

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

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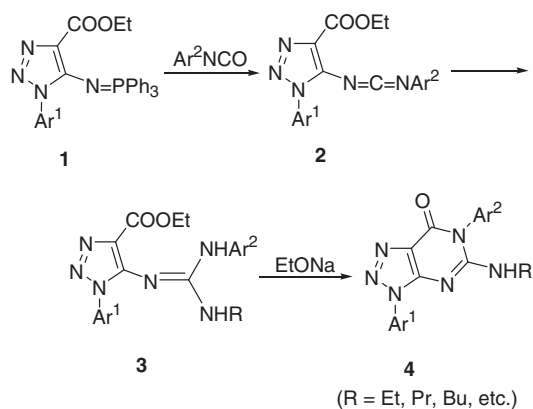
The carbodiimides **2**, obtained from aza-Wittig reactions of iminophosphorane **1** with aromatic isocyanates, reacted with primary amine RNH_2 ($\text{R} \neq \text{H, Me}$) to produce isolable guanidine intermediates **3**, which were further treated with sodium ethoxide in a mixed solvent to give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

7H-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 7H-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 quinoxalinones, 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 7H-1,2,3-triazolo[4,5-d]pyrimidin-7-ones **4** and **5**.

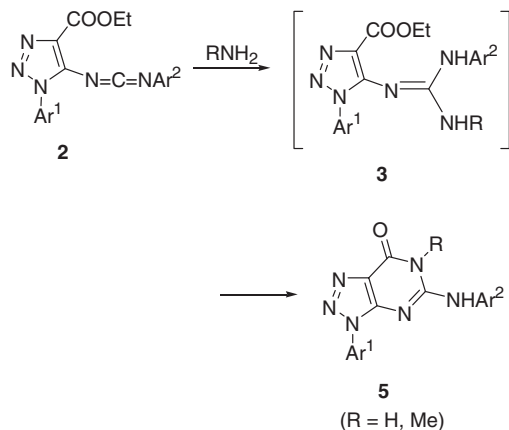
Iminophosphorane **1**^{15,16} reacted with aromatic isocyanates to give carbodiimides **2**, which were allowed to react with primary amines to provide isolable guanidine intermediates **3** as $\text{R} \neq \text{H, Me}$. When treated with sodium ethoxide in EtOH at room temperature, the guanidines **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 owing to unstability of the product at refluxing temperature under strong basic conditions. However, when a mixed solvent ($\text{CH}_2\text{Cl}_2/\text{EtOH}$) was used in the presence of EtONa, **3** cyclized easily at room temperature to provide only 5-alkylamino-7H-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 ¹H NMR analysis of the reaction mixture. The structure of **4** is deduced from its ¹H NMR data. For example, the ¹H 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 $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$ 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 $-\text{N}^-\text{Ar}$ from more acidic $-\text{NHAr}$ 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 ($\text{R} = \text{H, Me}$), generated the reversed selectivity. In this case, 5-arylmino-7H-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	<i>n</i> -Pr	88
4c	Ph	Ph	<i>n</i> -Bu	76
4d	Ph	Ph	PhCH ₂	84
4e	Ph	Ph	<i>i</i> -Pr	80
4f	Ph	Ph	cyclohexyl	78
4g	Ph	4-ClC ₆ H ₄	<i>i</i> -Pr	83
4h	4-ClC ₆ H ₄	Ph	Et	81
4i	4-ClC ₆ H ₄	Ph	<i>t</i> -Bu	74
4j	4-ClC ₆ H ₄	Ph	<i>i</i> -Pr	81
4k	4-ClC ₆ H ₄	Ph	cyclohexyl	90
5a	Ph	Ph	H	82
5b	Ph	Ph	CH ₃	87
5c	4-ClC ₆ H ₄	Ph	H	76
5d	4-ClC ₆ H ₄	Ph	CH ₃	83

^aIsolated 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.

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