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A New Synthesis of 3-Phenyl-5,6-Dihydropyridin-2(1*H*)-ones

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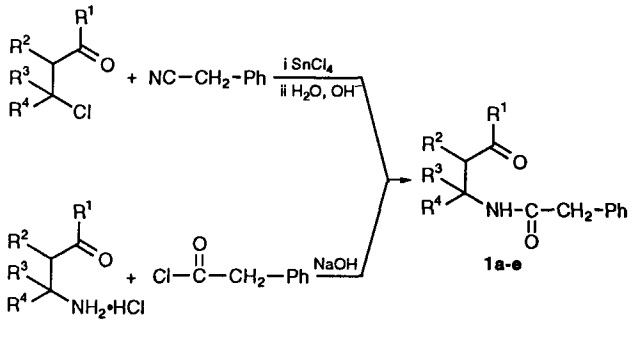
A new method has been developed for the synthesis of 5,6-dihydropyridin-2(1*H*)-ones by cyclization of *N*–3-oxoalkylamides in the presence of bases.

Well-known and accessible *N*–3-oxoalkylamides[1–7] have not yet found wide application in the synthesis of heterocyclic compounds. These substances have mostly been used as 4*H*-1,3-oxazine precursors. On the other hand, a corresponding carbanion can be generated from *N*-3-oxoalkylamide by deprotonation of the α-carbamoyl atom, and intramolecular attack on this intermediate at the carbonyl group may lead to formation of the cyclic amide. In order to examine this route of cyclization, we prepared *N*-3-oxoalkylamides of phenylacetic acid **1a–e**, according to the described procedures, from 1,3-chloroketones and benzyl cyanide (method A) and from 1,3-aminoketones by acylation (method B).†



a $R^1 = R^2 = Me$, $R^3 = R^4 = H$
b $R^1 = R^3 = R^4 = Me$, $R^2 = H$
c $R^1 = R^2 = R^3 = R^4 = Me$
d $R^1 = Et$, $R^2 = R^3 = R^4 = Me$
e $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Ph$

† *Experimental procedure.* N-3-*Oxoalkylphenylacetamides* **1a–e**. *Method A.* **1b,d,e** were prepared according to refs. 4 and 5. 4-Chloro-4-phenylbutan-2-one for the synthesis of **1e** was obtained by saturation of a solution of benzylideneacetone in absolute $CHCl_3$ with dry hydrogen chloride and was used without isolation.

Method B. **(1a,c)**. A three-necked flask equipped with two funnels and a magnetic stirrer was charged with 0.145 mol 1,3-aminoketone hydrochloride, 10 ml water and 35 ml ether. A solution of 0.29 mol NaOH in 18 ml of water and 0.15 mol phenylacetyl chloride were simultaneously added dropwise at −10 °C. The reaction mixture was stirred for 0.5 h at room temperature, 10 ml water was added to dissolve precipitated NaCl and the aqueous layer was extracted by $CHCl_3$ (3 × 25 ml). The combined organic phases were dried and evaporated and the residue purified by column chromatography (SiO_2/$CHCl_3$:ethyl acetate = 95:5).

3-*Phenyl*-5,6-*dihydropyridin*-2(1H)-*ones* **2a–e**. 2 mmol of an appropriate *N*-3-oxoalkylphenylacetamide was refluxed in 50 ml 10% KOH ethanolic solution under a stream of nitrogen for a certain time (Table 1). The reaction mixture was then cooled, neutralized with 10% aqueous HCl and evaporated *in vacuo*. The residue was extracted by $CHCl_3$ (2 × 15 ml), the extracts concentrated and the crude reaction product was purified by recrystallization. The recyclization of **3** was carried out in the same manner. The refluxing of 0.303 g (3.53×10^{-4} mol) **3** in 10 ml 10% KOH ethanolic solution followed by column chromatography (SiO_2/$CHCl_3$:EtOAc = 95:5) yielded 0.089 g (96%) of **2e**.

3,6-*Diphenylpyridin*-2(1H)-*one* **4**. Compound **2e** (0.600 g) and 0.20 g 10% Pd/C in dry xylene were refluxed for 1 h and the reaction mixture was filtered and cooled. The precipitated product was separated and recrystallized to give 0.470 g (79.5%) **4**, m.p. 224–225 °C (ethanol). IR data: ν/cm^{-1} ($CHCl_3$):1633 (CONH), 1615 (C=C); ^1H NMR data: δ ($CDCl_3$) 7.80–7.20 (m, 10H, 2Ph), 6.55 (s, 1H, 5–H), 2.00 (s, 3H, CH_3).

