Tetrahedron Letters,Vol.31,No.1,pp 131-134,1990
Printed in Great Britain

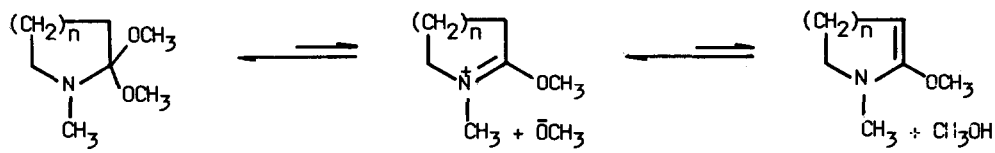
0040-4039/90 $3.00 + .00
Pergamon Press plc

A NOVEL SYNTHESIS OF DI(1-METHYLAZACYCLOALKENO)[2,3-b:2',3'-d]PYRIDINES THROUGH ANNULATION ON LACTAM ACETALS[1,2]

Sanjay Jain, Rahul Jain, Jujhar Singh and Nitya Anand*
Central Drug Research Institute
Lucknow 226 001, India

Summary: *Annulation reaction of lactam acetals* ***1****a and b with primary amides provided a facile synthesis of di(1-methylazacycloalkeno)[2,3-b:2',3'-d]pyridines* ***6****(a-i). Dehydrogenation of* ***6****a,b,d formed dipyrrolo[2,3-b:2',3'-d]pyridines* ***7****a,b,d.*

Lactam acetals belong to a unique class of reactive intermediates which exist in equilibrium with highly reactive immonium species **2**, a counterpart methoxide ion, and enamine **3** (Scheme 1)[3]. This property confers on them the ability to react with nucleophiles, electrophiles



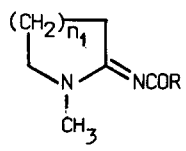
1 a, n = 1
b, n = 2

2

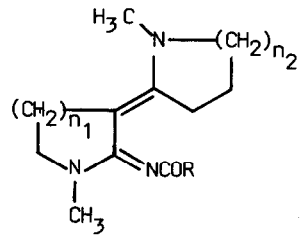
3

Scheme 1

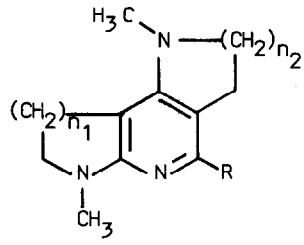
and bifunctional species to yield 2- and 3-substituted and 2,3-annulated products[4] and thus provides a useful platform for the construction of a variety of heterocycles. In our continuing study of the synthetic utility[5,6] of lactam acetals, it has been observed that their reaction with primary amides provides a facile synthesis of di(1-methylazacycloalkeno)[2,3-b:2',3'-d]pyridines **6**a-i; the ring systems dipyrrolo[2,3-b:2',3'-d]pyridine[5,6,5] and pyrrolo[3,2-c]-1,8-naphthyridine[5,6,6] are hitherto not known in literature while the formation of the parent pyrido[2,3-h]-1,6-naphthyridine[6,6,6] is reported[7] only as a bye product in the Hofmann reaction of 2,3'-bipyridine-2',3-dicarboxamide.



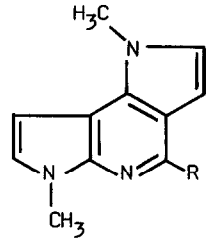
4 a-d



5 a,b



6 a-i



7 a,b,d

Chart 1

Reaction of **1**a & b with equimolar amounts of benzamide and p-substituted benzamides at room temperature in THF yielded N-acylcyclicamidines **4**a-d in 74-84% yield. Keeping in view, the low nucleophilicity of amides, it appears that the methoxide ion available in the equilibrium mixture of lactam acetals, abstracts a proton from the amide nitrogen and thus generates corresponding anion which readily condenses with the immonium species **2** leading to the formation of **4**. Amidines **4**a,b (1 g) possessing an activated 3-CH_2 group, reacted with N-methyl-2-pyrrolidone acetal **1**a (5 ml) at 150° for 3 h to furnish 2-acylimino-3-(1-methyl-2-pyrrolidinylidene)-1-methylpyrrolidines **5**a and b which were cyclized in refluxing $POCl_3$ (3 h) to give di(1-methyl-3,4-dihydropyrrolo)[2,3-b:2',3'-d]pyridines **6**a, b in fair yield (43-55%)[8]. In an one-pot synthesis, a mixture of arylamide (1 g) and **1**a (5 ml) was heated at 150° for 3 h and the resulting mixture was refluxed in $POCl_3$ (10 ml) for 3 h to yield the cyclized products **6**a-d in 35-61% yield which were crystallized from acetone. Structure **6** for the compounds was further supported by dehydrogenation of **6**a,b,d with Pd-C in refluxing diphenyl ether (6 h) to give aromatized dipyrrolo[2,3-b:2',3'-d]pyridines[9] **7**a,b,d (76-81%) (Table 1).

