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A NOVEL RING CLOSURE REACTION FOR THE PREPARATION OF 6-AMINOURACILS WITH AN α-BRANCHED 1-SUBSTITUENT

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Abstract- The preparation of 6-aminouracil derivatives is described involving a novel, silicon-promoted ring closure reaction. Condensation of *N*-substituted urea with cyanoacetic acid yields cyanoacetylureas, which are heated in hexamethyldisilazane/trimethylchlorosilane to afford *N*-substituted 6-amino-uracils. Previously unaccessible derivatives bearing an α-branched 1-substituent, including 6-amino-1-(1-phenylethyl)uracil were obtained.

6-Aminouracil derivatives (6-aminopyrimidine-2,4(1*H*,3*H*)-diones) are important precursors for the synthesis of a variety of condensed heterocycles, including pharmacologically active compounds such as xanthines.[1] Our ongoing efforts to investigate the structure-activity relationships of xanthine derivatives as adenosine receptor antagonists[2] necessitated the synthesis of 6-aminouracils bearing α-branched 1-substitutents, such as 1-phenylethyl or *tert*-butyl, as precursors for the preparation of the corresponding 3-substituted xanthines.

The classical preparation of 6-aminouracils involves condensation of *N*-mono- or *N*,*N'*-disubstituted urea with cyanoacetic acid yielding cyanoacetylureas, which are ring-closed by means of sodium hydroxide to afford the corresponding *N*-substituted 6-aminouracils.[3] In the case of *N*,*N'*-disubstituted cyano-acetylureas, the base-catalyzed ring closure proceeds exothermically affording high yields of 1,3-disubstituted 6-aminouracils. If *N*-monosubstituted ureas are employed, however, only moderate to low yields of 1-substituted 6-aminouracils are obtained due to deprotonation of the cyanoacetylurea.[3] Monosubstituted 6-aminouracils bearing an α-branched substitutent in the 1-position, such as isopropyl, cyclohexyl or *sec*-butyl, are not accessible by alkaline ring closure according to *Papesch* and *Schroeder*, due to steric hindrance.[3] To our knowledge, there is only one report of the preparation of such a monosubstituted 6-aminouracil with an α-branched 1-substituent, namely 1-isopropyl-6-aminouracil, the preparation of which was described in a Japanese patent in very low yield.[4] In our hands, however, the reported sodium hydroxide-catalyzed ring closure of *N*-isopropyl-cyanoacetylurea was not successful.

Initially, we attempted to optimize the conditions for the basic ring closure of the phenylethyl derivative (**2e**). Variation of the temperature (0-100°C), the sodium hydroxide concentration (1-50%), and the nature of the base (NaOH, Na_2CO_3, K_2CO_3, Cs_2CO_3, DBU) resulted in no reaction or degradation of the starting

compound. On the other hand, acid-catalyzed ring closure (CH_3COOH, HCl, H_2SO_4) was not successful either.

Therefore, we developed a novel ring closure method of cyanoacetylureas to synthesize 6-aminouracil derivatives with α-branched 1-substituents. The cyanoacetylureas (**2a-g**) were prepared by condensation of mono- or di-substituted ureas (**1a-g**) with cyanoacetic acid in acetic anhydride as described.[3] Compounds (**2a**-**2g**) were then suspended in excess hexamethyldisilazane (HMDS) containing catalytic amounts of trimethylchlorosilane, and refluxed for up to 24 hours. The reaction was finished when the solution had become clear, as monitored by thin layer chromatography. After removal of excess HMDS and subsequent hydrolysis by the addition of a saturated sodium hydrogencarbonate solution (**3a**,**b**,**d**,**f**,**g**) or methanol (**3c** and **3e**), uracils (**3a-g**) precipitated and could be isolated in fair to high yields.

The silyl-promoted ring closure of cyanoacetylureas did not only allow for the preparation of mono-substituted 6-aminouracils with α-branched 1-substituents, such as **3b**, **3c** and **3e**, but in most cases it was also superior to the classical method[3] for the preparation of other 1-substituted 6-aminouracils such as **3a**, **3d** and **3f**, resulting in improved yields (see table). Furthermore, 1,3-disubstituted 6-aminouracils, such as 1,3-dimethyl-6-aminouracil (**3g**), could also be obtained by this method in high yields (see Table).

