaction of **6b** and **7b** furnished compound **8e** and **8f** (1 : 4 ratio from ^{1}H NMR data) in excellent overall yield.

In one of our recent papers[12] we reported the attack of a cyano stabilised carbanion on 6-azido uracils which yielded 1,2,3-triazolo fused tricyclic analogues of uracil *via* an intramolecular cycloaddition of azide to nitriles. There are a few other reports of the reaction of azidouracils all of which involve intramolecular cycloaddition of azide to the C5–C6 double bond[13] or other transformations[14] and sometimes results in the rupturing of the uracil moiety.[15] The present report is the first example of trapping of an external dipolarophile by the azide functionality of 6-azidouracils keeping the uracil moiety intact. Although there was the possibility of the formation of cycloadduct **10** from intramolecular cycloaddition of the azide at the C5 atom we have not observed the formation of any such compound under the reaction conditions. More interestingly neither intramolecular cycloaddition of the azide to the allylic bond took place to yield compound **9**, nor rupturing of the uracil ring under the reaction conditions.

Further studies on this series of compounds are in progress. In conclusion we have demonstrated a versatile method for the synthesis of functionalised complex uracils as novel candidates in the HEPT series.

Experimental

Mps were determined in open capillary tubes on a Buchi apparatus and are uncorrected. The 90 MHz ^{1}H NMR spectra were recorded in a JEOL EX 90A spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) as the internal standard. The chemical shift values are recorded in δ units (ppm). The IR spectra were recorded on a Perkin-Elmer 237B IR spectrometer as KBr discs. Mass spectra were recorded on a INCOS - 50 GC MS instrument. Elemental analyses were performed on a Hitachi 026 CHN analyser.

General procedure for the synthesis of 1-alkyl-6-chlorouracils 5a,b

To a suspension of 6-chlorouracil **4** (10 mmol) in dichloromethane (20 ml) was added tetrabutylammonium bromide (4 mmol), 10% aqueous NaOH (20 ml) and alkyl bromide (30 mmol), and the reaction mixture was heated at 40 °C. The progress of the reaction was monitored by TLC, and at completion, the reaction mixture was cooled and diluted with water (20 ml). The organic layer was separated and the aqueous layer extracted with dichloromethane. The organic extract was washed with 20 ml water and dried over anhydrous sodium sulfate, and evaporated to obtain compound **5** in 85–90% yield. **5a**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.00 (s, 3H), 3.40 (d, 2H), 5.15 (m, 2H), 5.70 (s, 1H), 5.80 (m, 1H). MS 200 (M^+), mp 124 °C. **5b:** ($CDCl_3$) 3.10 (s, 3H), 3.15 (s, 3H), 5.65 (s, 1H). MS 174 (M^+), mp 113 °C.

General procedure for the synthesis of 1-alkyl-6-azidouracil 6a,b

A solution of 6-chlorouracils **5** (5 mmol) and sodium azide (9 mmol) in ethanol (15 ml) was refluxed for 2 h. Ethanol was removed by evaporation and the residue was washed with water and dried. A pale yellow product was obtained in 60% yield. **6a**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.00 (s, 3H), 3.40 (d, 2H), 5.15 (m, 2H), 5.70 (s, 1H), 5.80 (m, 1H). MS 207 (M^+). IR ν_{max} 2135 cm^{-1}. Mp 168 °C. **6b**: ($CDCl_3$) 3.10 (s, 3H), 3.15 (s, 3H), 5.65 (s, 1H). MS 181 (M^+). IR ν_{max} 2135 cm^{-1}. Mp 150 °C.

General procedure for the reaction of *N*-alkyl-6-azidouracil with acetylene

A mixture of 6-azidouracils (0.20 mmol) and acetylenes (0.30 mmol) in toluene (10 ml) were refluxed for 1–2 h. Initially a clear solution was formed and after a few minutes a thick precipitate appeared. The reaction mixture was cooled, filtered, and the solid product washed with toluene and dried. The reaction of **6a** and **7b** yielded **8c** and **8d** (1 : 4 ratio from ^{1}H NMR data) in a 90% overall yield. The compounds were separated by column chromatography using chloroform–methanol as eluent. Similarly the reaction of **6b** and **7b** furnished compound **8e** and **8f** (1 : 4 ratio from ^{1}H NMR data) in excellent overall yield. **8a**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.00 (s, 3H, >N-Me), 3.40 (d, 2H, -CH_2-), 3.60 (s, 3H, -OMe), 3.70 (s, 3H, -OMe), 5.15 (m, 2H, =CH_2), 5.70 (s, 1H, C5-H), 5.80 (m, 1H, =CH-). MS *349 (M*$^+$), mp > 250 °C. Elemental analysis (%) Calc. C, 48.13, H, 4.29; N, 20.05. Found: C, 48.10; H, 4.20; N, 20.15. **8b:** ^{1}H NMR 90 MHz ($CDCl_3$) 3.10 (s, 3H, >N-Me), 3.15 (s, 3H, >N-Me), 3.60 (s, 3H, -OMe), 3.70 (s, 3H, -OMe), 5.65 (s, 1H, C5-H). MS 323 (M^+), mp >250 °C. Elemental analysis (%) Calc. C, 44.58; H, 4.02; N, 21.67. Found: C, 44.50; H, 4.00; N, 21.65. **8c**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.10 (s, 3H, >N-Me), 3.40 (d, 2H, -CH_2-), 5.15 (m, 2H, =CH_2), 5.60 (s, 1H, C5-H), 5.80 (m, 1H, =CH-), 7.15 (m, 5H, -Ph), 8.30 (s, 1H, =CH-N=). MS 309 (M^+), mp >250 °C. Elemental analysis (%) Calc. C, 62.13; H, 4.85; N, 22.65. Found: C, 62.15; H, 4.80; N, 22.65. **8d**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.10 (s, 3H, >N-Me), 3.40 (d, 2H, -CH_2-), 5.20 (m, 2H, =CH_2), 5.55 (s, 1H, C5-H), 5.75 (M, 1H, =CH-), 7.15 (m, 5H, -Ph), 9.10 (s, 1H, =CH-N<). MS 309 (M^+), mp >250 °C. Elemental analysis (%) Calc. C, 62.13; H, 4.85; N, 22.65. Found: C, 62.15; H, 4.80; N, 22.65. **8e**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.10 (s, 3H, >N-Me), 3.15 (s, 3H, >N-Me), 5.65 (s, 1H, C5-H), 7.15 (m, 5H, -Ph), 8.35 (s, 1H, =CH-N=). MS 283 (M^+), mp >250 °C. Elemental analysis (%) Calc. C, 59.36; H, 4.59; N, 24.7. Found: C, 59.30; H, 4.60; N, 24.7. **8f**: ^{1}H NMR 90 MHz ($CDCl_3$) 3.10 (s, 3H, >N-Me), 3.15 (s, 3H, >N-Me), 5.60 (s, 1H, C5-H), 7.20 (m, 5H, -Ph), 9.15 (s, 1H, =CH-N<). MS 283 (M^+), mp >250 °C. Elemental analysis (%) Calc. C, 59.36; H, 4.59; N, 24.7. Found: C, 59.30; H, 4.60; N, 24.7.

