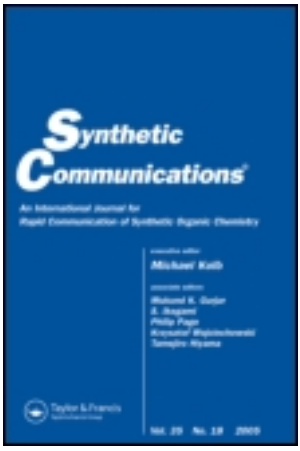


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# Synthesis of 1-Aryl-2-acyltetrahydroisoquinolines with an Electron Withdrawing Group in the Aromatic Ring of Heterocycle

Atanas P. Venkov [a] & Stela Statkova-Abeghe [a]
[a] Department of Chemistry, University of Plovdiv, 4000, Plovdiv, Bulgaria
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# SYNTHESIS OF 1-ARYL-2-ACYLTETRAHYDROISOQUINOLINES WITH AN ELECTRON WITHDRAWING GROUP IN THE AROMATIC RING OF HETEROCYCLE

Atanas P. Venkov* and Stela Statkova-Abeghe
Department of Chemistry, University of Plovdiv
4000 Plovdiv, Bulgaria



**ABSTRACT**: The intermolecular α-amidoalkylation reaction of adducts **3** obtained from acyl chlorides and 3,4-dihydroisoquinoline with an electron withdrawing group in the aromatic ring such as 7-nitro-3,4-dihydroisoquinoline towards aromatics has been investigated.

Classical synthesis of the isoquinoline ring system generally involve electrophilic cyclization onto an activated aromatic ring.[1] Thus, preparations of isoquinolines via the Pomeranz-Fritsch cyclization, dihydroisoquinolines via the Bischler-Napieralski cyclization, and tetrahydroisoquinolines via the Pictet-Spengler cyclization are usually unsuccessful or low yielding when electron withdrawing groups are present in the aromatic ring.[2,3]

Recently we reported the application of adducts from 3,4-dihydroisoquinolines and acyl chlorides as electrophilic reagents towards electron rich aromatics such as hydroxy- and alkoxybenzenes in an intermolecular

*To whom correspondence should be addressed.

α–amidoalkylation reaction for the synthesis of 1-aryl-2-acyltetrahydroisoquinolines.[4] The yields of the products showed that the reaction as an electrophilic substitution depended on the nucleophilicity of the aromatics and the nature of acyl chloride used for the preparation of the adducts **3**.

The acylation of imines has been shown to be an equilibrium, which shifts to the side of adduct when the temperature was lowered as it was determined by $^1$H-NMR investigation.[5,6] The position of the equilibrium will naturally be highly dependent on the structure of starting imine and the nature of acyl chloride, but no systematic study has been directed to this point.

Adducts **3** of 3,4-dihydroisoquinolines **1** and acyl chlorides **2** can be presented by their covalent structure **3a** or as N-acyl iminium salt **3b**. It can be assumed that in the presence of Lewis acid they reacted with aromatics by their covalent structure. The formation of this structure can be also influenced by the presence of electron withdrawing groups in the aromatic ring of the heterocycle.

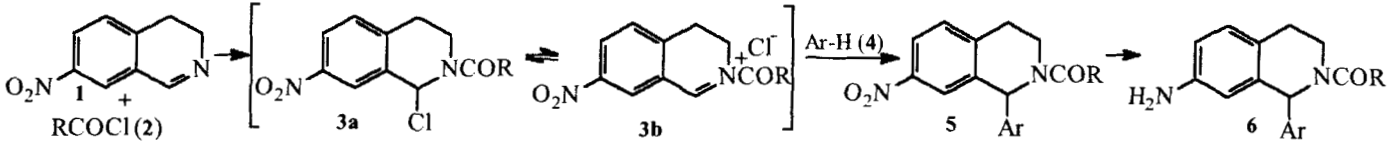
Now we report our investigations on the electrophilic reactivity towards aromatics of adducts **3** obtained from acyl chlorides and 3,4-dihydroisoquinoline with an electron withdrawing group in the aromatic ring such as 7-nitro-3,4-dihydroisoquinoline. Their reaction with aromatics **4** will lead to 7-nitro-2-acyltetrahydroisoquinolines **5**, some of which are known as pharmaceutical active compounds.[7]

