An efficient hetero Diels-Alder approach to imidazo[4,5-c]pyridazines as purine analogues

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Abstract

A general approach to 3-deaza-6-azapurine by a hetero Diels-Alder reaction is described. Reaction of sulfonamide protected 5-vinylimidazole with 4-phenyl-1,2,4-triazoline-3,5-dione in methanol gave the Diels-Alder adduct 8 in 85% yield. Deprotection of the resulting N-phenyltriazole was efficiently accomplished by ring opening with hydrazine followed by heating in DMSO. The completely deprotected and aromatized purine analogue 1 was obtained directly from this one-pot reaction in 48% yield. © 1998 Elsevier Science Ltd. All rights reserved.

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Modified nucleosides and nucleic acid bases have been the subject of many studies due to their potential activity as enzyme inhibitors resulting in antiviral and antitumor activity. Therefore, improved syntheses of such compounds or their precursors are of considerable interest. In connection with our interest in inhibitors of nucleic acid synthesis [1,2] we decided to synthesize 3-deaza-6-azapurine 1 and the corresponding riboside 2. This modified purine ring system, an imidazo[4,5-c]pyridazine, has not received much attention in literature, probably because its reported synthesis requires the use of hazardous starting materials and high pressure reaction conditions [3].

Recently the synthesis of benzimidazoles by [4+2] cycloaddition of a carbon dienophile with a protected vinylimidazole was described [4]. We reasoned that the use of an analogous diazo dienophile in a hetero Diels-Alder reaction would lead directly to the desired 3-deaza-6-aza-purine ring system (Scheme 1).
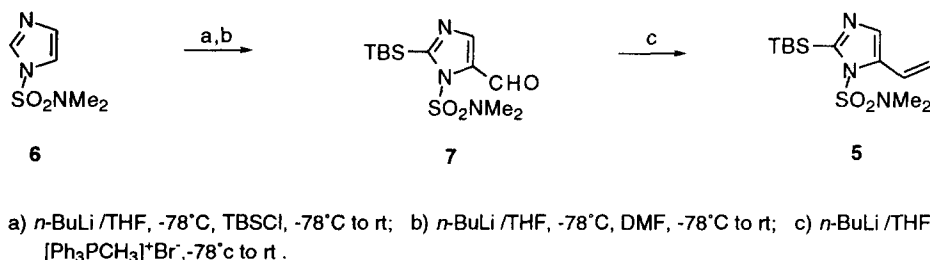

1 R¹ = H
2 R¹ = 1-ß-D-ribofuranosyl

3

4 R² = MOM
5 R² = SO₂NMe₂
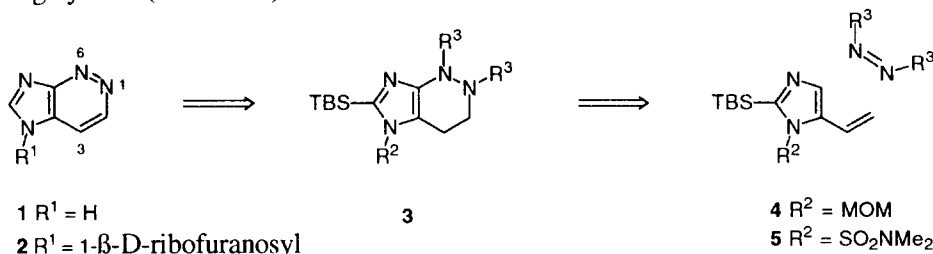
Scheme 1

Two different N-protecting groups were used for the vinylimidazole: methoxymethyl (MOM) (4) which was used before for this type of compound [4] and *N,N*-dimethylsulfonyl

(5), an electron withdrawing substituent which will influence the diene character of the vinylimidazole.

MOM-protected 5-vinylimidazole **4** was prepared according to a literature procedure [5-8]. Synthesis of N,N-dimethylsulfonyl protected 5-vinylimidazole **5** was accomplished from N,N-dimethylsulfonylimidazole **6** [8] via the same route (Scheme 2). Aldehyde **7** was prepared from **6** in a one-pot procedure and converted to vinyl imidazole **5** by Wittig reaction in an overall yield of 75%. The TBS-protecting group at C_2 which was required for selective C_5 lithiation was not be removed at this stage but in the last step of the purine synthesis.

