Chemistry of Heterocyclic Compounds, Vol. 30, No. 6, 1994

NOVEL SYNTHESIS OF 3-ARYL-5,6-DIHYDROPYRIDIN-2(1H)-ONES

A. S. Fisyuk, M. A. Vorontsova, and S. A. Ivanov

Cyclization of N-3-oxoalkylamides of substituted phenylacetic acids under the influence of bases produces 3-aryl-substituted 5,6-dihydropyridin-2(1H)-ones. Dehydrogenation of these latter compounds yields substituted pyridin-2(1H)-ones.

5,6-Dihydropyridin-2(1H)-ones are of interest as compounds that are biologically active [1, 2]; also, they are used in organic synthesis as intermediates, for example in the preparation of natural alkaloids and their analogs [3, 4].

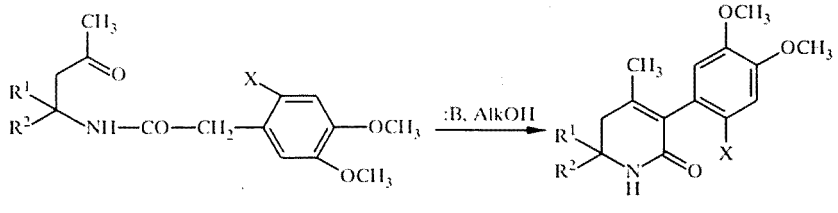
At the same time, there are no general methods for preparation of these compounds that are effective in all cases. Most of the known methods of synthesis are limited by low yields, low selectivity, or lack of availability of the starting materials for the synthesis [5, 6].

We had shown previously [7] that 3-phenyl-5,6-dihydropyridin-2(1H)-ones can be obtained by cyclization of the accessible N-3-oxoalkylphenylacetamides [8-11] under the influence of bases.

With the aim of expanding the synthetic possibilities of the method and obtaining new 3-aryl-substituted 5,6-dihydropyridin-2(1H)-ones, which are of interest as compounds with potential biological activity, we have investigated the cyclization of N-3-oxoalkylamides of 3,4-dimethoxy- and 2-nitro-4,5-dimethoxyphenylacetic acids (Ia-d) under the influence of bases. The N-3-oxoalkylamides Ia and Ib were obtained, as described in [8], from 1,3-chloroketones and homoveratronyl; the amides Ic and Id were obtained by nitration of compounds Ia,b, using a procedure described in [12].

The IR, PMR, and ^{13}C NMR spectra provide full confirmation of the structures of compounds Ia-d (see Experimental section and Tables 1 and 2).

We found that the N-3-oxoalkylamides Ia-d, under the influence of bases, are converted to 5,6-dihydropyridin-2(1H)-ones (IIa-d). In the nitro-substituted N-3-oxoalkylamides Ic, d, the α-carbamoyl hydrogen atoms are more mobile, so that these compounds are cyclized more readily than compounds Ia, b. At the same time, the amides Ib,d require more severe conditions to convert them to the corresponding 5,6-dihydropyridin-2(1H)-ones (in comparison with the conversion of the amides Ia, c); this difference can be attributed to the influence of the substituents in the N-3-oxoalkyl chain, which we had investigated previously [7].



Ia-d IIa-d

I, IIa) $R^1 = R^2 = Me$, X = H; b) $R^1 = X = H$, $R^2 = Ph$; c) $R^1 = R^2 = Me$, $X = NO_2$; d) $R^1 = H$, $R^2 = Ph$, $X = NO_2$

Omsk State University, Omsk 644077. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 812-815, June, 1994. Original article submitted May 6, 1994.

0009-3122/94/3006-0709$12.50

TABLE 1. Characteristics of Synthesized Compounds I-III

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}					Yield, %
			NH	CO	CONH	C=C	NO_2	
Ia	$C_{16}H_{23}NO_4$	87...88	3410	1720	1680	—	—	74,5
Ib	$C_{20}H_{23}NO_4$	159...160	3420	1725	1690	—	—	32,0
Ic	$C_{16}H_{22}N_2O_6$	126...127	3400	1713	1680	—	1339	81,4
Id	$C_{20}H_{22}N_2O_6$	168...169	3420	1727	1680	—	1339	87,4
IIa	$C_{16}H_{21}NO_3$	161...163	3400	—	1680	1640	—	92,0
IIb	$C_{20}H_{21}NO_3$	130...131	3400	—	1675	1630	—	83,4
IIc	$C_{16}H_{20}N_2O_5$	201...202	3406	—	1673	1640	1353	75,0
IId	$C_{20}H_{20}N_2O_5$	176...177	3400	—	1673	1642	1339	62,5
IIIb	$C_{20}H_{19}NO_3$	226...227	3385	—	1630		—	72,7
IIId	$C_{20}H_{18}N_2O_5$	256...257		—	1625		1339	74,9

