AN UNUSUAL CONDENSATION OF PYRIMIDINONES: SYNTHESIS OF BIPYRIMIDINONES AND BIPYRIMIDINYLMETHANE

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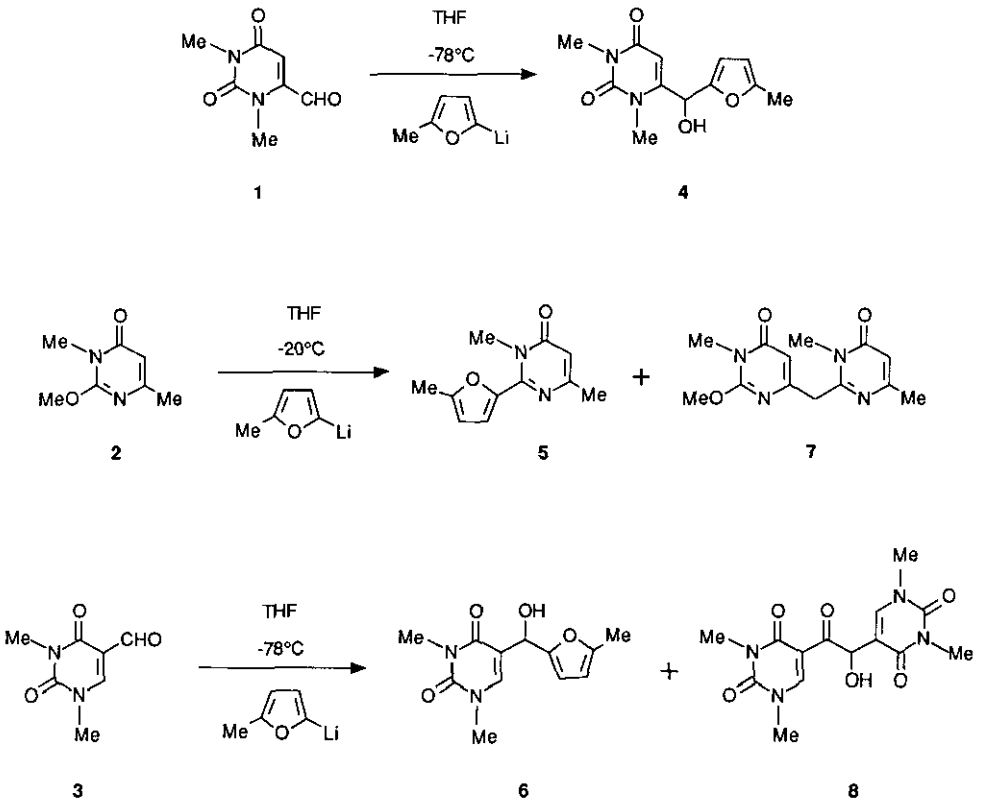
Abstract - An unusual condensation of pyrimidinones (2), (3), and (12) in the presence of lithiated furan derivatives or LiHMDS leads to the formation of 7, 8 and 13. In the case of the self condensation of 3, a novel acyloin reaction is invoked to explain the formation of product (8) where the substrate acts as the catalyst in the reaction.

Due to their biological and pharmacological importance, pyrimidines continue to attract much interest.[1] Although such compounds are relatively simple from a structural point of view, they have been the subject of a great deal of chemical work, and new transformations are frequently reported.[2]

During the course of our work on the synthesis of C-nucleoside analogs as potential antiviral agents, we planned to prepare furylpyrimidines by condensation of the pyrimidinones (1), (2) and (3) with furyllithium derivative and to subsequently subject them to an oxidative rearrangement of the furan ring according to Lefebvre.[3] The study of the products of these reactions enabled us to put into

evidence the unexpected behaviour of pyrimidinones (2) and (3) in basic media and their conversion respectively into bipyrimidinylmethane (7) and the acyloin

Scheme 1



derivative (8).

