REACTIONS OF 3-ACYLPYRIDINIUM SALTS WITH ELECTROPHILIC OLEFINS. A ONE-POT RING ANNELATION REACTION OF PYRIDINES

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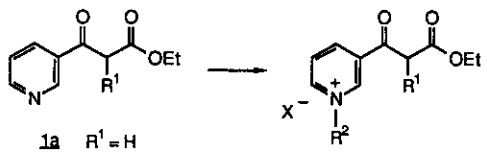
Abstract - The base-mediated addition of N-alkylated 3-pyridyl ketones (2a-d) to diethyl methylenemalonate (3) and ethyl α-phenylthioacrylate results in the formation of hexahydroisoquinoline derivatives in a one-pot reaction.

Nucleophilic additions to 3-acylpyridinium salts favour the C(4)-position to give the thermodynamically controlled 1,4-dihydropyridine derivatives. The reaction has been advantageously employed in the strategic step of a number of synthetic schemes[2]. The reaction of ester anions to N-substituted quaternary nicotinamide salts, leading to partially reduced 2,7-naphthyridinediones[3], has been studied broadly in this laboratory[4a,b]. Utilizing the principle of this reaction, we have achieved the facile syntheses of the alkaloids sesbanine[4a] and naucleofine[4b]. These results have prompted us to search for other ring-annelation strategies which are dependent upon the addition of a nucleophilic moiety to the C(4)-position of a pyridinium system. In this context, it was visualized that a nucleophilic attack by a carbonyl anion of a 3-acylpyridinium salt upon an electrophilic olefin, would generate a new nucleophile which should add to the C(4)-position to result in the C(3)-C(4)-annelation of the pyridine system. In this communication we present some examples of such a one-pot ring-annelation of pyridinium salts to isoquinoline derivatives.

The salts 2a-d[5] were readily obtained by alkylation of pyridyl β-keto esters 1a,b. The reactions of the salts (2a-d) with electrophilic olefins were mediated by sodium hydride in HMPT/THF (1:9, 5° — 20°C). The results of the reaction with two electrophiles are discussed in the following.

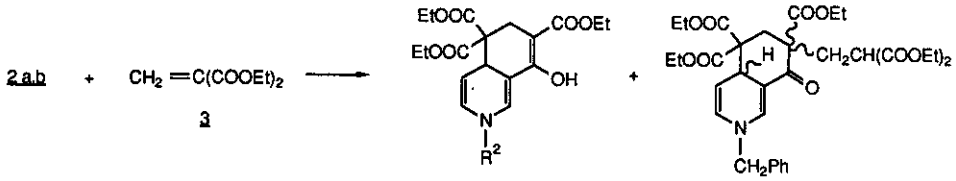
The salt 2a reacted with diethyl methylenemalonate (3) to give a reaction mixture in which product 4a[6] could be identified by nmr spectroscopy. When diester 3 was added to pyridinium salt 2b, the isoquinoline derivative 4b[7] could be isolated as a crystalline product in 22% yield. In addition, two further products, namely, the 1:2 adduct 5[5] (8%), of as yet undetermined stereochemistry, and a crystalline compound, mp 123-125°C (13%), whose structure is currently under investigation, were isolated.

It was apparent from the aforementioned results that the second enolizable hydrogen present in the



1a $R^1 = H$
1b $R^1 = Me$

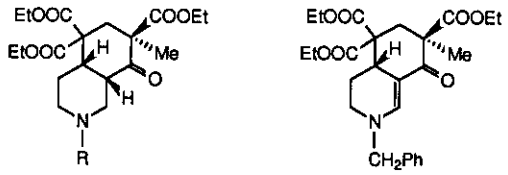
	R^1	R^2	X
2a	H	Me	I
2b	H	$PhCH_2$	Br
2c	Me	Me	I
2d	Me	$PhCH_2$	Br



