Ugi-Smiles couplings of purine derivatives.

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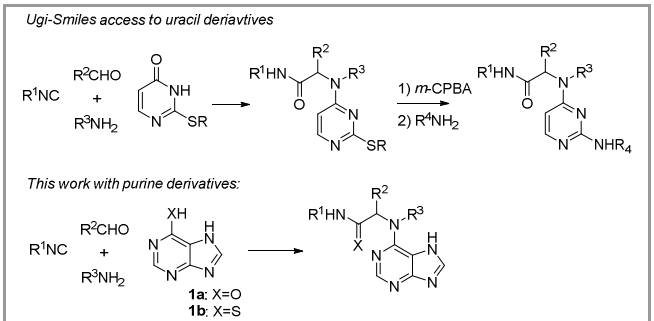
Abstract: Purines may be involved in Ugi-Smiles coupling as shown by the successful formation of thiocarboxamide derivatives from 6-mercaptopurine. This multicomponent coupling affords a very straightforward access to functionalized adenine derivatives, which are widely represented among natural products of medicinal interest.

Key words: Isocyanide, multicomponent, Ugi-Smiles, Purines, Adenines, thioamides.

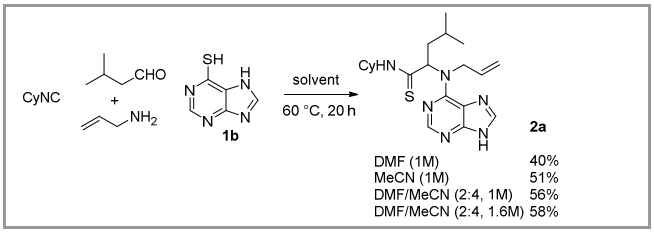
Ugi-Smiles reactions are 4-component couplings of isocyanides with aldehydes, primary amines and electron-deficient phenol leading to *N*-aryl carboxamide derivatives.[1] Compared with traditional Ugi couplings,[2] the reaction involves as a key step a Smiles transfer from an intermediate *O*-aryl imidate.[3] Following its initial disclosure with 2 and 4-nitrophenols,[1a] the scope of electron-deficient phenol amenable to participate has been significantly extended due to the ability of various nitrogen-based heterocycles to undergo Smiles rearrangements. Indeed, various hydroxy-substituted pyridines, pyrimidines and triazines were successfully used to afford fast 4-component accesses to amino heterocycles.[4] In this context, the ability to offer a Ugi-Smiles access to libraries of nucleobase derivatives represents an important goal due to the high medicinal impact of these scaffolds which can be found in numerous therapeutic agents with antibiotics and anticancer activities.[5] Though the potential of uracil derivatives in Ugi-Smiles reaction has already been explored by our group (Scheme 1),[6] purines remained more challenging as the fused imidazole ring should enrich the pyrimidine core of the structure and lower the efficiency of the Smiles step. Herein we wish to report on the successful 4-component formation of adenine derivatives from 6-mercaptopurine (Scheme 1).



Scheme 1 Ugi-Smiles reactions of nucleobase derivatives

Due to the lack of selectivity encountered in the Ugi-Smiles reaction of uracil,[6] we decided to focus on the behaviour of mono-hydroxy substituted purines. 6-hydroxypurine **1a**, known as hypoxantine and best pictured by its more stable tautomeric oxo form, was selected due to its low price and its previous use as precursors in many purine syntheses.[7] Heating hypoxanthine for 24 hours at 60°C with equimolar amounts of hydrocinnamaldehyde, allylamine and cyclohexyl isocyanide in MeOH or toluene (1M) failed to give any coupling. Though these components and conditions usually afford good yields in Ugi-Smiles reactions with simple hydroxy pyrimidines, the low solubility of hypoxanthine coupled with the need to work at high concentration may explain this lack of reactivity. The rather high pKa of **1a** (pKa = 8.9) might be also associated with a less efficient protonation of the intermediate imine prior to isocyanide addition.[8] Choosing DMF or DMSO to increase the solubility of **1a** did not lead to the expected adduct as well. In search for purine derivatives with higher solubility and a better pKa profile, we next turned our attention to 6-mercaptopurine **1b**. We have already shown that mercapto heterocycles are good partners in Ugi-Smiles reactions leading to the corresponding thiocarboxamide derivatives.[9] 6-mercaptopurine **1b** is a commercially available purine that has been used for many years in the treatment of acute leukemia and other cancers.[10] Its pKa of 7.7 should favour the initial step of the Ugi-Smiles coupling but no reaction occurred either in MeOH or toluene. However, when heating a DMF solution (1 M) of **1b**, allylamine,

