Chemistry of Heterocyclic Compounds, Vol. 40, No. 10, 2004

SYNTHESIS OF 7-OXOPYRROLO-[3,2-*d*]PYRIMIDINE 5-OXIDES BY THE REARRANGEMENT OF 6-ALKYNYL-5-NITROPYRIMIDINES

S. Tumkevicius, I. Susvilo, and A. Brukstus

A method is proposed for the synthesis of 6-substituted 4-amino-7-oxopyrrolo[2,3-d]pyrimidine 5-oxides which includes a Sonogashira reaction of 4-amino-6-chloro-5-nitropyrimidine with terminal alkynes and subsequent rearrangement of the 6-alkynyl-5-nitropyrimidines obtained.

Keywords: alkynes, nitropyrimidines, palladium, pyrrolo[3,2-*d*]pyrimidines, catalysis, rearrangement.

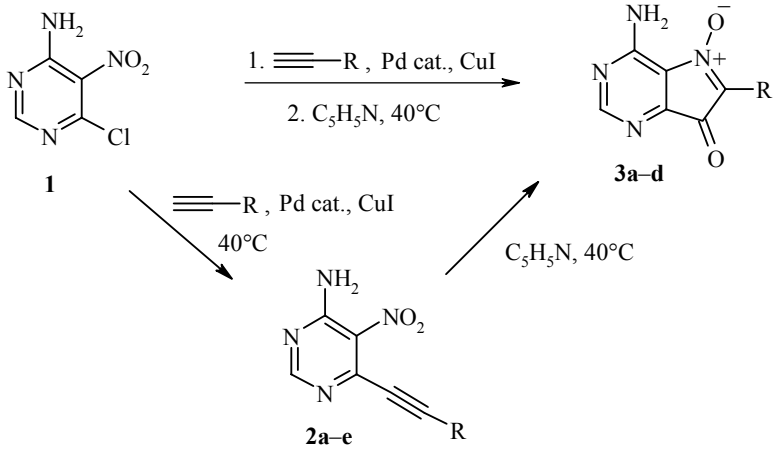
One of the routes for the synthesis of the pyrrolo[3,2-*d*]pyrimidine heterocyclic system involves the formation of a pyrrole ring by an intramolecular cyclization of the corresponding substituted pyrimidine. Analysis of the literature has shown that 5-aminopyrimidines are most frequently chosen as starting materials in achieving this goal [1-8]. There are only a few reports in the literature concerning the synthesis of pyrrolo[3,2-*d*]pyrimidines from 6-alkynylpyrimidines [9] and 5-nitropyrimidines [10-15]. The latter usually form pyrrolopyrimidines under reductive cyclization conditions. However, according to our study of the literature, the synthesis of pyrrolo[3,2-*d*]pyrimidines from 5-nitropyrimidines having alkyl substituents in the position 6 has not been reported. We have recently published a preliminary report of the possible synthesis of pyrrolo[3,2-*d*]pyrimidine 5-oxides by the rearrangement of certain 1-(4-amino-5-nitro-6-pyrimidinyl)-2-arylethynes in pyridine solution [16]. In the current work we continue the investigation to provide additional data for the synthesis of 7-oxo-7H-pyrrolo[3,2-*d*]pyrimidine 5-oxides. These compounds are aza analogs of isatogens [17-19] and are of interest as materials which bind radicals in a biological medium.

The readily prepared 4-amino-6-chloro-5-nitropyrimidine (**1**) [10] was chosen as the starting material in the synthesis. Investigation of the cross conjugation reaction of compound **1** with terminal alkynes in the presence of $PdCl_2(PPh_3)_2$ and CuI catalysts in triethylamine has shown that the best results are achieved by carrying out this reaction with a small excess of the appropriate acetylene at 40°C. The compounds **2a-e** are formed in 68-89% yields.

Study of the properties of the alkynylpyrimidines has shown that, when heated for a short time (15 min) in pyridine, they undergo a rearrangement to form the 6-substituted 4-amino-7-oxopyrrolo[2,3-*d*]pyrimidine 5-oxides **3a-d** (method A).

