Antiviral Agents: Synthesis of Furylpyrimidinones and Evaluation of Their Cytostatic and Antiviral Activity[1)]

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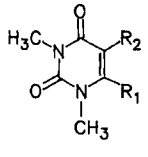
Condensation between furyllithium reagents and pyrimidinones **1**, **2**, **3**, and **4** has been studied. The product composition is strongly dependent upon the reaction conditions and purification methodologies. Cytostatic and antiviral activities of some substrates and reaction products is reported.

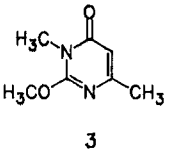
Antivirale Verbindungen: Synthese von Furylpyrimidonen und Prüfung ihrer cytostatischen und antiviralen Eigenschaften

Die Kondensation von Furyllithium-Reagentien mit den Pyrimidinonen **1**, **2**, **3** und **4** wurde untersucht. Die Zusammensetzung des Produktgemisches hängt stark ab von den Reaktionsbedingungen und der Art der Aufarbeitung. Über cytostatische und antivirale Eigenschaften einiger Substrate und Reaktionsprodukte wird berichtet.

During the last few years there has been a growing interest in the biological activity of substituted pyrimidines[2-4)]. Being involved in the synthesis and evaluation of new pyrimidine derivatives as potential antitumor and antimicrobial agents[5-8)], we deemed useful the introduction of a furyl residue in different positions of the pyrimidine ring in order to obtain intermediates to be further modified. Well known is, in fact, the great susceptibility of the furan ring to be chemically transformed into different heterocyclic nuclei such as pyrroles and pyridines[9)], sugar derivatives[10,11)] and butenolides[12)].

This paper describes some preliminary results on the coupling between furyllithium reagents and the pyrimidinone derivatives **1**, **2**, **3**, and **4** (Scheme 1) and reports the *in vitro* results obtained with some substrates and reaction products in cytostatic and antiviral assays.





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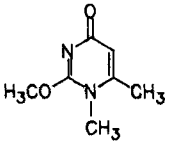
1 R_1 = H R_2 = CHO
2 R_1 = CHO R_2 = H
13 R_1 = $CH(OCH_3)_2$ R_2 = H



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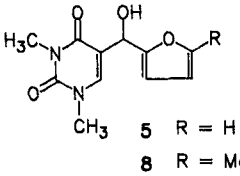
Scheme 1

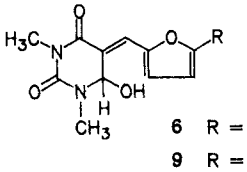
Chemistry

Compound **1** has been synthesized by methylation of uracil with Me_2SO_4 in KOH (5%, aqueous solution) followed by *Vilsmeier-Haack* formylation[13)]. Substrate **1** was added dropwise to a furyllithium solution in THF (1.2 mole equiv.) at -78°C. The mixture, quenched with NH_4Cl after 2 h, was processed as usual and purified by column chromatography. As a result, the furylpyrimidines **5**, **6**, and **7** were obtained (Scheme 2) along with unreacted substrate **1**. These structures are consistent with spectroscopic data (^{1}H-NMR, IR, MS).

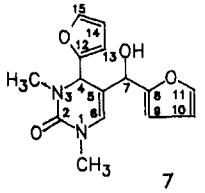
As far as the formation of **6** is concerned, we postulate that this compound was originated from **5** by isomerization on silica gel (allylic shift of the OH group), the driving force being the conjugation of the double bond with the furan ring. A similar shift has been observed in the transformation of 1-alkenyl-2-furylcarbinols to furylidencarbinols (*A. Scettri*, personal communication), and has been reported by *Lam* et al.[4)] for pyrimidines similar to compound **5**. In our case the occurrence of the shift was proved in separate experiments (see below).