4a $R^2 = Me$
4b $R^2 = PhCH_2$

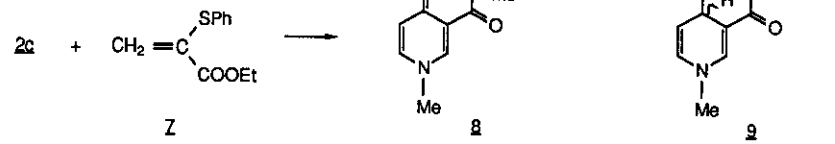
5

6a $R^2 = Me$, 6b $R^2 = PhCH_2$



11 $R = CH_2Ph$, 12 $R = H$

10



Z

8

9

ß-keto ester moiety of salts 2a and 2b complicated the course of the reaction. In view of this, the pyridinium salts 2c,d were selected for further study. Reaction of diester 3 with 2c,d led in a one-pot reaction to the formation of crystalline isoquinoline derivatives 6a,b[8,9] in high yields. Interestingly, the reactions were highly stereoselective, with only minor amounts of the cis:H,CH_3 isomer being formed. The stereochemical assignments in 6a,b are based upon the stereochemistry of the reduction product of 6b, described in the sequel. In 6a,b themselves, the assignments could not be made since, in both cases, the nmr signals of the C(4a)-hydrogens fall under the quartets of the ester methylenes.

Product 6b was reduced in two steps (a. H_2/Pd-C; b. $NaCNBH_3$, HCl/ethanol), via 10[5], to the decahydroisoquinoline derivative 11[10], mp 89-91°C. The N-debenzylation of the latter to 12[5] (62%) could be achieved by reduction with cyclohexene over Pd/C. The stereochemistry of 11 (See Fig. 1) could be deduced from nmr (COSY and NOE) studies[11]. Critical to the stereochemical assignment were the following Nuclear Overhauser experiments (C_6D_6). Irradiation of C(4a)-H at δ 2.95 gave signals at δ 3.85, corresponding to C(8a)-H, and at δ 1.7, representing C(1)-H_{ax} and C(3)-H_{ax}. When the C(7)-Me group was irradiated, a strong signal was observed at δ 2.55 [C(6)-H_{ax}] and a weak one at δ 3.40 [C(6)-H_{eq}]. Distinction between the signals of C(6)-H_{eq} and C(6)-H_{ax} could be made by identifying C(6)-H_{eq} due to its long distance W-coupling with C(4a)-H ($CDCl_3$). The stereochemical assignments, namely a cis- ring junction of the two cyclohexane ring and the trans-relationship between the C(7)-Me group and C(4a)-H, based upon the nmr data, was fully substantiated by the X-Ray structure of the compound (Fig. 2)[12].

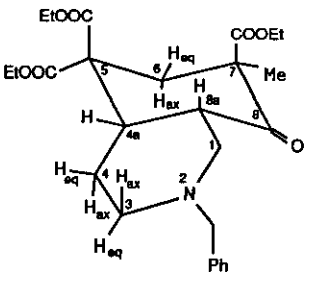


Fig. 1 (11)

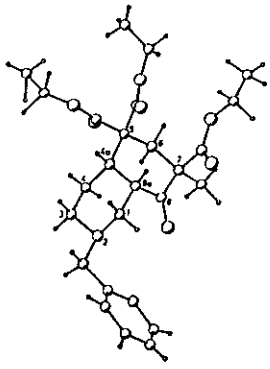


Fig. 2

The structure of 11 allowed the stereochemical assignments at C(4a) and C(7) in 4b and, by analogy in 4a. The high stereoselectivity of the cyclization steps leading to 4a and 4b, and during the reduction of 10, is related to the difference in steric interactions in the transition states, between two axially located ester groups on one hand and between an axial ester and an axial methyl group on the other. Models suggest that the first named interaction is less severe. In the case of

the reduction step, the cis-junction is favoured in the product (11) since the C(4a)-C(4) bond has a trans-diaxial and an axial-equatorial relationship with the two esters at C(5). In the trans-fused isomer of 11, the C(4a)-C(4) bond has two axial-equatorial interactions with the same ester groups. It should be noted in this connection, that the reduction conditions require the formation of the thermodynamically controlled product. A detailed discussion of the stereochemical course of the aforementioned reactions will be presented in a forthcoming paper.

The addition of α-phenylthioacrylate (7) to the anion of 2c results, in the case of homogeneous reaction conditions, in the formation of a mixture of 8 (16%)[13] and 9 (15%)[5], while a heterogeneous reaction leads to compound 8 (21%). It is obvious that the primary annelation product (9) eliminates phenyl thiolate under basic conditions to give 8. Not unexpectedly, attempts to isolate 9 in a pure state were thwarted due to its instability, leading to the formation of 8. The stereochemistry of the compound could, therefore, not be determined.