7-Nitro-3,4-dihydroisoquinoline **1** was obtained by the literature modified method [8] and was characterized. Adducts **3** were obtained from equimolar amounts of 7-nitro-3,4-dihydroisoquinoline **1** and acyl chlorides **2** in dry 1,2-dichloroethane or benzene (when it was used and as nucleophile) for 30 min at room temperature. The reaction of **3** with benzene proceeded

only at reflux in the presence of anh. $AlCl_3$ (**Table, 5a-c**), while with 3,4-dimethoxybenzene it can be carried out at room temperature (**Table, 5d-f**). The reaction of **3** with phenol and 1,2-dihydroxybenzene was carried out without a Lewis acid at reflux (**Table, 5g-j**) and led to two products that were separated by column chromatography and characterized as isomers. The above results showed that the intremolecular α-amidoalkylation reaction of aromatics with adducts **3** depended on the nucleophilicity of the aromatic compound.

To compare the electrophilic reactivity of adducts **3** towards aromatics we carried out reactions with adducts without electron withdrawing group and with electron donating groups in the aromatic ring of imine **1**. It was found that the reaction of adduct of 3,4-dihydroisoquinoline and ethyl chloroformate with 3,4-dimethoxybenzene proceeded in the presence of equimolar amount of anh. $AlCl_3$ and after 3 h at room temperature the yield of 1-(3,4-dimethoxyphenyl)-2-ethoxycarbonyltetrahydroisoquinoline was only 37%. As expected, the presence of electron donating groups in the aromatic ring acted unfavourably on the electrophilic properties of adducts **3**. Thus, the reaction of adduct of 6,7-dimethoxy-3,4-dihydroisoquinoline and ethyl chloroformate with 3,4-dimethoxybenzene in 1,2-dichloroethane in the presence of equimolar amount of anh. $AlCl_3$ did not proceed at room temperature for 24 h and the yield of the product after 6 h at 80°C was only 10%. The experiments showed that adducts of **3** of 7-nitro-3,4-dihydroisoquinoline are better electrophilic reagents toward aromatics than those without electron withdrawing group reported previously.[4]

The above investigations also showed that the method allows the synthesis of 1-aryl-2-acyltetrahydroisoquinolines with an electron withdrawing group in the aromatic ring of the heterocycle that can not be




**Table**

| Product | R | Ar | yield (%) | mp (°C) | $^1$H-NMR ($CDCl_3$/TMS) δ, ppm, J(Hz) |
|---|---|---|---|---|---|
| **5a** | Me | $C_6H_5$ | 66 | 128-130 | 2.16 (s,3H), 2.97(t,2H,J=7), 3.35-3.70(m,2H),6.92(s,1H), 7.09-7.17(m,5H), 7.25(d,1H,J=8), 7.82(d,1H,J=2),7.87and 8.00(d,d,1H,J=2) |
| **5b** | $C_6H_5$ | $C_6H_5$ | 30 | 147 | 2.82-3.07(m,2H),3.19-3.52(m,2H),7.05(s,1H),7.15(s,5H), 7.24(s,5H), 7.27(d,1H,J=10),7.80(s,1H,7.89) and 7.98(d,d,1H,J=2) |
| **5c** | OEt | $C_6H_5$ | 60 | oil | 1.27(t,3H,J=7),2.80-3.02(m,2H),3.07-3.37(m,2H),4.12(q,2H,J=7),6.35 (s,1H),6.95(s,5H),7.22(d,1H,J=8),7.77(d,1H,J=2),7.87 and 7.98(d,d,1H,J=2) |
| **5d** | Me | 3,4-$(MeO)_2C_6H_3$ | 75 | 138 | 2.16(s,3H),2.87-3.07(m,2H),3.26-3.52(m,2H),3.75(s,6H),6.32 (d,1H,J=8), 6.62(d,1H,J=8),6.85(s,1H),7.10(d,1H,J=10),7.86(d,1H,J=2),7.90 and 8.10 (d,d,1H,J=2) |

