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A one-pot approach to 10-(1*H*-1,2,3-triazol-1-yl)pyrimido[1,2-*a*]indoles via aryne-mediated transformations of 3-(pyrimidin-2-yl)-1,2,4-triazines

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ABSTRACT

An efficient synthetic approach toward 10-(1*H*-1,2,3-triazol-1-yl)pyrimido[1,2-*a*]indoles, including fluorinated derivatives, has been developed. The transformation of the 1,2,4-triazine ring of readily available 3-(pyrimidin-2-yl)-1,2,4-triazines proceeds via reaction with in situ generated aryne intermediates. Improved methods have been developed for the synthesis of the starting 5,6-diaryl- and 6-aryl-3-(pyrimidin-2-yl)-1,2,4-triazines. The influence that the nature of the aryne intermediate has on the reaction pathway was studied. The structure of the obtained pyrimido[1,2-*a*]indoles was confirmed by single crystal X-ray crystallography.

Introduction

Pyrido[1,2-*a*]indoles and pyrimido[1,2-*a*]indoles are of wide interest due to their presence in naturally occurring compounds (Fig. 1). They exhibit a wide range of biological activities,[1,2] in particular, against atherosclerosis,[3] depression,[4] and hypoglycemic activity,[4] as well as 5-HT4-receptor antagonists.[1,5]

So far, existing methods for the synthesis of these structures do not always involve the use of readily available and/or inexpensive reagents, or simple procedures. Thus, pyrimido[1,2-*a*]indoles can be obtained by the intramolecular condensation of 2-((2-pyridyl)methyl)pyridine *N*-oxide[6] or diphenyl(pyrimidin-2-yl)methanol,[7] or via the intermolecular heterocyclization reaction between 2-aminoindoles[8–13] or their aza-analog, i.e., 1*H*-benzimidazol-2-amine,[2] with 1,2-diketones. In addition, the synthesis of pyrimido[1,2-*a*]indoles can be performed via the transformations of 1-(2-ethynylphenyl)-3,3-dialkyltriazenes,[14] 1-acetylamino-2-iodobenzenes,[15] 3-formylindole,[16,17] or azidobenzylazide.[18] Modern synthetic methods involve the Pd-catalyzed reactions of phenylpropanedinitriles or ethyl phenylcyanoacetates with 2-cyanoaniline derivatives[19] or the Cu-catalyzed coupling of gem-dibromovinylanilides with sulfonamides.[20]

We have recently reported[21–23] one-pot methods for the synthesis of 1,2,3-triazole-substituted pyrido[1,2-*a*]indoles via the rearrangement of 3-(2-pyridyl)-1,2,4-triazine during their reactions with in situ generated aryne intermediates. Herein, we wish to report a new approach toward the synthesis of pyrimido[1,2-*a*]indoles via the transformations of 3-(pyrimidin-2-yl)-1,2,4-triazines when treated with arynes.

For the synthesis of the starting 3-(pyrimidine-2-yl)-1,2,4-triazines **4**, an improved procedure has been developed (ESI). The most convenient method for obtaining the various 5,6-diaryl-3-(het)aryl-1,2,4-triazines is the one-pot condensation reaction of amidrazones with aromatic 1,2-diketones, most of which are commercially available. However, for the synthesis of 3-pyrimidine-substituted 1,2,4-triazines, this approach is reported only in very few cases,[24,25] while the less accessible pyrimidine–carboxylic acid hydrazide is used as a starting material in other cases.[26,27]

We proposed an approach toward 3-(pyrimidine-2-yl)-1,2,4-triazines **4** involving the reaction of commercially available 2-cyanopyrimidine **1** with hydrazine hydrate. Reaction between

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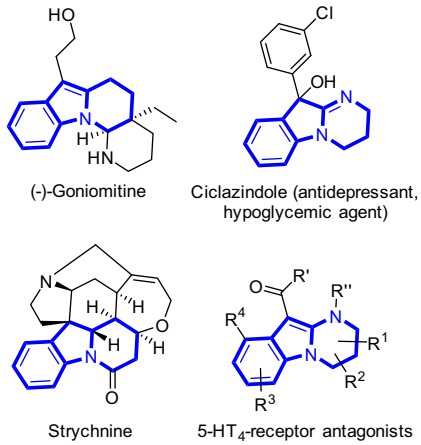


Figure 1. Representative examples of pyrido[1,2-*a*]- or pyrimido[1,2-*a*]indole containing biologically important molecules.

the formed amidrazone **2** and aromatic 1,2-diketones afforded the desired compounds (Scheme 1). It is noteworthy that purification of amidrazone **2** is not needed, which makes our approach more convenient than previously reported examples. In most reported cases tedious purification and separation steps involving extraction[28] or precipitation[29] were required, thereby reducing the product yield.

