A Selective Synthesis of 3,6-Dihydro-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones

Jun-Feng Zhao, Chang Xie, Ming-Wu Ding,* and Hong-Wu He*
Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan, 430079, P. R. China

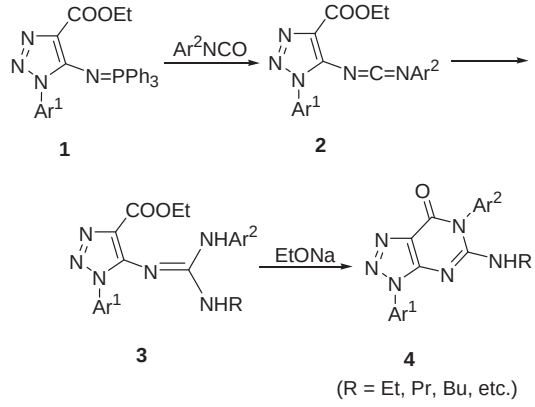
(Received April 8, 2005; CL-050474)

The carbodiimides **2**, obtained from aza-Wittig reactions of iminophosphorane **1** with aromatic isocyanates, reacted with primary amine RNH_2 ($R \neq H$, Me) to produce isolable guanidine intermediates **3**, which were further treated with sodium ethoxide in a mixed solvent to give selectivly one of the regioisomer **4** via a base catalytic cyclization mechanism. However, another regioisomers **5** were obtained directly as RNH_2 (R = H, Me) were used in the absence of sodium ethoxide, via a direct cyclization mechanism.

7*H*-1,2,3-Triazolo[4,5-*d*]pyrimidin-7-ones (azaguanines) are of great importances because of their remarkable biological properties such as antitumor, antiviral, anti-HIV, and antifungal activities.[1–7] The methods described for the preparation of this ring system either involves the reaction of properly substituted diaminopyrimidines with sodium nitrate and acetic acid, or the reaction of aminotriazolecarbonamides with orthoformate, or the cyclization of 5-acetamido-4-ethoxycarbonyl-1,2,3-triazoles with amine in the presence of phosphorus pentoxide.[7–13] However, these methods often require relatively harsh acid, dehydrating conditions or the heating at high temperature, and there is no report of a generally useful synthesis of 5-amino substituted 7*H*-1,2,3-triazolo[4,5-*d*] pyrimidin-7-ones starting from easily accessible 5-amino-4-ethoxycarbonyl-1,2,3-triazoles.

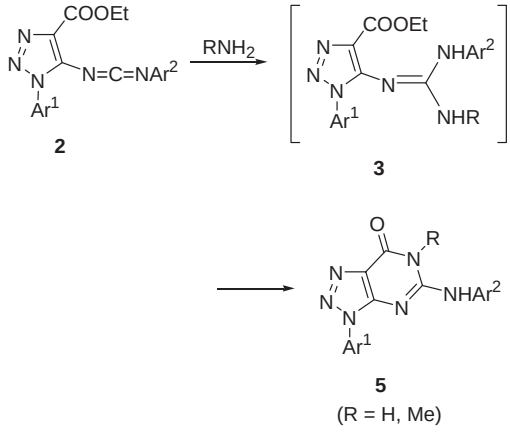
Recently we have been interested in the synthesis of quinazolinones, thienopyrimidinones and imidazolinones via the aza-Wittig reaction of α or β-ethoxycarbonyl iminophosphorane with aromatic isocyanate and the subsequent reaction with various nucleophile under mild conditions.[14] Here we wish to report a new selective approach to the synthesis of 7*H*-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-ones **4** and **5**.