5 R = H
8 R = Me



6 R = H
9 R = Me



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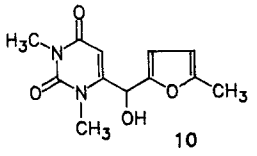


10

Scheme 2

Numbering arbitrarily chosen for ^{1}H–NMR purpose

  0365-6233/91/0404-0203 $ 3.50 + .25/0

The formation of **7** while substrate **1** is still present in the reaction mixture merits some comments. The higher reactivity of C-4 carbonyl in the product **5**, as compared to the reactivity of the same carbonyl in **1**, might be explained by chelation of the lithium cation as shown in Fig. 1. Such an interaction would enhance the positive character of the C-4 carbonyl-C, and promote the addition of a second equivalent of furyllithium at C-4.

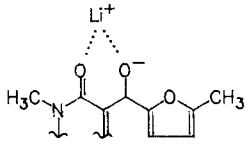


Fig. 1

The hypothesis of activation of the carbonyl in the lithium salt of **5** was tested by reacting **1** with an excess of furyllithium at -20°C: Under these conditions **7** was obtained in 75% yield along with approximatively 15% of unreacted substrate. On the other hand, 1,3-dimethyluracil failed to react with furyllithium, even at room temp., confirming the role of the side chain present in **1**.

When the condensation was conducted under different conditions by varying temp., solvents or substrate/furyllithium ratio, no dramatic changes in the composition of the reaction mixture were observed. Formation of **7** can be eliminated by adding the furyllithium solution to the substrate (THF solution) in one pot at -20°C, and quenching before the reaction is complete. Subsequent purification by flash chromatography affords **5** as the sole product in 62% yield. This purification condition prevents the formation of the isomerized compound **6**.

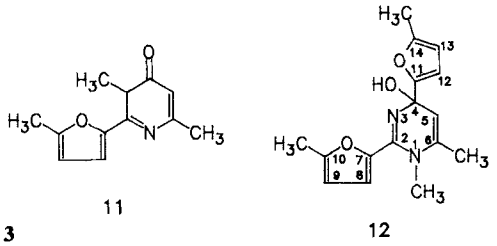
In a similar way, 5-methyl-2-furyllithium was reacted with **1**, affording **8** in 70% yield, with some starting material still present in the mixture. Both in the case of **5** and **8**, complete conversion into compounds **6** and **9**, respectively, took place by simply eluting through a silica gel column.

5-Methyl-2-furyllithium was then reacted with 1,3-dimethyl-6-formyluracil (**2**), prepared from readily available 6-methyluracil. Oxidation of the latter with SeO_2 in acetic acid[14], followed by protection of the aldehyde with trimethyl orthoformate pyridinium tosylate, and *N*-methylation gave the acetal **13**. Deprotection in aqueous acetic acid afforded the aldehyde **2** in 62% overall yield. The protection of the aldehyde was necessary since methylation of the unprotected aldehyde gave a complex mixture. On the other hand, SeO_2 oxidation of 1,3,6-trimethyluracil did not occur.

When a solution of 5-methyl-2-furyllithium in THF (1.1 mole equiv.) was reacted with **2** at -20°C, **10** was the only product obtained (50%) along with some starting material. Purification by flash chromatography gave pure **10** without formation of an isomerized product.

Because of our earlier involvement with the functionalization of 2-methoxy-6-alkyl-4(3*H*)-pyrimidinones[5,7] and in view of the potential biological interest of related compounds[2], we also reacted the pyrimidinones **3** and **4**[7,8] with 5-methyl-2-furyllithium.

Under the usual experimental conditions **3** gave **11** in 80% yield. Spectroscopic data are in accord with the proposed structure (Scheme 3).



Scheme 3

Numbering arbitrarily chosen for ^{1}H–NMR purpose

On the other hand, **4** reacted only with a large excess of the nucleophile to give a product (yield 45%) the spectroscopic data of which agree with structure **12**.

In conclusion, we have described a simply entry to some new pyrimidine derivatives. Their transformation into new highly functionalized pyrimidines of potential medicinal interest is in progress.

