Pergamon

Tetrahedron Letters 40 (1999) 1793–1794

TETRAHEDRON LETTERS

Studies on Uracils : A Simple and Efficient Method for the Synthesis of Novel Pyrimido[4,5-c]pyridazines

Pulak J. Bhuyan, Kushal C Lekhok and Jagir S Sandhu*.

Regional Research Laboratory, Jorhat-785 006. Assam, India.

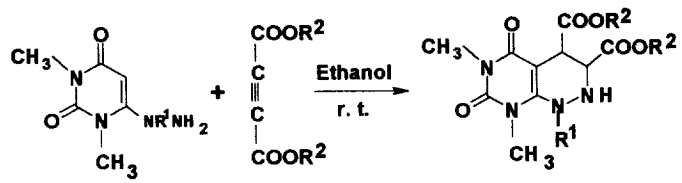
Received 3 November 1998; accepted 23 December 1998

Abstract : **The reaction of 6-hydrazino uracils 1 and acetylenedicarboxylates 2 at room temperature affords tetrahydro-pyrimido[4,5-c]pyridazines 3 in excellent yield.**

Keywords: Uracil, Cycloaddition, Pyridazine.

Uracil derivatives continue to be of great interest due to their wide range of biological activities.[1] The preparation of naturally occuring complex molecules containing a uracil ring poses significant synthetic challenges.[2] Pyrimido[4,5-c]pyridazines are an important class of annulated uracils of biological importance. 4-Deazatoxoflavin (1,6-Dimethyl-1,5,6,7-tetrahydropyrimido[4,5-c]pyridazine-5,7-dione), a member of the pyrimido- [4,5-c]pyridazines, inhibits the growth of *Pseudomonas 568* and also binds to herring sperm DNA .[3] But interestingly, only a few reports are available in literature[4] for the synthesis of pyrimido[4,5-c]pyridazines, and these usually require high temperatures, long reaction times and complex synthetic pathways.

In the present communication we report a very simple, mild and efficient method for the synthesis of pyrimido[4,5-c]pyridazines by exploring the nucleophilic double-bond of 6-hydrazino uracils. The reaction of 6-hydrazino uracils **1** and acetylenedicarboxylates[5] **2** at room temperature affords tetrahydro-pyrimido[4,5-c]pyridazines **3** in excellent yields **(Scheme-1).**



1. a, R^1=H; b, R^1=CH_3 2. a,R^2=CH_3 b,R^2=C_2H_5 3. a,R^1=H, R^2=CH_3 b, R^1=CH_3, R^2=CH_3 c, R^1=H, R^2=C_2H_5 d, R^1=CH_3, R^2=C_2H_5

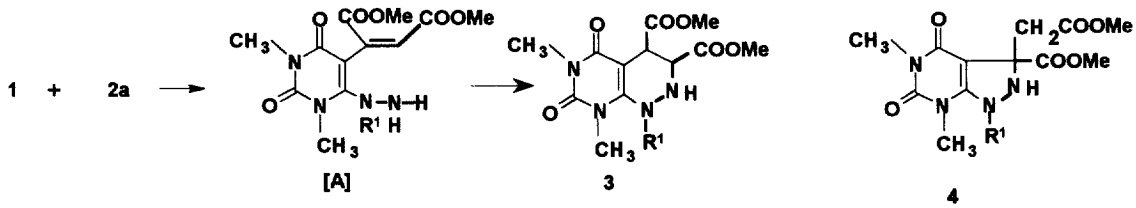
Scheme-1

In a simple experimental procedure dimethyl acetylenedicarboxylate **2a** (0.170g, 1 mmol) was added to a suspension of 1,3-dimethyl-6-hydrazino uracil **1a** (0.142g, 1 mmol) in ethanol (5ml) and the mixture was stirred at room temperature for 1 hr. The suspension of hydrazino uracil **1a** first disappeared with the addition of DMAD to a clear solution and then a thick

