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Atanas P. Venkov [a], Stela M. Statkova [a] & Ilian I. Ivanov [a]
[a] Department of Chemistry, University of Plovdiv, 4000, Plovdiv, Bulgaria
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SYNTHESIS OF 1-PHENYL-2-ACYL-TETRAHYDROISOQUINOLINES BY INTERMOLECULAR α-AMIDOALKYLATION REACTION

Atanas P. Venkov*, Stela M. Statkova, Ilian I. Ivanov
Department of Chemistry, University of Plovdiv,
4000 Plovdiv, Bulgaria

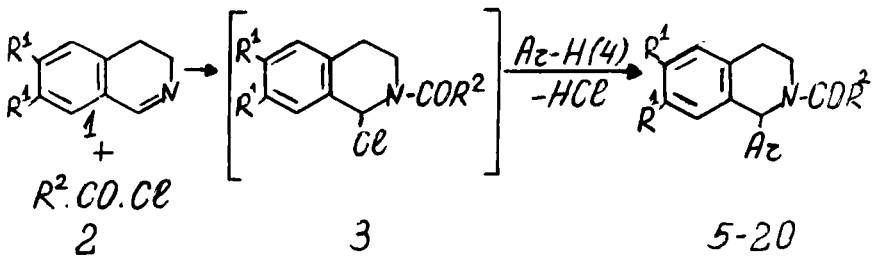
1-Phenyl-2-acyl-tetrahydroisoquinolines are obtained by an intermolecular α- amidoalkylation reaction of aromatics 4 with the adducts 3 of 3,4-dihydroisoquinolines and acyl chlorides.

The adducts of imines and acyl chlorides are one of the most reactive electrophilic reagents used in the inter- and intramolecular α-amidoalkylation reaction.[1,2] They have been successfully used for the synthesis of N-heterocyclic compounds as 2-azethidinones[3,4] and isoquinoline derivatives.[5-7] It was also

*To whom correspondence should be addressed.

shown that the adducts of acyl chlorides and azomethines[8-10] act as α-amidomethylating agents toward the number of aromatics in the presence of Lewis acids as anhydrous aluminum chloride.

Recently we used adducts of 3,4-dihydroisoquinolines and phenylacetyl chlorides for the synthesis of dibenzo /a,h/ quinolizine derivatives.[11] The reaction showed that the adducts display a good electrophilic reactivity in an intramolecular α-amidoalkylation reaction. These results prompt us to investigate the electrophilic properties of adducts 3 from 3,4-dihydroisoquinolines 1 and acyl chlorides 2 towards aromatics 4 in an intermolecular α-amidoalkylation reaction. The reaction will lead to 1-phenyl-tetrahydroisoquinolines, known as naturally occuring alkaloids.[12] Their synthesis have been carried by Bischler-Napieraski method as well as some other methods.[13] However, it is well known that according to these methods, the cyclization strongly depends upon the electron density at the ring closure position and is facilated at the presence of electron donating groups. The methods are limited also for the synthesis of 1-phenyl-tetrahydroisoquinolines with electron donating groups in the aromatic ring at position 1 and especially with hydroxyl groups.



We investigated first the electrophilic properties of adducts 3 towards electron rich aromatics as phenol, dihydroxybenzenes (pyrocatechol, resorcinol, etc.) and alkoxybenzenes (anizol, veratrole). It was found that the reaction of adducts 3 with phenol proceeds at a room temperature for 24 h to the corresponding 1-(hydroxyphenyl)-2-acyl-tetrahydroisoquinolines as a mixture of ortho and para isomers (Table, 5-9). The reaction of 3 with dihydroxybenzenes and dihydroxynaphthalene, proceeds also at a room temperature or for 4 h at 80°C to the corresponding 1-aryl-2-acyl-tetrahydroisoquinolines (Table, 10-14). However, the reaction of 3 with benzene and alkoxybenzenes proceeds sluggishly even for 8-10 h at 80°C. It was found that the yields can be considerablly improved when the reaction is carried in the presence of anhydrous aluminum chloride for 4 h at 80°C (Table, 15-20).

Table: 1-Phenyl-2-acyl-tetrahydroisoquinoline prepared[14,15]

