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Synthesis of 5,6-Dihydropyridin-2(1H)-ones, 1,5,6,8,8a-Hexahydroisoquinolin-3(2H)-ones and 4a,5,6,7,8,8a-Hexahydroquinolin-2(1H)-ones by Intramolecular Wittig Reaction

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Abstract: A new, universal and diastereospecific method has been developed for the synthesis of 5,6-dihydropyridin-2(1H)-ones, 1,5,6,8,8a-hexahydroisoquinolin-3(2H)-ones and 4a,5,6,7,8,8a-hexahydroquinolin-2(1H)-ones (**4**) based on the intramolecular Wittig cyclization of the triphenyphosphonium salts **2** derived from the N-(3-oxoalkyl)–chloroacetamides **1**.

Keywords: 5,6-dihydropyridin-2(1H)-one, Wittig reaction, intramolecular cyclization, N-(3-oxoalkyl)chloroacetamide.

Introduction

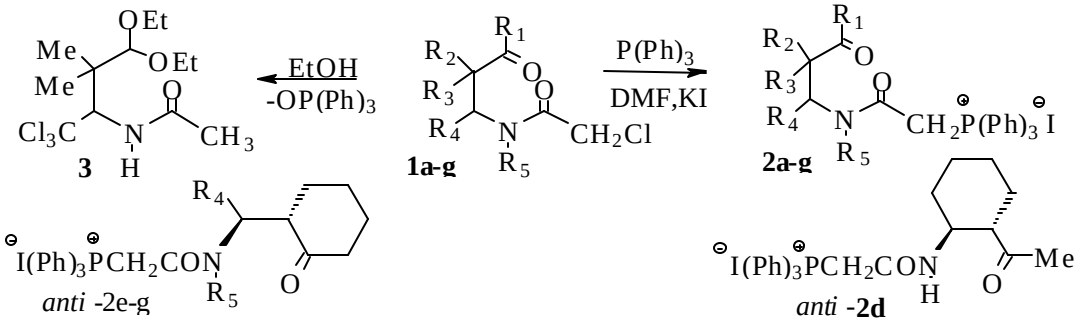
5,6-Dihydropyridin-2(1H)-ones possess significant importance due to both their biological activity [1] and their utilization in the synthesis of more complex compounds [2]. The main method for their synthesis is dehydrogenation of δ-valerolactams, but this route is limited by the availability of the required starting materials [1,3]. Although the Wittig reaction is widely used for the synthesis of heterocycles [4], the cyclization of N-(3-oxoalkyl)amides derivatives using this reaction has not been investigated until now. N-(3-Oxoalkyl)amides can be obtained by a number of synthetic methods [5-7], including diastero- and enantioselective ones [8], that makes them very promising precursors for the synthesis of 5,6-dihydropyridin-2(1H)-ones. The development

of the methodology for pyrid-2-ones and the formation their hydrogenated derivatives formation led to our interest in this reaction [9].

Results and Discussion

It is known that α-haloacetamides can be reduced in some cases when reacted with PPh_3 [10]. The interaction of compounds **1a-g** with PPh_3 under heating in ethanolic or dioxane [11] solutions proceeds with low yields and in some cases is accompanied by the formation of side products. For instance, the acetal **3** has been separated as a side product by reaction of compound **1c** with PPh_3 in ethanolic solution in presence of KI. We succeeded in finding of reaction conditions which afforded phosphonium salts **2a-g** in 80-90 % yields (Scheme 1).

Scheme 1



a) R_1=Me, R_2=R_3=R_5=H, R_4= Ph; **b**) R_1=R_4=Ph, R_2=R_3=R_5=H;
c) R_1=R_5=H, R_2=R_3=Me, R_4=CCl_3; **d**) R_1=Me, R_2=R_5=H, R_3+R_4= –$(CH_2)_4$–;
e) R_1+R_2= –$(CH_2)_4$–, R_3=R_5=H, R_4=Ph; **f**) R_1+R_2= –$(CH_2)_4$–, R_3=H, R_4=Ph, R_5= Me;
g) R_1+R_2= –$(CH_2)_4$–, R_3=R_5=H, R_4=CCl_3

5,6-Dihydropyridin-2(1H)-ones **4a-c** have been obtained in high yields from compounds **2a-c** by treatment with an equimolar amount of methanolic sodium methoxide at room temperature. Cyclization of the *anti*-**2d-g** phosphonium salts under the same conditions proceeds diasterospecifically and leads to 1,8a-*trans*-1,5,6,7,8,8a-hexahydroisoquinolin-3(2H)-ones (**4e-g**) and 4a,8a-*trans*-4a,5,6,7,8,8a-hexa-hydroquinolin-2(1H)-one (**4d**) (Scheme 2, Tables 1 and 2).

