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N-3-OXOALKYLAMIDES AND -THIOAMIDES IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS. 7*. STUDY OF THE CYCLIZATION OF N-(3-OXOALKYL)-AMIDES OF TOSYLACETIC ACID

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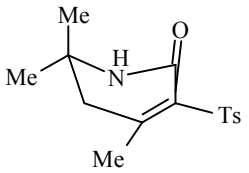
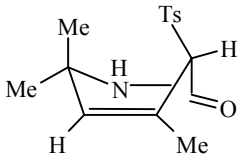
Alkyl-substituted N-(3-oxoalkyl)amides of tosylacetic acid are cyclized under the action of bases with the formation of 3-tosyl-3,6-dihydropyridin-2(1H)-ones. In the presence of a phenyl substituent at position $C_{(1)}$ of the 3-oxoalkyl chain the reaction proceeds with the formation of 2-pyridones. The principles influencing the regiodirection of cyclization are explained.

Keywords: N-(3-oxoalkyl)amides, 2-pyridones, 3-tosyl-3,6-dihydropyridin-2(1H)-ones, intramolecular cyclization.

We previously reported [2] that N-(3-oxoalkyl)phenylacetamides are capable of cyclization in basic media, proceeding according to an aldol type reaction with the formation of 5,6-dihydropyridin-2(1H)-ones. As in the case of the crotonization, where the reaction products may be not only α,β-unsaturated but also β,γ-unsaturated carbonyl compounds, the cyclization of N-(3-oxoalkyl)phenyl-acetamides may lead to the formation of 3,6-dihydropyridin-2(1H)-ones [3]. It might have been assumed that any factors destabilizing the double bond in the $C_{(3)}$=$C_{(4)}$ position of the ring of 5,6-dihydropyridin-2(1H)-ones will be capable of isomerizing it into the $C_{(4)}$=$C_{(5)}$ position. It is known [4] that if the substituent displays π_p-π_d conjugation and a large *-I* effect then it destabilizes the adjacent double bond and the equilibrium is displaced in the direction of the compound in which the double bond is removed from this substituent. The tosyl group possesses such qualities, consequently as a result of cyclizing N-(3-oxoalkyl)amides having a tosyl substituent in α-position in relation to the carbamoyl group, the formation of 3,6-dihydropyridin-2(1H)-ones might have been expected. Calculated data (MNDO/MOPAC 7.0) indicate that the energy of formation of 4,6,6-trimethyl-3-tosyl-5,6-dihydropyridin-2(1H)-one (**3a**) proves to be 2.8 kcal/mol higher than that of 3,6-dihydropyridin-2(1H)-one (**4a**).



3a



4a

* For Part 6 see [1].

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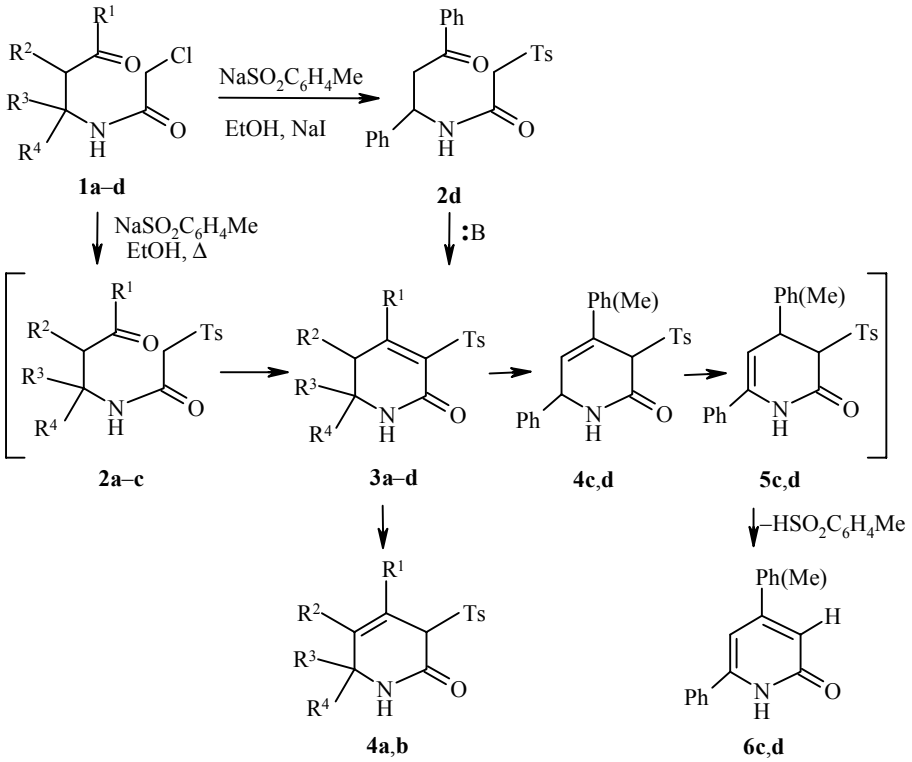
In this connection we have studied the possibility of the directed synthesis of 3,6-dihydropyridin-2(1H)-ones **4a-d** by the cyclization of N-(3-oxoalkyl)amides of tosylacetic acid **2a-d** and have established that the reaction of N-(3-oxoalkyl)chloroacetamide **1a** with sodium *p*-toluenesulfinate in reality leads to the formation of compound **4a**. Under analogous conditions *cis*- and *trans*-3,6-dihydropyridin-2(1H)-ones (**4b**) in a ratio of 2:3 were obtained from a mixture of *anti* and *syn* isomers of **1b**. The yields of compounds **4b** and **4a** were 45 and 70%. At the same time compound **1c** is converted under analogous conditions into 4-methyl-6-phenylpyrid-2-one (**6c**). For the synthesis of compounds **4,6** the sodium *p*-toluenesulfinate used was obtained from an aqueous solution of *p*-toluenesulfinic acid by salting out with Na_2CO_3 [5] and contains 10-15% sodium carbonate.

