Central European Science Journals
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Central European Journal of Chemistry
Central European Science Journals
CEJC 2(1) 2004 234–246

Amidoalkylation of Heteroaromatic Compounds with Adducts of Acyl Chlorides and 3,4-Dihydroisoquinoline and Isoquinoline

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Received 9 July 2003; revised 3 November 2003

Abstract: The N-acyliminium intermediates of 3,4-dihydroisoquinoline and salts of isoquinoline with acyl chlorides were successfully used as amidoalkylating reagents toward synthesis of heterocyclic aromatics as indole, pyrrole, thiophene and pyrazine.

Keywords: isoquinoline, amidoalkylation, heterocycles

1 Introduction

Reactions with formation of C-C bonds have continued to play a central role in synthetic approaches to numerous natural and unnatural heterocycles. Among the employed species for this purpose, Reissert compounds [1] and *N*-acyliminium ions [2] have proven particularly useful for effecting selective carbon-carbon bond formation. In the last several years, N-acyliminium intermediates of 3,4-dihydroisoquinolines with acyl chlorides have been successfully used as electrophilic reagents in intermolecular α-amidoalkylation for synthesis of tetrahydroisoquinoline derivatives. The electrophilic properties of reagents **6** toward aromatics, Grignard reagents and active methylene carbonyl compounds [3] were investigated. Similar examinations concerning N-acyliminium ions of isoquinoline and their reactivity have been published [4]. Reagents **2** have demonstrated high reactivity in reaction of heteroarylation toward aromatic π-nucleophiles.

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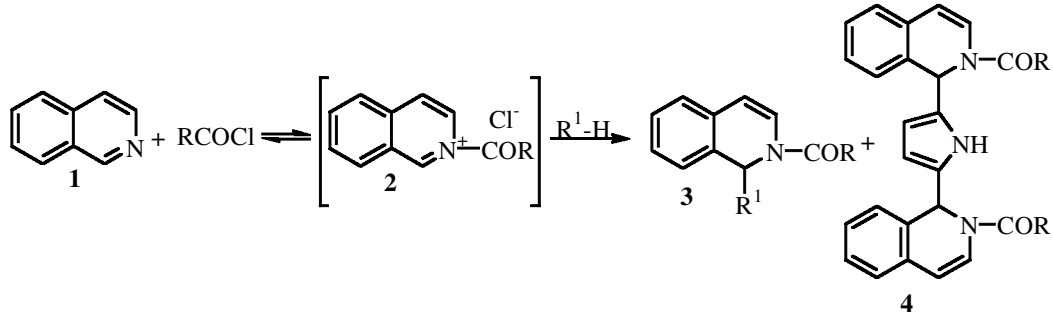
2 Results

We report here, our investigations concerning reactivity of N-acyliminium intermediates **6** in comparison with N-acyliminium ions of isoquinoline **2** and their further synthetic application in the amidoalkylation of some aromatic heterocycles as indole, pyrrole, thiophene and pyrazine. The heteroarylation of **6** with these heteroaromatic compounds, so far has not been studied.

As mentioned above, the application of salts **2** of isoquinoline as amidoalkylating reagents toward indole and pyrrole is known [4]. The original paper, however, lacked detailed description of the experimental procedures. That is why we repeated this study and as a result, the following procedure was found as optimal: the salts, **2,** were obtained in CH_3CN at 0^oC and the amidoalkylation of indole and pyrrole was carried out at room temperature in the presence of Et_3N for the time given (Scheme 1, Table 1). The amidoalkylation of indole led only to one product (**3a-3c**, Table 1), while the reaction with pyrrole afforded a mixture of products **3** and **4** (**3d-3f** and **4d-4f**, Table 1). The reactions of **2** with thiophene and pyrazine were not successful even in the presence of Lewis acids.



Scheme 1 Synthesis of the 1,2-dihydroisoquinoline derivatives **3** and **4**.

Entry	R	R^1	React. cond. [hrs]	**3** Yelds [%]	**3** Mp [^oC]	**4** Yelds [%]	**4** Mp [^oC]
a	Me	3-indolyl	3	61	175-176	-	-
b	OEt	3-indolyl	3	78	139-140	-	-
c	C_6H_5	3-indolyl	24	68	232[a]	-	-
d	Me	2-pyrrolyl	24	31	181-182	26	267-268[b]
e	OEt	2-pyrrolyl	24	25	93	50	135-136
f	C_6H_5	2-pyrrolyl	24	53	137-138[c]	37	198-200[d]

