Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 3-Oxo-2,3-Dihydroisoquinolines from Ethyl 2-Acylphenylacetates and Formamides

A. P. Venkov [a] & I. I. Ivanov [a]
[a] Department of Chemistry, University of Plovdiv, 4000, Plovdiv, Bulgaria
Published online: 23 Sep 2006.

To cite this article: A. P. Venkov & I. I. Ivanov (1994) Synthesis of 3-Oxo-2,3-Dihydroisoquinolines from Ethyl 2-Acylphenylacetates and Formamides, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 24:8, 1145-1150, DOI: 10.1080/00397919408011710

To link to this article: http://dx.doi.org/10.1080/00397919408011710

SYNTHETIC COMMUNICATIONS, 24(8), 1145-1150 (1994)

SYNTHESIS OF 3-OXO-2,3-DIHYDROISOQUINOLINES FROM ETHYL 2-ACYLPHENYLACETATES AND FORMAMIDES

A.P. Venkov* and I.I. Ivanov

Department of Chemistry, University of Plovdiv, 4000 Plovdiv, Bulgaria

ABSTRACT: 1- and 1,3-substituted 3-oxo-2,3-dihydroisoquinolines 4 are obtained from ethyl 2-acylphenylacetates 3 and formamides.

3-Oxo-2,3-dihydroisoquinolines are of considerable interest from the structural point of view and for the synthesis of tetrahydroisoquinoline alkaloids.[1-4] They show reactivity expected of the ortho-quinoid tautomers, participating readily in Diels-Alder and photodimerisation reactions.[1,4,7] Some of them are known as pharmacologically active and display a cardiovascular, bactericidal activity or after a cycloaddition reactions have been transformed to adducts useful as central nervous system active agents.[2,4,5]

Some 3-oxo-2,3-dihydroisoquinolines have been obtained from 2-hydroxymethyl arylacetic acid lactones via 2-formimino-N,N-dimethyl arylacetamides[4] and from phenylacetic acids and N-alkylbenzamides.[8]

*To whom correspondence should be addressed.

Their synthesis has been carried out also from 2-acyl-4,5-dimethoxy-phenylacetic acid, its esters[6] or lactones[1,2] and ammonia or alkyl amines but the reaction is limited and usually the corresponding 2-hydroxy-1,4-naphthaquinones[6] or aminonaphthols[3] are obtained.

Looking for the preparation of a new pharmacologically interesting 3-oxo-2,3-dihydroisoquinolines it was obvious that no generally useful preparative method is available.

In a search of a new approach for thier synthesis we found that they can be obtained in a very good yields from ethyl 2-acylphenylacetates 3 and formamides instead of amines.

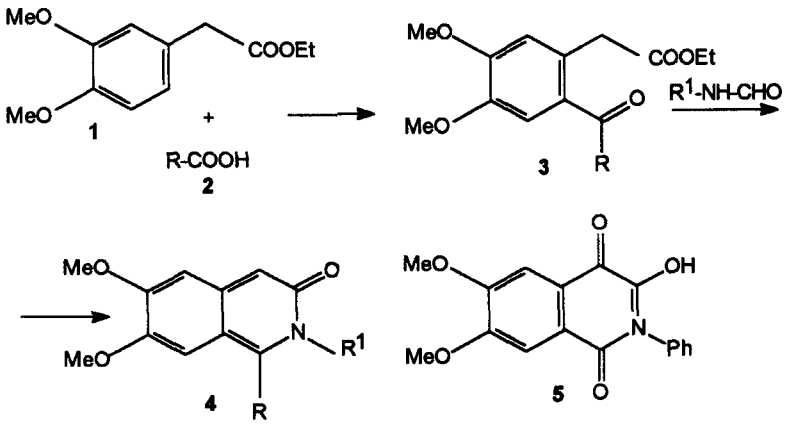
Some methyl 2-acylphenylacetates 3 have been obtained from methyl 3,4-dimethoxyphenylacetate and acyl chlorides in the presence of anh.$AlCl_3$ but in a poor yields (30-51%).[6]

We found that different ethyl 2-acyl-4,5-dimethoxyphenylacetates 3 can be obtained from ethyl 3,4-dimethoxyphenylacetate and carboxylic acids 2 and that way was possible to prevent the preferable intermolecular acylation of 3,4-dimethoxyphenylacetic acid.

Ethyl 2-acylphenylacetates 3 were obtained in a very good yields by acylation of ethyl 3,4-dimethoxyphenylacetate with carboxylic acids in dichloroethane in the presence of P_2O_5 (Table, 3a-g).

The reaction of ethyl 2-acyl-4,5-dimethoxyphenylacetates 3 with formamides to the corresponding 3-oxo-2,3-dihydroisoquinolines 4 proceeds in acetic acid at reflux for 6 h (Table, 4a-j).