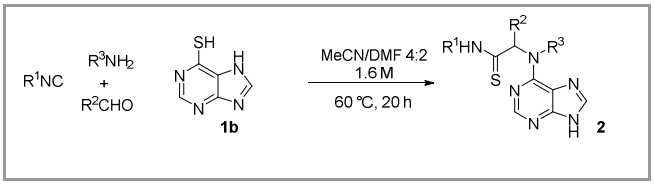
isovaleraldehyde and cyclohexyl isocyanide, we were delighted to observe after 20 h at 60 °C the formation of the thioamide **2a** in a 40% isolated yield (Scheme 2).

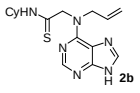
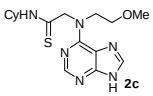
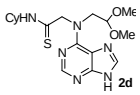
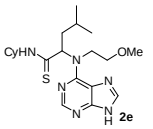
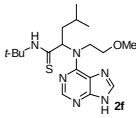
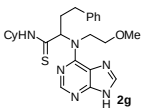
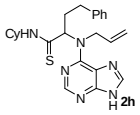
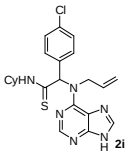
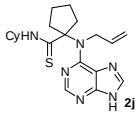


Scheme 2 formation of aminopurine **2a** from 6-mercaptopurine **1b**.

Acetonitrile improved slightly the efficiency of the coupling and mixing both solvents, acetonitrile and DMF, together with an increase of the concentration of the solution afforded the best yields. These optimized experimental conditions were thus selected for the various examples displayed in Table 1.

Table 1



Entry	Adduct **2**	Yield (%) (time (h))	Entry	Adduct **2**	Yield (%) (time (h))
1		75 (13)	2		38 (17)
3		28 (36)	4		70 (12)
5		58 (16)	6		40 (17)
7		47 (18)	8		0 (48)
9		0 (96)			

Whereas aliphatic aldehydes afforded Ugi-Smiles adducts in moderate to good yields (Table 1, entries 1-7), aromatic aldehydes (Table 1, entry 8) as well as ketones (Table 1, entry 9) failed to react under these conditions. This is consistent with the lower reactivity of these carbonyl derivatives in most Ugi-type reactions. Cyclohexyl isocyanide could be replaced by a bulkier isocyanide such as *t*-butylisocyanide leading however to a lower yield even after longer reaction time (Table 1, entries 4 and 5).

Even if limited to aliphatic aldehydes, this Ugi-Smiles transformation of 6-thiopurine affords a very convenient access to adenine derivatives. These compounds either as their free bases or their *N*-glycosylated derivatives are widely represented among natural products and have found huge applications in medicinal chemistry. Figure 1 gathers some representative compounds of this family. Cytokinines **3**[11] and **4**[12] belong to a group of natural phytohormones that promote cell growth. Isopentyladenine **4** displays as well strong antimetabolic and anticancer activities. The *N*-cyclopropyl purine **5** has been reported as potential analgesic for the treatment of chronic pain,[13] the purine aminoacide derivative **6** have shown strong activity against multidrug-resistant tubercolisis[14] and the adenylosuccinic acid **7** has been known for a long time to be the intermediate in the biosynthetic conversion of inosine 5'-phosphate into adenosine 5'-phosphate.[15]

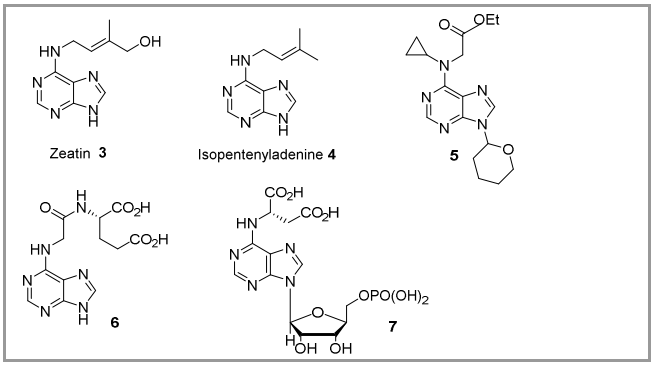


Figure 1 some *N*-alkylated adenine derivatives of biological importance.