| | | | | | |
|---|---|---|---|---|---|
| **5e** | $C_6H_5$ | 3,4-$(MeO)_2C_6H_3$ | 55 | 151-152 | 2.77-3.07(m,2H),3.15-3.40(m,2H),3.75(s,6H),6.25(d,1H,J=2),6.35(d,1H, J=2),6.62(d,1H,J=8),6.80-7.00(m,1H),7.22(d,1H,J=8),7.26(s,5H),7.82 (d,1H,J=2),7.93and 8.02(d,d,1H,J=2) |
| **5f** | OEt | 3,4-$(MeO)_2C_6H_3$ | 75 | 118 | 1.27(t,3H,J=7),2.82-3.02(m,2H),3.15-3.42(m,2H),3.75(s,6H), 4.17(q,2H,J=7), 6.30(d,1H,J=2),6.40(d,1H,J=2),.62(d,1H,J=8),6.77(s,1H), 67.20(d,1H,J=9),7.80(d,1H,J=2),7.87 and 7.97(d,d,1H,J=2) |
| **5g** | OEt | 4-HO-$C_5H_4$ | 58 | 171-172 | 1.30(t,3H,J=7),2.80-3.05(m,2H),3.07-3.35(m,2H), 4.02 (q,2H,J=7),6.27 (s,2H),6.60(d,2H,J=8),6.85(d,2H,J=8),7.05(d,1H,J=10),7.50(d,1H,J=2), 7.82 and 7.92(d,d,J=2) |
| **5h** | OEt | 2-HO-$C_5H_4$ | 23 | 182-183 | 1.28(t,3H,J=7),2.82-3.12(m,2H),3.20-3.42(m,2H),4.12(q,2H,J=7), 6.30-6.67(m,3H),6.80-7.07(m,2H), 7.25(d,1H,J=8),7.65(d,1H,J=2),7.85 and 7.93(d,d,1H,J=2),9.00(s,1H) |
| **5i** | OEt | 3,4-$(HO)_2C_6H_3$ | 68 | 190-192 | 1.27(t,3H,J=7),2.75-3.00(m,2H),3.07-3.32(m,2H),4.13(q,2H,J=7),6.22(s,1H), 6.25-6.35(m,1H),6.52(s,1H),6.60-6.77(m,3H),7.15 (d,1H,J=10),7.75(d,1H,J=2), 7.82 and 7.92(d,d,1H,J=2) |
| **5j** | OEt | 2,3-$(HO)_2C_6H_3$ | 14 | 204-205 | 1.27(t,3H,J=7),2.87-3.10(m,2H),3.15-3.35(m,2H),4.17(q,2H,J=7),5.82 and 5.92(d,d,2H,J=2),6.40(s,1H),6.55(d,1H,J=7),6.70, 6.78(d,d,1H,J=2),7.22 (d,1H,J=8), 7.67(d,1H,J=2),7.87 and 7.97(d,d,1H,J=2), 9.50(s,1H) |

prepared by the classical methods.[1] The obtained compounds are of interest themselves or can be converted to new derivatives. For example, the treatment of **5** in a solution of ethanol and conc. hydrochloric acid with zinc led to the corresponding 7-amino derivatives **6**.

## EXPERIMENTAL

**7-Nitro-3,4-dihydroisoquinoline:** Solution of 3,4-dihydroisoquinoline (0.6g, 4.6 mmol) in conc. $H_2SO_4$ (2.5 mL) was added dropwise to a stirred mixture of $KNO_3$ (0.5g) in conc. $H_2SO_4$ (2.5 mL) at -5°C. The mixture was allowed to attain room temperature for 2 h and heated at 60°C for 4 h, then poured on ice. The neutralization with ammonia afforded a light brown material that was extracted with $CH_2Cl_2$ (3x20 mL). The combined extracts were dried ($Na_2SO_4$) and the solvent removed under reduced pressure.. The product was purified by column chromatography on a neutral $Al_2O_3$ using $Et_2O$ as eluent and obtained as colourless crystals, mp 86-87°C, yield 0.66 g (89%); IR(KBr) $\nu_{max}$ :1640 $cm^{-1}$ (C=N); $^1$H-NMR ($CDCl_3$), δ, ppm: 2.83 (t, 2H, J=8), 3.82 (t, 2H, J=8), 7.32 (d, 1H, J=9), 8.10 (d, 1H, J=2), 8.17 and 8.20(d,d,1H,J=2),8.39(t,1H,J=2);MS,mz($M^+$),176(Calc.for$C_9H_8N_2O_2$,176.17)

