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Graphical Abstract

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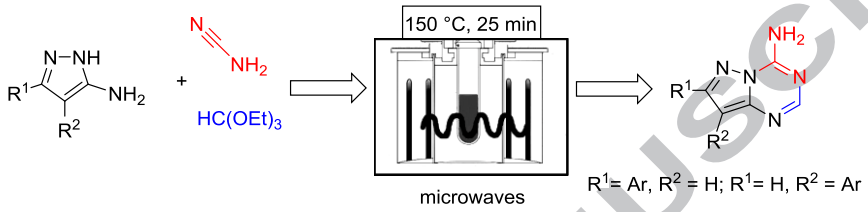

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A new, one-pot, multicomponent synthesis of 5-aza-9-deaza-adenines under microwave irradiation[§]

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ABSTRACT

A new, practical, three-component method for the synthesis of 5-aza-9-deaza-adenines is developed. Aminopyrazoles react in a one-pot fashion with triethyl orthoformate and cyanamide under microwave irradiation affording 5-aza-9-deaza-adenines in good yields and high purity. The main advantages of this method are the operational simplicity, accessibility and high efficiency.

[§] Part 25 in the series 'Fused heterocyclic systems with *s*-triazine ring', for part 24 see Ref. 1

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In Nature, purine is the most ubiquitous nitrogen-containing heterocycle.[2] Its derivatives encode 50% of the genetic information and are involved in functioning over 3250 proteins in the human body.[3] Being a privileged scaffold for drug discovery,[4] purines also motivate the development of the chemistry of structurally related isosteric heterocyclic systems. Changing the location of a nitrogen atom from position 9 to position 5 in the purine ring leads to the 5-aza-9-deazapurine (pyrazolo[1,5-*a*][1,3,5]triazine) system,[5] which has been recognised as the most promising purine isostere incorporating the 1,3,5-triazine ring.[6] Compounds with the pyrazolo[1,5-*a*][1,3,5]triazine scaffold were found to possess various biological activities. Thus, potent inhibitors of the enzymes xanthine oxidase,[7] thymidine phosphorylase,[8] phosphodiesterases[9] and cyclin-dependent kinases[10] have been constructed on the basis of the pyrazolo[1,5-*a*][1,3,5]triazine skeleton. Highly potent and selective antagonists of CB_1 canabinoid,[11] corticotropin-releasing factor[12] and $P2Y_1$ receptors[13] were identified among pyrazolo[1,5-*a*][1,3,5]triazines. Compounds with this ring system have also demonstrated antiviral,[14] anti-inflammatory,[15] anti-allergic and anti-asthmatic[16] activities. Interest in bioactive pyrazolo[1,5-*a*][1,3,5]triazines has resulted in the continued development of new and effective methods for the synthesis of compounds bearing this heterocyclic core.[17]

There has been significant attention devoted to the derivatives of the 5-aza-9-deaza- isostere of adenine (4-aminopyrazolo[1,5-*a*][1,3,5]triazine) as natural nucleoside analogues and potential therapeutic agents. For example, anti-leukemic properties were discovered for 5-aza-9-deaza-adenosine (**1**) (Figure 1), which was significantly more active than the reference compounds, formycins A and B.[18] Inhibition of *S*-adenosylhomocysteinase leading to an antiviral effect was observed for another related structure **2**.[19] Recently, a 5-aza-9-deaza- analogue of deoxyadenosine (**3**) was successfully incorporated into artificial oligodeoxyribonucleotides possessing increased resistance to hydrolysis.[20]