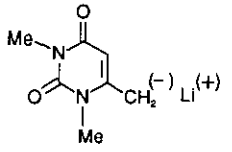
During the condensation of 2 with 2-methylfuryllithium, in THF at -20°C, adding a THF solution of the anion to the substrate in one pot, we noticed the presence of a by-product in the reaction mixture, along with the condensation product 5.[4] When the addition of the anion was done dropwise, the by-product (7) became the major product of the reaction and no traces of the condensed product (5) was detectable in the reaction mixture (see Table 1). The condensation of pyrimidinone (3) with 2-methylfuryllithium showed an analogous behaviour. The products of these reactions have been identified as the bipymiridinylmethane (7) and the acyloin (8), respectively, on the basis of their spectroscopic data.

Bipyrimidines are usually formed from nucleic acids as a result of uv induced mutation of human cells.[5] They are synthetized in different ways, such as by lithiation of bromopyrimidines and subsequent condensation with a second pyrimidine molecule, via condensation of a pyrimidinone derivative with dimethyl malonate or ethyl acetoacetate to construct the second pyrimidine ring,[6] by electrochemical oxidation[7] and by radical additions.[8]

Considering the interest in bipyrimidines and spurred by the novelty of our results, it deemed worthy to study the reactions further.

We rationalize the formation of bipyrimidinylmethane (7) based on a transmetallation reaction between the furyllithium and the relatively acidic C-6 methyl group in 2, thus giving the anion (9). In a second step, this anion displaces the C-2 methoxy group of another molecule of the substrate (2) leading to the product (7).[9]

Scheme 2



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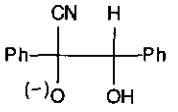

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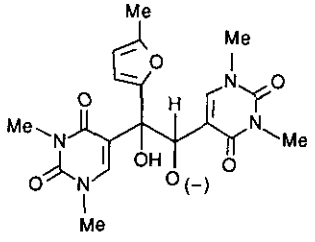

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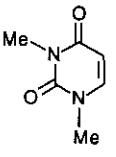

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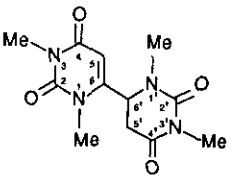

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This mechanism explains why 7 is the only reaction product when the base is added dropwise to the substrate since the substrate is always in large excess as compared to the base.

Bipyrimidine (8) has the structure of an acyloin. In particular ^{1}H-nmr spectrum showed a doublet (one proton) at δ 7.12 and a very broad signal at δ 10.34 (one proton). The latter signal disappeared after the addition of D_2O and concomitantly, the doublet became a singlet at δ 7.12. Same results were obtained by a decoupling experiment operated by irradiation of the δ 10.34 signal, showing in this way the presence of a secondary alcohol between quaternary carbons. No aldehyde carbonyl absorbtions are present in the ir spectrum.

With the purpose to optimizing the yield of products (7) and (8) and in order to better understand the reaction course, we changed the nature of the base. As reported in Table 1, a stronger base (LiHMDS) leads to an increase in the yield of bipyrimidines (7) and (8). More difficult is to formulate a possible mechanism of the reaction giving 8. Benzoin condensation is in fact a well known reaction but is usually described for aromatic substrates, this case is one of the few examples[10] of non aromatic substrate.