**7-Nitro-1-phenyl-2-acyltetrahydroisoquinolines (5a-c); General procedure:** Acyl chloride **2** (3 mmol) was added to a stirred solution of 7-nitro-3,4-dihydroisoquinoline **1** (3 mmol) in dry benzene (5 mL) at room temperature. Anh. $AlCl_3$ (3 mmol) was added after 30 min and the mixture as refluxed for 3 h, then cooled and 10% aq. HCl (10 mL) was added. The resulting emulsion was extracted with $CH_2Cl_2$ (3x20 mL), the combined extracts were dried ($Na_2SO_4$) and the solvents evaporated. The products were purified by recrystallization or column chromatography on silica gel using p.ether, ether as eluents.

**7-Nitro-1-(alkoxyphenyl)-2-acyltetrahydroisoquinolines (5d-f); General procedure:** Acyl chloride **2** (3 mmol) was added to a solution of 7-nitro-3,4-dihydroisoquinoline **1** (3 mmol) in dry 1,2-dichloroethane (5 mL) and the mixture was stirred for 30 min at room temperature. Alkoxybenzene **4** (3 mmol) and anh. $AlCl_3$ (3 mmol) were added and the mixture was stirred for 3 h at room temperature, then worked up as above.

**7-Nitro-1-(hydroxyphenyl)-2-acyltetrahydroisoquinolines (5g-j); General Procedure:** Acyl chloride **2** (3 mmol) was added to a solution of 7-nitro-3,4-dihydroisoquinoline **1** (3 mmol) in dry 1,2-dichloroethane (5 mL) and the mixture was stirred for 30 min at room temperature. Hydroxybenzene **4** (3 mmol) was added and the mixture was stirred at reflux for 3 h, then cooled and worked up as above.

**7-Amino-1-(3,4-dimethoxyphenyl)-2-acyltetrahydroisoquinolines (6d-f); General procedure:** Zinc (0.5g, powder) was added in a small portions for 1 h to a stirred solution of 7-nitro-1-(3,4-dimethoxyphenyl)-2-acyltetrahydroisoquinolines **5d** or **5f** (1 mmol) in EtOH (5 mL) and conc. hydrochloric acid. The mixture was diluted with water (10 mL), alkalized with ammonia and extracted with $CH_2Cl_2$ (3x10mL) to obtain pure products **6** after evaporation of the solvents.

**7-Amino-1-(3,4-dimethoxyphenyl)-2-acetyltetrahydroisoquinoline (6d)** as oil in a yield of 98%; IR (KBr) $\nu_{max}$ $cm^{-1}$: 3351 (NH), 1630 (CO); $^1$H-NMR ($CDCl_3$), δ, ppm: 2.10 (s,3H), 2.62-2.87 (m,2H), 3.30-3.62 (m,2H), 3.80 (s,6H), 6.39 (d,1H,J=2), 6.50 (d,1H,J=2), 6.62 (d,2H,J=2), 6.75 (s,1H), 6.87 (s,1H), 6.95 (d,1H,J=4), 7.22 (d,2H,J=6).

**7-Amino-1-(3,4-dimethoxyphenyl)-2-ethoxycarbonyltetrahydro-isoquinoline (6f)** as oil in a yield of 93%; IR (KBr) $\nu_{max}$ $cm^{-1}$: 3361 (NH), 1684 (CO); $^1$H-NMR ($CDCl_3$), δ, ppm: 1.32 (t,3H,J=7), 2.60-2.92 (m,2H), 2.95-3.20 (m,2H), 3.80 (s,6H), 4.02 (q,2H,J=7), 6.25 (s,1H), 6.35 (d,1H,J=2), 6.50 (d,1H,J=8), 6.67 (s,2H), 6.87 (s,2H), 6.95 (s,1H), 7.20 (s,1H).



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