Iminophosphorane **1**[15,16] reacted with aromatic isocyanates to give carbodiimides **2**, which were allowed to react with primary amines to provide isolable guanidine intermediates **3** as $R \neq H$, Me. When treated with sodium ethoxide in EtOH at room temperature, the guanidines **3** were recovered unchanged probably because of the low solubility of **3** in EtOH. In refluxing EtOH in presence of EtONa, a complex mixture was obtained probably owning to unstability of the product at refluxing temperature under strong basic conditions. However, when a mixed solvent (CH_2Cl_2/EtOH) was used in the presence of EtONa, **3** cyclized easily at room temperature to provide only 5-alkylamino-7*H*-1,2,3-triazolo[4,5-*d*] pyrimidin-7-ones **4**, one of the possible regioisomers (Scheme 1). This may be due to the good solubility of **3** in the mixed solvent. Different from the early result in similar cases,[17] we obtained only **4** from the reaction mixture after recrystallization; the other isomer was not found by ^{1}H NMR analysis of the reaction mixture. The structure of **4** is deduced from its ^{1}H NMR data. For example, the ^{1}H NMR spectrum in **4c** shows the signals of NH at 4.48 ppm as triplet and NCH_2 at 3.41–3.46 ppm as multiplet, which strongly suggest the existence of $NHCH_2CH_2CH_2CH_3$ group in **4c**. When the primary amine used is from ethylamine to bulky *t*-butylamine, the cyclization was achieved all in good yields with similar selectivity. The results are listed in Table 1. The solitary formation of **4** can be rationalized in terms of a base catalytic cyclization of the guanidine intermediate **3** to give **4** across the arylamino group rather than the alkylamino one. This may probably be due to the preferential generation of $-N^-Ar$ from more acidic –NHAr under the catalysis of EtONa.



Scheme 1.

On the other hand, the reaction of carbodiimides **2** with a small amine, such as ammonia or methylamine (R = H, Me), generated the reversed selectivity. In this case, 5-arylamino-7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-one **5**, another of the possible regioisomers, was directly precipitated from the reaction mixture when the small amine was added to the solution of



Scheme 2.

Table 1. Preparation of compounds **4** or **5**

	Ar^1	Ar^2	R	Yield /%[a]
4a	Ph	Ph	Et	85
4b	Ph	Ph	*n*-Pr	88
4c	Ph	Ph	*n*-Bu	76
4d	Ph	Ph	$PhCH_2$	84
4e	Ph	Ph	*i*-Pr	80
4f	Ph	Ph	cyclohexyl	78
4g	Ph	4-ClC_6H_4	*i*-Pr	83
4h	4-ClC_6H_4	Ph	Et	81
4i	4-ClC_6H_4	Ph	*t*-Bu	74
4j	4-ClC_6H_4	Ph	*i*-Pr	81
4k	4-ClC_6H_4	Ph	cyclohexyl	90
5a	Ph	Ph	H	82
5b	Ph	Ph	CH_3	87
5c	4-ClC_6H_4	Ph	H	76
5d	4-ClC_6H_4	Ph	CH_3	83

[a]Isolated yields based on iminophosphorane **1**.

carbodiimide **2**. It is deduced that the intermediate **3** has generated but cyclizes quickly and the catalysis by sodium ethoxide is not needed (Scheme 2). The reversed-selective formation of **5** can be rationalized in terms of a direct cyclization of the guanidine intermediate **3** to give **5** across the little steric and strong nucleophilic amino or methylamino group rather than the arylamino one.

It is worth noting that the selectivity of the reaction between α- or β-ethoxycarbonyl carbodiimide and amine seems to be controversial. Sometimes the alkylamino substituted heterocycle was isolated as the major or sole product,[17,18] whereas the arylamino substituted heterocycle was produced as the sole product in other cases.[19] The results we report here reveal firstly that the different selectivity is probably due to the different reaction condition (in the presence or absence of a base catalyst) and then different reaction mechanism (base catalytic cyclization mechanism or direct cyclization mechanism).

In conclusion, we have developed an efficient and selective synthesis of 7*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-7-ones via the aza-Wittig reaction. Owing to the mild reaction conditions, good yields, easily accessible starting materials and straightforward product isolation, we think that the versatile synthetic approach discussed here in many cases compares favorably with other existing methods.

We gratefully acknowledge financial support of this work by the National Basic Research Program of China (2003CB114400) and the National Natural Science Foundation of China (Project Nos. 20372023 and 20102001).