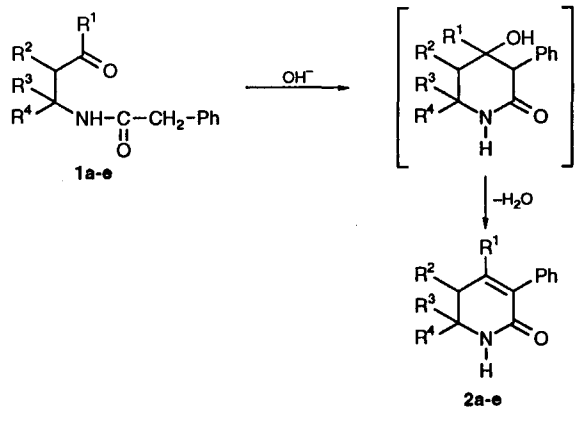
Table 1 Some data for the *N*-3-oxoalkylamides and 5,6-dihydropyridin-2(1*H*)-ones.

Compound	M.p./°C	Yield(%)	Method, **1a–e** (τ/h, **2a–e**)	^{1}H NMR (δ); *J*/Hz	IR,ν/cm^{-1}		
					C=O	NHCO	NH
1a	*a*	25.2	B	7.73–7.56 (m, 5H), 6.58 (br. s, 1H, NH), 3.89 (s, 2H), 3.80–3.60 (m, 2H), 3.30–3.10 (m, 1H), 2.47 (s, 3H), 1.44 (d, 3H, ^3J=7.0)	1720	1685	3420
1b	82–83 (hexane)	82.0	A	7.13–6.98 (m, 5H), 5.86 (br. s, 1H, NH), 3.19 (s, 2H), 2.48 (s, 2H), 1.51 (s, 3H), 1.13 (s, 6H)	1720	1685	3410
1c	43–44 (hexane)	97.5	B	7.46–7.37 (m, 5H), 6.03 (br. s, 1H, NH), 3.54 (s, 2H), 3.26 (q, 1H, ^3J=7.0), 2.19 (s, 3H), 1.44 (s, 3H), 1.04 (d, 3H, ^3J=7.0)	1715	1680	3410
1d	82–83 (hexane)	35.9	A	7.32–7.16 (m, 5H), 5.89 (br. s, 1H, NH), 3.40 (s, 2H), 3.17 (q, 1H, ^3J=7.0), 2.38 (q, 2H, ^3J=7.1), 1.31 (s, 3H), 1.23 (s, 3H), 0.91 (t, 3H, ^3J=7.1), 0.89 (d, 3H, ^3J=7.0)	1710	1680	3420
1e	144–145 (ethanol)	63.0	A	7.40–7.20 (m, 10H), 6.63 (br. d, 1H, ^3J=8.5, NH), 5.41 (m, 1H, ^3J=8.5, ^3J=6.0), 3.56 (s, 2H), 3.03 (d. d, 1H, ^2J=17.0 ^3J=6.0), 2.80 (d. d, 1H, ^2J=17.0, ^3J=6.0), 2.00 (s, 3H)	1730	1680	3430
2a	132–134 (hexane)	87.2	(0.75)	7.32–7.05 (m, 5H), 6.47 (br. s, 1H, NH), 3.57 (d, d, 1H, ^2J=12.4, ^3J=5.2), 3.03 (m, 1H, ^2J=12.4, ^3J=3.8, ^3J=5.2), 2.33 (m, 1H), 1.70 (s, 3H), 1.16 (d, 3H, ^3J=7.0)	—	1665	3420
2b	179–180 (ethanol)	93.0	(0.01)	7.40–7.26 (m, 5H), 5.97 (br. s, 1H, NH), 2.36 (s, 2H), 1.46 (s, 3H), 1.29 (s, 6H)	—	1665	3390
2c	147–148 (hexane)	92.0	(0.4)	7.32–7.02 (m, 5H), 5.38 (br. s, 1H, NH), 2.05 (q, 1H, ^3J=6.5), 1.74 (s, 3H), 1.32 (s, 3H), 1.16 (s, 3H), 1.09 (d, 3H, ^3J=6.5)	—	1665	3390
2d	151–152 (hexane)	89.0	(2.5)	7.37–7.04 (m, 5H), 5.31 (br. s, 1H, NH), 2.03 (q, 2H, ^3J=7.3), 2.01 (q, 1H, ^3J=7.3), 1.32 (s, 3H), 1.19 (s, 3H), 1.09 (d, 3H, ^3J=7.3), 0.92 (t, 3H, ^3J=7.3)	—	1680	3400
2e	149–150 (ethanol)	89.9	(0.2)	7.30–7.00 (m, 10H), 5.85 (br. s, 1H, NH), 4.83 (m, 1H, ^3J=9.0, ^3J=7.0), 2.78 (d.d, 2H, ^2J=17.0, ^3J=9.0), 2.55 (d. d, 1H, ^2J=17.0, ^3J=7.0), 1.79 (s, 3H)	—	1667	3400

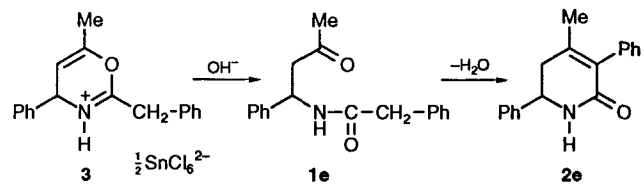
[a] Liquid.