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00011-8

precipitate appeared rapidly. The precipitate was filtered, washed with a small amount of cold ethanol and dried. The product **3a** was obtained in quantitative yield and recrystallised from ethanol, m.p. 140°C. ^{1}H NMR 90 MHz ($CDCl_3$) 2.90(d, *J*=4, 1H), 3.00(s, 3H), 3.15(s, 3H), 3.60(s, 3H), 3.70(s, 3H), 3.88(d, *J*=3.8, 1H). MS 312 M^+. CHN analyses (calculated %) C, 46.15; H, 5.13; N, 17.94; (found %) C, 46.20; H, 5.15; N, 17.90. Similarly, compound 3b-d were prepared and the structures confirmed from spectroscopic data and elemental analyses. 3b. m.p. 135°C. ^{1}H NMR ($CDCl_3$) 2.90(d, *J*=4.2, 1H), 3.00(s, 3H), 3.10(s, 3H), 3.15(s, 3H), 3.65(s, 3H), 3.75(s, 3H), 3.80(d, *J*=3.8, 1H). MS 326 M^+. CHN analyses (calculated %) C, 47.85; H, 5.52; N, 17.17; (found %) C, 47.80; H, 5.45; N, 17.10. 3c. m.p. 172°C. ^{1}H NMR ($CDCl_3$) 1.45 (t, 3H), 1.65 (t, 3H), 2.85(d, *J*=4.6, 1H), 3.05(s, 3H), 3.15(s, 3H), 3.80(d, *J*=4, 1H), 4.25-4.65(m, 4H). MS 340 M^+. CHN analyses (calculated %) C, 49.41; H, 5.88; N, 16.47; (found %) C, 49.40; H, 5.80; N, 16.40. 3d. m.p. 165°C. ^{1}H NMR ($CDCl_3$) 1.35(t, 3H), 1.55(t, 3H), 2.95(d, *J*=4.6, 2H), 3.00(s, 3H), 3.10(s, 3H), 3.20(s, 3H), 3.85(d, *J*=3.8, 1H), 4.25-4.60(m, 4H). MS 354 M^+. CHN analyses (calculated %) C, 50.84; H, 6.21; N, 15.90; (found %) C, 50.80; H, 6.15; N, 15.75.

Although we could not isolate any intermediates, a resonable mechanism for the formation of the pyrimido[4,5-c]pyridazines is outlined in **scheme 2**. The reactions may occur via a Michael addition of the nucleophilic double bond of the uracils on to the acetylenedicarboxylates to form a hydrazinodiene system (A), which rearranges to give the product. Although there was a possibility of the formation of the 1,5-cycloadduct **4**, we did not observe any such compound in the reaction mixture.



Scheme-2.

Further study of this effective synthetic method is in progress. In conclusion our results demonstrate a simple mild and efficient method for the synthesis of complex pyrimido[4,5-c]-pyridazines of biological importance.

References :,

1. (a) Jones, A. S., Sayers, J. R., Walker, R.T. Clercq, E.D., *J. Med. Chem.*,**1988**, *31*, 268. (b) Mitsuya, H. Yarchoan, R. Broder, S., *Science*, **1990**, *249*, 1533. (c) Pontikis, R., Monneret, C., *Tetrahedron Lett.*, **1994**, *35*,4351.
2. (a) Lunt, E., *Comprehensive Organic Chemistry;* Barton, D. H. R., Ollis, W.D., Eds. Pergamon Press, Oxford, **1979**, vol.4, p-493. (b) Brown, D. J., *Comprehensive Heterocyclic Chemistry*, Katritzky, A.R., Rees, C. W., Eds. Pergamon Press, Oxford, **1984**, vol. 3, p-57. (c) Sasaki, T., Minamoto, K., Suzuki, T., Yamashita, S., *Tetrahedron*, **1980**, *36*, 865. (d) Bhuyan, P.J., Boruah, R.C., Sandhu, J.S., *J. Org. Chem.*, **1990**, *55*, 568.
3. Billings, B.K., Wagner, J.A., Cook, P.D., Castle, R.N. *J. Het. Chem.*, **1975**, *12*, 1221.
4. (a) Mallory, W.R.; Morrison, R.W.Jr.; Styles,V.L. *J. Org. Chem.*, **1982**, *47*, 667 and references cited therein. (b) Miyamoto, T.; Kimura, Y.; Matsumoto J-I.; Minami. S. *Chem. Pharm. Bull.*, **1978**, *26*, 14 and references cited therein.
5. Bhuyan, P.J., Sandhu, J.S., Ghosh, A.C., *Tetrahedron Lett.*, **1996**, *37*, 1853 and references cited therein.