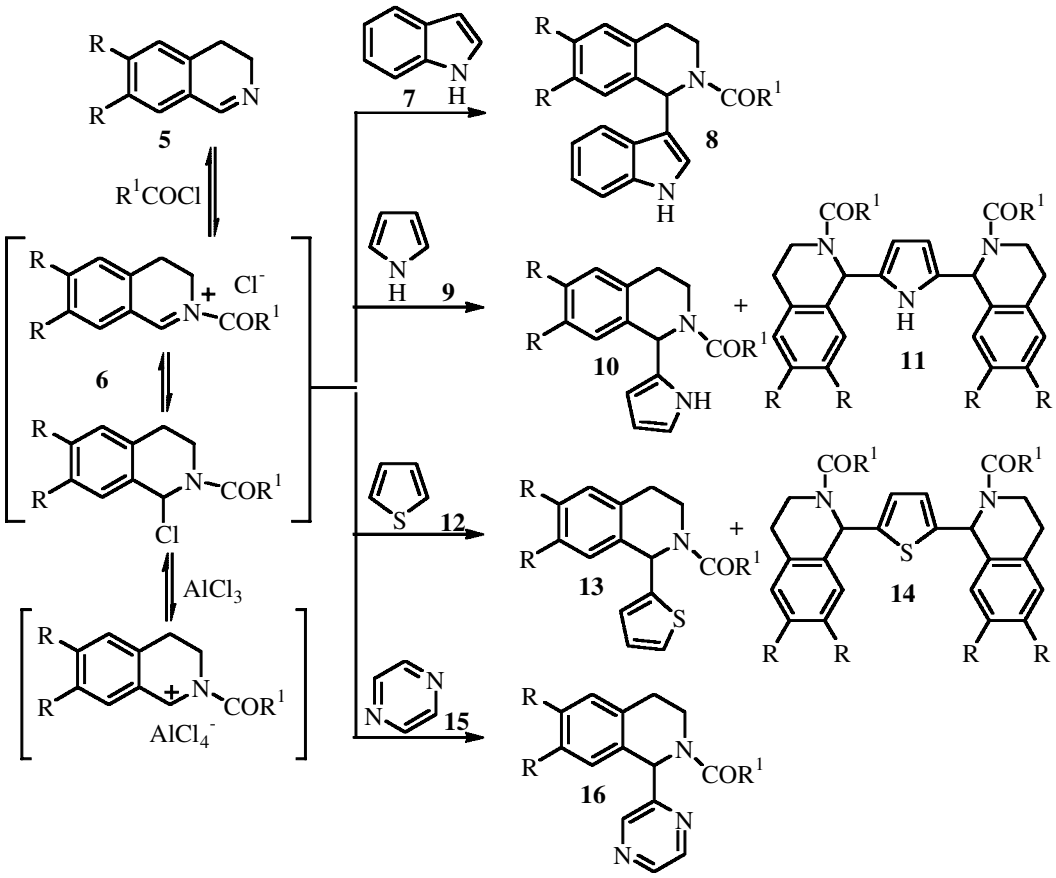
[a]Mp 228^oC in ref.[5]; [b]Mp $263\text{-}264^oC$, [c]Mp $136\text{-}138^oC$, [d]Mp $197\text{-}198^oC$ in ref. [6].

Table 1 Reaction conditions, yelds and melting points of compounds **3** and **4**.

We used Et_3N as a base, whereas Sheinkman et al. carried out these reactions in excess of isoquinoline. The results from our study are in good agreement with the previously published data. The yields of known compounds **3b**, **4d**, **3e**, **4e** are similar to those cited

in references. In the literature there is also an observation that salts of isoquinoline do not react with thiophene. There is no information about reactions with pyrazine.

Extending our study, we found that the reaction of N-acyliminium intermediates **6** obtained from equimolar amounts of 3,4-dihydroisoquinoline **5** and ethyl chloroformate in dichloromethane with indole **7** afforded at room temperature a product which was characterized as ethyl 1-(1*H*-3-indolyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate (**8b,** Table 2) but in a moderate yield (40%).



Scheme 2 Synthesis of the 1,2-disubstitutedtetrahydroisoquinolines (**8**, **10**, **11**, **13**, **14**, **16)** via α-amidoalkylation toward heteroaromatics (**7**, **9**, **12**, **15**).

The yield of the product was improved to 77%, when the reaction was carried out in the presence of Et_3N. The reactions of N-acyliminium intermediates **6** of 3,4-dihydroisoquinoline and acetyl chloride or benzoyl chloride with indole were carried out under the same reaction conditions and afforded the corresponding 1-(3-indolyl)-2-acyltetrahydroisoqunolines (**8a**, **8c**, Table 2). It is observed that the products **8a** and **8c** were obtained in higher yields with a shorter reaction time than the corresponding **3a** and **3c** (Table 1 and Table 2). In the case when a cyclic imine like 6,7-dimethoxy-3,4-dihydroisoquinoline was used, the products **8d** and **8e** were obtained in lower yields. This could be explained due to the electron-donating effect of the methoxy groups, which lowers the electrophilicity of the corresponding adducts **6**.

