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Alkoxy base-mediated selective synthesis and new rearrangements of 1,2,4-triazolodipyrimidinones

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ABSTRACT

A versatile approach for the synthesis of [1,2,4]triazolodipyrimidinones with various annulations of the triazole and pyrimidine rings was developed. The isomeric triazolodipyrimidinones were obtained by the stepwise condensation of partially hydrogenated [1,2,4]triazolo[1,5-*a*]pyrimidin-2-amines with β-ketoesters or diethyl ethoxymethylenemalonate, alkoxy base-mediated cyclization of the enamines, and subsequent cascade rearrangement of the 10-oxo-[1,2,4]triazolo[1,5-*a*:4,3-*a*′]dipyrimidines.

Introduction

[1,2,4]Triazolo[1,5-*a*]pyrimidines are purine analogs that exhibit beneficial biological properties and are widely applied in agrochemistry and medicine.[1] For example, the triazolopyrimidine sulfonamide herbicides flumetsulam and metosulam have been employed in agriculture for approximately twenty years,[1c,2] and in the last decade, a new fungicide ametoctradin (Initium®)[1c,1d] and herbicide pyroxsulam[2b,3] have seen agricultural applications in many countries. Trapidil (Rocornal®), which is a coronary vasodilator and anti-platelet agent, has been used in medicine since the 1960s.[1a,1b,4] Furthermore, derivatives of [1,2,4]triazolo[1,5-*a*]pyrimidine exhibit anticancer,[5] antiparasitic,[6] antibacterial,[7] antiviral (including anti-HIV and anti-HCV),[8] anti-inflammatory,[9] hypoglycemic,[10] anticonvulsant,[11] microtubule-stabilizing CNS,[12] hypnotic,[13] and cannabinoid CB_2 antagonistic[14] activities.

In recent years, polycyclic molecules containing the [1,2,4]triazolo[1,5-*a*]pyrimidine fragment annulated with different carbo- and heterocycles have received considerable attention in view of their pronounced anticancer and anti-inflammatory activities.[5a,5b,9,15] Commonly applied approaches for the synthesis of these compounds are based on various electrophilic reactions of partially hydrogenated triazolopyrimidines at the electron-rich C6 atom and a substituent in position 5 or 7.[13,15b,15c,16] However, the potential of triazolopyrimidines as *N*-nucleophilic synthons for the annulation of new rings from the side of the triazole fragment remains poorly studied.

Recently, we demonstrated the possibility of annulating new rings to the triazole moiety of partially hydrogenated aminotriazolopyrimidines (Scheme 1).[17] The proposed strategy was based on the reactions between readily available 2-aminosubstituted [1,2,4]triazolo[1,5-*a*]pyrimidines **I-III** with various degrees of saturation of the pyrimidine ring,[16a,18] and 1,2- or 1,3-biselectrophilic reagents.

β-Ketoesters and alkoxymethylenemalonates are useful biselectrophilic reagents for the synthesis of various types of heterocycles, especially pyrimidine derivatives.[1a,19] However, potential reactions between aminotriazolopyrimidines **I-III** and β-ketoesters or alkoxymethylenemalonates have not yet been investigated.

In the current article, we describe a new approach for the preparation of multi-substituted polycondensed heterocycles with various annulations of the triazole and pyrimidine rings *via* the reactions between aminotriazolopyrimidines **I-III** and β-ketoesters or diethyl ethoxymethylenemalonate. The structural features and

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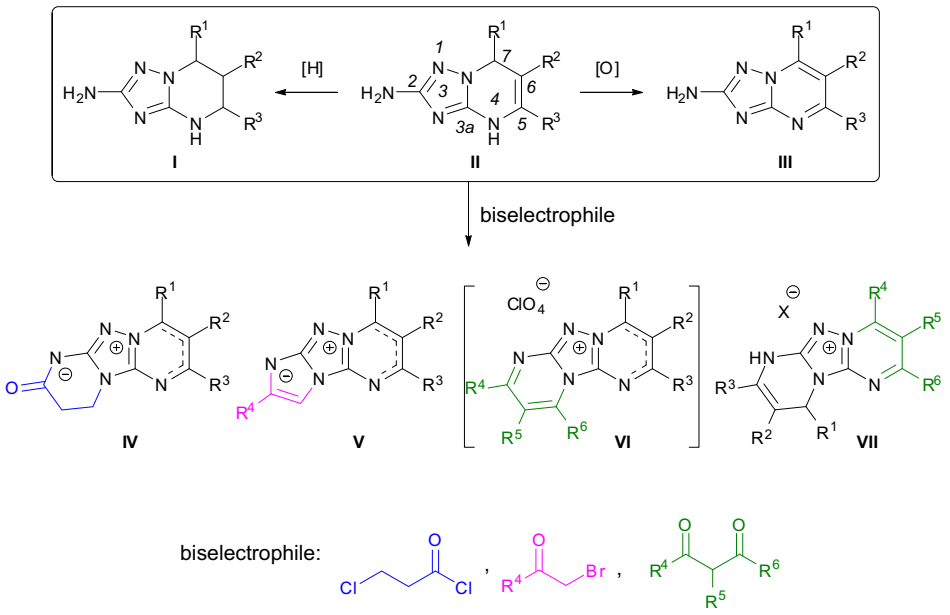


Scheme 1. Synthesis of polycondensed heterocycles **IV**-**VII** from aminotriazolopyrimidines **I**-**III** and various biselectrophiles.

new rearrangements of the obtained polycondensed heterocycles are also discussed.