The first reported synthesis of 5-aza-9-deaza-adenine was performed *via* a seven-step transformation of 5-aminopyrazole.[21] To date, several more straightforward methods for the preparation of 5-aza-9-deaza-adenines have been proposed (Scheme 1), however, all possess various limitations. A common route toward these compounds involves the construction of an amino-substituted 1,3,5-triazine ring on the 5-aminopyrazoles **4**. 5-Aminopyrazole-1-carboxamidines **5** underwent ring closure upon treatment with triethyl orthoformate[22] or its synthetic equivalent, diethoxy methyl acetate,[23] functioning as a one-carbon inserting reagent (Method A). The main drawback of this method for the synthesis of 5-aza-9-deaza-adenines **6** is the low yield of the key precursor **5**.[24] Alternative methods for the synthesis of 5-aminopyrazole-1-carboxamidines **5** also suffered from very low yields.[22a] 5-Aza-9-deaza-adenines **6** can be prepared directly from 5-aminopyrazoles **4** *via* reaction with ethyl *N*-cyanoformimidate, the product of condensation of cyanamide and triethyl orthoformate (Method B).[25] The preparation of ethyl *N*-cyanoformimidate requires fractional distillation, which together with the low stability of the product[26] makes this approach less attractive. Its synthetic equivalent, methyl *N*-cyanoformimidate, was also used in this approach,[27] but in addition to its instability, was reported[28] to be a highly irritating reagent. Recently, we developed a more practical method based on the condensation of 5-aminopyrazoles **4** with *N*,*N*-dimethylformamide dimethyl acetal followed by treatment of the resulting amidine **7**, with cyanamide (Method C).[17a] Analysis of the above approaches revealed that the known methods represent all the possible stepwise sequential approaches for the reaction of 5-aminopyrazoles, triethyl orthoformate and cyanamide, sometimes using their synthetic equivalents. Since the reaction outcome does not depend on the sequence of reagent introduction, we anticipated that the reaction could be run in a one-pot multicomponent format. Herein, we report our attempts to further improve on the synthesis of 5-aza-9-deaza-adenines **6** by combining the two operational steps required for these methods into one multicomponent reaction using 5-aminopyrazoles, triethyl orthoformate and cyanamide as building blocks.

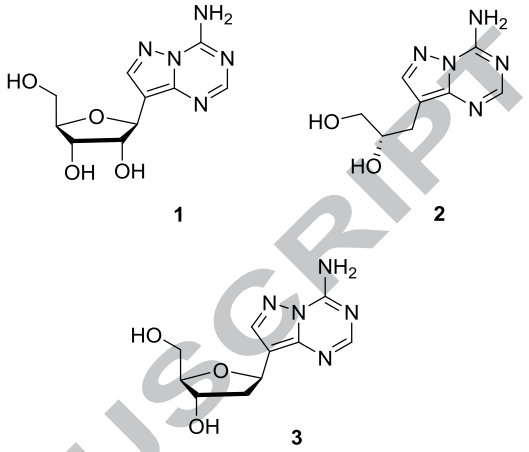


Figure 1. Some biologically active 5-aza-9-deaza-adenine derivatives **1**-**3**.

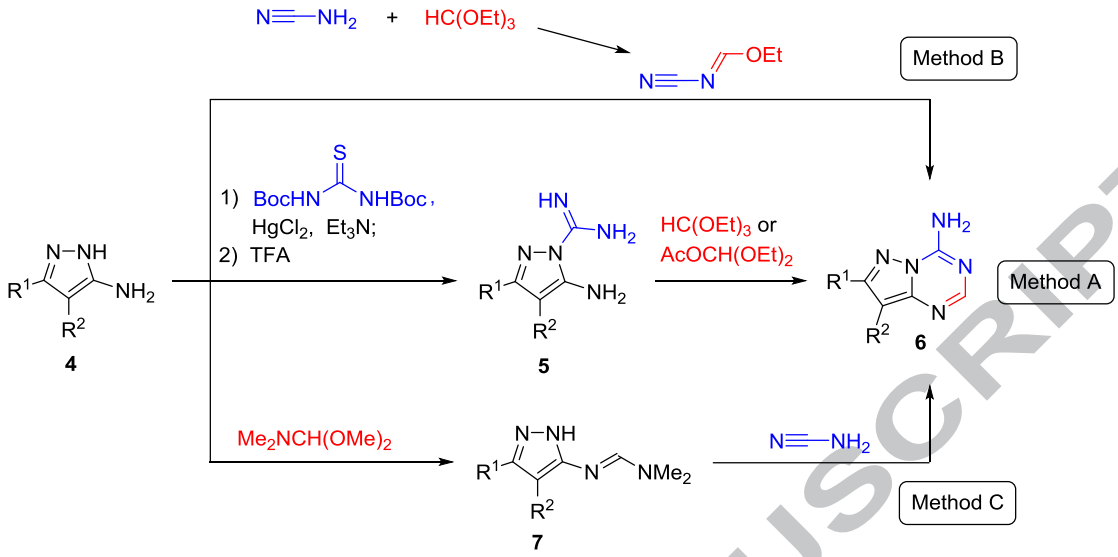
Using one-pot multicomponent reactions in synthesis has been well recognised as a very efficient and practical approach to the construction of biologically active heterocyclic compounds.[29] In a variety of multicomponent reactions, 5-aminopyrazoles **4** have proved to be very useful building blocks.[30] However, only two multicomponent reactions of 5-aminopyrazoles leading to the pyrazolo[1,5-*a*][1,3,5]triazine ring system have been reported: Mannich condensation with primary amines and formaldehyde,[31] and the reaction of 5-aminopyrazoles with aryl cyanates and acetone.[32] Considering the wide synthetic utility of triethyl orthoformate, particularly when used as a one-carbon synthon in multicomponent heterocyclic synthesis,[33] we assumed that it would be able to play the same role in our multicomponent reaction.