The reaction of N-acyliminium intermediates **6** with pyrrole **9** was carried out un-

der similar reaction conditions as with indole. The reagent **6** so obtained was cooled to 0^{o}C and then a solution of equimolar amounts of pyrrole and Et_3N was added to the stirred mixture. The α-amidoalkylation and α-diamidoalkylation reactions of pyrrole with the adducts **6,** obtained from 3,4-dihydroisoquinoline and ethyl chloroformate, led to a mixture of two products which were characterized as ethyl 1-(1*H*-2-pyrrolyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate (**10b**) and ethyl 1-[5-(2-ethyloxycarbonyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate (**11b**) (Table 2). TLC and IR monitoring of the reaction mixtures showed that the reactions to **10** and **11** are parallel and depend on the ratio of adduct **6** and pyrrole. E.g., when the ratio of adduct **6** and of pyrrole in the reaction was 2:1 mmol instead of 1:1, the yield of **10b** decreased from 61% to 5%, and the yield of **11b** increased from 28% to 82% (Table 2, yields in brackets). It was also established that the second amidoalkylation of product **10b** with the N-acyliminium intermediates **6** (R=H, R^1=OEt), for 1 hour in the presence of Et_3N afforded **11b** in a 76 % yield. Similarly in the reaction between intermediates **6** (R=H, R^1=Me; R=H, R^1=C_6H_5) and pyrrole, parallel amidoalkylation and diamidoalkylation was observed and mixtures of products **10a**, **11a** and **10c**, **11c** were obtained.

Entry	R	R^1	Reaction time [hrs]	Yield [%]	Mp [^{o}C]
8a	H	Me	0.5	87	212-214
8b	H	OEt	3	77	141-143
8c	H	C_6H_5	1	80	216-217
8d	MeO	Me	1	37	226-227
8e	MeO	OEt	3	66	76-77
10a	H	Me	1	8	111-112
11a	H	Me	1	63	165-166
10b	H	OEt	1	61 (5)	93-94
11b	H	OEt	1	28(82)	67-68
10c	H	C_6H_5	1	72	oil
11c	H	C_6H_5	1	20	70-72
10d	MeO	OEt	1	13	175-176
11d	MeO	OEt	1	57	oil
13a	H	Me	2	35 (60)*	94-95
13b	H	OEt	4	31	oil
14b	H	OEt	4	54	oil
16	H	OEt	4 (80^{o}C)	54	oil

* With anh. $AlCl_3$ at the same reaction time.

Table 2 Reaction conditions, yields and melting points of the compounds (**8**, **10**, **11**, **13**, **14**, **16**).

As indicated in Table 2, the reaction time sufficient for completion of the reaction of reagents **6** and pyrrole is 1 hour in comparison with 24 hours for the corresponding

reactions of salts **2** of isoquinoline (Table 1). And once again the total yields of products **10** and **11** were higher than corresponding total yield of products **3** and **4** (Table 1, Table 2). The collected results from the reactions with indole and pyrrole demonstrated that N-acyliminium intermediates **6**, obtained from 3,4-dihydroisoquinoline and acyl clorides are more reactive than the salts **2** of isoquinoline.

The results from the reactions of adducts **6** of 3,4-dihydroisoquinoline and acyl chlorides toward thiophene and pyrazine support the conclusion concerning the reactivity of reagents **6** and **2**. The reaction of reagents **6** with unsubstituted thiophene **12** was successful in the presence of Lewis acids as $BF_3{\cdot}Et_2O$ (we have used successfully this catalyst in our previous investigations concerning the reaction of N-acyliminium intermediates of 3,4-dihydroisoquinoline toward aromatics). The adduct **6** of 3,4-dihydroisoquinoline and ethyl chloroformate afforded a mixture of two products (**13b** and **14b**, Table 2), while the adduct of 3,4-dihydroisoquinoline and acetyl chloride led only to **13a** albeit in a low yield. When the last reaction was carried out in the presence of anhydrous $AlCl_3$, the yield of **10b** increased to 60%. From the literature it is known that so far salts of isoquinoline have been reacted only with activated thiophene derivatives. The reaction of adduct **6** with pyrazine **15** was successful also in the presence of $BF_3{\cdot}Et_2O$ and at reflux in CH_3CN (**15**, Table 2).

The above investigations demonstrated that the N-acyliminium intermediates **6** of 3,4-dihydroisoquinoline and acyl chlorides possess higher electrophilic reactivity than salts **2** of isoquinoline in the reaction of α-amidoalkylation toward heteroaromatics. As a result of the examinations, reaction conditions for heteroarylation of indole and pyrrole with salts of isoquinoline are proposed. The products obtained were spectrally characterized. On the other hand, the application of the α-amidoalkylation was successfully extended with investigations of the reaction between reagents **6** and heterocyclic compounds. This way were easily obtained compounds combining two different kinds of heterocycles in their molecules.

3 Experimental

All melting temperatures were determined using Boettus heat plate apparatus and are uncorrected. The ^{1}H NMR, ^{13}C NMR spectra were recorded on a Bruker DRX 250 spectrometer in the indicated solvent (δ, ppm) and MS spectra on a Jeol JMS-D300 spectrometer (70 eV). Infrared spectra were recorded with Perkin-Elmer 1750 IFTS spectrometer.