The 5-unsubstituted-6-aryl-3-(pyrimidin-2-yl)-1,2,4-triazines have not been previously prepared in high yields. Only in a few cases[30,31] were these compounds isolated in very low yields as side-products. On the other hand, the cyclocondensation reaction of in situ generated iminoesters with *iso*-nitrosoacetophenone hydrazones has been previously used to obtain 6-aryl-3-pyridyl-1,2,4-triazines in moderate yields.[32] This method was used to obtain 3-(pyrimidin-2-yl)-1,2,4-triazine **4c** in 45% yield. Due to both the use of the one-step procedure and the extremely low availability of these compounds by other methods, such yields can be considered as acceptable.

The structures of the compounds were determined by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. Thus, in the ^{1}H NMR spectra of products **4a–c**, signals in the range of 7.30–9.40 ppm, ascribed to the proton resonance of the pyrimidine moiety (doublet of doublets and doublet with integrated intensity of two protons) and aromatic substituents are observed. In the case of triazine **4c** the additional signal of the C-5 proton of the 1,2,4-triazine ring is observed as a one-proton singlet at 9.53 ppm.

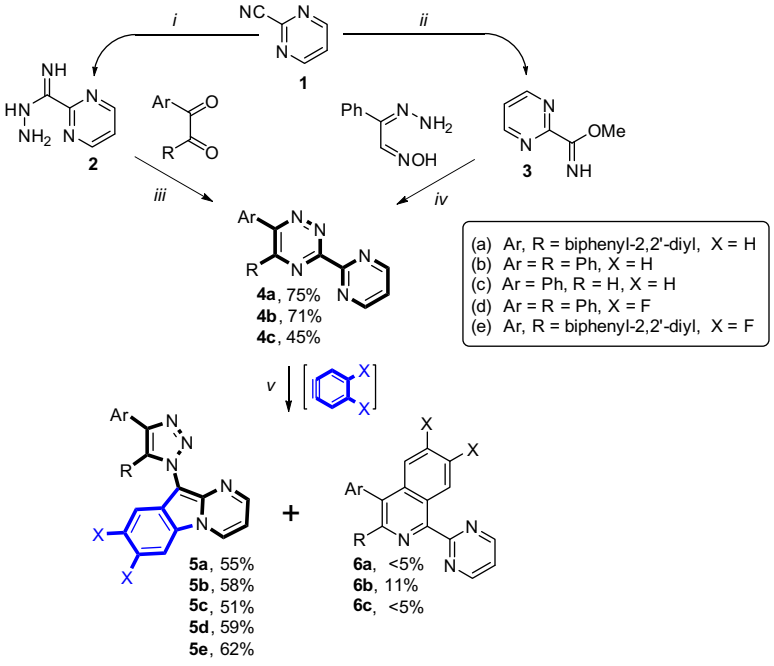
In the next step, in order to study the influence of the aryne intermediate substituents on the reaction pathway, we investigated the reactions of 3-(pyrimidin-2-yl)-1,2,4-triazines **4** with in situ generated aryne intermediates.

Thus, under typical conditions,[21–23] the reaction of 3-(pyrimidin-2-yl)-1,2,4-triazines with the unsubstituted aryne, benzyne, afforded 10-(1*H*-1,2,3-triazol-1-yl)pyrimido[1,2-*a*]indoles **5a–c** as the major products, i.e., the reaction proceeds by the same mechanism as for 3-(2-pyridyl)-1,2,4-triazines (Scheme 2).[21–23]

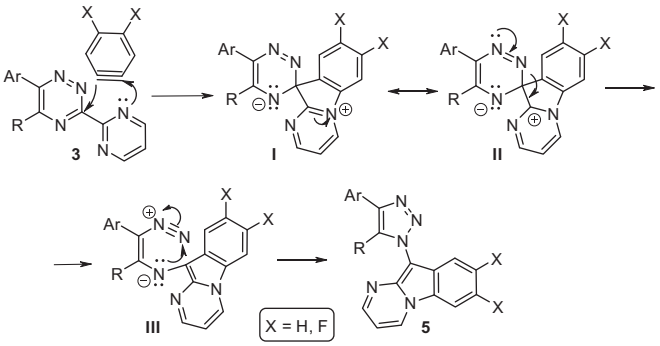
However, compared to pyridine, the nucleophilicity of each of the two pyridine-type nitrogen atoms in the pyrimidine moiety is reduced. Therefore, the reaction also afforded the aza-Diels–Alder reaction products, namely 1-(pyrimidin-2-yl)isoquinolines **6a–c**, as minor products in 3–11% yields. The product ratios were determined by ^{1}H NMR of the crude products and ESI-MS. Product **6b** was isolated as an analytically pure sample (see Scheme 1).

Due to the presence of two electron-donating methoxy-groups, 4,5-dimethoxy-1,2-dehydrobenzene is less susceptible to nucleophilic attack by the nitrogen of the pyrimidine ring. For this reason the reaction between 3-(pyrimidin-2-yl)-1,2,4-triazines **4** and 4,5-dimethoxy-1,2-dehydrobenzene under both typical[21–23] and harsh (boiling *o*-xylene) reaction conditions afforded neither the desired products nor the aza-Diels–Alder reaction products, and only starting compounds were isolated from the reaction mixture.