While investigating the cyclization of **1a–e** in boiling 1–10% KOH ethanolic solution, it was observed that 3-phenyl-5,6-dihydropyridin-2(1*H*)-ones **2a–e**, which otherwise are very hard to obtain, were formed in high (87–93%) yields. The reaction time was observed to vary from 1–2 min (**1b**) to 2.5 h (**1d**) and depended on the effective volume of the substituents in the oxoalkyl fragment of the molecule. Enlarging the effective volume of R^1 and R^2 substituents is found to slow down the cyclization rate; this becomes clear when comparing the reaction times of **1b,c** and **1c,d**. The effect is probably caused by steric hindrance in the process of ring closure. On the contrary, enlarging the effective volume of R^3 and R^4 substituents is shown to increase the reaction rate, as established by comparison of **1a** and **1c**, due to the *gem*-dimethyl effect known for the substituted cyclohexanes.[8]

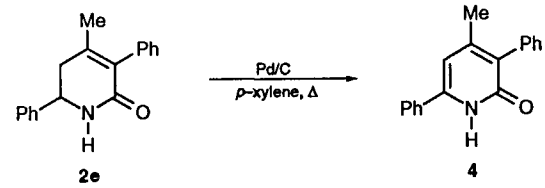
In our previous publication we reported that a similar influence of the substituents was observed while investigating heterocyclization of *N*-3-oxoalkyldithiocarbaminic acids.[9]



It was found that the proposed route for the synthesis of 3-phenyl-5,6-dihydropyridin-2(1*H*)-ones made it possible to use 4*H*-1,3-oxazinium salts as starting materials. The latter were hydrolysed into *N*-3-oxoalkylamides under the reaction conditions. Bis(2-benzyl-6-methyl-4-phenyl-4*H*-1,3-oxazinium)hexachlorostannate **3**, prepared according to the procedure reported by Schmidt,[5] was found to give **2e** in 96% yield under reflux in 1–10% KOH ethanolic solution. This transformation of **3** to **2e** seems to be an isomerisation recyclization that formally occurs in a similar manner to pyrimidinium salt rearrangement in the presence of bases.[10]



Dihydropyridin-2(1*H*)-ones were shown to readily dehydrogenate. Thus, refluxing of **2e** with 10% Pd/C in xylene gave 4-methyl-3,6-diphenylpyridin-2(1*H*)-one **4** in high yield.



We have therefore investigated the influence of structural factors on the cyclization of *N*-3-oxoalkylphenylacetamides and developed new preparative methods for the synthesis of 3-phenyl-substituted 5,6-dihydropyridin-2(1*H*)-ones. It was proved that accessible *N*-3-oxoalkylphenylacetamides could be available precursors for the synthesis of 3-phenyl-substituted 5,6-dihydropyridin-2(1*H*)-ones and pyridin-2(1*H*)-ones.

References

1 S. Gabriel and P. Elfeldt, *Chem. Ber.*, 1892, **24**, 3213.
2 H. E. Zaugg, *Synthesis*, 1984, **2**, 85–110, 181–212.
3 R. Ikeda, Y. Terao and M. Sekiya, *Chem. Pharm. Bull.*, 1981, **29**, 4,1156.
4 M. Lora-Tamayo, R. Madronero, G. Garsia Munos and H. Leipprand, *Chem. Ber.*, 1964, **97**, 2234.
5 R. Schmidt, *Chem. Ber.*, 1965, **98**, 334.
6 J. Jochims, R. Abu-El-Halawa, M. Glocker, L. Zsolnai and G. Huttner, *Synthesis*, 1990, **9**, 763.
7 A. Shastin and E. Balenkova, *Zh. Org. Khim*, 1984, **20**, 1357 [*J. Org. Chem. USSR (Engl. Transl.)*, 1984, **20**, 1235].
8 N. Allinger and V. Zalkov, *J. Org. Chem.*, 1969, **25**, 701.
9 A. Fyssiuk, A. Moskovkin, I. Miroshnitchenko, N. Botlicov and B. Unkovsky, *Khim. Geterotsikl. Soedin*, 1992, **7**, 985 [*Chem. Heterocycl. Compd. (Engl. Transl.)*, 1992, **7**, 823].
10 R. Sagitullin, A. Kost and G. Danagulyan, *Tetrahedron Lett.*, 1978, **43**, 4135.

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