

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

Alexander S. Fisyuk* and Nikolai V. Poendaev

Department of Organic Chemistry, Omsk State University, Omsk, 644077, Russian Federation.
Tel. 7-3812-64-24-47.

* Author to whom correspondence should be addressed; e-mail: fis@univer.omsk.su

Received: 7 May 2001; in revised form: 15 January 2002 / Accepted: 16 January 2002 / Published: 28 February 2002

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 triphenylphosphonium 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

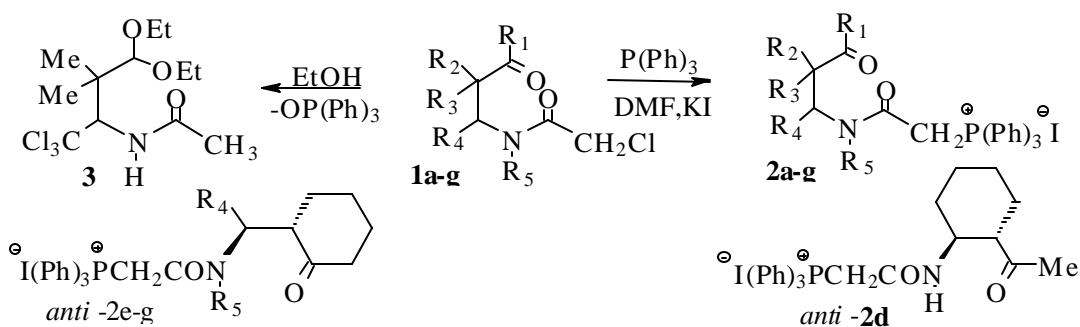
5,6-Dihydropyridin-2(1H)-ones possess significant importance due to both their biological activity [1] and their utilization in the synthesis of more complex compounds [2]. The main method for their synthesis is dehydrogenation of δ -valerolactams, but this route is limited by the availability of the 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 diastereo- 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) $\text{R}_1=\text{Me}$, $\text{R}_2=\text{R}_3=\text{R}_5=\text{H}$, $\text{R}_4=\text{Ph}$; b) $\text{R}_1=\text{R}_4=\text{Ph}$, $\text{R}_2=\text{R}_3=\text{R}_5=\text{H}$;
 c) $\text{R}_1=\text{R}_5=\text{H}$, $\text{R}_2=\text{R}_3=\text{Me}$, $\text{R}_4=\text{CCl}_3$; d) $\text{R}_1=\text{Me}$, $\text{R}_2=\text{R}_5=\text{H}$, $\text{R}_3+\text{R}_4=-(\text{CH}_2)_4-$;
 e) $\text{R}_1+\text{R}_2=-(\text{CH}_2)_4-$, $\text{R}_3=\text{R}_5=\text{H}$, $\text{R}_4=\text{Ph}$; f) $\text{R}_1+\text{R}_2=-(\text{CH}_2)_4-$, $\text{R}_3=\text{H}$, $\text{R}_4=\text{Ph}$, $\text{R}_5=\text{Me}$;
 g) $\text{R}_1+\text{R}_2=-(\text{CH}_2)_4-$, $\text{R}_3=\text{R}_5=\text{H}$, $\text{R}_4=\text{CCl}_3$

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 diastereospecifically 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

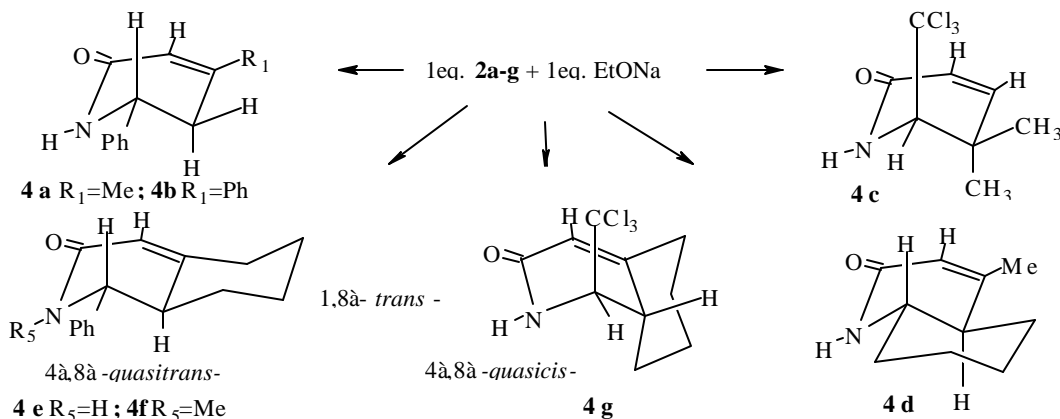


Table 1. Melting Points and Yields of Compounds **4a-g**.

