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Synthesis of 9-alkyl-6-amino[1,2,4]triazolo[3,4-*c*]-5-azaquinoxalines. Mild and effective S_NAr amination of highly electron-poor heterocycles

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ABSTRACT

The synthesis and characterization of five different 9-alkyl-6-amino[1,2,3]triazolo[3,4-*c*]-5-azaquinoxalines is described. Due to the notable electrophilic character of the C-6 position of the [1,2,4]triazolo[3,4-*c*]-5-azaquinoxaline tricyclic system, S_NAr amination was achieved simply by reacting the corresponding 6-chloro derivative with ammonia-saturated acetonitrile (a non-nucleophilic polar solvent) in a sealed reaction vessel, using microwave-mediated or conventional heating.

Many nitrogen-containing heterocycles are regarded as privileged structures due to their ability to bind to multiple cell receptors with high affinity.[1,2] Among them, 6:6:5 fused nitrogen-containing tricycles have been investigated for their binding affinity to adenosine receptors,[3,4] with many examples showing excellent activities as adenosine antagonists of different receptor subtypes and a selectivity highly modulated by the nature of the substituents attached to the polycyclic ring system.[5,6] Based on their structural similarity with adenosine (see Fig. 1) and related structures with high selectivity for the adenosine A2a receptor,[6] we decided to investigate the synthesis of [1,2,4]triazolo[3,4-*c*]-5-azaquinoxaline tricycles[7] with an amino group at the C-6 position.

Electron-poor heterocycles undergo nucleophilic aromatic substitution (S_NAr) in the presence of a variety of nucleophiles at the electrophilic carbon to which a good leaving group is attached.[8–10] This reaction is widely used for displacing halogen atoms with strong nucleophiles (e.g., alkoxides, hydrazine, alkylamines, etc.) in deactivated aromatic rings.[11–14] While this direct displacement is generally disallowed for weaker nucleophiles such as ammonia (thus, requiring the employment of ammonia surrogates and metal catalysis[15–20]), if the aromatic ring is highly deactivated by the presence of several electron-withdrawing groups or pyridine-like nitrogen atoms, metal-free direct S_NAr amination can be achieved using either methanolic or liquid ammonia.[21–23] Herein, we report a study of the synthesis of five distinct 9-alkyl-6-amino[1,2,4]triazolo[3,4-*c*]-5-azaquinoxalines (Fig. 1) which were obtained by direct S_NAr amination of the 6-chloro derivative using an effective and convenient procedure that avoids the use of liquid ammonia.

The construction of the 6:6:5 fused tricyclic system was carried out from commercially available 2,3-diaminopyridine **1** using the three-step pathway outlined in Scheme 1.[7] 2,3-Dichloro-5-azaquinoxaline **2** was synthesized by condensation of compound **1** with

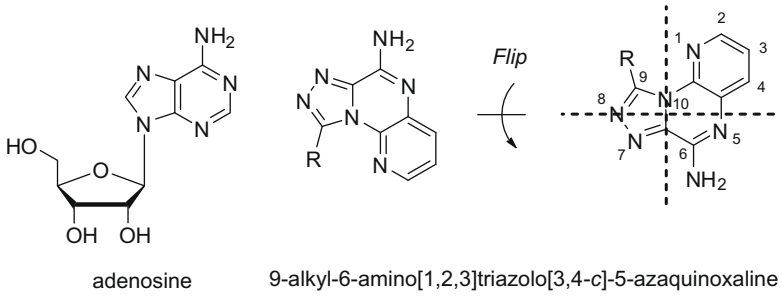

Figure 1. Adenosine and 9-alkyl-6-amino[1,2,4]triazolo [3,4-*c*]-5-azaquinoxaline.

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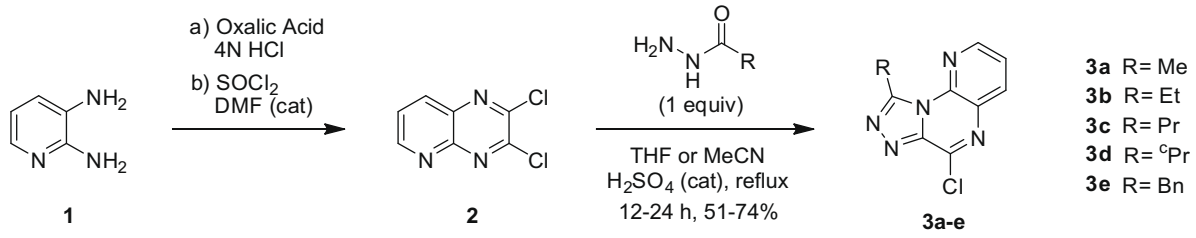


Scheme 1. Synthesis of 9-alkyl-6-chloro[1,2,4]triazolo[3,4-*c*]-5-azaquinoxalines **3a**–**e** from commercially available 2,3-diaminopyridine **1**.[7]