The scope and applications of the annelation strategy described in this communication are being actively studied in this laboratory.

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REFERENCES

1. Taken in part from the forthcoming doctorate thesis of Ir. K.M.J. Brands.
2. For some recent examples of synthetic applicaitons of nucleophilic addition to pyridinium salts see:
   (a) K. Akiba, A. Ohtani, and Y. Yamamoto, J. Org. Chem., 1986, 51, 5328;
   (b) E. Wenkert, E.C. Angell, J. Drexler, P.D.R. Moeller, J.T. Pyrek, Y. Shi, M. Sultana, and Y.D. Vankar, ibid., 1986, 51, 2995;
   (c) D.D. Weller, E.P. Stirchak, and D.L. Weller, ibid., 1983, 48, 4597;
   (d) W.H. Gündel and S. Bohnert, Ann., 1986, 395.
3. M.N. Pattreyman and K.R.H. Wooldridge, J. Chem. Soc. Perkin I, 1974, 57.
4. (a) M.J. Wanner, G.J. Koomen, and U.K. Pandit, Tetrahedron, 1982, 38, 2748;
   (b) M.J. Wanner, G.J. Koomen, and U.K. Pandit, ibid., 1983, 39, 3673.
5. Spectral data of compounds 2a-d, 5, 9, 10 and 12 are in full agreement with the assigned structures.
6. 4a: Yield 21%; nmr ($CDCl_3$): δ 2.97 (s, 3H, N-CH_3), 5.14 (dd, 1H, J = 8.2, J = 3.3, H_4), 5.71 (m,

1H, H_3), 7.19 (d, 1H, J = 1.7, H_1).

7. 4b: Yield 22%; m.p. 85-88°C; nmr ($CDCl_3$): δ 2.57 (d, 1H, J = 16.1, H_6), 3.07 (d, 1H, J = 16.1, H_6), 4.85 (dd, 1H, J = 8.2, J = 2.4, H_4), 5.78 (m, 1H, H_3).
8. 6a: Yield 90%; nmr ($CDCl_3$): δ 1.37 (s, 3H, CH_3), 2.19 (d, 1H, J = 14.9, H_6), 2.84 (d, 1H, J = 14.9, H_6), 2.97 (s, 3H, NCH_3), 5.13 (dd, 1H, J = 8.2, J = 3.3, H_4), 5.69 (m, 1H, H_3), 7.17 (d, 1H, J = 1.6, H_1).
9. 6b: Yield 66%; m.p. 98-99°C; nmr ($CDCl_3$): δ 1.37 (s, 3H, CH_3), 2.23 (d, 1H, J = 14.9, H_6), 2.84 (d, 1H, J = 14.9, H_6), 4.32 (m, CH_2Ar), 5.14 (dd, 1H, J = 8.2, J = 3.4, H_4), 5.71 (m, 1H, H_3), 7.17 (d, 1H, J = 1.5, H_1).
10. 11: Yield 57%; m.p. 89-91°C; nmr (C_6D_6): δ 1.39 (s, 3H, CH_3), 2.52 (d, 1H, J = 15.1, H_{6ax}), 2.69 (m, 1H, H_3), 2.95 (m, 1H, H_{4a}). nmr ($CDCl_3$), δ 1.36 (s, 3H, CH_3), 2.31 (d, 1H, J = 15.1, H_{6ax}), 2.72 (m, 1H, H_3), 2.91 (m, 1H, H_{4a}), 2.98 (dd, 1H, J = 15.1, J = 1.8, H 6_{eq}).
11. Details of these will be described in a forthcoming paper.
12. Thanks are due to Dr. C.H. Stam and Drs. K. Goubits of the Laboratory of Crystallography of the University of Amsterdam, for determination of the X-Ray structure of compound 11.
13. 8: M.p. 139-141°C; nmr ($CDCl_3$): δ 1.34 (s, 3H, CH_3), 2.43 (d, 1H, J = 16.7, H_6), 3.28 (d, 1H, J = 16.7, H_6), 3.42 (s, 3H, NCH_3), 6.45 (dd, 1H, J = 7.9, J = 1.9, H_3), 7.61 (d, 1H. J = 1.9, H_1), 7.93 (d, 1H, J = 7.9, H_4).

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