The yields of compounds **3a-d** are 87-95%. Only the reaction of compound **2e** occurs differently. In this case a complex mixture of products is formed along with tarring of the reaction mixture and the expected product could not be separated. The reason could be the instability of compound **2e**, which is partially decomposed even when attempts are made to purify it using column chromatography or crystallization.

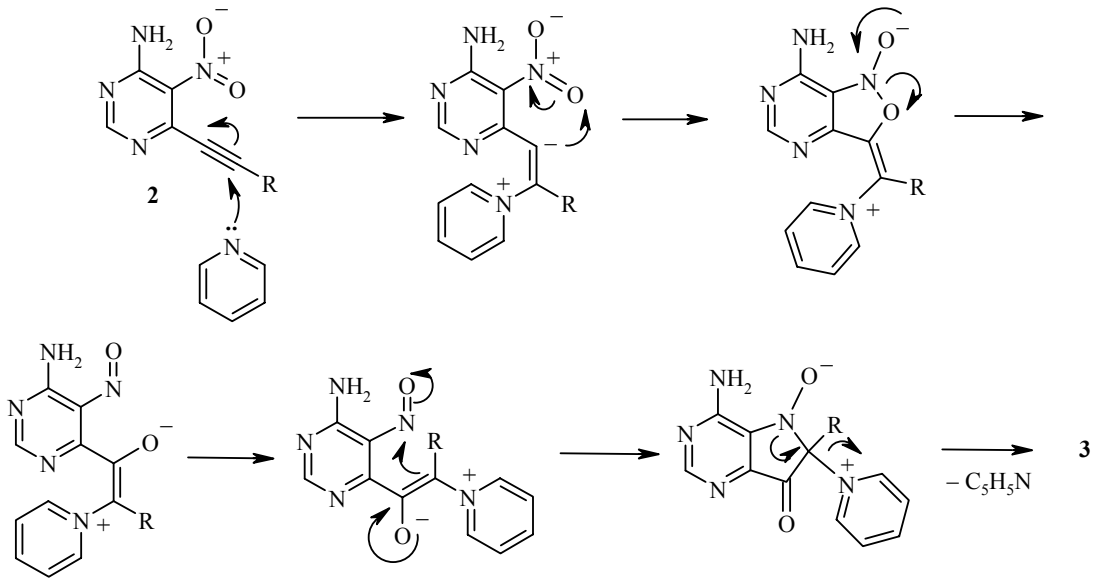
Organic Chemistry Department, Vilnius University, Vilnius LT-03225, Lithuania; e-mail: sigitas.tumkevicius@chf.vu.lt. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10. pp. 1546-1550, October, 2004. Original article submitted July 7, 2004.



a R = Bu, **b** R = Ph, **c** R = 4-MeC$_6$H$_4$, **d** R = 4-F-C$_6$H$_4$, **e** R = SiMe$_3$

In view of the fact that the preparation of the alkynylpyrimidines and the conversion of compounds **2a-e** to the pyrrolo[3,2-*d*]pyrimidine 5-oxides **3a-e** occur in the presence of a tertiary amine base it seemed appropriate to us to study the possible preparation of compound **3** in a single stage, directly from the chloropyrimidine **1**. It was found that the triethylamine used in the cross conjugation stage does not cause the rearrangement of the alkynylpyrimidines formed. At the reflux temperature of triethylamine only a tarring of the reaction mixture occurs which markedly lowers the yields of the alkynylpyrimidines and hinders their separation. The formation of compound **3** was not observed. Upon addition of pyridine to the reaction mixture and carrying out the reaction at 40°C the 6-substituted 7-oxopyrrolo[3,2-*d*]pyrimidine 5-oxides **3a-c** are formed (method B). The yields of compounds **3a-c** as obtained using method B were less than the overall yields *via* the synthesis in the two stage method A. However, method B has the advantage that it avoids the procedure of the separation and purification of the intermediate alkynylpyrimidines.

The data obtained shows that pyridine can serve as catalyst in the rearrangement of the 6-alkynyl-5-nitropyrimidines to the corresponding 7-oxopyrrolo[2,3-*d*]pyrimidine 5-oxides. Evidently the pyridine adds to the triple bond and activates the alkyne. Subsequent nucleophilic attack on the oxygen of the nitro group leads to formation of an isoxazole derivative which then rearranges to the 7-oxopyrrolo[2,3-*d*]pyrimidine 5-oxide.