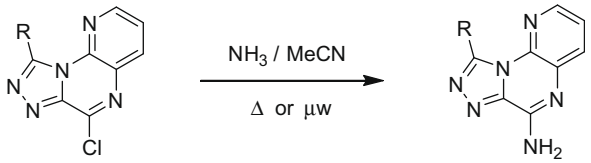
oxalic acid in 4 N HCl followed by chlorination of the dihydroxy intermediate using excess of thionyl chloride and DMF in catalytic amount. To introduce the triazolo-fused ring we used the one-pot synthetic procedure developed by our group,[7] involving the use of aliphatic hydrazides to first perform regioselective S_NAr reaction of the 3-chloro atom of compound **2** followed by heat-induced cyclocondensation. Thereby, tricycles were synthesized by refluxing compound **2**, aliphatic hydrazides and H_2SO_4 (catalytic amount) in THF or acetonitrile for 12–24 h (Scheme 1), giving 6-chloro derivatives **3a–e** in moderate to good yields (51–74%). The unique formation of the [1,2,4]triazolo[3,4-*c*]-5-azaquinoxaline system is due to the pyridine-type nitrogen atom in position 5 of compound **2**, which dictates the regiochemistry of the reaction by inducing different electrophilicity between the 2- and the 3-carbon positions.

It has been recently reported that the use of microwave-mediated heating significantly improves the rate of the cyclization step in the synthesis of a similar tricyclic system.[24] In order to investigate this trend in the synthesis of compounds **3a**–**e**, reactions were carried out under microwave heating at different temperatures. However, even though the reaction times were reduced, lower yields were obtained due to the increased formation of tetracyclic side products.[7]

Due to the anticipated high electrophilicity of the [1,2,4]triazolo[3,4-*c*]-5-azaquinoxaline ring system, direct amination by nucleophilic displacement of the 6-chloro atom was first attempted using saturated methanolic ammonia at room temperature. The reactions were monitored by TLC and, surprisingly, no traces of starting material were observed after 10 min. However, the 6-methoxy derivatives were the only products isolated from the reactions (see Supplementary data). An alternative procedure for the amination of electron-poor heterocycles involves (i) halogen displacement with hydrazine, and (ii) subsequent cleavage of the N–N bond using Raney Ni.[19,22] However, the use of this method resulted in very low yields, leading almost exclusively to the dehydrazination byproduct.[25] This result is in accordance with previous studies[12,26] in relation to the instability of hydrazino groups when attached to electron-deficient nitrogen-containing heterocycles.

The use of anhydrous ammonia in its liquid form has also been employed for performing S_NAr amination of electron-poor heterocycles; a protocol that requires the application of high pressure in a steel bomb.[23] In order to explore a milder procedure, dry acetonitrile was saturated with ammonia gas and then used for the direct S_NAr amination of compounds **3a–e** in a sealed glass vessel. Reactions were carried out using conventional oil-bath heating at 80 °C for 4–8 h, affording the expected 6-amino derivatives **4a–e** in quantitative yield (Scheme 2). As the reagent (ammonia) and solvent (acetonitrile) were easily evaporated under vacuum, reaction work-up consisted simply of re-dissolving in ethyl acetate, washing with water (to remove ammonium chloride) and evaporation to dryness, with no further purification required.

Different non-nucleophilic, high-boiling point, polar solvents such as dioxane and DMF were also investigated, requiring shorter reaction times but providing slightly lower yields. In order to improve the reaction rates while still using acetonitrile as solvent, microwave-mediated heating was explored under a pressure-monitored system using a biotage initiator. Thereby, compounds **3a–e** were treated with ammonia-saturated acetonitrile under microwave heating (using conventional microwave caps and vials), leading to pure 6-amino compounds **4a–e** after 30 min irradiation at 100–110 °C (Scheme 2).



Product	R	Temp, °C	Time, h	Yield, %
4a	Me	80 (100)	4 (0.5)	99 (98)
4b	Et	80 (110)	6 (0.5)	98 (99)
4c	Pr	80 (110)	8 (0.5)	95 (96)
4d	^{c}Pr	80 (110)	8 (0.5)	98 (98)
4e	Bn	80 (110)	6 (0.5)	97 (98)

[a] Conditions and yields using microwave heating in brackets.

Scheme 2. Treatment of 6-chloro derivatives **3a–e** with ammonia-saturated acetonitrile.[a]

In conclusion, the synthesis and characterization (see Supplementary data) of five 9-alkyl-6-amino[1,2,4]triazolo[3,4-*c*]-5-azaquinoxalines has been described. The [1,2,4]triazolo[3,4-*c*]-5-azaquinoxaline ring system was demonstrated to be exceptionally electron-poor, hindering access to the 6-amino derivatives by traditional methods. Substitution of the chloro atom at C-6 by an amino group was carried out by heating the chloro derivative with ammonia-saturated acetonitrile (non-nucleophilic solvent) in a sealed reaction vessel, thus avoiding the employment of liquid ammonia and allowing the use of microwave-mediated heating.

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Supplementary data

Supplementary data (experimental procedures and characterization data of all the compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.109.

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