Table : Yields and reaction times for 1-mono- and 1,3-disubstituted 6-aminouracils (**3a-g**)

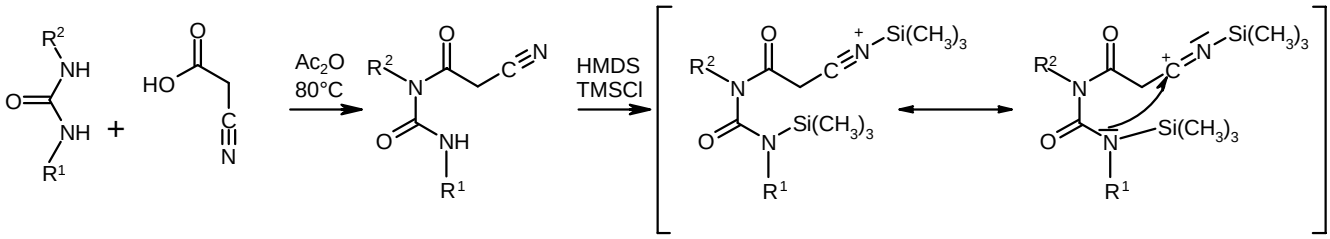
compd	**R^1**	**R^2**	**yields (%)**		**Reaction time (h)**
			ring closure with NaOH[a]	ring closure with HMDS/TMSCl	(HMDS method)
3a	methyl	H	59	87	24
3b	isopropyl	H	0	16	48
3c	*tert*-butyl	H	0	25	48
3d	benzyl	H	55	62	24
3e	1-phenylethyl	H	0	44	48
3f	phenyl	H	94	92	12
3g	methyl	methyl	83	79	24

[a] optimized reaction conditions in analogy to Papesch and Schroeder[3]

The new *tert*-butyl-substituted 6-aminouracil derivative (**3c**) proved to be rather unstable and tended to decompose to yield unsubstituted 6-aminouracil. The compound was particularly sensitive to alkaline conditions (pH ≥ 9), or high temperature (≥ 90 °C). Under these conditions, the *tert*-butyl group was rapidly split off. Futhermore, sensitivity towards UV light was observed. Thus, a 0.5 M solution of **3c** in methanol was completely degraded within 2 hours when subjected to UV light (254 nm).

The 1-phenylethyl derivative (**3e**) proved to be quite stable. The phenylethyl group could, however, be quantitatively removed by strong acids, e.g. 50 % sulfuric acid at room temperature. Similar observations regarding *N*-phenylethyl-substituted heterocyclic compounds have been described by Pichler *et al*.[6] Thus, the 1-phenylethyl moiety might be useful as a protecting group in heterocyclic chemistry, e.g. for the preparation of 3-unsubstituted xanthine derivatives. It might be superior to the benzyl group, which has been shown to be difficult to remove, particularly in xanthine synthesis.[7]

The described synthesis is a novel addition to the series of silicon-promoted reactions developed by Vorbrüggen and others.[8,9] Silicon-promoted ring closure of cyanoacetylureas may proceed *via* silylation of the cyano function yielding intermediate trimethylsilylnitrilium cations (see reaction scheme below); nitrilium cations show largely increased electrophilicity.[10,11] The reaction could be envisaged as being analogous to the well-known Ritter reaction[12] and therefore be classified as a "Silyl-Ritter reaction".
In conclusion, we developed a general, silicon-promoted ring closure of cyanoacetylureas to obtain 6-aminouracils in high yields, including derivatives with α-branched 1-substituents, such as 6-amino-1-(1-phenylethyl)uracil and 6-amino-1-*tert*-butyluracil which had not been previously accessible. This putative Silyl-Ritter reaction might be of broader scope in addition reactions of nucleophiles to nitriles.



	R^1	R^2
a	methyl	H
b	isopropyl	H
c	*tert*-butyl	H
d	benzyl	H
e	1-phenylethyl	H
f	phenyl	H
g	methyl	methyl

EXPERIMENTAL SECTION

Melting points were measured with a Büchi 530 melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AC-250 spectrometer. DMSO-d_6 was used as solvent. The chemical shifts of the remaining protons of the deuterated solvent served as internal standard. Elemental analyses were performed by the Institute of Inorganic Chemistry, University of Würzburg, using an Elemental Analyser, Carlo Erba Instruments.

General procedure for the preparation of 6-aminouracils (**3a-g**)

A mixture of cyanoacetylurea (**2a-g**, 0.2 mol), 150 mL (10.13 mol) of hexamethyldisilazane (HMDS) and 3 mL (23.7 mmol) of trimethylchlorosilane (TMSCl) was heated for 20-24 h under reflux until the solution became clear. After cooling to rt, excess HMDS was evaporated under reduced pressure. The residue was hydrolyzed by the addition of a saturated aqueous solution of $NaHCO_3$ with ice-cooling (for **3a**,**b**,**d**,**f**,**g**). Compounds (**3c**) and (**3e**) were hydrolyzed by the addition of methanol. A solid precipitated, which was collected by filtration and washed with three 10 mL portions of H_2O (**3a**,**b**,**d-g**). Compound (**3c**) was isolated as follows: The solvent was removed by rotary evaporation. The residue was taken up in DMF and **3c** was precipitated by the addition of 1.5 mL of water and subsequently washed with three 5 mL portions of ice water.