Heating N-(3-oxo-1,3-diphenylpropyl)-2-(*p*-toluenesulfonyl)acetamide (**2d**), synthesized by substituting the halogen atom in compound **1d** by a tosyl group, in an alcoholic solution of EtONa, also leads to the formation of 4,6-diphenyl-2-pyridone (**6d**). It should be noted that a mixture of *cis* and *trans* isomers of **4b** was not converted into 3,6-dimethylpyrid-2-one under analogous conditions. Probably the increase in acidity of the proton at position 6 aids isomerization of dihydropyridin-2(1H)-ones **4c,d** into **5c,d**, which form pyrid-2-ones **6c,d** after cleavage of *p*-toluenesulfinic acid.



1–4 a $R^1 = R^3 = R^4 = Me$, $R^2 = H$; **b** $R^1 = R^2 = R^3 = Me$, $R^4 = H$; **c** $R^1 = Me$, $R^2 = R^4 = H$, $R^3 = Ph$; **d** $R^1 = R^3 = Ph$, $R^2 = R^4 = H$

In the IR spectra of compounds **4a,b** in $CDCl_3$ solution systems of bands were present at 1140-1330 cm^{-1} for the vibrations of the sulfo group (Table 1). The vibrations of the C=C and NH bonds were located at 1600 and 3400 and of the N–C=O group at 1680 cm^{-1}.

In the ^1H NMR spectrum of compound **4a** a multiplet signal was present at 5.84 ppm for the $C_{(5)}$–H proton with $^4J_{5,4\text{-}CH_3} = 1.5$ and $^4J_{5,NH} = 1.5$ Hz. The character of the splitting of the $C_{(4)}$–CH_3 methyl group signals in **4a,b** confirms the presence of an allylic interaction with the $C_{(5)}$–H proton in compound **4a** and a homoallylic interaction with the $C_{(5)}$–CH_3 methyl substituent in compound *cis*-**4b** ($^5J_{5\text{-}CH_3,4\text{-}CH_3} = 0.9$ Hz). The $C_{(3)}$–H proton of compound **4a** is recorded as a singlet at 4.31 ppm. The absence of long-range spin-spin interactions of $C_{(5)}$–H

TABLE 1. Spectral Characteristics and Yields of Compounds **1a,b**, **2d**, **4a,b**, and **6s,d**