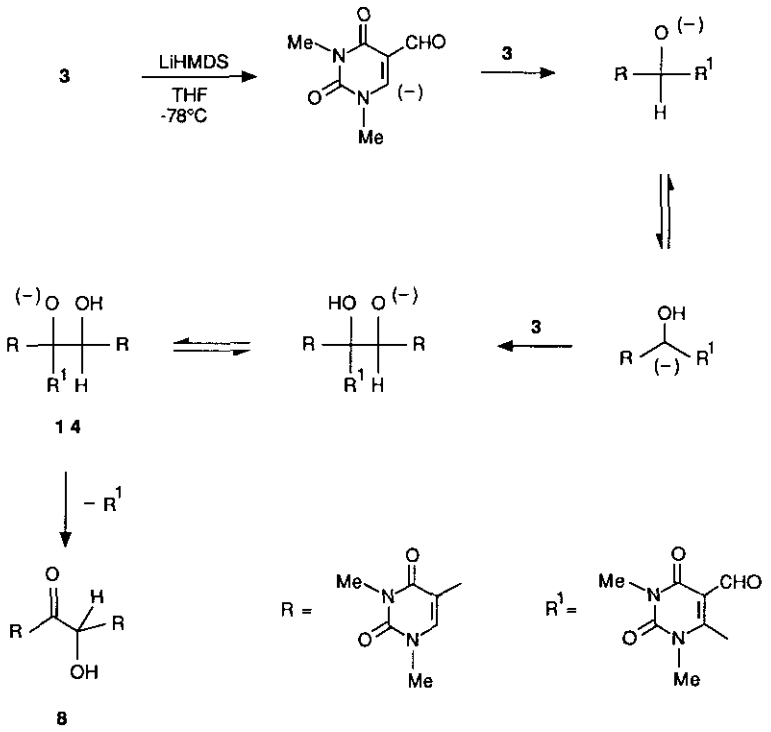
The intramolecular condensation of an aromatic aldehyde is usually catalyzed by cyanide ion[11] through the tetrahedric intermediate (10) to give the corresponding acyloin. Breslow showed that the condensation can be catalyzed by thyamine[12] and more recent reports are available in the literature in which other heterocycles[11] act as good catalysts for the benzoin condensation. It is worthy to note that, in the condensation of 3, no catalyst has been added to the reaction mixture. In principle, two mechanism could be reasonably formulated. The first one, in which the furyl ion, similarly to what described by Lapworth[11] and then by Breslow,[12] plays the role of the cyanide ion through the intermediate (11) to give then the product (8).

A second mechanism is outlined in Scheme 3.

The base removes a C-6 hydrogen of the substrate (3) to generate an anion which adds intramolecularly to the formyl group of an other molecule of the substrate. The new anion formed can react with one more molecule of the substrate to give an intermediate (14) similar to 10, that subsequently gives the acyloin (8). In such a mechanism the pyrimidinone (3) acts as substrate and also as the catalyst.

A mechanism in which the base (furyllithium) itself plays the role of the catalyst instead of the pyrimidinone, as for the first hypothesis, has to be ruled out considering the experimental observation that the condensation is even more efficient when LiHMDS is used as the base and it is hard to imagine an addition of LiHMDS to the carbonyl.

Scheme 3



Furthermore, the fact that benzaldehyde did not condense under our experimental conditions (furyllithium, 2-methylfuryllithium, LiHMDS), confirms the second mechanism hypothesis. Nevertheless the second proposed mechanism is reasonable only if the C-6 hydrogen is acidic. In order to prove this hypothesis we tried the same condensation using 1,3-dimethyluracil (12) as the substrate.

We have obtained a product with the analytical data in accordance with the structure (13). In particular the ^{1}H-nmr showed an ABX system where $J_{AB}>>J_{BX}>>J_{AX}\cong 0$ formed

by a quartet centered at δ 3.29 (one of the $C_{5'}$-H) partially hidden by the N-methyls, a doublet (one proton) at δ 4.50 and a broad doublet (one proton) at δ 2.80.

Decoupling experiments performed by irradiating the δ 2.80 signal transform the quartet in a doublet while the irradiation of the doublet centered at δ 4.50 transforms the quartet to a doublet as well, showing the reciprocal situation of C-5' and C-6'protons. ^{13}C-Nmr spectrum and ms are in accordance with the proposed structure.

When 1,3-dimethyl-6-formyl-4-pyrimidinone (1) was subjected to the lithiated bases, no bipyrimidinones were obtained since the C-5 proton is not acidic enough.[13]

In conclusion, we have shown that 6-methylalkoxypyrimidinones can be transformed into their anions at primary carbon atom and that these undergo intermolecular condensations to give products of type 7. 5-Formyl-N,N-dimethylpyrimidinones undergo an unprecedented acyloin condensation in which the pyrimidinones are the substrate and the catalyst at the same time.

Table 1 - Yields of 7, 13, and 8 with different bases[a]

Substrate	Product	Yield (%)[b]	Base
		20	Furyllithium[c]
2	7	40	2-Methylfuryllithium[c]
		60	LiHMDS
		30	Furyllithium
12	13	70	2-Methylfuryllithium
		70	LiHMDS
		10	Furyllithium[c]
3	8	30	2-Methylfuryllithium[c]
		60	LiMDS

a) Reactions run by adding the base dropwise.

b) Yields of isolated products.

c) No product of condensation between the substrate and the base was detected.