Condensation of six membered acetal **1**b with arylamides was found to be more facile. Thus heating a mixture of arylamides (1 g) and **1**b (5 ml) at 150° for 3 h yielded directly the cyclized products **6**e-g (53-59%), while reaction of 2-benzoylimino-1-methylpiperidine **4**d with N-methyl-2-pyrrolidone acetal **1**a furnished the cyclized product **6**h demonstrating a greater

synthetic flexibility of N-acylamidines **4** in the development of various di(1-methylazacycloalkeno)-[2,3-b:2',3'-d]pyridines, depending upon their reaction with lactam acetals of various ring sizes. These observations indicate an ease of formation of [6,6,6] and [6,6,5] ring systems compared to [5,6,5].

Table 1: *Physical constants of compounds* **4-7***

Compound No.	n_1	n_2	*R*	*m.p.°C*	*% Yield*
4a	1	-	C_6H_5	Oil	80
4b	1	-	p-ClC_6H_4	124-25	83
4c	1	-	p-$NO_2C_6H_4$	153-54	76
4d	2	-	C_6H_5	139-40	84
5a	1	1	C_6H_5	124-25	50
5b	1	1	p-ClC_6H_4	102-03	56
6a	1	1	C_6H_5	141-42	46
6b	1	1	p-ClC_6H_4	132-33	56
6c	1	1	p-$NO_2C_6H_4$	151-52	35
6d	1	1	3-C_5H_4N	155-56	61
6e	2	2	C_6H_5	Oil	53
6f	2	2	p-ClC_6H_4	147-48	59
6g	2	2	3-C_5H_4N	Oil	54
6h	2	1	C_6H_5	104-05	38
6i	1	1	H	Oil	32
7a	1	1	C_6H_5	144-46	81
7b	1	1	p-ClC_6H_4	117-18	78
7d	1	1	3-C_5H_4N	156-57	76

*Compounds were characterized by their IR, ^{1}H NMR and MS data and satisfactory elemental analysis

This reaction was also studied with aliphatic amides. Reactions with formamide, yielded the expected cyclized product **6i** in 32% while reaction with acetamide and propionamide resulted in the formation of intractable mixture.

REFERENCES AND NOTES

1. C.D.R.I. Communication No.4573.
2. This is part XX of the 'Studies on Lactam Acetals'.
3. J. Singh, V. Sardana and N. Anand, Indian J. Chem., **22B**, 1141 (1983).
4. N. Anand and J. Singh, Tetrahedron, **44**(19), 5975 (1988).
5. P. Ahuja, J. Singh and N. Anand, Indian J. Chem., **22B**, 723 (1983).
6. P. Ahuja, J. Singh and N. Anand, Indian J. Chem., **27B**, 166 (1988).
7. W. Brydowna, Roczniki Chem., **14**, 304 (1934); Chem. Abstr., **29**, 2535^{7} (1935).
8. Spectral data of **6a**: ^{1}H NMR ($CDCl_3$, δ ppm): 2.85 (s, 6H, 2xN-C$\underline{H}_3$), 2.80-3.45 (m, 8H, 4xC$\underline{H}_2$), 7.00-7.40 (m, 3H, 3'-, 4'- and 5'-Ar$\underline{H}$) and 7.50-7.80 (m, 2H, 2'- and 6'-Ar$\underline{H}$). MS: $\underline{m/z}$ 265 (M^+).
9. Spectral data of **7a**: ^{1}H NMR ($CDCl_3$, δ ppm): 3.94 and 3.99 (2s, 6H, 2xN-C$\underline{H}_3$), 6.62 and 6.72 (2d, 3- and 8-Ar$\underline{H}$, J = 4.0Hz), 6.88 and 7.02 (2d, 2- and 7-Ar$\underline{H}$, J = 4.0Hz), 7.25-7.60 (m, 3H, 3'-, 4'- and 5'-Ar$\underline{H}$) and 7.80-8.10 (m, 2H, 2'- and 6'-Ar-$\underline{H}$). MS: $\underline{m/z}$ 261 (M^+).

(Received in UK 14 November 1989)