Compound	IR spectrum, ν, cm^{-1}*		Empirical formula	Found, % / Calculated, %		^1H [^{13}C] NMR spectrum, δ, ppm (*J*, Hz)**	Yield, %
	(N–C=O) SO_2	(NH) C=S, C=O		C	H		
1	2	3	4	5	6	7	8
1a	1680	(3410) 1710	$C_8H_{14}ClNO$	—	—	7.29 (1H, br. s, NH); 3.98 (2H, s, CH_2Cl); 2.99 (2H, s, CH_2CO); 2.15 (3H, s, $COCH_3$); 1.43 (6H, s, $2CH_3$)	59
anti-**1b**, *sin*-**1b**	1670	(3420) 1710	$C_8H_{14}ClNO_2$	49.98 / 50.14	7.35 / 7.36	*anti*-**1b**, 6.94 (1H, br. s, NH); 4.30 (1H, m, ^3J = 9.5, ^3J = 7.0, ^3J = 5.5, $C_{(1)}$–H); 4.03 (2H, s, CH_2Cl); 2.72 (1H, dd, ^3J = 7.3, ^3J = 5.5, $C_{(2)}$–H); 2.21 (3H, s, $COCH_3$); 1.22 (3H, d, ^3J = 7.0, $C_{(1)}$–CH_3); 1.18 (3H, d, ^3J = 7.3, $C_{(2)}$–CH_3) *sin*-**1b**, 7.50 (1H, br. s, NH); 4.18 (1H, m, $C_{(1)}$–H); 4.04 (2H, s, CH_2Cl); 2.83 (1H, dd, ^3J = 7.3, ^3J = 4.2, $C_{(2)}$–H); 2.22 (3H, s, $COCH_3$); 1.19 (3H, d, ^3J = 6.8, $C_{(1)}$–CH_3); 1.17 (3H, d, ^3J = 7.3, $C_{(1)}$–CH_3)	39
1c	1690	(3410) 1730	$C_{12}H_{14}ClNO_2$	60.15 / 60.13	5.88 / 5.89	7.84 (1H, d, ^3J = 8.3, NH); 7.35-7.19 (5H, m, Ph); 5.38 (1H, m, ^3J = 8.3, ^3J = 6.0, ^3J = 6.0, $C_{(1)}$–H); 3.96 (2H, s, CH_2Cl); 3.12 (1H, dd, ^2J = 17.0, ^3J = 6.0, $C_{(2)}$–H); 2.91 (1H, dd, ^2J = 17.0, ^3J = 6.0, $C_{(2)}$–H); 2.06 (3H, s, $COCH_3$)	56
1d	1690	(3410) 1730	$C_{17}H_{16}ClNO_2$	67.71 / 67.66	5.48 / 5.34	7.90-7.21 (11H, m, NH, 2Ph); 5.58 (1H, m, ^3J = 6.0, ^3J = 5.5, ^3J = 5.5, $C_{(1)}$–H); 4.00 (2H, s, CH_2Cl); 3.75 (1H, dd, ^2J = 17.2, ^3J = 5.5, $C_{(2)}$–H); 3.43 (1H, dd, ^2J = 17.2, ^3J = 6.0, $C_{(2)}$–H)	81
2d	(1655) 1155, 1300, 1325	(3280) 1685	$C_{24}H_{23}NO_4S$	68.43 / 68.39	5.39 / 5.50	8.72 (1H, d, ^3J = 7.8, NH); 7.97-7.24 (14H, m, 2Ph, C_6H_4); 5.35 (1H, m, $C_{(1)}$-4); 4.24 (1H, d, ^2J = 13.7, $NCOCH_2Ts$); 4.27 (1H, d, ^2J = 13.7, $NCOCH_2Ts$); 3.55 (1H, dd, ^2J = 17.6, ^3J = 7.6, $PhCOCH_2$); 3.41 (1H, dd, ^2J = 17.6, ^3J = 7.6, $PhCOCH_2$); 2.37 (3H, s, CH_3)	87
4a	(1690) 1145, 1290, 1310, 1325	(3400) 1600	$C_{15}H_{19}NO_3S$	61.44 / 61.41	6.50 / 6.53	7.80 (2H, d, ^3J = 8.0, Ar); 7.34 (2H, d, ^3J = 8.0, Ar); 6.42 (1H, br. s, NH); 5.84 (1H, m, ^4J = 1.5, ^4J = 1.5, 5-H); 4.31 (1H, s, 3-H); 2.44 (3H, s, Ar–C<u>H</u>$_3$); 2.10 (3H, d, ^4J = 1.5, 4-CH_3); 1.38 (3H, s, 6-CH_3); 1.28 (3H, s, 6-CH_3) [162.2 (NCO); 145.0, 136.1, 2 × 129.5, 2 × 129.3 (Ar); 135.2 ($C_{(5)}$); 122.4 ($C_{(4)}$); 71.7 ($C_{(3)}$); 55.2 ($C_{(6)}$); 31.3 (6-CH_3); 30.2 (4-CH_3); 22.5 (6-CH_3); 21.7 (Ar–<u>C</u>H$_3$)]	70

TABLE 1 (continued)