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Biological Part

Materials and Methods

Cells. The following cell lines were used:

H9/HTLV-IIIB, a human T cell line that produces Human Immunodeficiency Virus (HIV, HTLV-III); C8166, a CD4+ T cell line containing a genome of HTLV-I and expressing only the tat gene. In these cells the HIV-1 induces an easily detectable syncytium-forming cytopathic effect (CPE); Raji, human lymphoblast-like cells from a Burkitt lymphoma; L1210, lymphocytic mouse leukemia cells; HEL 299, diploid fibroblast-like cells from human embrionic lung tissue; Vero, fibroblast-like cells from African Green Monkey kidney. All the cell lines were mycoplasma-negative. The lymphoblastoid cell lines were grown in RPMI-1640 medium supplemented with 10% foetal calf serum (FCS), 100 U/ml penicillin and 100µg/ml streptomycin, at 37°C in a CO_2 incubator. HEL 299 and Vero cells were grown in *Dulbecco's* modified MEM supplemented with 10% newborn calf serum (NCS).

Viruses. The HIV-1 was obtained from culture supernatants of H9/HTLV-IIIB cells collected at the end of an exponential growth phase. The titer of the virus suspensions varied between 2 and $4x10^5$ cell culture infectious dose fifty ($CCID_{50}$)/ml.

Virus stocks of Herpes Simplex type 1 (HSV-1, ATCC VR 733), Herpes Simplex type 2 (HSV-2, ATCC VR 734), Vaccinia (VV, ATCC VR 117), African Swine Fever (ASFV, Istituto Zooprofilattico di Sassari), Adeno type 1 (ATCC VR 1), Measles (Morbivax Sclavo), Vescicular Somatitis (VSC, ATCC VR 158), and Polio type 1 (Sabin strain), were obtained in Vero cells and had a titer of $5x10^8$ PFU per ml, $2x10^7$ PFU per ml, $3x10^7$ PFU per ml, $5x10^6$ PFU/ml, 10^7 PFU/ml, $5x10^8$ PFU/ml, 10^9 PFU/ml, and $2x10^8$ PFU/ml, respectively.

Toxicity tests. C8166, Raji, and L1210 cells were resuspended at a density of 1x105 cells/ml in growth medium and cultured with various concentrations of the test compounds. Cell numbers were determined with a Coulter counter after 96 h (36 h for L1210). HEL 299 and Vero cells were seeded at a density of 1x105 cells/well in 6-well plates and were allowed to adhere overnight. Growth medium containing various concentrations of the compounds was added and the cultures were incubated for 72 h. Cell numbers were determined with a Coulter counter after trypsinization of the monolayers.

Anti-HIV assays. Exponentially growing C8166 cells were resuspended at a density of 1x107 cells/ml and then infected with HIV-1 at a multiplicity of infection (m.o.i.) of 0.05. After 2 h of incubation at 37°C the inoculum was removed, the cells were washed three times and then resuspended at $1x10^5$/ml in RPMI-1640 medium containing 10% FCS, in the absence or in the presence of the test drugs. After a 4 days incubation at 37°C, the number of syncytia was evaluated at the inverted microscope and the amount of infectious virus produced was determined by end point titration.

Titration of HIV. Titrations were performed by the standard limiting dilution method (log 10 ratio, 4 replicas per dilution) in C8166 cells seeded at 10 cells/ml in 96-well plates. The infectious virus titer was measured by light microscope scoring of syncytia after 4 days of culture and virus titers were expressed as CCID50 per ml using the Reed and Muench method.

Anti-DNA and -RNA virus assays. Confluent monolayers of Vero cells (2x105 cells/well) were infected with 100 ml of viral suspensions so as to obtain 100-200 plaques in the untreated controls after incubation for 24 h (VSV, Adeno), 48 h (HSV-1, VV) or 96 h (ASFV).

Results and Discussion

Cytostatic activity. Results of the *in vitro* assays on cytostatic activity of some of the precursors and reaction products are shown in Tab. 1. The compounds have been listed in two main groups, 6-substituted and 5-substituted pyrimidines, to facilitate the analysis of the structure-activity relationships. Also included in the assays were 6-formyluracil and compound **11**, which was the sole available representative of 2-substituted pyrimidines and 5-fluorouracil (5-FU), used as reference.

Vero cells were included in toxicity assays because of their susceptibility to the infection by a range of DNA and RNA viruses against which the above drugs had to be tested. This was the same for C8166, which was a suitable cell line for anti-HIV assays due to the easily detectable syncytia produced by replicating HIV-1.