3.1 General Procedure for preparation of products 3a-f and 4d-f (Table 1):

Acyl chloride (2 mmol) was added dropwise to a stirred and ice cold solution of isoquinoline (2 mmol) in MeCN (5 mL). The mixture was stirred for 30 min for the preparation of salt **2** and then a solution of indole (2 mmol) or pyrrole (2 mmol) and Et_3N (2 mmol) in MeCN (1 mL) was added dropwise. The reaction mixture was stirred for the time given

(Table 1), then treated with 10% aq. HCl (10 mL) and rapidly extracted with $CHCl_3$ (3×10 mL). The combined extract was washed with 10% aq. $NaHCO_3$ (2×10 mL), dried (Na_2SO_4) and the solvent was removed by distillation. The products were separated and purified by recrystallization or column chromatography on neutral Al_2O_3.

3a: **1-[1-(1*H*-3-indolyl)-1,2-dihydro-2-isoquinolinyl]-1-ethanone**,
(eluent: $CHCl_3$)
^{1}H-NMR ($CDCl_3$) δ: 2.21 (s, 3H, CH_3), 6.21 (d, 1H, J=8, CH-3), 6.37 (d, 1H, J=8, CH-4), 6.71 (s, 1H, CH-1), 7.12-7.48 (m, 8H), 7.92-8.15 (m, 1H), 8.31 (s, 1H, NH); IR (KBr): ν (cm^{-1}) : 3219 (NH), 1651 (CO), 1619 (C=C); ^{13}C-NMR ($CDCl_3$) δ: 19.16 (CH_3), 28.15 (C-1), 109.40 (C-4), 110.60, 117.80, 120.38, 120.80, 123.40 (C-3), 123.80, 124.55, 126.70, 127.80, 129.45, 130.15, 134.50, 135.90, 138.60, 168.90 (CO)- $C_{19}H_{16}N_2O$ (288.34): calcd. C 79.14, H 5.59, N 9.72; found C 79.30, H 5.78, N 9.60.

3b: **ethyl 1-(1*H*-3-indolyl)-1,2-dihydro-2-isoquinolinecarboxylate**,
(eluent: mixture petroleum ether/ether - 3/1)
^{1}H-NMR ($CDCl_3$) δ: 1.35 (t, 3H, J=7, CH_3), 4.35 (q, 2H, J=7, CH_2), 6.15 (d, 1H, J=8, CH-3), 6.77-7.05 (m, 2H, CH-4, CH-1), 7.17-7.45 (m, 8H), 7.92-8.40 (m, 2H); IR (KBr): ν (cm^{-1}) =3299 (NH), 1688 (CO); ^{13}C-NMR ($CDCl_3$) δ: 14.13 (CH_3), 29.60 (C-1), 64.17 (CH_2), 108.30 (C-4), 113.20, 115.20, 120.30, 120.80, 124.60, 125.30, 126.16, 127.50, 127.80, 128.30, 133.40, 137.50, 140.15, 151.20 (CO) - $C_{20}H_{18}N_2O_2$ (318.37): calcd. C 75.45, H 5.70, N 8.80; found C 75.55, H 5.90, N 8.65.

3c: **1-(1*H*-3-indolyl)-1,2-dihydro-2-isoquinolinyl-phenylmethanone**,
(recrystallization: Et_2O)
^{1}H-NMR (DMSO-d_6) δ: 6.27 (d, 1H, J=7, CH-3), 6.90-7.05 (m, 2H, CH-4, CH-1), 7.10-7.30 (m, 4H), 7.43 (s, 4H), 7.61 (s, 5H), 7.87-8.07 (m, 2H); IR (KBr): ν= 3257 (NH), 1642 (CO), 1615 cm^{-1} (C=C); ^{13}C-NMR ($CDCl_3$) δ: 40.15 (C-1), 108.35 (C-4), 112.30, 117.15, 120.75, 121.80, 122.30, 123.15, 124.70, 125.60, 125.80, 127.10, 127.80, 128.16, 129.70, 132.16, 133.25, 134.28, 136.35, 138.90, 170.95 (CO) - $C_{24}H_{18}N_2O$ (350.41): calcd. C 82.26, H 5.18, N 7.99; found C 82.34, H 5.30, N 7.80.

3d: **1-[1-(1*H*-2-pyrrolyl)-1,2-dihydro-2-isoquinolinyl]-1-ethanone**,
(eluent: mixture petroleumether/ether – 1/1)
^{1}H-NMR ($CDCl_3$): 2.25 (s,3H,CH_3), 5.52 (s,1H), 6.00-6.25 (m,2H), 6.60 (d,1H,J=8,CH-4), 6.75-6.90 (m,1H), 6.98 (s,1H,CH-1), 7.25-7.50 (m,4H), 9.05 (s,1H,NH); IR (KBr): ν =3303 (NH), 1647 (CO), 1618 cm^{-1} (C=C); ^{13}C-NMR($CDCl_3$): 21.63 (CH_3), 50.31 (C-1), 105.84, 107.41 (C-4), 108,09, 110.23, 117.93, 123.86, 124.72, 127.41, 127.66, 128.08, 130.41, 132.65, 170.18 (CO) - $C_{15}H_{14}N_2O$ (238.28): calcd. C 75.61, H 5.92, N 11.76; found C 75.85, H 6.10, N 11.50.