A catalytic role for the pyridine was also noted in a study of the photochemical isomerization of 2-nitrotolanes [20]. It was also shown that electron-acceptor substituents stabilize the carbanion formed and facilitate the reaction. In our case the electron deficient pyrimidine ring is such a group. It evidently also dictates that the 6-alkynyl-5-nitropyrimidines **2** readily undergo rearrangement to the 7-oxopyrrolo[2,3-*d*]pyrimidine 5-oxides **3** in the absence of UV irradiation.

We therefore propose a novel and convenient method for the synthesis of compounds of type **3** from 6-alkynyl-5-nitropyrimidines which are readily prepared by a Sonogashira reaction of 6-chloro-5-nitropyrimidine with terminal alkynes.

EXPERIMENTAL

IR spectra were recorded using vaseline oil on an FT-IR Spectrum BX II spectrometer (Perkin-Elmer). ^{1}H NMR spectra were taken on a Tesla 587A (80 MHz) or a Varian INOVA (300 MHz) spectrometer using TMS as internal standard. The course of the reaction and the purity of the compounds obtained were monitored using TLC on Alufol Silica Gel 60 F_{254} plates (Merck).

The characteristics of the compounds **2b-d**, **3b-d** are given in [16].

1-(4-Amino-5-nitro-6-pyrimidinyl)-2-substituted Acetylenes 2a-e (General Method). A mixture of compound **1** (0.2 g, 1.16 mmol), $PdCl_2(PPh_3)_2$ (0.015 g, 0.021 mmol), and CuI (1.98 mg, 0.0105 mmol) in dry triethylamine (5 ml) was stirred in an argon atmosphere for 1-3 min. The corresponding acetylene (1.25 mmol) was added and the reaction mixture was stirred for 2-3 h at 40°C. After cooling, the precipitate was filtered off and recrystallized (in the case of compounds **2a-d**) or washed with water (in the case of compound **2e**) to give the compounds **2a-e**.

Compound 2a. Yield 70%; mp 159°C (octane). IR spectrum, ν, cm^{-1}: 3382, 3220 (NH_2), 2209 (C≡C), 1569 (NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.98 (3H, t, *J* = 5.6, CH_3); 1.56 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$); 2.85 (2H, t, *J* = 5.6, CH_2); 7.88 (2H, br. s, NH_2); 8.74 (1H, s, H-2). ^{13}C NMR spectrum (CD_2Cl_2): 13.48, 21.01, 22.03, 37.49, 84.47, 87.06, 122.48, 144.91, 162.82, 167.91. Found, %: C 54.48; H 5.42; N 25.38. $C_{10}H_{12}N_4O_2$. Calculated, %: C 54.54; H 5.49; N 25.44.

Compound 2b [16]. Yield 75%. **Compound 2c** [16]. Yield 89%. **Compound 2d** [16]. Yield 68%.

Compound 2e. Yield 86%; mp 149-150°C. IR spectrum, ν, cm^{-1}: 3344, 3198 (NH_2), 2215 (C≡C), 1568 (NO_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.26 (9H, s, $Si(CH_3)_3$); 8.45 (1H, s, H-2); 9.02 (2H, br. s, NH_2).

6-Substituted 4-Amino-7-oxo-7H-pyrrolo[3,2-*d*]pyrimidine 5-Oxides 3a-d. A. A solution of the corresponding compounds **2a-d** (1 mmol) in anhydrous pyridine (5 ml) was refluxed for 15 min. After cooling to room temperature the precipitate was filtered off and the filtrate was concentrated at reduced pressure. The precipitate formed was combined with that obtained previously and recrystallized to give compounds **3a-d**.

B. A mixture of compound **1** (0.2 g, 1.16 mmol), $PdCl_2(PPh_3)_2$ (0.015 g, 0.021 mmol), CuI (1.98 mg, 0.0105 mmol), and dry triethylamine (5 ml) was stirred under an argon atmosphere for 1-3 min. The corresponding acetylene (1.25 mmol) was added and the reaction mixture was stirred for 30 min at 40°C. Pyridine (0.5 ml) was added and stirring was continued for a further 2-24 h. The reaction mixture was cooled and the precipitate filtered off and recrystallized to give compounds **3a-c**.