Tab. 1: In Vitro Cytotoxic Activity[a)]

Tested substance	TD_{50} (μM) VERO	HEL	C8166	RAJI	L1210
6-formyluracil	35	180	350	350	350
2	300	300	300	300	300
10	400	400	400	400	400
13	1400	1400	1400	1400	1400
1	750	750	750	750	750
6	60	400	800	800	800
8	60	400	800	800	800
11	480	950	950	950	950
5-FU	45	45	45	45	45

a) TD_{50} (Toxic Dose 50) = drug concn. that reduced by 50% the number of cells after three cell cycles. The cell number in untreated controls were: Vero ($1x10^6$), HEL 299 ($5x10^5$), C8166 ($8x10^5$), Raji ($8x10^6$), L1210 ($1x10^6$).

Tab. 2: In Vitro Antiviral Activity[a)]

Tested substance	ED_{50} (μM) HIV-1	HSV-1	VACC	ASFV	ADENO	VSV
6-formyluracil	>350	>35	>35	>35	>35	>35
2	>150	>300	>300	>300	>300	>300
10		>400	>400	>400	>400	>400
13		>1400	>1400	>1400	>1400	>1400
1	1200	>750	>750	>750	>750	>750
6		>60	>60	>60	>60	>60
8		>60	>60	>60	>60	>60
11	960	>480	>480	>480	>480	>480
5-FU	>45	>45	>45	>45	>45	>45
AZT	0.01	>40	ND	ND	ND	ND
ACG	ND	0.2	>1150	ND	ND	>1150

a) ED_{50} (Effective Dose 50) = drug concn. that reduced by 50% either the yield of HIV-1 or the number of plaques of all the other viruses. The HIV-1 yield in untreated controls was $2.2x10^5$ $CCID_{50}$/ml. The plaque numbers in untreated controls were: HSV-1 (125), VV (135), ASFV (198), Adeno (175), VSV (160).
Not Determined

Among the 6-substituted pyrimidines the most toxic compound on fibroblast-like cell lines (Vero and HEL) was 6-formyluracil. On these cells the cytotoxicity decreased with the methylation of the N-atoms of the pyrimidine ring as in **2** and, more drastically, when also the aldehyde group lost its dipole character as in **10** and **13**. *Vice versa*, among the 5-substituted pyrimidines the formyl derivative **1** showed the lowest toxicity, while the furylpyrimidines **6** and **8** turned out to be ten times more toxic. When tested on the three lymphoid cell lines (C8166, Raji, and L1210, a human T cell line, a human B cell line, and a mouse leukemic cell line, respectively), none of the compounds showed a significant selective toxicity. Here, 6-formyluracil and compounds **6** and **8** were even much less toxic than for fibroblast-like cells. The toxicity of 5-FU was of a similar degree on all the cell lines tested.

Antiviral activity. The antiviral activity was evaluated against HIV-1, the etiological agent of AIDS, and against conventional RNA (VSV) and DNA (HSV-1, Vaccinia, ASFV and Adeno) viruses. Results are reported in Tab. 2: none of the compounds inhibited any of the viruses when tested at concentrations equal to the TD_{50}. Vice-versa, under the same experimental conditions, 3'-azidothymidine (AZT) and acyclovir (ACG) confirmed their selective activity against HIV-1 and HSV-1, respectively.

Chemical Experimental Part

M.p.: Büchi 530, not corrected.- IR-spectra: Perkin-Elmer 298, solvent CHCl3 passed through a Al2O3 column.- 1H-NMR-spectra: Varian EM 360 A (60 MHz) in CDCl3, TMS as int. standard.- Mass spectra: Kratos MS80.- Microanalyses: University of Siena. Column Chromatography: silica gel Merck (70-230 mesh); Column flash chromatography: silica gel Merck (230-400 mesh). TLC: precoated silica gel Merck 60 F254.- Organic extracts were dried over anhydrous Na2SO4. Evaporation of solvents under reduced pressure. Anhydrous THF was distilled from K before use.- Temp. in ÉC.