Initial optimization of the reaction conditions for the multicomponent reaction was performed using 5(3)-amino-3(5)-phenylpyrazole (**4a**) as the starting material (Table 1). Heating **4a** under reflux with triethyl orthoformate and cyanamide in methanol (entry 1) gave a complex mixture of products. In order to analyse the mixture of products, HPLC[34] was used with the reference compound **6a**, which was prepared using previously reported method C (Scheme 1). Analysis of the mixture identified that 23% of the targeted product **6a** had formed in the reaction under these conditions.

Microwave-assisted synthesis has become a very valuable tool, improving the outcome of multicomponent reactions[35] and is particularly useful for the preparation of various biologically active heterocyclic compounds.[36] In our attempts to find optimum conditions for the model reaction of **4a** with triethyl orthoformate and cyanamide, we observed a dramatic change in the outcome of the reaction when it was carried out under microwave irradiation instead of conventional heating under reflux.

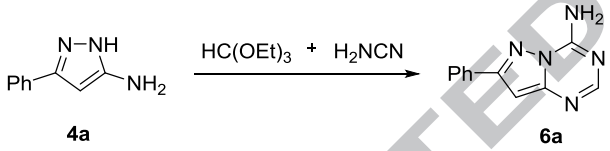
To our satisfaction, we observed the formation of **6a** as a solid, which was easily isolated in pure form *via* simple filtration. Screening of the solvents for the reaction (entries 2-6) identified that under identical conditions, using methanol led to better yields. Further optimization of the reaction parameters revealed that the product could be obtained in good yield and purity using microwave irradiation at 150 °C for 25 minutes in methanol (entry 9). Neither further increasing the reaction time (entry 10) or temperature (entry 8), nor increasing the ratio of reagents (entry 7) improved the reaction yield.

The reaction was highly regioselective with the cyano group of cyanamide reacting with the endocyclic nitrogen of **4** and triethyl orthoformate linking the amino groups of cyanamide and **4**.



Scheme 1. Existing approaches for the synthesis of 5-aza-9-deaza-adenines **6**.

Table 1. Optimization of the conditions for the model reaction[a]



Entry	Solvent	Temp (°C)	Time (min)	Yield (%)
1	MeOH	reflux[b]	480	23[d]
2	MeOH	150[c]	20	62[e]
3	EtOH	150[c]	20	26[e]
4	toluene	150[c]	20	58[e]
5	THF	150[c]	20	26[e]
6	MeCN	150[c]	20	39[e]
7[f]	MeOH	150[c]	20	59[e]
8	MeOH	160[c]	20	69[e]
9	MeOH	150[c]	25	73[e]
10	MeOH	150[c]	30	69[e]

[a] 1.0 equiv. **4a**, 1.2 equiv H_2NCN, 1.8 equiv. $HC(OEt)_3$.

[b] Conventional heating.

[c] Microwave irradiation.

[d] Determined by HPLC.[34]

[e] Isolated yield.

[f] 1.0 equiv. **4a**, 2 equiv. H_2NCN, 2.5 equiv. $HC(OEt)_3$.