CAUTION: All the azides are potentially explosive and should not be heated as neat solids or liquids. All reactions involving azides described in this paper were carried out in solution.

References

1 (*a*) E. Lunt, *Comprehensive Organic Chemistry*, eds. D. H. R. Barton and W. D. Ollis, Pergamon Press, Oxford, 1979, vol. 4, p. 493; (*b*) D. J. Brown, *Comprehensive Heterocyclic Chemistry*, eds. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, vol. 3, p. 57; (*c*) T. Sasaki, K. Minamoto, T. Suzuki and S. Yamashita, *Tetrahedron*, 1980, **36**, 865.

2 (*a*) A. S. Jones, J. R. Sayers, R. T. Walker and E. De Clercq, *J. Med. Chem.*, 1988, **31**, 268; (*b*) H. Mitsuya, R. Yarchoan and S. Broder, *Science*, 1990, **249**, 1533; (*c*) R. Pontikis and C. Monneret, *Tetrahedron Lett.*, 1994, **35**, 4351.

3 T. Miyasaka, H. Tanaka, M. Baba, H. Huyakawa, R.T. Walker, J. Balzarini and E. De Clercq, *J. Med. Chem.*, 1989, **32**, 2507.

4 (*a*) K. K. Gauri and H. Kohlage, *Chemotherapy*, 1969, **14**, 158; (*b*) K. K. Gauri and B. Rohde, *Klin. Wochenschr.*, 1969, **47**, 375.

5 (*a*) R. W. Sidmell, J. H. Huffman, G. P. Khare, L. B. Allen, J. T. Wotkowski and R. K. Robins, *Science*, 1972, **177**, 705; (*b*) R. K. Robins, P. C. Srivastava, V. L. Narayan, J. Plowman and K. D. Paull, *J. Med. Chem.*, 1982, **25**, 107.

6 (*a*) Y. Ueda, *Chemotherapy* (*Tokyo*), 1976, **24**, 1661; (*b*) R. J. Fass and R. B. Prior, *Curr. Ther. Res.*, 1978, **24**, 352.

7 U. Saha, A. Das, S. Chakraborty, M. Ghosh and D. K. Roy, *J. Inst. Chem.* (*India*), 1980, **52**, 196; (*Chem. Abstr.*, 1981, **44**, 139681).

8 (*a*) P. J. Bhuyan, R. C. Boruah and J. S. Sandhu, *J. Org. Chem.*, 1990, **55**, 568; (*b*) P. J. Bhuyan, J. S. Sandhu and A. C. Ghosh, *Tetrahedron Lett.*, 1996, **37**, 1853; (*c*) P. J. Bhuyan, K. C. Lekhok and J. S. Sandhu, *Tetrahedron Lett.*, 1999, **40**, 1793.

9 G. Nubel and W. Pfleiderer, *Chem. Ber.*, 1962, **95**, 1605.

10 M. Hedayatullah, *J. Heterocycl. Chem.*, 1981, **18**, 339.

11 S. Senda, K. Hirota, T. Asao and K. Maruhashi, *J. Am. Chem. Soc.*, 1978, **100**, 7661.

12 P. J. Bhuyan, K. C. Lekhok and J. S. Sandhu, *J. Chem. Res. (S)*, 1999, 232.

13 M. Jokic and V. Skaric, *J. Chem. Soc., Perkin Trans. 1*, 1989, 757.

14 K. Hirota, K. Maruhashi, T. Asao, N. Kitamura, Y. Maki and S. Senda, *Chem. Pharm. Bull.*,1983, **31**, 3959.

15 T. Sasaki, K. Minamoto, T. Suzuki and S. Yamashita, *Tetrahedron*, 1980, **36**, 865.

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