1,3-Dimethyl-5-formyluracil (**1**)

4 g (0.036 mol) of uracil were dissolved in KOH (40 ml, 5% aqueous solution) and 9.5 ml (0.1 mol) of Me_2SO_4 were added. When the reaction was complete (TLC; SiO_2, $CHCl_3$/MeOH: 9/1) NH_4OH (2 ml) was added. The resulting solution was extracted with $CHCl_3$ and the org. layer was washed with saturated NaCl solution. Evaporation of the dried (Na_2SO_4) solvents afforded *1,3-dimethyluracil* (4.8 g, 95%) as an amorphous solid homogeneous in TLC, which was used in the next reaction without further purification. MS: m/z = 140 (M^+).- IR: 1700; 1665 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 5.60 (1H, d, J = 9 Hz, H-5), 7.20 (1H, d, J = 9 Hz, H-6).- A mixture of $POCl_3$ (5 ml) and dry DMF (7 ml) was added to a stirred solution of 1,3 -dimethyluracil (4 g, 0.028 mol) in dry DMF (8 ml) at 0°. After 2 h at 90° the reaction was complete (TLC: SiO_2; $CHCl_3$/MeOH - 9/1). The solution was cooled down to 0°C and was neutralized using 5% NaOH; the hydrolysis was complete in a few min. Extraction of the mixture with EtOAc was followed by washing of the org. extracts with 10% $NaHCO_3$ and H_2O. Evaporation of the dried solvents (Na_2SO_4) afforded 4.6 g of crude product which was recrystallized (CH_2Cl_2) to give pure **1** (3.8 g, 93%, m.p. 125-28°). MS: m/z 168 (M^+).- IR: 1725 (aldehyde); 1700, 1665 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.30 (3H, s, NCH_3), 3.50 (3H, s, NCH_3), 8.00 (1H, s, H-6), 9.90 (1H, s, CHO).- $C_7H_8N_2O_3$: Calcd. C 50.0 H 4.80 N 16.1 Found C 49.9 H 4.65 N 16.1.

1,3-Dimethyl-6-formyluracil (**2**)

The procedure of Zee-Cheng[14] for the synthesis of orotaldehyde was altered.

A well stirred solution of 6-methyluracil (2 g, 0.016 mol) and SeO_2 (2.57 g, 0.023 mol) in glacial acetic acid (48 ml) was refluxed for 24 h. The hot mixture was filtered under reduced pressure through a celite pad and the solid was washed with hot acetic acid. To the clear solution, after evaporation to a small volume, SiO_2 (10 g) was added and the volatiles were removed *in vacuo*.

This silica gel was poured on the top of an already prepared flash chromatography column, which was eluted with $CHCl_3$/MeOH: 9.5/0.5. Evaporation of the solvents afforded the crystalline orotaldehyde (1.8 g, 72%, m.p. 274-75°, reported 273-75°[14]).

A solution of orotaldehyde (1 g, 7.14 mmol) in MeOH (50 ml) and trimethyl orthoformate (30 ml) was refluxed for 36 h in the presence of pyridinium tosylate (300 mg). Solvents were evaporated *in vacuo* and the residue (1.52 g, homogeneous in TLC) was used in the next reaction without further purification. For analytical purposes a sample of the protected aldehyde was recrystallized (MeOH, m.p. 185-86°). MS: m/z 186 (M^+).- IR: 3400 (NH), 1725, 1695 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.33 (6H, s, 2 x OCH_3), 5.03 (1H, s, $CH(OCH_3)_2$), 5.73 (1H, s, H-5).

1.52 g of the crude material from the preceding reaction was dissolved in KOH (10 ml, 5% aqueous solution) and Me_2SO_4 (1.6 ml) was added. The mixture was stirred for 15 min at 50°, then quenched with NH_4OH (1 ml). Extraction with $CHCl_3$ and evaporation of the dried (Na_2SO_4) solvents gave 1.31 g of the crude product (TLC showed a single spot), which was used in the next reaction without further purification. For analytical purposes a sample was purified by PTLC (SiO_2; $CHCl_3$/MeOH: 9.5/0.5) to afford **13** as an amorphous solid. MS: m/z = 214 (M^+).- IR: 1710, 1670 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.29 (3H, s, NCH_3), 3.33 (6H, s, 2 x OCH_3), 3.40 (3H, s, NCH_3), 4.99 (1H, s, $CH(OCH_3)_2$), 5.90 (1H, s, H-5).