With optimized reaction conditions in hand,[37] we decided to explore the scope of the method using a variety of 3-/4-aryl substituted 5-aminopyrazoles **4**, which were prepared from the corresponding β-cyano carbonyl compounds **7** and **8** under microwave irradiation using previously reported methods (Scheme 2).[38]

The synthesized 5-aminopyrazoles **4** were utilized as substrates for the multicomponent reaction with cyanamide and triethyl orthoformate under microwave irradiation using the optimized conditions. This one-pot, three-component reaction proceeded with formation of the desired products **6** regardless of the position of the aryl group. Both electron-donating and electron-withdrawing substituents on the aromatic ring of 5-amino-3-arylpyrazoles **4a-e** and 5-amino-4-arylpyrazoles **4f-l** were equally tolerated, allowing the preparation of a series of 5-aza-9-deaza-adenines **6** in satisfactory yields (Table 2). In all cases, 5-aza-9-deaza-adenines **6**[39] were isolated as the exclusive products, therefore confirming the chemo- and regioselectivity of this reaction under microwave irradiation.

The high level of delocalization of the lone pair of electrons on the amino group nitrogen over the heterocyclic system resulted in hindered rotation around the C-N bond. In the ^{1}H NMR spectra of 5-aza-9-deaza-adenines **6**, this phenomenon is reflected in the downfield shift (compared to the corresponding purine analogues[40]) and splitting of the signal attributed to the amino group into two separate broad signals at 8.26-8.52 ppm and 8.68-8.85 ppm.

In summary, we have successfully developed a new one-pot, three-component, microwave-assisted synthesis of 5-aza-9-deazapurines. This method allows the efficient and clean synthesis of 5-aza-9-deaza-adenines **6** from easily obtainable reagents, *viz*. 5-aminopyrazoles (**4**), cyanamide and triethyl orthoformate. Short reaction times and operational simplicity together with good product yields and purities makes this method a practical and attractive approach for the generation of libraries of purine-like compounds for drug discovery processes.

Acknowledgements

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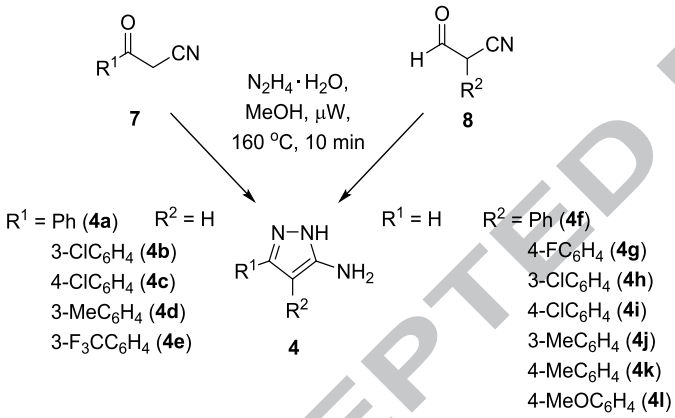
Supplementary data

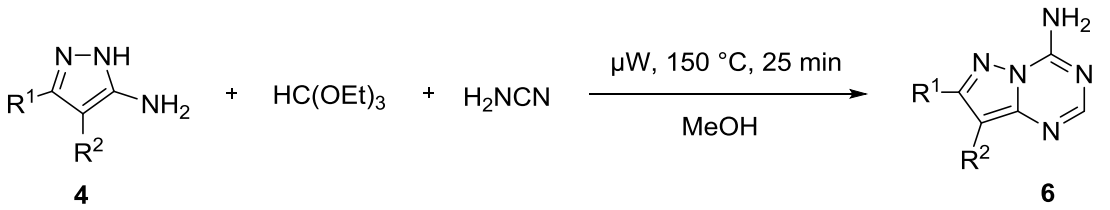
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.