Scheme 2

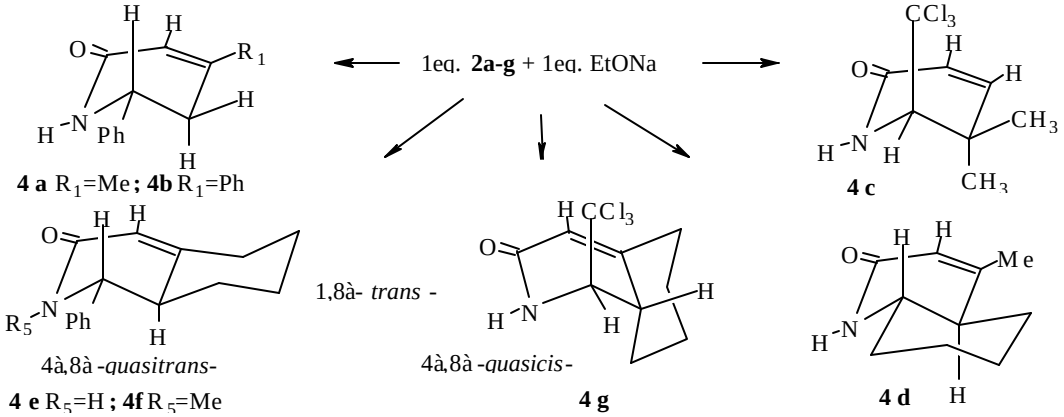


Table 1. Melting Points and Yields of Compounds **4a-g**.

Compound	**4a**	**4b**	**4c**	*trans*-**4d**	*trans*-**4e**	*trans*-**4f**	*trans*-**4g**
m.p. °C	135-6[1)]	>210 decom	147-8[1)]	176-7[1)]	183-4[1)]	Oil	172-3[1)]
Yield %	94	29[2)]	96	97	91	85	91

[1] sealed capillary, compound sublimes; [2] unstable compound, decomposes in air

Table 2. ^{1}H-NMR Data of Compounds **4a-g**.

Compound	**Chemical shifts d (ppm) and coupling constants J (Hz)**						
	=C-H (^{3}J, ^{4}J)	**R$_1$(^{3}J, ^{4}J)**	**R$_2$(^{2}J, ^{3}J)**	**R$_3$(^{2}J, ^{3}J)**	**R$_4$**	**NCH (^{3}J, ^{4}J)**	**R$_6$**
4a	5.79 m (1.5,1.5,1.5)	1.93 m (1.5,1.0)	2.58-2.40 m		7.36 s	4.72 m (9.0, 7.5, 0.6)	5.70 s
4b	5.53 d (3.8)	7.30-7.01 m	2.85 dd (16.1,7.0)	2.67 dd (16.1,10.1)	7.30-7.01 m	3.93 m (10.1, 7.0, 3.8)	8.10 m
4c	5.86 dd (10.1, 2.0)	6.30 dd (10.1, 1.3)	1.57 s	1.43 s	–	3.97 dd (4.6,1.3)	7.37 s
trans-**4d**	5.72 m (1.6, 1.6, 1.6)	1.86 dd (1.6,1.6)	2.17-1.02 m			3.15 m (12.4, 10.8, 3.6)	6.47 s
trans-**4e**	5.76 dd (2.1, 2.1, 2.1)	2.58-1.06 m			7.37 s	4.25 d (11,1)	5.39 s
trans-**4f**	5.82 dd (2.5, 2.5)	2.53-0.60 m		3.10-2.94 m	7.30-7.15 m	4.42 d (8.2)	2.82 s
trans-**4g**	5.70 dd (1.4, 1.4, 1.4)	2.47-1.23 m		2.80-2.72 m	–	3.82 dd (3.5,1.3)	7.00 s