It was found that the presence of AcOH is important for the reaction of ethyl 4,5-dimethoxy-2-acylphenylacetates 3 with formamides leading to 3-oxo-2,3-dihydroisoquinolines 4 and especially for those with 2-phenyl-acetyl group. For example, the reaction of 3e and 3f in formamide for 1 h at 140°C led only to the



5a Ph = C_6H_5, **5b** Ph = 4-O_2N-C_6H_4

Table: Ethyl 2-acyl-4,5-dimethoxyphenylacetates 3 and 3-oxo-2,3-dihydroisoquinolines 4 prepared[9,10]

Entry	R	R^1	3 yield (%)	3 mp (°C)	4 yield (%)	4 mp (°C)
a	CH_3	H	84	94-95	89	212-213
b	$(CH_3)_2CH.CH_2$	H	86	76-78	56	193-196
c	C_6H_5	H	90	78-79	82	204-206
d	4-NO_2-C_6H_4	H	60	90-92	68	239-241
e	$C_6H_5CH_2$	H	62	73-75	54	212-214
f	4-NO_2-$C_6H_4.CH_2$	H	70	115-117	65	249-250
g	3,4$(CH_3O)_2C_6H_3CH_2$	H	80*	153-154	85	216-218
h	CH_3	CH_3	-	-	65	182-183
i	C_6H_3	CH_3	-	-	70	178-179

*Obtained from homoveratric acid in PPA, overnight at r.t. as described in the literature.[1]

corresponding 2-phenyl-3-hydroxy-5,7-dimethoxy-1,4-naphthaquinones 5a,b,.[6] However, the reaction of 3c only in formamide for 3 h at 180°C led to 4c in a yield of 80%.

EXPERIMENTAL

Ethyl o-acyl-4,5-dimethoxyphenylacetates (Table,3a-e) General Procedure:To a solution of ethyl 3,4-dimethoxy phenylacetate (5 mmol) and the corresponding carboxylic acid 2 (10 mmol) in dichloroethane (30 mL) is added P_2O_5 (5 g). The suspension is stirred vigorously for 8-10 h at room temperature, then water is added dropwise to the cooled mixture. The organic layer is washed with water (50mL), 10% aq.NaOH (30mL), water (50mL) and dried (Na_2SO_4). The products, after the removal of the solvent, are purified by recrystallization or column chromatography on a silica gel using Et_2O as eluent.

3-Oxo-2,3-dihydroisoquinolines (Table,4a-g);General Procedure: Ethyl 2-acyl-4,5-dimethoxyphenylacetate 3 (3 mmol) is dissolved in AcOH (15mL) and then formamide (3 mL) is added. The solution is stirred for 6 h at reflux, then cooled and water (50mL) is added. The mixture is extracted with $CHCI_3$ (3x20mL) and the combined organic layer is washed with water (3x50mL), aq. Na_2CO_3 (2x25mL), water, then dried (Na_2SO_4). The products, after the removal of the solvent are purified by recrystallization (EtOH) or column chromatography on a neutral AI_2O_3, using CH_2CI_2, $CHCI_3$, MeOH as eluents. For the reaction of 3 with N-mehtylformamide in AcOH (Table, 3h-i) the ratio is 1 mmol: 2 mL: 2 mL.

2-Phenyl-3-hydroxy-6,7-dimethoxy-1,4-naphthaquinone 5a and 2-(4-Nitrophenyl)-3-hydroxy-5,7-dimethoxy-1,4-naphthaquinone 5b: 3e or 3g (3mmol) in 5 mL formamide is heated for 1 h at 140°C. Water is added to a cooled mixture and extracted several times with $CHCI_3$. After the evaporation of the solvent the product is purified by recrystallization (EtOH) or column chromatography.

5a: yield 80%; mp 255°C (lit.[6] 255°C); ^{1}H-NMR (DMSO):3.75(s,6H), 7.22(s,5H), 7.26(s,2H); MS: m/z=310 (M^+); IR (NaCl): 3326 cm^{-1} (OH), 1646 cm^{-1} (CO).

5b: yield 62%; mp 309-310°C; ^{1}H-NMR (DMSO): 3.87(s,6H), 7.26 (s,2H), 7.48(d,2H,J=10 Hz), 8.10(d,2H,J=10 Hz); MS: m/z=355 (M^+); IR (NaCl): 3335 cm^{-1}(OH), 1659 cm^{-1} (CO).