1.3 g of crude **13** were dissolved in 80% aqueous solution of acetic acid (5 ml) and 2N HCl (3 ml) was added. The reaction was stirred for 1 h at 70°, then cooled in an ice bath and neutralized by careful addition of solid $NaHCO_3$. The mixture was extracted with $CHCl_3$ and the org. layer was washed with 10% $NaHCO_3$ followed by H_2O. Evaporation of the dried (Na_2SO_4) solvents and purification by column chromatography (SiO_2; $CHCl_3$/MeOH: 9/1) gave **2** (872 mg, overall yield in three steps 73%) as an amorphous solid, homogeneous in TLC. MS: m/z = 168 (M^+).- IR: 1710 (aldehyde and lactam), 1665 (lactam) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.33 (3H, s, NCH_3), 3.60 (3H, s, NCH_3), 6.19 (1H, s, H-5), 9.40 (1H, s, CHO). $C_7H_8N_2O_3$:: Calcd. C 50.0 H 4.80 N 16.1 Found C 50.0 H 4.78 N 16.0.

Condensation of furan with 1,3-dimethyl-5-formyluracil (**1**)

To a stirred solution of n-butyllithium (1.8 mmol) in anhydrous THF (4 ml) under N_2 at -20°, furan (0.26 ml) was added. After 2 h, **1** (200 mg, 1.2 mmol) dissolved in anhydrous THF (4 ml) was added. After 2 h, the temp. was allowed to rise to 0°, then the reaction was quenched with a saturated solution of NH_4Cl (2 ml). Separation of the org. layer followed by extraction with EtOAc and evaporation of the collected org. solvents gave a crude material which was chromatographed (SiO_2; $CHCl_3$/MeOH: 9.5/0.5). Products **7** (48 mg, 13%), **6** (28 mg, 10%), **5** (28 mg, 10%) along with starting material **1** (90 mg, 45%) were obtained.

7: MS: m/z = 286 (M^+-H_2O).- IR: 3600, 3450 (OH), 1650 (lactam) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 2.80 (3H, s, NCH_3), 3.23 (3H, s, NCH_3), 5.33 (1H, s, H-7), 6.20-6.50 (3H, m, H-9, H-10, H-13), 6.90-7.10 (2H, m, H-6, H-14), 7.30 (1H, bs, H-11), 7.49 (1H, bs, H-15). $C_{15}H_{16}N_2O_5$: Calcd. C 59.2 H 5.30 N 9.2 Found C 59.2 H 5.26 N 9.2.

5: MS: m/z = 236 (M+).- IR: 3600 (OH), 1710, 1670 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.19 (3H, s, NCH_3), 3.30 (3H, s, NCH_3), 4.80 (1H, s, H-7), 6.06 (1H, m, H-9), 6.23 (1H, m, H-10), 7.10 (1H, s, H-6), 7.26 (1H, m, H-11). $C_{11}H_{12}N_2O_4$: Calcd. C 55.9 H 5.12 N 11.9 Found C 55.9 H 5.16 N 11.8.

6: MS: m/z = 236 (M^+).- IR: 3600 (OH), 1705, 1665 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 3.30 (3H, s, NCH_3), 3.33 (3H, s, NCH_3), 5.63 (1H, bs, H-6), 6.26 (2H, bs, H-9, H-10), 7.03 (1H, s, H-7), 7.26 (1H, m, H-11). $C_{11}H_{12}N_2O_4$: Calcd. C 55.9 H 5.12 N 11.9 Found C 55.9 H 5.14 N 11.8.

A similar reaction was done using a substrate/2-furyllithium ratio = 1/3 and gave, after column chromatography, **1** (15%) and **7** (72%).

Transformation of **5** *into* **6**

5 (50 mg, 0.21 mmol) was passed through a SiO2 column (CHCl3/MeOH: 9.5/0.5). Evaporation of the solvents afforded **6** (32 mg, 64%).