3e: **ethyl 1-(1*H*-2-pyrrolyl)-1,2-dihydro-2-isoquinolinecarboxylate**,
(eluent: mixture p. ether/ether – 2/1)
^{1}H-NMR ($CDCl_3$): 3.37 (t,3H,J=7,CH_3), 4.44 (q,2H,J=7,CH_2), 5.52-5.72 (m,1H), 5.97

(d,1H,*J*=8,CH-3), 6.07-6.21 (m,1H), 6.75 (d,1H,*J*=8,CH-4), 6.80-6.97 (m,2H), 7.20-7.47 (m,4H), 9.05 (s,1H,NH); IR (KBr): ν =3329 (NH), 1689 (CO), 1632 cm^{-1} (C=C); ^{13}C-NMR($CDCl_3$): 13.70 (CH_3), 43.70 (C-1), 59.60 (CH_2), 105.16 (C-4), 107.15, 109.70, 124.15, 125.60, 126.30, 127.11, 128.35, 129.40, 134.15, 137.26, 139.60, 153.63 (CO) - $C_{16}H_{16}N_2O_2$(268.31): calcd. C 71.62, H 6.01, N 10.44; found C 71.80, H 6.20, N 10.30.

3f: **phenyl-1-(1*H*-2-pyrrolyl)-1,2-dihydro-2-isoquinolinylmethanone**, (eluent: mixture p.ether/ether – 2/1)
^{1}H-NMR ($CDCl_3$): 5.48-5.65 (m,1H), 6.07 (d,1H,*J*=8,CH-3), 6.12-6.32 (m,1H), 6.50 (d,1H,*J*=8,CH-4), 6.85-7.00 (m,1H), 7.05 (s,1H,CH-1), 7.35-7.47 (m,3H), 7.52 (s,2H), 7.58-7.90 (m,4H), 9.50 (s,1H,NH); IR (KBr): ν =3376 (NH), 1651 (CO), 1624 cm^{-1} (C=C); ^{13}C-NMR($CDCl_3$): 39.16 (C-1), 104.60, 105.60 (C-4), 109.17, 124.15, 124.80, 125.08, 125.60, 126.30, 126.80, 129.35, 129.95, 131.16, 132.36, 135.39, 140.37, 168.23 (CO) - $C_{20}H_{16}N_2O$ (300.35): calcd. C 79.98, H 5.37, N 9.33; found C 80.13, H 5.52, N 9.17.

4d: 1-1-[5-(2-acetyl-1,2-dihydro-1-isoquinolinyl)-1*H*- 2-pyrrolyl] -1,2-dihydro-2-isoquinolinyl-1-ethanone, (recrystallization: MeCOMe)
^{1}H-NMR ($CDCl_3$): 2.23 (s, 6H, 2CH_3) 5.38 (d, 2H, *J*=3), 6.02 (d, 2H, *J*=8, 2CH-3), 6.62 (d, 2H, *J*=8, 2CH-4), 6.90 (s, 2H, 2CH-1), 7.18-7.50 (m, 8H), 9.18 (s, 1H, NH); IR (KBr): ν =3349 (NH), 1662 (CO),1626 cm^{-1} (C=C); ^{13}C-NMR ($CDCl_3$): 21.37 (CH_3), 21.55 (CH_3), 50.26 (C-1), 52.18 (C-1), 106.85, 108.03 109.76, 124.29, 124.65, 127.29, 127.46, 127.59, 127.94, 129.97, 130.19, 132.37, 169.47 (CO), 169.79 (CO) - $C_{26}H_{23}N_3O_2$ (409.48): calcd. C 76.26, H 5.66, N 10.26; found C 76.38, H 5.79, N 10.13.

4e: **ethyl 1-[5-(2-ethyloxycarbonyl-1,2-dihydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-1,2-dihydro-2-isoquinolinecarboxylate,** (recrystallization: MeCOMe)
^{1}H-NMR ($CDCl_3$): 1.32 (t,3H,*J*=7,CH_3), 1.40 (t,3H,*J*=7,CH_3), 4.32 (q,2H,*J*=7,CH_2), 4.42 (q,2H,*J*=7,CH_2), 5.32-5.55 (m,2H), 5.92 (d,2H,*J*=8,2CH-3), 6.57 (s,2H,2CH-1), 6.85 (d,2H,*J*=8,2CH-4), 7.15-7.50 (m,8H), 9.52 (s,1H,NH); IR (KBr): ν= 3425 (NH), 1698 (CO), 1634 cm^{-1} (C=C); ^{13}C-NMR ($CDCl_3$): 13.95 (2CH_3), 45.10 (C-1), 53.70 (C-1), 59.15 (2CH_2), 100.20, 100.80, 102.78 (2C-4), 122.45, 123.18, 125.32, 126.17, 129.34, 131.15, 132.28, 134.80, 135.35, 136.90, 140.50, 152.17 (CO), 169.35 (CO) - $C_{28}H_{27}N_3O_4$ (469.53): calcd. C 71.63, H 5.80, N 8.95; found C 71.75, H 5.93, N 8.80.