REFERENCES AND NOTES

1. Elliot,I.W. J. Heterocyclic Chemistry, 1972, 9, 853.

2. Kreighbaum,W.E., Kavanaugh,W.F., Comer,W.T., J. Med.Chemistry, 1972, 13, 1131.

3. Kreighbaum,W.E., Kavanaugh,W.F., Comer,W.T., J.Heterocyclic Chemistry 1973, 3, 317.

4. McCorkindale,N.J., McCulloch,A.W., Tetrahedron, 1971, 4653.

5. Denayer,R. Ger. Offen 2,152,232 (1972); Chem.Abstr. 1972, 77, 48288.

6. Bentley,H.R.,Dawson,W.,Spring,F.S. J. Chem.Soc., 1952, 1763.

7. Jones,D.W. J. Chem.Soc.(C) 1969, 1729.

8. Venkov,A.P., Lukanov,L.M., Mollov,N.M., Synthesis, 1982, 486.

9. The ^{1}H-NMR spectra were recorded on a Tesla BS 587A 80 MHz spectometer in $CDCl_3$ or DMSO* (TMS). The data in ppm are as follows: 3a 1.25(t,2H,J=7). 2.57 (s,3H), 3.82(s,2H), 3.90(s,6H), 4.12(q,2H,J=7), 6.62 (s,1H), 7.15(s,1H); 3b 0.95(d,6H,J=6), 1.25 (t,3H,J=6), 2.12-2.43(m,1H), 2.75(d,2H,J=8), 3.88(s,2H), 3.95(s,6H), 4.13(q,2H,J=6),6.73(s,1H) 7.25(s,1H); 3c 1.12(t,3H,J=8), 3.75(s,3H), 3.80(s,2H), 3.92(s,3H),4.12(q,2H,J=8), 6.83 (s,1H), 6.92(s,1H), 7.40-7.83(m,5H); 3d 1.16(t,3H,J=6), 3.75(s,3H), 3.88 (s,2H), 3.95(s,3H), 4.12(q,2H,J=8), 6.85(s,2H), 7.92(q,2H,J=10), 8.28(d,2H, J=10); 3e 1.25(t,3H,J=6), 3.60(t,2H,J=10), 3.78(s,3H),3.85(s,2H),3.92(s,3H),

4.10 (q,2H,J=6), 4.18 (s,2H), 6.68(s,1H), 7.15(s,1H),7.18- 7.80(m,5H); 3f 1.10(t,3H,J=6), 3.72(s,3H),3.80(s,2H), 3.92(s,3H), 4.10(q,2H,J=6), 4.18 (s,2H), 6.75 (s,1H),6.80(s,1H), 6.92(s,1H),7.50(s,1H); 4a 1.92(s,3H), 2.50 (s,1H), 3.83(s,6H), 6.48(s,1H), 6.92(s,1H), 7.08 (s,1H); 4b 1.02(d,6H,J=8), 1.98-2.30(m,1H), 3.06 (d, 2H,J=7), 3.93(s,3H), 3.98(s,3H), 6.63(s,2H), 6.85 (s,1H); 4c 3.68(s,3H), 3.92(s,3H), 6.78 (s,1H), 7.08 (s,1H), 7.13(s,1H), 7.40-7.70(m,5H); 4d 3.53(s,6H), 6.82 (s,1H), 6.96(s,1H), 7.08(s,1H), 7.92(d,2H, J=8), 8.38(d,2H,J=8); 4e 1.93(s,1H), 3.78(s,3H), 3.85 (s,3H), 4.45(s,2H), 6.63(s,1H), 7.00(s,1H), 7.12 (s,1H), 7.25(s,5H); 4f 3.78(s,3H), 3.83(s,3H), 4.55 (s,2H),6.55 (s,1H), 6.98(s,1H), 7.20(s,1H), 7.46(d, 2H, J=8), 8.05(d,2H, J=8); 4g 3.62(s,3H), 3.65(s,3H), 3.80(s,3H), 3.85(s,3H), 4.50(s,2H), 6.70 (s,2H), 7.00 (s,2H), 7.15(s,1H), 7.45(s,1H); 4h 2.62(s,3H), 3.60 (s,3H), 3.75 (s,6H), 6.15(s,1H), 6.48(s,1H), 6.95(s,1H); 4i 3.38(s,3H), 3.50(s,3H), 3.80 (s,3H), 5.93(s,1H), 6.39(s,1H), 6.56(s,1H), 7.10-7.48 (m,5H).

*spectra of 4a-g in DMSO.

10. The M.S. spectra were recorded on a JMS-D300 spectrometer and m/z (M^+) are as follows: 3a 266($C_{14}H_{18}O_5$, 266.3); 3b 308 ($C_{17}H_{24}O_5$, 308.4); 3c 328 ($C_{19}H_{20}O_5$, 328,4); 3d 373 ($C_{19}H_{19}NO_7$, 373.4);3e 342 ($C_{20}H_{22}O_5$, 342.4); 3f 402 ($C_{22}H_{26}O_7$, 402); 4a 219 ($C_{12}H_{13}NO_3$, 219.2); 4b 261 ($C_{15}H_{19}NO_3$,261.3) 4c 281 ($C_{17}H_{15}NO_3$, 281.3); 4d 326 ($C_{17}H_{14}N_2O_5$, 326.3); 4e 295 ($C_{18}H_{17}NO_3$, 295.3); 4f 340 ($C_{18}H_{16}N_2O_5$, 340.4); 4g 355 ($C_{20}H_{21}NO_5$, 355.4); 4h 233 ($C_{13}H_{15}NO_3$, 233.3); 4i 295 ($C_{18}H_{17}NO_3$,295.3)

(Received in the UK 04 August 1993)