6-Amino-1-methylpyrimidine-2,4(1*H*,3*H*)-dione (3a). mp >300°C (EtOH:H_2O = 50:50), (lit., mp 306-307°C)[3]; ^{1}H NMR δ 3.22 (s, 3H), 4.56 (s, 1H, H-5), 6.78 (s, 2H, NH_2), 10.41 (s, 1H, NH); ^{13}C NMR δ 28.43 (CH_3), 75.59 (C5), 151.45 (C2), 155.83 (C6), 162.30 (C4). Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.37; H, 4.93; N, 29.92.

6-Amino-1-isopropylpyrimidine-2,4(1*H*,3*H*)-dione (3b). mp 272°C (MeOH:H_2O = 50:50); ^{1}H NMR δ 1.24 (d, 6H, ^{3}J=6.3 Hz, CH_3), 3.69-3.89 (m, 1H, isopropyl CH), 4.54 (s, 1H, H-5), 6.83 (s, 2H, NH_2), 10.44 (s, 1H, NH); ^{13}C NMR δ 21.04 (C^b), 41.16 (C^a), 82.93 (C5), 150.26 (C2), 158.86 (C6), 163.34 (C4). Anal. Calcd for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 50.02; H, 6.50; N, 24.65.

6-Amino-1-(*tert*-butyl)pyrimidine-2,4(1*H*,3*H*)-dione (3c). mp >300°C (MeOH:H_2O = 70:30); ^{1}H NMR 1.18-1.43 (m, 9H; 3*CH_3), 5.40 (s, 1H, H-5), 6.71 (s, 2H, NH_2); 10.43 (br s, 1 H, NH);^{13}C NMR δ 28.44 (3*CH_3), 48.74 (*t* C), 74.09 (C5), 150.75 (C2), 154.97(C6), 164.08 (C6). Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.45, H, 7.15; N, 22.94. Found: C, 52.15; H, 7.47; N, 23.26.

6-Amino-1-benzylpyrimidine-2,4(1*H*,3*H*)-dione (3d). mp 286°C (EtOH:H_2O = 50:50) (lit., mp 285-286°C)[3]; ^{1}H NMR δ 4.63 (s, 1H, H-5), 5.03 (s, 2H, H^a), 6.80 (s, 2H, NH_2), 7.15-7.40 (m, 5H, H_{aromat}), 10.51 (s, 1H, NH); ^{13}C NMR δ 43.54 (C^a), 75.62 (C5), 126.34, 127.13, 128.38, 136.57 (C_{aromat}), 151.43 (C2), 155.85 (C6), 162.32 (C4). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 61.10; H, 4.93; N, 19.22.

6-Amino-1-(1-phenylethyl)pyrimidine-2,4(1*H*,3*H*)-dione (3e). mp 238°C (MeOH:H_2O = 70:30) (slight decomp); ^{1}H NMR 2.08 (d, 3 H, ^{3}J = 5.9 Hz) 4.32 (s, 1 H, H-5), 5.75 (br s, 1H), 6.41 (br s, 1H), 7.25-7.47 (m, 5 H), 10.26 (s, 1 H, NH); ^{13}C NMR δ 16.59 (C^b), 30.89 (C^a), 75.59 (C5), 125.93 (C^e), 126.97 (C^f), 128.51 (C^d), 139.82 (C^c), 150.53 (C2), 156.10 (C6), 163.34 (C4). Anal. Calcd for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 61.99; H, 6.00; N, 17.81.

6-Amino-1-phenylpyrimidine-2,4(1*H*,3*H*)-dione (3f). mp >280°C (EtOH:H_2O = 50:50) (lit., mp 285-287°C)[5]; ^{1}H NMR δ 4.67 (s, 1H, H-5), 6.11 (s, 2H, NH_2), 7.20-7.56 (m, 5H, H_{aromat}), 10.49 (s, 1H, NH); ^{13}C NMR δ 75.20 (C5), 129.45, 129.69, 129.94, 134.33 (C_{aromat}), 151.21 (C2), 155.86 (C6), 162.02 (C4). Anal. Calcd for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46; N, 20.68. Found: C, 59.31; H, 4.60; N, 20.60.

6-Amino-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (3g). mp >300°C (lit., mp 305-307°C)[3]; Anal. Calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.81; N, 27.08. Found: C, 46.32; H, 6.01; N, 26.97.

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