4f:1-[5-(2-benzoyl-1,2-dihydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-1,2-dihydro-2-isoquinolinyl-phenylmethanone, (recrystallization: MeCOMe)
^{1}H-NMR ($CDCl_3$): 5.40 (d,2H,*J*=2), 5.98 (d,2H,*J*=8,2CH-3), 6.45 (d,2H,*J*=8,2CH-4), 6.95 (s,2H,2CH-1), 7.18-7.25-7.45 (m,8H), 7.50-7.90 (m,10H), 9.65 (s,1H,NH); IR (KBr): ν= 3380 (NH), 1655 (CO), 1624 cm^{-1} (C=C); ^{13}C-NMR ($CDCl_3$): 42.18 (C-1), 50.29 (C-1), 98.35, 104.30, 115.38, 120.16, 124.30, 126.73, 128.16, 128.86, 132.35, 132.80, 133.15, 134.25, 138.50, 142.16, 173.25 (CO), 174.10 (CO) - $C_{36}H_{27}N_3O_2$(533.62): calcd. C 81.03, H 5.10, N 7.87; found C 81.23, H 5.23, N 7.79.

3.2 General Procedure for preparation of products 8a-e, 10a-d, 11a-d, 13a-b, 14b and 16 (Table 2):

Acyl chloride (2 mmol) was added dropwise to a stirred solution of 3,4-dihydroisoquinoline (2 mmol) in dichloromethane (3 mL) at room temperature. The mixture was stirred for 1 h (or 30 min at 40-50^{o}C) for the preparation of adducts **6**. For products **8**, **10** and **11** the reaction mixture was cooled to 0^{o}C and a solution of indole (2 mmol) or pyrrole (2 mmol) and Et_3N (2 mmol) in dichloromethane (3 mL) was added dropwise. For the preparation of products **13**, **14** and **16,** thiophene or pyrazine (2 mmol) and BF_3ĚEt$_2$O (0.5 mL) were added to the already obtained reagent **6** . The reactions were carried out at the conditions given in Table 2, then treated with 10% aq. HCl (10 mL) and rapidly extracted with $CHCl_3$ (3×10 mL). The combined extract was washed with 10% aq. $NaHCO_3$ (2×10 mL), dried (Na_2SO_4) and the solvent was removed by distillation. The products were separated and purified by recrystallization or column chromatography on a neutral Al_2O_3.

8a: **1-[1-(1*H*-3-indolyl)-1,2,3,4-tetrahydro-2-isoquinolinyl]-1-ethanone**, (eluent: $CHCl_3$)
^{1}H-NMR ([D6]DMSO): 2.09 (s, 3H, CH_3), 2.91-3.07 (m, 2H, CH_2-4), 3.71-3.79 (m, 2H, CH_2-3), 6.59 (s, 1H, CH-1), 6.92-7.21 (m, 7H), 7.35 (d, 1H, J=6), 7.58 (d, 1H, J=6), 10.96 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 21.60 (CH_3), 28.59(C-4), 38.91(C-3), 48.12 (C-1), 111.66, 117.25, 118.92, 119.42, 121.52, 125.58, 125.89, 126.76, 128.35, 129.04, 134.58, 136.37, 136.48, 168.02 (CO) - $C_{19}H_{18}N_2O$ (290.36): calcd. C 78.59, H 6.25, N 9.65; found C 78.73, H 6.38, N 9.50.

8b: **ethyl 1-(1*H*-3-indolyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate**, (eluent: mixture p.ether/ether – 3/1)
^{1}H-NMR ($CDCl_3$): 1.25 (t, 3H, J=6, CH_3) 2.69-2.77 (m, 2H, CH_2-4), 3.05-3.24 (m, 2H, CH_2-3), 4.12-4.22 (m, 2H, CH_2), 6.60 (s, 1H, CH-1), 6.61-6.76 (m, 1H), 7.02-7.20 (m, 6H), 7.29-7.33 (m, 1H), 7.75 (s, 1H), 8.21 (s,1H, NH); ^{13}C-NMR ($CDCl_3$): 14.77 (CH_3), 28.51 (C-4), 37.24 (C-3), 51.18 (C-1), 61.37 (CH_2), 111.05, 119.75, 120.12, 122.23, 124.97, 125.73, 126.63, 128.38, 128.96, 136.14, 136.35, 155.18 (CO) - $C_{20}H_{20}N_2O_2$ (320.38): calcd. C 74.98, H 6.29, N 8.74; found C 75.09, H 6.42, N 8.63.