Finally, the reactions involving 3-(pyrimidin-2-yl)-1,2,4-triazines **4** with the most electrophilic aryne, 4,5-difluoro-1,2-dehy-



Scheme 1. Synthesis of 3-(pyrimidin-2-yl)-1,2,4-triazines and their reactions with arynes. Reagents and conditions: (i) Hydrazine hydrate, ethanol, 20 °C, 2 h, 100%; (ii) NaOMe, methanol, 20 °C, 1 h, 100%; (iii) ethanol–THF (1:1), reflux, 10 h, 71–75%; (iv) methanol, 20 °C, 1 h, then AcOH, reflux, 30 min, 45%; (v) anthranilic acid, isoamyl nitrite, dry toluene–dioxane (7:1), reflux, 1.5 h, 51–62%.



Scheme 2. Proposed mechanism for the formation of 10-(1*H*-1,2,3-triazol-1-yl) pyrimido[1,2-*a*]indoles.

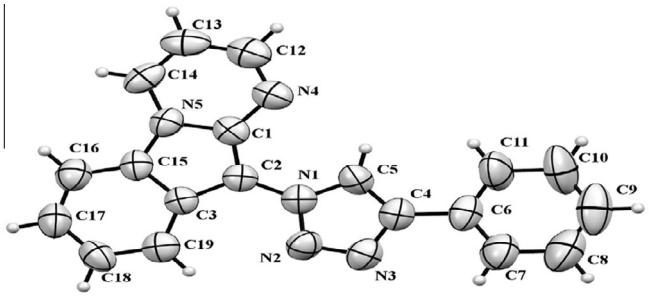
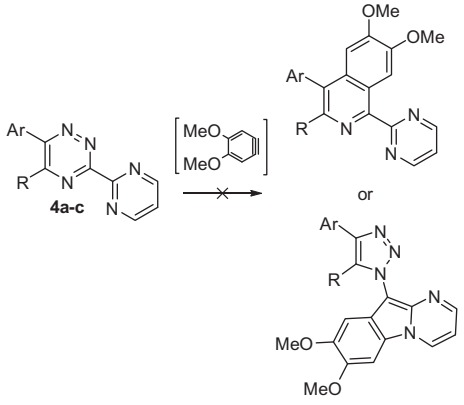


Figure 2. Molecular structure of compound **5c**.

drobenzene, afforded 2,3-difluoro-1*H*-1,2,3-triazol-1-yl)pyrimido-[1,2-*a*]indoles **5d–e** as the only products with no 6,7-difluoroisoquinolines detected.

The structures of products **5** and **6** were confirmed on the basis of ^{1}H, ^{13}C and ^{19}F NMR spectroscopy, mass spectrometry, and elemental analysis. In particular, for products **5**, the signals of the former pyrimidine ring protons, which have become non-equivalent, take the form of three doublets of doublets and the presence of the additional signal for the C-5 proton of the 1,2,3-triazole ring is observed as a one-proton singlet at 8.97 ppm in the case of compound **5c** (ESI). In addition, the ^{19}F NMR spectrum of compound **5d** shows two signals of non-equivalent fluorine atoms, observed as doublets. In the ^{13}C NMR spectra of compound **5d** the ^{13}C–^{19}F coupling is observed. In the case of isoquinoline **6b** the signals of the 2-substituted pyrimidine moiety in the ^{1}H NMR spectrum



Scheme 3. Attempted reaction between 4,5-dimethoxy-1,2-dehydrobenzene and 1,2,4-triazines **4a–c**. Reagents and conditions: (i) isoamyl nitrite, *o*-xylene–dioxane (7:1), reflux.

can be clearly detected. For example, the proton signals in the C4 and C6 positions of the isoquinoline moiety are observed as two doublets with coupling constants of $J = 4.8$ Hz. Ultimately, the structures of the representative compound **5c** was confirmed by single crystal X-ray crystallography (Fig. 2).[33]

In summary, we have developed an efficient synthetic approach toward 10-(1*H*-1,2,3-triazol-1-yl)pyrimido[1,2-*a*]indoles by the one-pot transformation of readily available 3-(pyrimidin-2-yl)-1,2,4-triazines **4** using in situ generated arynes. It has been shown that the reaction pathway and the product ratios depend strongly on the nature of the substituents in the aryne core. In the case of a less electrophilic aryne, benzyne addition to 3-(pyrimidin-2-yl)-1,2,4-triazines resulted in the formation of 1-(pyrimidin-2-yl)isoquinolines **6** as minor products. The reaction of **4** with the least electrophilic aryne, 4,5-dimethoxy-1,2-dehydrobenzene, did not afford any products (see Scheme 3).

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Supplementary data

Supplementary data (crystallographic data, ^{1}H, ^{13}C and ^{19}F NMR spectra of new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.07.052.

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