a) n-BuLi /THF, -78°C, TBSCl, -78°C to rt;   b) n-BuLi /THF, -78°C, DMF, -78°C to rt;   c) n-BuLi /THF, [Ph₃PCH₃]⁺Br⁻,-78°c to rt .
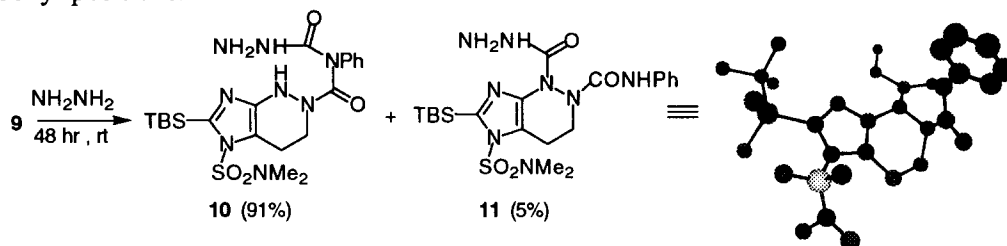
Scheme 2

Diels-Alder reaction of MOM-protected vinylimidazole **4** was attempted first using diethyl azodicarboxylate as a linear dienophile, but this reaction did not proceed to completion and the yield of only 10% could not be increased. Changing to the more reactive dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) did not give substantial improvement of the yield. Apparently, judging from these results in combination with observations made in the literature [4] this reaction is reversible, with the equilibrium lying on the side of the starting materials. N-Sulfonyl protected vinylimidazole **5** on the other hand gave a fast cycloaddition reaction with PTAD resulting in the desired ring system **8** in high yield (Scheme 3). Product **8**, which easily gave retro Diels-Alder reaction upon heating or with acid treatment, directly crystallized from the reaction mixture. The favorable shifting of the equilibrium towards the adduct is probably a result of this crystallization. Decrease of aromaticity in the imidazole ring in **5** by the presence of the electron withdrawing sulfonamide substituent may also influence the equilibrium.
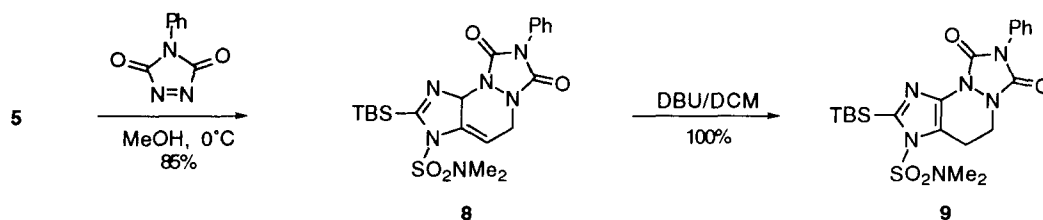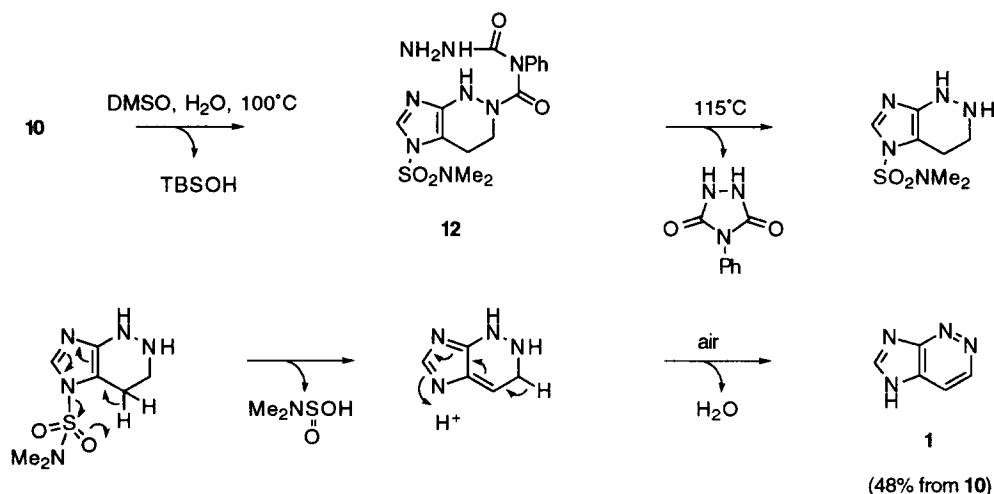

