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# A new strategy for the synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]-pyrimidines and pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines

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ABSTRACT

A series of pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines were prepared via oxidative cyclization of aldehyde *N*-(1,3-diphenylpyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones. Dimroth rearrangement of such a series yielded pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidines.



## 1. Introduction

Reports from our laboratory[1] and from others[2] revealed that the only possible route for the synthesis of pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives involves reaction of 5-amino-4-imino-pyrazolo[3,4-*d*]pyrimidine with one-carbon cyclizing agents. Furthermore, attempts to prepare the isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines via dehydrative cyclization of the 4-acylhydrazino-pyrazolo[3,4-*d*]pyrimidines was reported to give the corresponding pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]-pyrimidines.[3] In view of these findings and in continuation of our long standing interest for the utility of nitrilimines derived from either hydrazonoyl halides or hydrazones in the synthesis of heterocycles,[4–13] we wish to report herein a simple and convenient route for the synthesis of the title compounds. This route involves 1,5-electrocyclization of nitrilimines generated in situ from the hitherto unreported aldehyde *N*-(pyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones to give the respective pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines and Dimroth rearrangement of the latter to give their isomeric pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine derivatives.

Our interest in developing a new synthesis of these two ring systems results from the fact that some derivatives of both pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine and pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine exhibit interesting pharmacological activities.[14] For example, several 3- and/or 5-substituted 7*H*-pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines were reported to be potent xanthine oxidase (XO) inhibitors.[14] Also efforts made in medicinal chemistry in the past 25 years have revealed that the isomeric ring system pyrazolo[4,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine is one of the structural requirements for compounds that behave as selective antagonists for human $A_{2A}$ and $A_3$ adenosine receptor subtypes.[2] In addition, various derivatives have been used as a new pharmacological tool for characterization of human $A_3$ adenosine receptors.[15]

## 2. Results and discussion

The starting 5-amino-1,3-diphenyl-4-imino-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine **1** was prepared as previously reported from our laboratory.[1] When compound **1** was stirred in ethanol in the presence of excess hydrazine hydrate at room temperature, it underwent Dimroth type rearrangement to give 1,3-diphenyl-4-hydrazino-pyrazolo[3,4-*d*]-pyrimidine **2**, which has not been reported hitherto (Scheme 1). The isomerization of **1** into **2** seems to occur through base-catalyzed tandem ring opening and ring closure as shown in Scheme 2. This is consistent with a similar rearrangement that was reported recently.[16] The structure of **2** was evidenced by its spectra and elemental analysis (see Section 3).

The required aldehyde *N*-(1,3-diphenylpyrazolo[3,4-*d*]pyrimidin-4-yl)hydrazones **4** were prepared by condensation of the hydrazine derivative **2** with the appropriate aldehydes **3** (Scheme 1).

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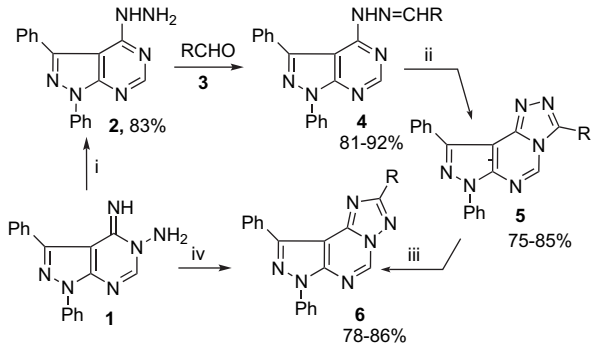
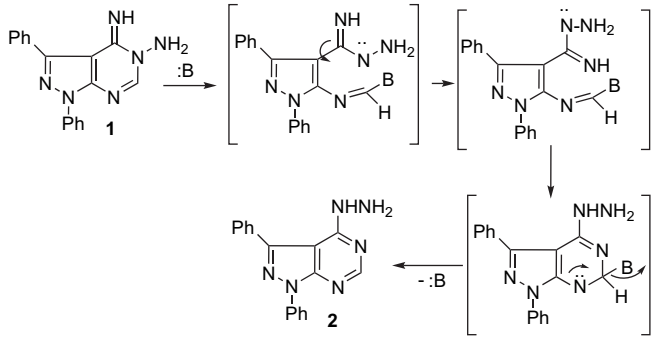


**Scheme 1.** Reagents: (i) $H_2NNH_2 \cdot H_2O$/rt; (ii) $FeCl_3$/EtOH/rt; (iii) MeCOONa/heat; (iv) RCOCl, $(RCO)_2O$ or RCOOH. R= (a) $C_6H_5$; (b) 4-$MeC_6H_4$; (c) R = 4-$ClC_6H_4$; (d) 4-$MeOC_6H_4$; (e) 4-$O_2NC_6H_4$; (f) 4-$Me_2NC_6H_4$; (g) PhCH=CH–; (h) 1-naphthyl; (i) 2-furyl; (j) 2-thienyl; (k) $CH_3$; (l) H.

All such hydrazones have not been reported hitherto. Their structures were confirmed by their elemental analyses and spectral (MS, IR and $^1$H NMR) data (see Section 3). For example, their $^1$H NMR spectra in $CDCl_3$ revealed, in each case, a characteristic signal in the region $\delta$ 8.0–8.2 assignable to the –N=CH– proton. Their IR spectra showed the characteristic band for the N–H stretch of the hydrazone group in the region 3393–3248 cm$^{-1}$.