Syntheses of *N*-alkylated adenine derivatives usually involve S_NAr reactions between amines and chloropurines.[16] The latter may be prepared from the related hydroxy derivatives using chlorinated derivatives such as $POCl_3$ or $SOCl_2$. The direct conversion of 6-thiopurines into adenine derivatives is poorly documented and known to occur only under vigorous conditions.[17] Faster and more efficient substitutions may however be observed if the thio derivative is oxidized with dimethyldioxirane prior to the addition of the amine.[18]

To conclude, we have disclosed new 4-component couplings of 6-mercaptopurine leading to adenine derivatives bearing a thiocarboxamide group.[19] Such purine thiocarboxamides have never been prepared

before and should display some interesting biological activities due to their structural relationship with many biologically active amino acid substituted purines. Furthermore, besides its potential in medicinal chemistry, this study represents the first report of a Ugi-Smiles reaction involving a purine derivative as acidic component.

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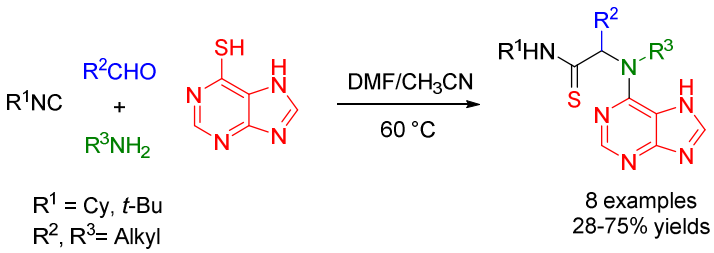
(19) Typical procedure given for **2a:** The Passerini adduct **1a** (102 mg, 0.338 mmol) and Cs_2CO_3 (1.0 equiv, 110 mg) were suspended in 3.0 mL of trifluoroethanol (TFE) in a 10 mL reaction glass vial containing a magnetic stir bar. The vial was flashed with argon, sealed and irradiated with stirring (CEM Discover Microwave. Settings: 140°C, 150 W) during 15 minutes. Upon completion of the reaction time, the vial was cooled to room temperature. The reaction mixture was diluted with water (30 mL) and extracted with CH_2Cl_2 (3×15 mL). Purification by flash column chromatography on silica gel (20:80 Dichloromethane/ Petroleum ether) gave **2a** as a white solid (m.p. = 86.0-86.5°C) isolated in 93% yield (81 mg). Rf: 0.6 (80:20 Dichloromethane/ Petroleum ether). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.30-7.26 (m, 2H, H-Ar), 7.22-7.17 (m, 3H, H-Ar), 6.82 (d, *J* = 6.3 Hz, 1H, NH), 3.77-3.67 (m, 1H), 3.28 (t, *J* = 7.5 Hz, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 1.91-1.87 (m, 2H, H-Cy), 1.76-1.60 (m, 3H, H-Cy), 1.42-1.32 (m, 2H, H-Cy), 1.25-1.13 (m, 3H, H-Cy). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 198.8, 159.0, 140.5, 128.6, 128.5, 126.3, 48.4, 38.4, 32.7, 29.2, 25.4, 24.8. HRMS: Calcd. for $C_{16}H_{21}NO_2$: 259.1572, Found: 259.1564. I.R. ($CHCl_3$): 3398, 2938, 2858, 1720, 1682, 1522, 1498, 1453, 1373, 1116, 892 cm^{-1}.



R^1 = Cy, *t*-Bu
R^2, R^3= Alkyl

8 examples
28-75% yields