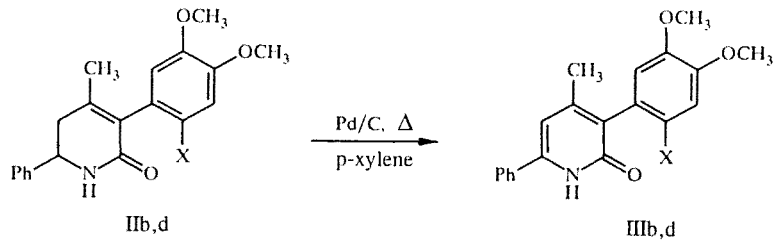
TABLE 2. PMR Spectra of Compounds Ia-d

Compound	Chemical shift, δ, ppm (and SSCC J, Hz)						
	NH	3-CH_3	2-CH_2	R^1	R^2	Ar (2-OCH_3)	CH—Ar
Ia	5,66 br.s	2,01 s	2,85 s	1,26 s		6,75...6,73 m (3,84 s & 3,81 s)	3,34 s
Ib	6,57 br.d ^3J = 9,0	2,14 s	2,95 dd, 3,66 dd ^2J = 20,0 $^3J_{12}$ = 7,0	5,48m, ^3J = 9,0 $^3J_{12}$ = 7,0	7,38...7,02 m	6,91...6,86 m (3,97 s & 3,94 s)	3,60 s
Ic	6,07 br.s	2,02 s	2,83 s	1,33 s		7,62 s, 3'-H 6,75 s, 5'-H (3,91 s & 3,88 s)	3,70 s
Id	6,89 d ^3J = 8,0	2,08 s	3,01 m ^2J = 17,0 $^3J_{12}$ = 6,0	5,39 m ^3J = 8,0 $^3J_{12}$ = 6,0	7,35...7,27 m	7,07 s, 3'-H 6,82 s, 5'-H (3,95 s & 3,94 s)	3,84 s

Here we must note that in the PMR spectrum of the 5,6-dihydropyridin-2(1H)-one IId, there are signals of two diastereomers with an equatorial position of the phenyl group at $C_{(6)}$ and different mutual orientations of the aryl ring and the dihydropyridine ring, owing to the presence of the asymmetric carbon atom $C_{(6)}$ and a chiral axis formed as a consequence of hindered internal rotation at the $C_{(3)}$–Ar bond. The magnitude of the SSCC $^3J_5H_BH$ indicates axial orientation of the proton at $C_{(6)}$ and, correspondingly, equatorial orientation of the 6-Ph group.

The 3-aryl-5,6-dihydropyridin-2(1H)-ones are readily dehydrogenated. When compounds IIb,d are refluxed in xylene with Pd/C, the corresponding substituted pyridin-2(1H)-ones IIIb,d are obtained in high yields.

Thus, the accessibility of the starting materials, the simplicity of the experimental procedures, and the high yields of product make the N-3-oxoalkylamides of arylacetic acids convenient synthons for obtaining not only 3-aryl-substituted 5,6-dihydropyridin-2(1H)-ones, but also pyridin-2(1H)-ones.



IIb,d IIIb,d

TABLE 3. PMR Spectra of Compounds IIa-e

Compound	Chemical shift, δ, ppm (and SSCC J, Hz)						
	NH	4-CH_3, s	5-H_a	5-H_e	6-Ra^1	6-R_e^2	3-Ar ($2OCH_3$)
IIa	5,39 br.s	1,74	2,35 s		1,27 s		6,74 m (3,81 s)
IIb	5,63 br.s	1,89	2,74 dd ^2J = 18,0 $^3J_{5a6a}$ =10,5	2,50 dd ^2J = 18,0 $^3J_{5e6a}$ = 6,6	4,80 m ^3J = 1,5 $^3J_{5a6a}$ = 10,5 $^3J_{5e6a}$ = 6,6	7,46 m	6,89 m (3,95 s & 3,96 s)
IIc	5,51 s	1,67	2,19 d ^2J = 16,0	2,52 d ^2J = 16,0	1,28 s	1,39 s	7,66 s, 3-H′ 6,56 s, 6-H′ (3,90 s & 3,87 d)
IId*	5,79 br.s	1,835	2,83 dd $^3J_{5a6a}$ =13,0 ^2J = 17,2	2,54 dd $^3J_{5e6a}$ = 5,0 ^2J = 17,2	5,02 m $^3J_{5e6a}$ = 5,0 $^3J_{5a6a}$ = 13,0	7,51...7,33 m	7,80 s, 3′-H 6,76 s, 6′-H (4,03 s & 4,02 s)
IIe*	5,76 br.s	1,831	2,85 dd $^3J_{5a6a}$ =11,2 ^2J = 17,0	2,68 dd $^3J_{5e6a}$ = 6,0 ^2J = 17,0	4,89 m $^3J_{6a5e}$ = 6,0 $^3J_{6a5a}$ = 11,2	7,51...7,33 m	7,79 s, 3′-H 6,70 s, 6′-H (4,02 s & 4,12 s)