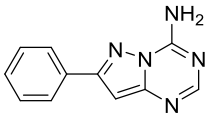
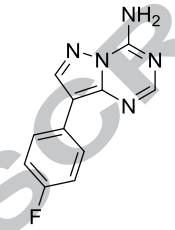
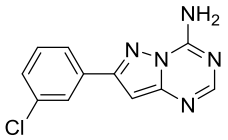
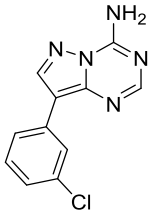
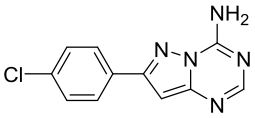
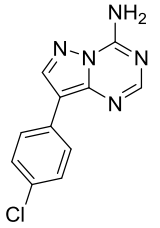
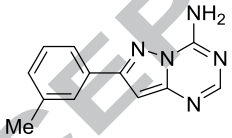
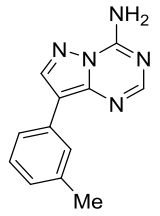
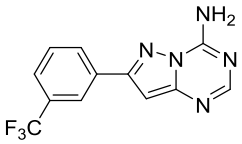
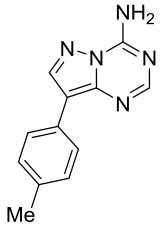
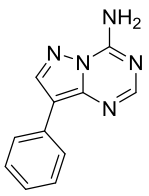
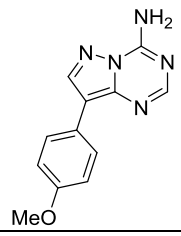
XX.XXX. These data include experimental details, copies of ^{1}H and ^{13}C NMR spectra of the prepared compounds and photographs of the products and corresponding reaction mixtures.



Scheme 2. Synthesis of 3-/4-aryl substituted 5-amino-pyrazoles **4**.

Table 2. Synthesis of aryl-substituted 5-aza-9-deaza-adenines **6**.



Product	Structure	Yield (%)	Product	Structure	Yield (%)
6a		73	**6g**		67
6b		71	**6h**		64
6c		64	**6i**		60
6d		71	**6j**		70
6e		61	**6k**		70
6f		68	**6l**		68

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39. *Data for representative products: 4-Amino-7-(3-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazine (**6b**)*: mp 311-313 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.02 (1H, s, H-8), 7.50-7.57 (2H, m, H-4′ and H-5′), 8.02 (1H, dt, ^3J = 7.2 Hz, ^4J = 1.6 Hz, H-6′), 8.07 (1H, s, H-2), 8.16 (1H, t, ^3J = 1.6 Hz, H-2′), 8.34 (1H, br s, NH), 8.74 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 92.7 (C-2), 125.1 (C-6′), 125.9 (C-2′), 129.0 (C-4′), 130.7 (C-5′), 133.68 (C-1′), 134.31 (C-3′), 150.0 and 150.7 (C-7 and C-8a), 153.7 (C-4), 154.1 (C-8). IR (KBr): ν 3179 (N-H), 3034 (C-H), 1685, 1595, 1566 cm^{-1}. Anal. Calcd for $C_{11}H_8ClN_5$: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.69; H, 3.30; N, 28.53. *4-Amino-8-(3-chlorophenyl)-pyrazolo[1,5-a][1,3,5]triazine (**6h**)*: mp 302-304 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (1H, ddd, ^3J = 8.0 Hz, ^3J = 4.1 Hz, ^4J = 0.9 Hz, H-4′), 7.45 (1H, t, ^3J = 7.9 Hz, H-5′), 8.06 (1H, dt, ^3J = 7.9 Hz, ^4J = 1.2 Hz, H-6′), 8.23 (1H, d, ^3J = 1.8 Hz, H-2′), 8.23 (1H, s, H-2), 8.52 (1H, br s, NH), 8.79 (1H, s, H-7), 8.85 (1H, br s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 106.7 (C-8), 123.8 (C-6′), 124.9 (C-2′), 125.6 (C-4′), 130.4 (C-5′), 133.5 (C-1′), 134.1 (C-3′), 143.2 (C-2), 145.4 (C-8a), 151.0 (C-4), 154.7 (C-7). IR (KBr): ν 3298 (N-H), 3071 (C-H), 1683, 1604, 1562 cm^{-1}. Anal. Calcd for $C_{11}H_8ClN_5$: C, 53.78; H, 3.28; N, 28.51. Found: C, 53.70; H, 3.33; N, 28.42.
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