8c: **1-(1*H*-3-indolyl)-1,2,3,4-tetrahydro-2-isoquinolinyl-phenylmethanone**, (eluent: mixture p.ether/ether – 1/2)
^{1}H-NMR ($CDCl_3$): 2.75-2.95 (m, 2H, CH_2-4), 3.66-3.83 (m, 2H, CH_2-3), 6.75 (s, 1H, CH-1), 7.08-7.25 (m, 5H), 7.30 (s, 4H), 7.42 (s, 4H), 7.82-7.95 (m, 1H), 8.96 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 29.56 (C-4), 40.20 (C-3), 45.30 (C-1), 108.50, 109.00, 112.60, 113.70, 118.50, 120.40, 121.20, 123.30, 123.70, 124.30, 125.50, 126.40, 128.30, 129.40, 129.70, 130.20, 132.12, 134.16, 135.35, 139.60, 160.25 (CO) - $C_{24}H_{20}N_2O$ (352.43): calcd. C 81.79, H 5.72, N 7.95; found C 81.91, H 5.90, N 7.83.

8d: **1-[1-(1*H*-3-indolyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolinyl]-1-ethanone,** (eluent: mixture p.ether/ether – 1/2)
^{1}H-NMR ([D6]DMSO): 2.08 (s, 3H, CH_3), 2.56-2.82 (m, 2H, CH_2-3), 3.55-3.65 (m, 2H, CH_2-4), 3.73 (s, 3H, MeO), 3.89 (s, 3H, MeO), 6.62 (s, 1H, CH-1), 6.67 (s, 1H), 6.78 (s, 1H), 6.88-6.98 (m, 2H), 7.07 (s, 1H), 7.34 (d, 1H, J=3), 7.60 (d, 1H, *J*=3), 10.91 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 21.55 (CH_3), 28.20 (C-4), 38.59 (C-3), 47.72 (C-1), 55.60, 111.41, 111.68, 111.82, 118.87, 119.48, 125.62, 126.36, 128.06, 136.52, 147.11, 167.84 (CO);) - $C_{21}H_{22}N_2O_3$ (350.41): C 71.98, H 6.33, N 7.99; found C 72.10, H 6.45, N 7.80.

8e: **ethyl 1-(1*H*-3-indolyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate,** (eluent: mixture p.ether/ether – 2/1)
^{1}H-NMR ($CDCl_3$): 1.26 (t, 3H, *J*=6, CH_3), 2.55-2.85 (m, 2H, CH_2-4), 3.15-3.25 (m, 2H, CH_2-3), 3.75 (s, 3H, MeO), 3.94 (s, 3H, MeO), 4.16-4.44 (m, 2H), 6.62 (s, 1H, CH-1), 6.75 (s, 2H), 7.20-7.48 (m, 5H), 8.46 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 13.80 (CH_3), 26.40 (C-4), 45.80 (C-3), 50.35 (C-1), 54.25 (CH_3), 55.80 (CH_3), 52.16 (CH_2), 104.30, 110.20, 111.30, 112.40, 117.20, 118.50, 124.30, 125.60, 132.50, 134.20, 136.20, 143.70, 148.60, 156.70 (CO) - $C_{22}H_{24}N_2O_4$ (380.44): calcd. C 69.46, H 6.36, N 7.36; found C 69.55, H 6.48, N 7.20.

10a: **1-[1-(1*H*-2-pyrrolyl)-1,2,3,4-tetrahydro-2-isoquinolinyl]-1-ethanone**, (eluent: $CHCl_3$)
^{1}H-NMR ($CDCl_3$): 2.16 (s, 3H, CH_3), 2.92-3.04 (m, 2H, CH_2-4), 3.44-3.55 (m, 1H, CH-3), 3.64-3.73 (m, 1H, CH-1), 5.50 (s,1H), 6.00 (s,1H), 6.70 (s,2H), 7.17-7.28 (m, 4H), 9.27(s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 21.78 (CH_3), 28.91 (C-4), 41.16 (C-1), 50.39 (C-3), 107.00, 107.58, 117.74, 126.19, 127.04, 128.23, 128.78, 133.71, 133.82, 134.33, 170.64 (CO) - $C_{15}H_{16}N_2O$ (240.30): calcd. C 74.97, H 6.71, N 11.66; found C 75.09, H 6.90, N 11.50.

10b: **ethyl 1-(1*H*-2-pyrrolyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate**, (eluent: mixture p.ether/ether – 3/1)
^{1}H-NMR ([D6]DMSO): 1.28 (t, 3H, *J*=6, CH_3), 2.76-2.93 (m, 2H, CH_2-4), 3.06-3.41 (m, 2H, CH_2-3), 4.19 (q, 2H, *J*=6, CH_2), 5.52 (s, 1H), 6.01 (s, 1H), 6.34 (s, 1H, CH-1), 6.71 (s, 1H), 7.12-7.26 (m, 4H), 9.15 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 14.65 (CH_3), 28.56 (C-4), 38.55 (C-1), 51.95 (C-3), 61.61 (CH_2), 107.20, 117.66, 125.85, 126.98, 128.48, 133.81, 134.88, 156.78 (CO) - $C_{16}H_{18}N_2O_2$ (270.33): calcd. C 71.09, H 6.71, N 10.36; found C 71.20, H 6.89, N 10.20.