*Mixture of two diastereomers.

EXPERIMENTAL

The IR spectra were recorded in a Specord 75-IR instrument in chloroform. The PMR spectra were recorded in a Bruker AC-200 P spectrometer (200 MHz) and a Tesla BS-587 spectrometer (80 MHz) in $CDCl_3$. The ^{13}C NMR spectra were recorded in a Tesla BS-587 spectrometer (20 MHz) in $CDCl_3$, internal standard HMDS. The mass spectra were recorded in a Mat-112 instrument (FINNIGAN MAT). The course of the reaction was monitored by TLC on Silufol UV-254 plates. Liquid column chromatography was performed on L 40/100 silica gel.

The characteristics of the synthesized compounds are listed in Tables 1-3. The results of elementary analyses matched the calculated values.

The 4-methyl-4-chloro-2-pentanone and 4-phenyl-4-chloro-2-butanone were obtained by a procedure given in [9].

N-3-Oxoalkylamides Ia,b. To a solution of 20 mmoles of 3,4-dimethoxyphenylacetonitrile and 20 mmoles of 4-methyl-4-chloro-2-pentanone (for Ia) or 4-phenyl-4-chloro-2-butanone (for Ib) in 100 ml of absolute chloroform, 20 mmoles of $SnCl_4$ was added dropwise with stirring at 0°C. The reaction mixture was stirred for 15 min at 0°C and then left for 2-3 h at room temperature. The solution was neutralized with a saturated Na_2CO_3 solution, the organic layer was separated and dried over $MgSO_4$, and the solvent was removed under vacuum.

N-(2-Methyl-4-oxopentyl-2)-3′,4′-dimethoxyphenylacetamide (Ia). After taking off the solvent, the residue was dissolved in 50 ml of hexane and chilled to 0°C; the Ia precipitated in the form of colorless crystals, which were filtered off and then recrystallized from a chloroform–hexane mixture.

^{13}C NMR spectrum: 208.13 (CO); 171.50 (CON); 149.04 ($C_{(3')}$); 148.14 ($C_{(4')}$); 127.63 ($C_{(1')}$); 121.51 ($C_{(6')}$); 112.53 ($C_{(5')}$); 111.56 ($C_{(2')}$); 73.04 ($-CH_2-Ar$); 55.81 ($C_{(1)}$); 51.99 and 50.72 (OMe); 43.86 ($C_{(2)}$); 31.67 (CH_3-CO); 27.24 (2Me).

N-(1-Phenyl-3-oxobutyl-1)-3′,4′-dimethoxyphenylacetamide (Ib). After taking off the solvent, the residue was purified by column chromatography (eluent 95:5 chloroform–ethyl acetate). The eluate was evaporated down, and the residue was recrystallized from ethanol.

N-3-Oxoalkylamides (Ic,d). To a solution of 5 mmoles of compound Ia,b in 100 ml of glacial acetic acid, 1.35 ml of HNO_3 (d = 1.50) was added dropwise at 10°C. The reaction mixture was held for 15 min at 10°C and then poured into ice water (60 ml); after 30 min, the precipitated product was filtered off, washed with ice water, and recrystallized from ethanol.

3-Aryl-5,6-dihydropyridin-2(1H)-ones (IIa,c,d). A 9-mmole quantity of the N-3-oxoalkylamide Ia,d in a 3% solution of MeONa was refluxed in a flow of inert gas for 7 h or 1 h, respectively. The reaction mixture was cooled and neutralized

with 10% aqueous HCl; the solvent was removed under vacuum, and the residue was extracted with chloroform (2 × 40 ml) and dried over $MgSO_4$; after taking off the solvent, the products IIa,d were obtained. The reaction with the amide Ic was performed by the same procedure, but at room temperature for 30 h.