General procedure for the condensation

To a stirred solution of the substrate (1.2 mmol) in anhydrous THF (4 ml) under N_2 at -20°, a solution of 5-methyl-2-furyl-lithium (1.3 mmol, previously prepared) in dry THF (3 ml) was added in one pot. After 0.5 h, the temp. was allowed to rise up to 0°, then the reaction was quenched with H_2O (2 ml). Extraction with EtOAc, evaporation of the dried solvents (Na_2SO_4) and purification by column chromatography (SiO_2; $CHCl_3$) afforded the pure products and some starting material (see below):

Product **5**: prepared from **1** by reaction with furyllithium. Yield: 62%. Recovered starting material: 22%.

Product **8**: obtained from **1** in 70% yield as an oil. Recovered starting material: 12%.- MS: m/z = 250 (M^+).- IR: 3600 (OH), 1705, 1665 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 2.30 (3H, s, C-CH_3), 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 5.23 (1H, s, H-7), 5.86 (1H, m, H-10), 6.16 (1H, d, J = 4 Hz, H-9), 7.33 (1H, s, H-6). $C_{12}H_{14}N_2O_4$: Calcd. C 57.6 H 5.64 N 11.2 Found C 57.5 H 5.65 N 11.2.

Product **10**: prepared in 50% yield from **2** as an oil. Recovered starting material: 25%.- MS: m/z = 250 (M^+).- IR: 3600 (OH), 1710, 1660 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 2.26 (3H, s, C-CH_3), 3.26 (3H, s, NCH_3), 3.30 (3H, s, NCH_3), 3.63 (1H, s, OH), 5.53 (1H, s, H-7), 5.86 (1H, m, H-10), 5.96 (1H, s, H-5), 6.13 (1H, d, J = 4 Hz, H-9). $C_{12}H_{14}N_2O_4$: Calcd. 57.6 H 5.64 N 11.2 Found C 57.6 H 5.67 N 11.2.

Product **11**: obtained from **3** in 80% yield. M.p. 140°. Recovered starting material: 17%.- MS: m/z = 204 (M^+).- IR: 3400 (NH), 1570 (lactam) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 2.45 (3H, s, C-6-CH_3), 2.50 (3H, s, C-CH_3), 3.70 (3H, s, NCH_3), 6.20 (1H, d, J = 4 Hz, H-9), 6.45 (1H, s, H-5), 6.85 (1H, d, J = 4 Hz, H-8). $C_{11}H_{12}N_2O_2$: Calcd. C 64.7 H 5.93 N 13.7 Found C 64.6 H 5.95 N 13.7.

Product 12: obtained as an oil in 45% yield by reaction with 3.6 mmol of 5-methyl-2-furyllithium. Recovered starting material: 21%.- MS: m/z = 286 (M+Ã).- IR: 3420 (NH and OH) cm-1.- 1H-NMR: d (ppm) = 1.99 (3H, s, C-6-CH3), 2.30 (6H, s, 2 x CH3), 2.83 (3H, s, NCH3), 4.80 (1H, bs, OH), 5.62 (1H, bs, H-5), 5.86 (2H, m, H-9 and H-10), 6.10 (2H, d, J = 4 Hz, H-8 and H-13). C16H18N2O3: Calcd. C 67.1 H 6.34 N 9.8 Found C 67.1 H 6.38 N 9.75.

Transformation of **8** *into* **9**

8 (150 mg, 0.6 mmol) was passed through a SiO_2 column ($CHCl_3$/MeOH: 9.5/0.5). Evaporation afforded **9** (26 mg, 17%) as an oil. MS: m/z = 250 (M^+).- IR: 3700 (OH), 1705, 1665 (lactams) cm^{-1}.- ^{1}H-NMR: δ (ppm) = 2.30 (3H, s, C-CH_3), 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 5.23 (1H, s, H-6), 5.86 (1H, m, H-10), 6.16 (1H, d, J = 4 Hz, H-9), 7.33 (1H, s, H-7). $C_{12}H_{14}N_2O_4$: Calcd. C 57.6 H 5.64 N 11.2 Found C 57.6 H 5.66 N 11.2.

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