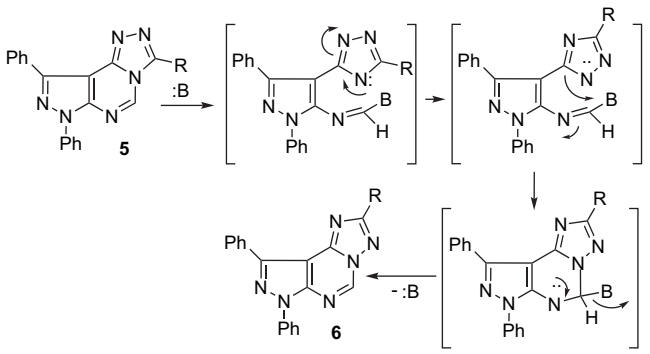


**Scheme 2.**

Treatment of each of the hydrazones **4** with 4 equiv of iron(III) chloride in ethanol for 12 h gave, in each case, a single product as evidenced by TLC analysis. Elemental analyses and mass spectra revealed that each of such isolated products has two hydrogens less than the respective hydrazone. This finding was confirmed by the $^1$H NMR spectra, which indicated the absence of the –N=CH– and hydrazone –NH-N=C protons. On the basis of this finding, the isolated products were assigned the structure of 3-substituted-7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidines **5a**–**l** (Scheme 1). The conversion of **4** into **5** is reminiscent of other related oxidative cyclization of aldehyde *N*-heteroarylhydrazones with iron(III) chloride, which have been reported to proceed via generation of the respective nitrilimines, which undergo in situ 1,5-electrocyclization to give the respective fused heterocycles.[17,18]

When each of the pyrazolo[4,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidine derivatives **5** was heated in ethanol in the presence of sodium acetate, they isomerized to the thermodynamically more stable pyrazolo[4,3-*e*][1,2,4] [1,5-*c*]pyrimidine derivative **6** through tandem ring opening and ring closure reactions (Scheme 3). This rearrangement is consistent with those reported in some earlier reports.[16, 19] The structures of 6 were determined by elemental analyses and spectral (MS, IR, $^1$H NMR) data (see Section 3).

To provide a decisive evidence for this rearrangement, the products **6a**, **6k** and **6l** were compared with authentic samples prepared by an alternative synthesis.[1] Thus, in our hands, treatment



**Scheme 3.**

of **1** with 1 equiv quantity of each of benzoyl chloride, acetic anhydride and formic acid gave products, [1] which proved identical in all respects (mp, mixed mp, IR and $^1$H NMR spectra) with those obtained above from base-catalyzed rearrangement of **5a**, **5k**, and **5l**, respectively (Scheme 1). This finding confirms the base-catalyzed rearrangement of **5** into **6** (Scheme 1). A further evidence for the rearrangement of **5** into **6** is provided by comparison of the $^1$H NMR spectrum of **5l** with that of **6l**. For example, the $^1$H NMR spectrum of **5l** reveals the triazole C3–H proton signal at $\delta$ 8.88, whereas that of **6l** shows the C2–H proton signal at $\delta$ 8.47. This feature is consistent with the literature reports, which indicate that the C3–H proton of *s*-triazolo[4,3-*c*]pyrimidine is more deshielded than that of C2–H of *s*-triazolo[1,5-*c*]pyrimidine.[20] The driving force for the observed rearrangement is the fact that [1,2,4]triazolo[1,5-*c*]pyrimidine ring system is thermodynamically more stable than its isomer namely [1,2,4]triazolo[4,3-*c*]pyrimidine.[21]

In conclusion, we have presented a facile strategy for the general synthesis of the title compounds **5** and **6**. Such new heterocycles will be evaluated in pharmacological assays to determine their activities as xanthine oxidase inhibitors and human adenosine antagonists.

## 3. Experimental

### 3.1. General

All melting points were determined on an electrothermal Gallenkamp apparatus. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The $^1$H NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz) in $CDCl_3$. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. The starting 5-amino-1,3-diphenyl-4,5-dihydro-4-imino-1*H*-pyrazolo[3,4-*d*]pyrimidine **1** was prepared according to a literature method.[1] The 2-phenyl-, 2-methyl- and 2-unsubstituted derivatives of 7,9-diphenylpyrazolo[4,3-*e*][1,2,4]triazolo[1,5-c]pyrimidines (**6a**, **6k**, **6l**) were also prepared as previously described from **1** and the respective one-carbon atom cyclizing agents.[1]

### 3.2. 4-Hydrazino-1,3-diphenylpyrazolo[3,4-*d*]pyrimidine (2)

#### 3.2.1. *Method A*

To 5-amino-1,3-diphenyl-4-imino-4,5-dihydro-1*H*-pyrazolo[3,4-*d*] pyrimidine **1** (1.51 g, 5 mmol) in ethanol (30 mL) was added hydrazine hydrate (80%, 8.5 mL). The mixture was stirred at room temperature for 24 h. The solid that precipitated was filtered and crystallized from dioxane to give **2** as white solid, yield 1.3 g (83%), mp 204 °C.