EXPERIMENTAL

Nmr spectra were recorded on a Varian XL 300 (300 MHz) spectrometer and are reported in δ values. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. Microanalysis were performed by Carlo Erba 1106 analyzer. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Mass spectra were recorded on a Kratos MS80 spectrometer. All solvents were ACS reagent grade and were redistilled and dried according to standard procedure.

General Procedure for the Synthesis of 7, 8 and 13.

To a solution of the substrate (2 mmol) in dry THF (10 ml) cooled to -78 °C[a] LiHMDS (2 mmol)[b] was added dropwise under nitrogen atmosphere. After 1 h the mixture was decomposed by addition of water (5 ml). The organic layer diluted with EtOAc was then separated, dried with anhydrous Na_2SO_4 and evaporated under reduced pressure. The resultant foam was purified by preparative tlc on silica gel (Merck) using 10% methanol in chloroform as mobile phase. Yields are reported in Table 1.

[a] For compound(7)the reaction was run at -20°C.

[b] The reaction was performed in the same experimental conditions when different bases were used.

Compound 7.

mp 188-189°C (MeOH/H_2O); ir (ν,cm^{-1}) ($CHCl_3$) 2800, 1680, 1550; ^{1}H-nmr(δ, ppm), ($CDCl_3$) 2.19(s, 3H, CH_3), 3.31(s, 3H, NCH_3), 3.51(s, 3H, NCH_3), 3.88(s, 3H, OCH_3), 3.90-4.03(m, 2H, CH_2), 5.99(s, 1H), 6.19(s, 1H); ^{13}C-nmr (δ, ppm) ($CDCl_3$) 22.66 (CH_3), 27.23(CH_2), 30.79(CH_3), 42.44(CH_3), 55.59(CH_3), 105.89(CH), 110.35(CH), 156.96(C), 157.85(C), 159.39(C), 162.88(C), 163.02(C), 163.35(C); ms +EI(m/z, M^+1) 277.

Anal.Calcd for $C_{13}H_{16}N_4O_3$:C,56.51; H,5.84; N,20.28. Found:C,56.84; H,5.80; N,20.34.

Compound 8.

Ir oil (ν, cm^{-1}) ($CHCl_3$) 3500, 2930, 1650; ^1H-nmr (δ, ppm) ($CDCl_3$) 2.78(s, 6H, NCH_3), 3.13(s, 6H, NCH_3), 7.10(d, J=16.3 Hz, 1H), 8.83(s, 2H), 10.15(s, br, 1H), ^{13}C-nmr (δ, ppm) ($CDCl_3$) 24.80(CH_3), 36.00(CH_3), 103.94(CH), 124.00(CH), 142.12(C), 165.92(C), 168.50(C), 187.61(C); ms -CI(m/z, M^-), -336 Anal.Calcd for $C_{14}H_{16}N_4O_6$: C,50.00; H,4.80; N,16.66. Found:C,50.44; H,4.55; N,16.79.

Compound 13.

mp 247-249°C ($MeOH/H_2O$); ir (ν, cm^{-1}) ($CHCl_3$) 1710, 1680; ^1H-nmr (δ, ppm) ($CDCl_3$) 2.80(br d, J_{AB}=16.5 Hz, 1H), 3.06(s, 3H, NCH_3), 3.20(s, 3H, NCH_3), 3.29(q, J_{AB}=16.5 Hz, J_{BX}=7.8 Hz, 1H, partially hidden by the N-methyls), 3.32(s, 3H, NCH_3), 3.40(s, 3H, NCH_3), 4.58(d, J_{BX}=7.8 Hz, 1H), 5.45(s, 1H); ^{13}C-nmr (δ, ppm) ($CDCl_3$), 27.91 (CH_3), 28.20(CH_3), 31.23(CH_3), 34.67(CH_3), 35.74(CH_2), 53.43(CH), 98.90(CH), 149.75(C), 152.75(C), 152.91(C), 161.70(C); ms +EI(m/z, M^++1)277. Anal. Calcd for $C_{12}H_{16}N_4O_4$:C,51.42; H,5.75; N,19.99. Found:C,51.44; H,5.73; N,19.97.

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