Compound 3a. Yield 92% (method A), 36% (method B, reaction time 24 h); mp 223°C (benzene). IR spectrum, ν, cm^{-1}: 3341, 3299 (NH_2), 1736 (CO), 1348 (NO). ^{1}H NMR spectrum (DMSO-d_6), δ, pm (*J*, Hz): 1.05 (3H, t, *J* = 5.6, CH_3); 1.51 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_3$); 2.99 (2H, t, *J* = 5.6, CH_2); 6.80 (1H, br. s, NH); 7.75 (1H, br. s, NH); 8.10 (1H, s, H-2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.28, 22.01, 22.63, 29.75,122.45, 136.96, 150.28, 154.89, 166.98, 187.93. Found, %: C 54.45; H 5.68; N 25.29. $C_{10}H_{12}N_4O_2$. Calculated, %: C 54.54; H 5.49; N 25.44.

Compound 3b. Yield 95% (method A) [16], 49% (method B, reaction time 2 h).

Compound 3c. Yield 90% (method A) [16], 38% (method B, reaction time 4 h).

This work was carried out with the financial support of the Lithuanian Fund for Science and Education, grant No. T-04220.

REFERENCES

1. M. Pfleiderer, *Chem. Ber.*, **90**, 738 (1957).
2. N. Kawahara, T. Nakajima, T. Itoh, and H. Ogura, *Chem. Pharm. Bull.*, **33**, 4740 (1985).
3. O. S. Sizova and R. G. Glushkov, *Pharm. Chem. J. (Eng. Ed.)*, **18**, 420 (1984).
4. M. Brahta and G. D. Daves, *J. Chem. Soc., Perkin Trans. 1*, 1883 (1992).
5. T. Sakamoto, C. Satoh, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, **41**, 81 (1993).
6. Y. Okamoto, K. Takagi, A. Takada, and T. Ueda, *J. Org. Chem.*, **49**, 908 (1984).
7. K. C. Majumdar, U. Das, and N. K. Jana, *J. Org. Chem.*, **63**, 3550 (1998).
8. R. L. De Jong, J. G. Davidson, G. J. Dozeman, P. J. Fiore, P. Giri, M. E. Kelly, T. P. Puls, and R. E. Seamans, *Org. Process Res. Dev.*, **5**, 216 (2001).
9. A. L. Rodriguez, C. Koradin, N. Dohle, and P. Knochel, *Angew. Chem. Int. Ed.*, **39**, 2488 (2000).
10. T. L. Cupps, D. S. Wise, and L. B. Townsend, *J. Org. Chem.*, **48**, 1060 (1983).
11. Yu. N. Tkachenko, E. B. Tsupak, and A. F. Pozharskii, *Khim. Geterotsikl. Soedin.*, 368 (2000).
12. T. L. Cupps, D. S. Wise, and L. B. Townsend, *Tetrahedron Lett.*, **23**, 4759 (1982).
13. M. Otmar, M. Masojidkova, and A. Holy, *Collect. Czech. Chem. Commun.*, **61**, 49 (1996).
14. M. Otmar, M. Masojidkova, M. Budesinsky, and A. Holy, *Tetrahedron*, **54**, 2931 (1998).
15. G. B. Evans, R. H. Furneaux, T. L. Hutchison, H. S. Kezar, P. E. Morris, L. T. Schramm, and P. C. Tyler, *J. Org. Chem.*, **66**, 5723 (2001).
16. I. Susvilo, A. Brukstus, and S. Tumkevicius, *Synlett*, 1151 (2003).
17. R. Nepveu, J.-P. Souchard, Y. Rolland, G. Dorey, and M. Spedding, *Biochem. Biophys. Res. Commun.*, **242**, 272 (1998).
18. G. M. Rosen, P. Tsai, E. D. Barth, G. Dorey, P. Casara, M. Spedding, and H. J. Halpern, *J. Org. Chem.*, **65**, 4460 (2000).
19. V. B. Genisson, A.-V. Bouniol, and F. Nepveu, *Synlett*, 700 (2001).
20. R. Huisgen, *Angew. Chem. Int. Ed.*, **2**, 565 (1963).