4,6,6-Trimethyl-3-(3′,4′-dimethoxyphenyl)-5,6-dihydropyridin-2(1H)-one (IIa) was recrystallized from a chloroform–hexane mixture. M^+ 275.0.

4,6,6-Trimethyl-3-(2′-nitro-4′,5′-dimethoxyphenyl)-5,6-dihydropyridin-2(1H)-one (IIc) was recrystallized from ethanol. ^{13}C NMR spectrum: 165.12 (CO); 153.04 ($C_{(4)}$); 148.37 ($C_{(5')}$); 144.31 ($C_{(4')}$); 141.46 ($C_{(2')}$); 128.42 ($C_{(3)}$); 126.23 ($C_{(1')}$); 114.22 ($C_{(6')}$); 108.1 ($C_{(3')}$); 56.54 ($2OCH_3$); 51.14 ($C_{(6)}$); 44.04 ($C_{(5)}$); 30.21 and 28.63 (C-CH_3); 21.78 (4-CH_3).

4-Methyl-3-(2′-nitro-4′,5′-dimethoxyphenyl)-6-phenyl-5,6-dihydropyridin-2(1H)-one (IId). Crystallized from ethanol, obtaining a mixture of two diastereomers.

4-Methyl-3-(3′,4′-dimethoxyphenyl)-6-phenyl-5,6-dihydropyridin-2(1H)-one (IIb). Refluxed 9 mmoles of Ib in 20 ml of a 10% alcoholic KOH solution for 20 min in a flow of inert gas. After treatment as indicated above, the residue was purified by column chromatography (eluent 1:1 benzene–ethyl acetate). The residue remaining after concentrating the eluate was crystallized from a benzene–heptane mixture.

4-Methyl-3-(3′,4′-dimethoxyphenyl)-6-phenylpyridin-2(1H)-one (IIIb). Refluxed 0.5 mmole of compound IIb and 0.1 g of 10% Pd/C in 10 ml of dry p-xylene for 3 h. The reaction mixture was filtered and cooled. The precipitate was separated and recrystallized from ethanol. PMR spectrum: 7.55 (5H, m, 6-Ph); 6.93 (3H, m, 3-Ar); 6.49 (1H, m, 5-H); 3.96 (3H, s, OCH_3); 3.85 (3H, s, CH_3); 2.20 (3H, s, 4-CH_3).

4-Methyl-3-(2′-nitro-4′,5′-dimethoxyphenyl)-6-phenylpyridin-2(1H)-one (IIId). Obtained in the same manner, from IId, by refluxing for 4 h. PMR spectrum: 7.79 (1H, s, 3′-H); 7.55 (5H, m, 6-Ph); 6.71 (1H, s, 6′-H); 6.45 (1H, s, 5-H); 4.03 (3H, s, OCH_3); 3.92 (3H, s, OCH_3); 2.11 (3H, s, 4-CH_3).

REFERENCES

1. M. Sekiya and Y. Watarase, Jpn. Pat. 54-70283.
2. N. Ohba, A. Ikeda, K. Matsunari, Y. Yamada, M. Hirata, Y. Nakamura, and A. Takeuchi, U.S. Pat. 5,006,157.
3. D. O. Imbroisi and N. S. Simpkins, Tetrahedron Lett., **30**, 4309 (1989).
4. M. Nakagawa, Z. Lai, Y. Tarisawa, and H. Hito, Heterocycles, **31**, 999 (1990).
5. M. Shamma and P. Rosenstock, J. Org. Chem., **26**, 718 (1961).
6. M. Komatsu, S. Yamamoto, Y. Oshiro, and T. Agawa, Tetrahedron Lett., **22**, 3769 (1981).
7. A. S. Fissiouk, M. A. Vorontsova, and R. S. Sagitullin, Mendeleev Commun., 249 (1993).
8. R. R. Schmidt, Chem. Ber., **98**, 334 (1965).
9. M. Lora-Tamayo, R. Madronero, G. Garcia Munos, and H. Leipprand, Chem. Ber., **97**, 2234 (1964).
10. K. Ikeda, Y. Terao, and M. Sekiya, Chem. Pharm. Bull., **29**, 1156 (1981).
11. A. V. Shastin and E. S. Balenkova, Zh. Org. Khim., **20**, 1357 (1984).
12. G. N. Walker, J. Am. Chem. Soc., **77**, 3844 (1955).