When an excess of the base is used, an epimerisation of the α-carbonyl asymmetric center occurs and consequently a mixture of *cis*- and *trans*-**4d-g** is obtained. The spin-spin coupling constants of the C$_{(1)}$-H (^{3}J$_{1,8a}$ 8.2-11.1 Hz) C$_{(4)}$-H (^{4}J$_{4,8a}$ 2.1-2.5 Hz) hydrogen atoms shows that *trans*-**4e,f** compounds exist in a conformation with an equatorial arrangement of the C$_{(1)}$-Ph substituent and a quasitransoidal ring junction (Table 1). At the same time, in compound *trans*-**4g** the C$_{(1)}$-CCl$_3$ substituent arranges axially and the rings are joined quasicisoidly (^{3}J$_{1,8a}$ 1.3, ^{3}J$_{1,NH}$ 3.5, ^{4}J$_{4,8a}$ 1.4 Hz). The structures of all the compounds obtained have been confirmed by ^{13}C- and ^{1}H-NMR spectroscopy and elemental analysis. Assignment of ^{1}H-NMR spin-spin constants was performed using COSY ^{1}H-^{1}H 2D spectroscopy.

Conclusions

We have developed a new, universal and diastereospecific synthetic method which affords 5,6-dihydropyridin-2(1H)-ones, 1,8a-*trans*-1,5,6,7,8,8a-hexahydroisoquinolin-3(2H)-ones and 4a,8a-*trans*-4a,5,6,7,8,8a-hexahydroquinolin-2(1H)-ones in high yields from versatile N-(3-oxoalkyl)chloro-acetamides.

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Experimental

General

^{1}H-NMR spectra ($CDCl_3$ solutions) were obtained using a Bruker AC-200 NMR spectrometer and were recorded at 200 MHz. N-(3-Oxoalkyl)amides **1a** (56%, m.p. 90-91°C); **1b** (81 %, m.p. 104-105°C) and *anti*-**1e** (14%, m.p.156-157°C) were obtained from the α,β-unsaturated ketones and chloroacetonitrile [6,9]; compounds **1c** (69%, m.p. 109-110°C) and *anti*-**1g** (55%, m.p. 74-75°C) — by reaction of $Cl_3CCH{=}NCOCH_2Cl$ with enamines [7]; compound *anti*-**1d** (88%, m.p.124-125°C) — by acylation of 1-(*trans*-2-aminocyclohexyl)-1-ethanone with chloroanhydride of chloroacetic acid [9]; compound **1f** (19%, m.p. 201-202°C) — by interaction of (1-cyclohexenyloxy)(trimethyl)silane with PhCH=NMe and $ClCH_2COCl$ in the presence of $TiCl_4$ [9]. Compounds *anti*-**1e**, *anti*-**1f** were separated by column chromatography on silica (eluent 95:5 $CHCl_3$–EtOAc).

Typical experimental procedure for the synthesis of salts **2a–g**.

KI (2.52 mmol) was added to a solution of **1a-g** (2.50 mmol) and PPh_3 (2.64 mmol) in DMF at 0 °C. The reaction mixture was kept at 0-7°C for 2-3 days and then poured into a 30 % aqueous solution of KI (30 mL). The reaction was monitored by TLC. After adding water (10 mL) the residue was extended until crystallization ocurred. The product was filtered off, dried over P_4O_{10}, recrystallized from chloroform-ether and dried again. Yields, melting points: **2a** - 74%, 191-192°C; **2b** - 93%, 119-120°C; **2c** - 78%, 203-205°C; *anti*-**2d** - 93%, 187-188°C; *anti*-**2e** - 83%, 200-201°C; *anti*-**2f** - 78%, 160-161°C; *anti*-**2g** - 89%, 159-150°C.

Typical experimental procedure for the syntheses of **4a-g**.

An equimolar amount of sodium methoxide (concentration: 2.5-3 mg Na/mL of methanol) was added dropwise to a solution of 0.40 g of phosphonium salt **2a-g** in methanol (10 mL) at 18-25 °C. The reaction

mixture was kept at this temperature for 12 h and afterwards the solvent was evaporated under reduced pressure. The residue was treated with benzene, filtered and filtrate was evaporated again. Compounds **4a-g** were separated by column chromatography on silicagel. Eluents: **4c** (2:1 CCl_4 - AcOEt); **4g** (2:1 CCl_4 - AcOEt,); **4a,e** (gradient of *n*-C_6H_{14} → 1:1 *n*-C_6H_{14} - DME); **4d** (gradient of $CHCl_3$ → 1:1 $CHCl_3$ - AcOEt, 1:1). Compound **4b** was separated by flash-chromatography on a dry column (silica, $CHCl_3$).

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Sample Availability: Available from the authors.