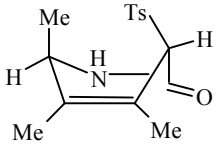
1	2	3	4	5	6	7	8
cis- and *trans*-**4b***[3]	(1680) 1140, 1290, 1300, 1320, 1330	(3400) 1600	$C_{15}H_{19}NO_3S$	61.32 / 61.41	6.59 / 6.53	*trans*-**4b** 7.80 (2H, d, ^3J = 8.2, Ar); 7.34 (2H, d, ^3J = 8.2, Ar); 7.13 (1H, br. s, NH); 4.34 (1H, br. s, 3-H); 3.81 (1H, br. q, ^3J = 6.7, 6-H); 2.44 (3H, s, Ar–C<u>H</u>$_3$); 1.98 (3H, s, 4-CH_3); 1.82 (3H, s, 5-CH_3); 1.41 (3H, d, ^3J = 6.7, 6-CH_3) [163.2 (NCO); 144.8, 136.3, 2 × 129.5, 2 × 129.2 (Ar); 136.3 ($C_{(5)}$); 117.1 ($C_{(4)}$); 73.6 ($C_{(3)}$); 54.9($C_{(6)}$); 21.8 (Ar–<u>C</u>H_3); 21.7 (4-CH_3); 19.5 (6-CH_3); 16.8 (5-CH_3)] *cis*-**4b** 7.75 (2H, d, ^3J = 9.2, Ar); 7.34 (2H, d, ^3J = 8.2, Ar); 7.03 (1H, br. s, NH); 4.33 (1H, br. s, 3-H); 3.70 (1H, br. q, ^3J = 7.0, 6-H); 2.44 (3H, s, Ar–C<u>H</u>$_3$); 1.98 (3H, s, 4-CH_3); 1.74 (3H, q, ^5J = 0.9, 5-CH_3); 1.15 (3H, d, ^3J = 7.0, 6-CH_3) [163.1 (NCO); 145.1, 136.1, 2 × 129.6; 2 × 129.3 (Ar); 135.0 ($C_{(5)}$); 118.1 ($C_{(4)}$); 74.2 ($C_{(3)}$); 52.1 ($C_{(6)}$); 21.8 (Ar–<u>C</u>H_3); 21.7 (4-CH_3); 20.4 (6-CH_3); 15.5 (4-CH_3)]	43
6c	1645	(3370)	$C_{12}H_{11}NO$	77.82 / 77.81	6.09 / 5.99	12.7 (1H, br. s, NH); 7.80-7.20 (5H, m, Ph); 6.33 (1H, d, $^4J_{35}$ = 1.2, $C_{(3)}$–<u>H</u>); 6.32 (1H, d, $^4J_{35}$ = 1.2, $C_{(5)}$–H); 2.23 (3H, s, CH_3) [165.5 (NCO); 152.9 ($C_{(4)}$), 146.0 ($C_{(6)}$), 133.6, 129.8, 129.0, 126.8 (Ph) 117.2 ($C_{(3)}$) 107.5 ($C_{(5)}$), 21.7 (CH_3)]	79
6d	1645	(3380)	—	—	—	7.80-7.28 (10H, m, 2Ph); 6.84 (1H, d, $^4J_{35}$ = 1.6, $C_{(3)}$–<u>H</u>); 6.50 (1H, d, $^4J_{35}$ = 1.6, $C_{(5)}$–H)	87

* The IR spectra were taken in $CHCl_3$.

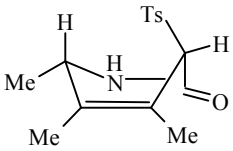
*[2] The ^{13}C NMR spectra for compounds **4a,b** and **6c** are given in square brackets; the ^1H NMR spectra of compounds **2d** and **6d** were taken in DMSO-d_6, the ^1H and ^{13}C NMR spectra of the remaining compounds in $CDCl_3$.