Scheme 3

Since acid catalyzed aromatization of the imidazolidine ring in **8** was not possible due to retro Diels-Alder reaction, DBU was used producing **9** in quantitative yield. Removal of the protecting groups in **9** was examined next, beginning with the 4-phenylurazole ring system. Conversion of urazoles to hydrazines is a difficult process, e.g. prolonged treatment with potassium hydroxide in refluxing water-ethylene glycol or lithium aluminum hydride in refluxing tetrahydrofuran are necessary [9]. Refluxing **9** with saturated potassium hydroxide

in methanol, which is also one of the known procedures, was not successful. Only one of the urea bonds was cleaved and even after longer reaction times the second bond was not affected. Hydrazinolysis of **9** with neat hydrazine hydrate proved to be very effective. Two isomers **10** and **11** were formed as a result of ring opening by attack on either of the two carbonyl positions.

Scheme 4

The structure of these compounds was established by NMR and mass spectroscopy and by X-ray analysis of the crystalline isomer **11**. Intramolecular deprotection of the main isomer **10** was a simple process performed just by heating in DMSO (Scheme 5). During this reaction in DMSO several other reactions occurred, leading directly to completely deprotected **1**.[1]
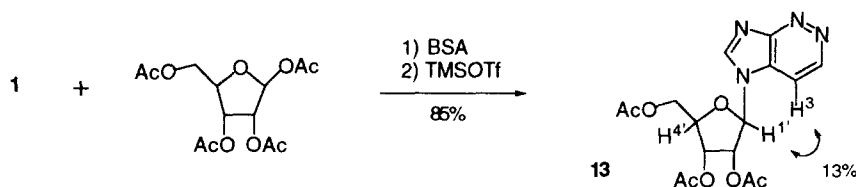

Scheme 5

Thermolysis in aqueous DMSO (100°C, 5h) started with removal of the TBS-group from the 2-position, giving **12**. A comparable process was described recently for the removal of several TBS-ethers [10]. When the temperature was increased to 115°C, 4-phenylurazole was formed from **12** as was mentioned before, producing the unprotected hydrazine. At the same time elimination of the N,N-dimethylsulfonyl substituent occurred. Although a simple sulfonamide hydrolysis reaction was expected, the isolation of the completely aromatized ring system gives an indication that an intramolecular reaction takes place as is shown in Scheme

[1] ^{1}H NMR data for **1** (400MHz, CD$_3$OD) 9.06 (d, J = 5.7 Hz, H$_2$), 8.70 (s, H$_8$), 7,96 (d, J = 5.7 Hz, H$_3$); UV max (methanol): 253 nm (ε, 6,045) and 272 nm (ε, 4,590).

5. In a 6-membered transition state sulfite is eliminated, while at the same time a double bond is formed in the tetrahydropyridazine ring. Finally complete aromatization by oxidation with oxygen from the air completes this intriguing series of reactions. This one-pot deprotection procedure (48% yield of **1**) could be reproduced on multigram scale.[1]

Ribosylation of **1** was accomplished via silylation with *N,O*-bis-(trimethylsilyl)acetamide (BSA) and subsequent coupling with tetra-acetyl-ß-D-ribofuranose in the presence of TMS-triflate (Scheme 6) [11]. Although this reaction could give rise to either N_7 or N_9 substitution only the N_9-riboside **13** was obtained, probably due to the lower nucleophilicity of N_7 compared to the normal purine system.

Scheme 6

The structure of nucleoside **13** was confirmed by NMR experiments. In contrast to normal purine systems, the presence of a H-atom at C_3 in 3-deazapurines makes NOE measurements possible. Upon irradiation of $H_{1'}$ 13% enhancement of the H_3 signal was observed, confirming N_9 ribosylation. In the same experiment a positive NOE of the $H_{4'}$ signal (2.6%) established the ß-configuration of the riboside [12].

In summary, a short and efficient synthesis of 3-deaza-6-azapurine *via* a hetero Diels-Alder reaction was accomplished. Since MOM protection gave unsatisfactory results in the cycloaddition reaction a strongly electron withdrawing sulfonyl protecting group was introduced on the imidazole-N_1. Crystallization of the DA-adduct and reduced aromatic stabilization of the starting imidazole may explain the observed strongly improved yield. Introduction of substituents at C_3 in order to influence the substitution pattern with ribose derivatives is currently underway.

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[1] Since oxygen is present throughout, it is also possible that dehydrogenation to the fully aromatic system takes place first and is then followed by straightforward hydrolysis of the dimethylsulfonyl group.