Product	R^1	R^2	Ar	Yield (%)	m.p. (°C)
5	H	OEt	4-HO-C_6H_4	85	130-131
6a	H	CH_2Cl	4-HO-C_6H_4	45	oil
6b	H	CH_2Cl	2-HO-C_6H_4	40	114-115
7a	H	C_6H_5	4-HO-C_6H_4	62	oil
7b	H	C_6H_5	2-HO-C_6H_4	13	oil
8a	H	Me	4-HO-C_6H_4	28	184-185
8b	H	Me	2-HO-C_6H_4	38	174-175
9	MeO	OEt	4-HO-C_6H_4	30	77-78
10	H	OEt	3,4-$(HO)_2$-C_6H_3	82	158-159
11a	H	OEt	2,4-$(HO)_2$-C_6H_3	55	133-134
11b	H	OEt	2,6-$(HO)_2$-C_6H_3	20	238-240
12	H	OEt	2,5-$(HO)_2C_6H_3$	90	oil
13	H	OEt	2,3-$(HO)_2$-5-NO_2-C_6H_2	62	203-204
14	H	OEt	2,3-$(HO)_2$-naphthyl	75	183-184
15	H	OEt	4-MeO-C_6H_4	85	oil
16	H	OEt	3,4-$(MeO)_2$-C_6H_3	90	oil
17	H	C_6H_5	3,4-$(MeO)_2$-C_6H_3	83	oil
18	H	CH_2Cl	3,4-$(MeO)_2$-C_6H_3	77	92-93
19	H	Me	3,4-$(MeO)_2$-C_6H_3	50	107-108
20	H	C_6H_5	3,4-$(MeO)_2$-C_6H_3	40	119-120

The yields of the obttained 1-aryl-2-acyl-tetra-hydroisoquinolines (Table, 5-20) show that the reaction of the adducts 3 with aomatics 4 proceeds as an electrophilic substitution, depending from the nucleophilicity of the aromatic compound and the electron accepting properties of the N-acetyl group. The developed reaction allowed to be obtained 1-phenyl-tetrahydroisoquinolines without electron donating groups in the aromatic moiety of the isoquinoline. It is convenient for the synthesis of 1-phenyl-tetrahydro-isoquinolines with electron donating groups in the aromatic ring at 1-position and especially with hydroxyl groups as substituents.

EXPERIMENTAL

1-(Hydroxyphenzyl)-2-acyl-tetrahydroisoquinolines (Table,5-14); General Procedure: To a solution of 3,4-dihydroisoquinoline 1 (3 mmol) in dry CH_2Cl_2 (5 mL) is added an acyl chloride 2 (3 mmol) at a room temperature and the reaction mixture is stirred for 30 min. An equimolar amount (3 mmol) of phenol or dihydroxybenzene 4 is added and the reaction mixture is stirred at a room temperature for 24 h. The solution is washed with 10% aq. HCl (5 mL), water (10 mL) and dried (Na_2SO_4). The products are separated or purified by column

chromatography on a silica gel with petroleum ether and ether as eluents.

1-(Methoxyphenyl)-2-acyl-tetrahydroisoquinolines (Table,15-20); General Procedure: Acyl chloride 2 (3 mmol) in dry dichloroethane (5 mL) is added to a solution of 3,4-dihydroisoquinoline 1 (3 mmol) in dry dichloroethane (5 mL) at a room temperature. The mixture is stirred for 30 min and then methoxybenzene (3 moll) and anh. $AlCl_3$ (3 mmol) are added. The mixture is stirred for 4 h at 80°C, then cooled and 10% aq. HCl (5 mL) is added. The resulting emulsion is extracted with CH_2Cl_2 (3x10 mL), the combined extracts are dried (Na_2SO_4), and the solvent evaporated. The crudes 15-20 (Table) are purified by recrystallization or column chromatography on a silica gel using Et_2O as eluent.

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14. The ^{1}H-NMR spectra were measured at 60 MHz with Perkin-Elmer R-24B spectrometer.The data in δ ppm in $CDCl_3$ (TMS) are as follows: 5 1.30(t,3H,J=10), 2.70-2.90(m,2H),3.18(t,2H,J=10),4.15(q,2H,J=10), 6.21(s,1H),6.57(s,1H),6.72(s,1H),6.90(s,2H),7.20 (s,5H); 6a 2.72-3.05(m,2H),3.20-3.50 (m,2H),4.45 (s,2H),6.30(s,1H),6.55(s,1H),6.70(s,2H),6.85(s,1H), 7.05(s,1H),7.12(s,4H); 6b 3.00(t,2H,J=10),3.40-3.60 (m,2H),4.10(s,2H),6.55(s,1H),6.60(s,1H),6.68(s,1H), 6.95(s,2H),7.15(s,4H),9.22(s,1H)*; 7a 2.78-3.00 (m,2H),3.36(t,2H,J=9),5.90(s,1H),6.58(s,1H),6.69 (s,2H),6.90(s,2H),7.10(s,2H),7.18(s,2H),7.30(s,5H); 7b 2.60-2.88(m,2H),3.20(t,2H,J=9),6.22(s,1H),6.28