*[3] Ratio of *cis:trans* isomers was 63:37.

and $C_{(3)}$–H is characteristic of allylic protons [6] and indicates the closeness of the value of the dihedral angle $C_{(5)}=C_{(4)}–C_{(3)}–H$ to θ ~180°, and consequently the pseudoequatorial orientation of $C_{(3)}$–H. The $C_{(6)}–CH_3$ protons of *cis*-**4b** (δ 1.15) are shielded by the tosyl group, and in comparison with *trans*-**4b** (δ 1.41), give a doublet signal towards higher field. In the ^{13}C NMR spectrum of compounds **4a,b** characteristic signals are present for the nuclei of the carbon atoms of the NC=O group (δ 163.2-162.2), double bond (δ 136.3-135.0 and 122.4-117.1), the aromatic ring (δ 145.1-129.2), and the $C_{(3)}$ atom (δ 74.2-71.7 ppm). It is known that the presence of van der Waals interactions between spatially adjacent alkyl groups leads to a high field chemical shift of the carbon atom nuclei [7]. In the spectrum of *trans*-**4b** having the interaction between $C_{(6)}–\underline{C}H_3$ and $C_{(5)}–\underline{C}H_3$ the signals of the carbon nuclei of the respective methyl groups are present at 19.5 and 16.8 ppm.



cis-**4b**



trans-**4b**

The absence of such an interaction in *cis*-**4b** leads to a low field displacement of the shift of the $C_{(5)}–\underline{C}H_3$ signal (15.5 ppm). At the same time the signal of $C_{(6)}–\underline{C}H_3$ of compound *cis*-**4b** is located at high field (20.4 ppm) as a result of spatial interactions with the tosyl group.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC 200 P instrument (200 and 50 MHz). Internal standard was TMS. The IR spectra were recorded on a Specord IR-75 spectrometer. A check on the progress of reactions and the purity of the compounds obtained was carried out by TLC on Silufol UV 254 plates, visualizing with iodine vapor or UV light.

Compounds **1a,b** were obtained by the acylation of 1,3-amino ketones with chloroacetyl chloride [2], and **1c,d** from the corresponding 1,3-chloroketones and chloroacetonitrile in the presence of $SnCl_4$ [2, 8]. Compound **1b** had mp 56-76°C (hexane), **1c** mp 90-91°C (ethanol). The properties of compounds **1a,d** are given in [9].

2-[(4-Methylphenyl)sulfonyl]-N-(3-oxo-1,3-diphenylpropyl)acetamide (2d). A solution of chloroacetamide **1d** (0.88 g, 2.92 mmol), KI (0.50 g, 3.01 mmol), and sodium *p*-toluenesulfinate dihydrate (1.918 g, 6.00 mmol) in DMSO (25 ml) was stirred at room temperature for 48 h. The reaction mixture was then poured into water (150 ml), the solid filtered off, washed with water, dried in the air, and crystallized from C_6H_6–EtOH, 1:4. Compound **2d** (1.037 g) was obtained; mp 190-191°C.

4,4,6-Trimethyl-3-[(4-methylphenyl)sulfonyl]-3,6-dihydropyridin-2(1H)-one (4a). Compound **1a** (1.00 g, 5.2 mmol) and tetrabutylammonium iodide (0.10 g) were added to a solution of sodium *p*-toluenesulfinate dihydrate (2.44 g, 11.2 mmol) in 50% aqueous ethanol (15 ml). The reaction mixture was boiled under reflux for 2 h, cooled, and the precipitated solid was filtered off. After crystallization from 50% ethanol compound **4a** (1.07 g) was obtained; mp 231-232°C.

4,5,6-Trimethyl-3-[(4-methylphenyl)sulfonyl]-3,6-dihydropyridin-2(1H)-one (4b) was obtained analogously to compound **4a** from a mixture of the *syn* and *anti* isomers of compound **1b** (0.153 g, 0.83 mmol), sodium *p*-toluenesulfinate dihydrate (0.295 g, 1.35 mmol), and KI (0.276 g) in alcohol (10 ml), and boiling for 24 h. The reaction mixture was evaporated, chloroform (5 ml) added, the salt was filtered off, and the product purified by column chromatography on silica gel with a solvent gradient of $CHCl_3 \rightarrow CHCl_3$–AcOEt–EtOH, 6:3:1. A mixture of *cis*- and *trans*-**4b** (0.104 g) was obtained; mp 198-203°C.

4-Methyl-6-phenylpyridin-2(1H)-one (6c) was obtained analogously to compound **4a** from compound **1c** by boiling for 6 h. The product was purified by recrystallization from a mixture of ethyl acetate–benzene. Mp 159-160°C.

4,6-Diphenylpyridin-2(1H)-one (6d). Potassium hydroxide (0.20 g) was added to a solution of compound **2d** (0.20 g, 0.474 mmol) in a mixture (20 ml) of benzene and alcohol (1:5). The reaction mixture was boiled for 1 h, evaporated, and diluted with water. The precipitated solid was filtered off, and crystallized from alcohol. Compound **6d** (0.102 g) was obtained; mp 211-212°C (lit. 211-212°C [10]).

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