References

1 K. A. Jacobson, J. W. Daly, and V. Manganiello, "Purines in Cellular Signaling: Targets for New Drugs," Spinger-Verlag, New York (1990).
2 L. Santana, M. Teijeira, E. Uriarte, J. Balzarini, and E. De Clercq, *Eur. J. Med. Chem.*, **37**, 755 (2002).
3 J. M. Blanco, O. Caamano, F. Fernandez, X. Garcia-Mera, A. R. Hergueta, C. Lopez, J. E. Rodriguez-Borges, J. Balzarini, and E. De Clerco, *Chem. Pharm. Bull.*, **47**, 1314 (1999).
4 M. I. Nieto, O. Caamano, F. Fernandez, M. Gomez, J. Balzarini, and E. De Clercq, *Nucleosides Nucleotides*, **21**, 243 (2002).
5 W. A. Slusarchyk and R. Zahler, U. S. Patent 5723609 (1988); *Chem. Abstr.*, **128**, 230636c (1998).
6 E. Matthes, M. Von Janta-Lipinski, K. Reimer, W. Mueller, H. Meisel, C. Lehmann, and J. Schildt, Eur. Patent 409227 (1991); *Chem. Abstr.*, **115**, 159680m (1991).
7 F. E. Nielsen, E. B. Pedersen, and M. Begtrup, *Liebigs Ann. Chem.*, **1984**, 1848.
8 M. Nogueras, M. Melguizo, M. L. Quijano, and A. Sanchez, *J. Heterocycl. Chem.*, **28**, 1417 (1991).
9 A. R. Asenjo, S. M. Melgarejo, M. M. Noqueras, A. M. Rodriquez, M. C. Rodriquez, and R. A. Sanchez, *Nucleosides Nucleotides*, **3**, 207 (1984).
10 W. Ried, R. Guryn, and J. Laoutidis, *Liebigs Ann. Chem.*, **1990**, 819.
11 P. Scheiner, S. Arwin, M. Eliacin, and J. Tu, *J. Heterocycl. Chem.*, **22**, 1435 (1985).
12 M. L. Sznaidman and L. M. Beauchamp, *J. Heterocycl. Chem.*, **33**, 1605 (1996).
13 F. Chretien and B. Gross, *Tetrahedron*, **38**, 103 (1982).
14 a) M. W. Ding, S. Z. Xu, and J. F. Zhao, *J. Org. Chem.*, **69**, 8366 (2004). b) M. W. Ding, Y. F. Chen, and N. Y. Huang, *Eur. J. Org. Chem.*, **2004**, 3872. c) M. W. Ding, S. J. Yang, and J. Zhu, *Synthesis*, **2004**, 75. d) M. W. Ding, G. P. Zeng, and T. J. Wu, *Synth. Commun.*, **30**, 1599 (2000). e) M. W. Ding, Y. Sun, X. P. Liu, and Z. J. Liu, *Org. Prep. Proced. Int.*, **35**, 391 (2003).
15 a) M. D. Chen, G. P. Yuan, and S. Y. Yang, *Chin. J. Org. Chem.*, **20**, 357 (2000). b) M. Chen, G. Yuan, and S. Yang, *Synth. Commun.*, **30**, 1287 (2000). c) M. Chen, Y. Zheng, G. Gao, S. Fan, and S. Lu, *Heterocycl. Commun.*, **9**, 395 (2003).
16 H. Wamhoff and G. Haffmanns, *Chem. Ber.*, **117**, 585 (1984).
17 a) M. W. Ding, Y. Sun, X. P. Liu, and Z. J. Liu, *Chin. J. Chem.*, **21**, 577 (2003). b) Y. Liang, M. W. Ding, Z. J. Liu, and X. P. Liu, *Synth. Commun.*, **33**, 2843 (2003). c) M. W. Ding, Z. F. Xu, Z. J. Liu, and T. J. Wu, *Synth. Commun.*, **31**, 1053 (2001).
18 a) P. Molina, P. M. Fresneda, and P. Almendros, *Tetrahedron Lett.*, **33**, 4491 (1992). b) P. Molina, P. Almendros, and P. M. Fresneda, *Tetrahedron*, **50**, 2241 (1994). c) T. Saito, K. Tsuda, and Y. Saito, *Tetrahedron Lett.*, **37**, 209 (1996). d) D. V. Vilarelle, C. P. Veira, and J. M. Q. Lopez, *Tetrahedron*, **60**, 275 (2004).
19 a) E. C. Taylor and M. Patel, *J. Heterocycl. Chem.*, **28**, 1857 (1991). b) M. Watanabe, H. Okada, T. Teshima, M. Noguchi, and A. Kakehi, *Tetrahedron*, **52**, 2827 (1996).

Published on the web (Advance View) June 18, 2005; DOI 10.1246/cl.2005.1022