Results and discussion

Partially hydrogenated 2-aminosubstituted triazolopyrimidines **1a-c**[18b] and **2a-d** as well as aromatic aminotriazolopyrimidine **3**[18c] were used as substrates with various degrees of saturation of the pyrimidine ring. Commercially available β-ketoesters **4a-c** and diethyl ethoxymethylenemalonate **5** were applied as 1,3-biselectrophilic reagents (Fig. 1).

Compounds **2a-d** were obtained using a two-step procedure including condensation of acetoacetic ester with benzaldehydes in the presence of the AcOH-piperidine catalytic system to give intermediate enones **6a-d**,[20] followed by the one-pot condensation of **6** with diaminotriazole **7** in DMF to give compounds **2a-d** in 71–83% yield (Scheme 2).

Attempts to perform the condensation of partially hydrogenated aminotriazolopyrimidines **1a** and **2** or aromatic **3** with β-ketoesters **4a-c** in ethanol, THF, or acetonitrile, analogously to the previously described procedures for the preparation of enaminoesters of 1-substituted 3,5-diamino[1,2,4]triazoles,[19c,19e] were

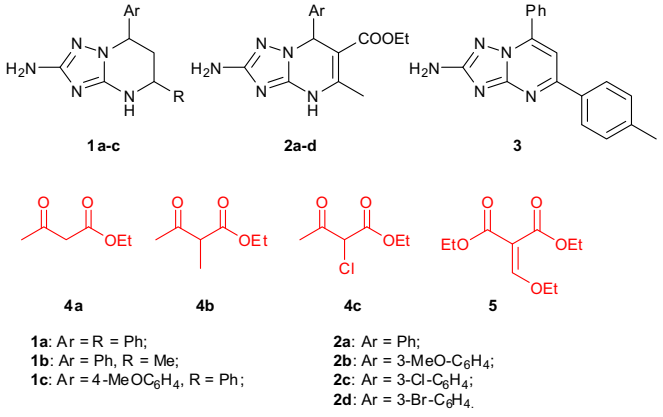
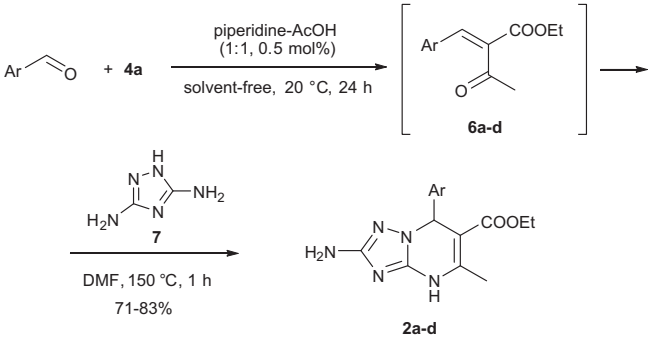


Fig. 1. Starting compounds.



Scheme 2. Synthesis of starting compounds **2a-d**.

unsuccessful due to insufficient solubility of the aminotriazolopyrimidines. Heating compound **2a** with ketoester **4a** in DMF at 90 °C afforded a complex mixture from which enaminoester **8d** was isolated in 63% yield (Scheme 3). At higher temperatures, significant tarring of the reaction mixtures was observed. However, at lower temperatures, the reaction time was too long. In contrast to ketoesters **4a-c**, the condensation of diethyl ethoxymethylenemalonate **5** with amines **1a-c**, **2a**, **b**, **d**, **3** in DMF at 90 °C afforded well-crystallized enaminoesters **8a-c**, **e-h** in 69–82% yield (Scheme 3).

The cyclization of enaminoesters **8** was investigated under a variety of reaction conditions (ESI, Table S01). The cyclization failed upon heating compounds **8** in acidic and neutral conditions, or in the presence of KOH: complex mixtures were obtained from which only aminotriazolopyrimidines **1**–**3** were separated after neutralization and crystallization. However, we observed that heating compounds **8** in the presence of sodium ethoxide in absolute ethanol and subsequent neutralization resulted in formation of the corresponding 10-oxo-[1,2,4]triazolo[1,5-*a*:4,3-*a*′]dipyrimidines **9** or **10** (Scheme 4). The highest yields of compounds **9** and **10** were observed upon heating compounds **8** with sodium ethoxide in absolute ethanol (**8**:EtONa = 1:3) at reflux for 0.5 h. Based on the optimized conditions (ESI, Table S01), the selective cyclization of enaminoesters **8a-g** into the 10-oxo-[1,2,4]triazolo[1,5-*a*:4,3-*a*′]dipyrimidines **9a-c** and **10a-d** was performed in good