Compound	4a	4b	4c	<i>trans-4d</i>	<i>trans-4e</i>	<i>trans-4f</i>	<i>trans-4g</i>
m.p. °C	135-6 ¹⁾	>210 decomp	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. ¹H-NMR Data of Compounds **4a-g**.

Compound	Chemical shifts δ (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
<i>trans-4d</i>	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
<i>trans-4e</i>	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
<i>trans-4f</i>	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
<i>trans-4g</i>	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 (³J_{1,8a} 8.2-11.1 Hz) C₍₄₎-H (⁴J_{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₎-CCl₃ substituent arranges axially and the rings are joined quasicisoidly (³J_{1,8a} 1.3, ³J_{1,NH} 3.5, ⁴J_{4,8a} 1.4 Hz). The structures of all the compounds obtained have been confirmed by ¹³C- and ¹H-NMR spectroscopy and elemental analysis. Assignment of ¹H-NMR spin-spin constants was performed using COSY ¹H-¹H 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.

Acknowledgments

We are grateful to the Russian Foundation for Basic Research (grant No 99-03-33013) and Russian Ministry of Education (grant No E00-5.0-282) for financial support of this work.

Experimental

General

¹H-NMR spectra (CDCl₃ 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 Cl₃CCH=NCOCH₂Cl 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 ClCH₂COCl in the presence of TiCl₄ [9]. Compounds *anti*-**1e**, *anti*-**1f** were separated by column chromatography on silica (eluent 95:5 CHCl₃-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 PPh₃ (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 occurred. The product was filtered off, dried over P₄O₁₀, 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 CCl₄ - AcOEt); **4g** (2:1 CCl₄ - AcOEt); **4a,e** (gradient of *n*-C₆H₁₄ → 1:1 *n*-C₆H₁₄ - DME); **4d** (gradient of CHCl₃ → 1:1 CHCl₃ - AcOEt, 1:1). Compound **4b** was separated by flash-chromatography on a dry column (silica, CHCl₃).

References

1. Fisyuk, A. S.; Bundel, Yu. G. 5,6-Dihydropyridin-2(1H)-ones and 5,6-dihydropyridine-2(1H)-thiones. *Chem. Heterocycl. Compd. (N. Y.)*, **1999**, *35*, 125-145.
2. Davis, D.A.; Gribble, G.W. A regioselective Diels-Alder synthesis of ellipticine. *Tetrahedron Lett.*, **1990**, *31*, 1081-1084.
3. Amat, M.; Llor, N.; Bosch, J.; Solans, X. Preparation of Enantiopure 6-(3-Indolyl)-2-piperidones and Conjugate Additions to a 3,4-Didegido Derivative. *Tetrahedron*, **1997**, *53*, 719-730.
4. Heron, B.M. Heterocycles from Intramolecular Wittig, Horner and Wadsworth-Emmons Reactions. *Heterocycles*, **1995**, *41*, 2357-2385.
5. Marson, Ch.M.; Fallah, A. Catalytic C-amidoalkylations: synthesis of β-amido aldehydes by three-component condensations. *Chem. Commun.*, **1998**, 83-84.
6. Lora-Tamayo, M.; Madroñero, R.; Leipprand, H. Beitrag zum chemischen Verhalten der 4H-1,3-Oxazine. *Chem. Ber.*, **1964**, *97*, 2244-2250.
7. Ikeda, K.; Terao, Y.; Sekiya, M. New Syntheses of α-N-Alkylacetamidomethylated Carbonyl Compounds. *Chem. Pharm. Bull.*, **1981**, *29*, 1156-1159.
8. Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W.; Reuter, H.; Puff, H. Synthesis of diastereo- and enantiomerically pure α-amino-γ-oxo acid esters by reaction of acyliminoacetates with enamines derived from 6-membered ketones. *Tetrahedron*, **1985**, *41*, 1693-1701.
9. Fisyuk, A.S.; Vorontsova, M.A.; Sagitullin, R.S. A New Synthesis of 3-Phenyl-5,6-Dihydropyridin-2(1H)-ones. *Mendeleev Commun.*, **1993**, 249-251.
10. Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Kutsuna, T.; Saigo, K. Triphenylphosphine/ Germanium (IV) Chloride Combination: A New Agent for the Reduction of α-Bromo Carboxylic Acid Derivatives. *Tetrahedron Lett.*, **1998**, *39*, 1203-1206.
11. Fisyuk, A. S.; Poendaev, N. V.; Bundel, Y.G. A New Route for Synthesis of 5,6-Dihydropyridine-2(1H)-ones, Pyridones-2 and (4-Hydroxy-2-oxopiperidyl-3)pyridinium chlorides by Intramolecular Cyclization of N-3-Oxoalkylchloroacetamides Derivatives. *Mendeleev Commun.*, **1998**, 12-14.
12. Zaugg, H. E. α-Amidoalkylation at Carbon: Recent Advances – Part II. *Synthesis*, **1984**, 181-211.

Sample Availability: Available from the authors.