(s,1H),6.50(s,1H),6.69(s,2H),6.90(s,2H),7.00(s,4H), 7.20(s,1H), 7.60(s,1H),7.90(s,1H),9.70(s,1H)*; 8a 2.17(s,3H),2.88(t,2H,J=8),3.55(t,2H,J=9),5.85 (s,1H),6.60(s,1H).6.80(s,2H),6.90 (s,2H),7.10 (s,4H); 8b 2.15(s,3H),3.00(t,2H,J=11),3.65(t,2H, J=10),6.55(s,1H),6.61(s,1H),6.78(s,2H),6.98 (s,1H), 7.18(s,4H),9.60(s,1H)*; 9 1.29(t,3H,J=11),2.84 (t,2H,J=9),3.32(t,2H,J=10),3.70 (s,3H),3.82(s,3H), 4.15(q,2H,J=11),6.20(s,1H),6.40(s,1H),6.58(s,2H), 6.70(s,2H),6.90(s,1H),7.04(s,1H); 10 1.24(t,3H, J=11),2.75(t,2H,J=10),3.20-3.50(m,2H),4.08(q,2H, J=12),6.12(s,1H),6.40(s,1H),6.52(s,1H),6.70(s,1H), 7.00(s,4H),7.10(s,2H); 11a 1.25(t,3H,J=11),2.85 (t,2H,J=9),3.65(t,2H,J=10),4.15(q,2H,J=11),6.19 (s,1H),6.30(s,2H),6.42(s,1H),6.82(s,1H),7.02(s,2H), 7.10(s,2H),9.30(s,1H)*; 11b 1.22(t,3H,J=11),2.55-2.80 (m,2H),3.76(t,2H,J=10),4.14(q,2H,J=12),5.49 (d,1H,J=14),6.18(s,2H),6.48(s,1H),6.73-7.00(m,4H), 7.15(s,1H),9.10(d,1H,J=14)*; 12 1.25(t,3H,J=12), 2.80-3.02(m,2H),3.60(t,2H,J=9),4.14(q,2H,J=12), 6.02(s,1H),6.30(s,1H),6.68(s,1H),7.00(s,2H),7.10 (s,4H),9.30(s,1H)*; 13 1.30(t,3H,J=12),2.86-3.04 (m,2H),3.20-3.52(m,2H),4.17(q,2H,J=11),6.40(s,1H), 6.90(s,1H),6.99(s,1H),7.18(s,4H),7.57(d,1H,J=6), 7.95(s,1H); 14 2.80-3.02(m,2H),3.80-4.15(m,2H),

6.28(s,1H),6.79(s,1H),6.99(s,2H),7.15(s,4H),7.34 (s,5H),7.50(s,1H),7.70(s,1H),8.02(s,1H),8.80(s,1H); 15 1.28(t,3H,J=12),2.70-2.95(m,2H),3.08-3.22(m,2H), 3.70(s,3H),4.15(q,2H,J=10),6.30(s,1H),6.62(s,1H), 6.78(s,1H),7.00(s,2H),7.05(s,2H),7.11(s,2H); 16 1.30((t,3H,J=10),2.60-2.80 (m,2H),3.40(t,2H,J=8), 3.80(s,6H),4.20(q,2H,J=8),6.34(s,1H),6.69(s,1H), 6.82(d,2H,J=6),7.00-7.20(m,4H); 17 2.60-2.90(m,2H), 3.25(t,2H,J=7),3.80(s,6H),6.35(s,1H),6.68(s,2H), 6.80(s,1H),7.15(s,2H),7.22(s,2H),7.35(s,4H),7.90 (s,1H); 18 2.85-3.10(m,2H),3.28(t,2H,J=7),3.80 (s,6H),4.15(s,2H),6.10(s,1H),6.64(d,2H,J=8),7.18 (s,2H),7.22(s,2H),7.95(s,1H); 19 2.10(s,3H),2.50-3.00(m,2H),3.20-3.60(m,2H),3.80(s,6H),6.08(s,1H), 6.61(s,2H),6.85(s,1H),7.12(s,2H),7.21(s,1H),7.50 (s,1H); 20 2.70-3.00(m,2H),3.25-3.53(m,2H),6.55 (s,1H),6.68(s,1H),7.08(s,2H),7.18(s,5H),7.28(s,5H), 7.90(s,1H).

* For the proton of phenolic hydroxyl group at ortho position.

15. The M.S. spectra were recorded on a JMS-D300 spectrometer and m/e (M^+) are as follows: 5 297 ($C_{18}H_{19}NO_3$, 297.3); 6a and 6b 301 ($C_{17}H_{16}NO_2Cl$, 301.8); 7a and 7b 329 ($C_{22}H_{19}NO_2$, 329.4); 8a and 8b 267 ($C_{17}H_{17}NO_2$, 267.3); 9 357 ($C_{20}H_{23}NO_5$, 357.4);

10 313 ($C_{18}H_{19}NO_4$, 313.3); 11a and 11b 313 ($C_{18}H_{19}NO_4$, 313.3); 12 313 ($C_{18}H_{19}NO_4$, 313.3); 13 358 ($C_{18}H_{18}N_2O_6$, 358.3); 14 395 ($C_{26}H_{21}NO_3$, 395.3); 15 311 ($C_{19}H_{21}NO_3$, 311.4); 16 341 ($C_{20}H_{23}NO_4$, 341.4); 17 389 ($C_{24}H_{23}NO_4$, 389.4); 18 346 ($C_{19}H_{20}NO_3Cl$, 345.8); 19 311 ($C_{19}H_{21}NO_3$, 311.4); 20 313 ($C_{22}H_{19}NO_3$, 313.4).

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