10c: phenyl-1-(1*H*-2-pyrrolyl)-1,2,3,4-tetrahydro-2-isoquinolinylmethanone, (eluent: mixture p.ether/ether – 2/1)
^{1}H-NMR ($CDCl_3$): 3.00-3.20 (m, 2H, CH_2-4), 3.56-3.70 (m, 2H, CH_2-3), 6.13 (s, 1H, CH-1), 6.18-6.35 (m, 1H), 6.78-6.92 (m, 2H), 7.15-7.28 (m,3H), 7.50-7.83 (m,6H), 8.63 (s,1H,NH); ^{13}C-NMR ($CDCl_3$): 25.16 (C-4), 42.18 (C-3), 43.80 (C-1), 107.07, 113.12, 122.30, 123.80, 124.10, 125.16, 126.70, 127.15, 128.50, 129.24, 131.18, 132.10, 135.19, 142.60, 169.70 (CO): $C_{20}H_{18}N_2O$ (302.37): calcd. C 79.44, H 6.00, N 9.26; found C 79.80, H 6.35, N 9.00.

10d: ethyl 6,7-dimethoxy-1-(1*H*-2-pyrrolyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate, (eluent: mixture p.ether/ether – 2/1)
^{1}H-NMR ($CDCl_3$): 1.35 (t, 3H, J=7, CH_3), 2.74-3.00 (m, 2H, CH_2-4), 3.10-3.45 (m, 2H, CH_2-3), 3.87 (s, 3H, MeO), 3.97 (s, 3H, MeO), 4.31 (q, 2H, J=7, CH_2), 5.71 (s, 1H), 6.10-6.25 (m, 1H), 6.40 (s, 1H, CH-1), 6.80 (s, 1H), 6.85 (s, 1H), 6.86-7.00 (m, 1H), 9.92 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 13.90 (CH_3), 22.60 (C-4), 43.80 (C-1), 45.20 (C-3), 54.90 (CH_3), 55.20 (CH_3), 60.20 (CH_2), 102.30, 108.30, 110.50, 113.60, 118.90, 124.60, 125.80, 137.80, 145.20, 147.80, 156.20 (CO) - $C_{18}H_{22}N_2O_4$ (330.38): calcd. C 65.44, H 6.71, N 8.48; found C 65.57, H 6.89, N 8.30.

11a: **1-1-[5-(2-acetyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-1, 2, 3, 4-tetrahydro-2-isoquinolinyl-1-ethanone,** (eluent: $CHCl_3$)
^{1}H-NMR ($CDCl_3$): 2.24 (s, 6H, 2CH_3), 3.00 (t, 4H, J=7, 2CH_2-4), 3.72 (q, 4H, J=6, 2CH_2-3), 5.42 (d, 2H, J=2), 6.82 (s, 2H, 2CH-1), 7.12-7.30 (m, 1H), 7.32 (s, 8H); ^{13}C-NMR ($CDCl_3$): 19.60 (CH_3), 20.70 (CH_3), 23.60 (2C-4), 40.15 (C-1), 42.16 (C-3), 44.15 (C-3), 51.40 (C-1), 100.70, 123.26, 124.60, 125.10, 126.60, 127.10, 129.01, 130.70, 136.90, 140.25, 165.15 (CO), 178.60 (CO) - $C_{26}H_{27}N_3O_2$ (413.51): calcd. C 75.52, H 6.58, N 10.16; found C 75.70, H 6.73, N 10.04.

11b: **ethyl 1-[5-(2-ethyloxycarbonyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate,** (eluent: mixture p.ether / ether – 3/1)
^{1}H-NMR ($CDCl_3$): 1.25 (t, 3H, J=7, CH_3), 1.33 (t, 3H, J=7, CH_3), 2.77-3.05 (m, 4H, 2CH_2-4), 3.10-3.40 (m,4H,2CH_2-3), 3.75 (q, 2H, J=6, CH_2), 4.10-4.58 (m,2H,CH_2), 5.45 (s,2H), 6.38 (s, 2H, 2CH-1), 7.27 (s,8H), 9.72 (s,1H,NH); ^{13}C-NMR ($CDCl_3$): 13.90 (2CH_3), 23.60 (2C-4), 42.80 (C-1), 44.60 (2C-3), 52.80 (C-1), 61.40 (2CH_2), 101.20, 124.60, 125.40, 126.70, 128.60, 130.60, 132.40, 135.26, 136.70, 139.60, 149.15 (CO), 165.17 (CO) – $C_{28}H_{31}N_3O_4$ (473.56): calcd. C 72.02, H 6.60, N 8.87; found C 71.15, H 6.78, N 8.79.

11c: 1-[5-(2-benzoyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-1,2, 3,4-tetrahydro-2-isoquinolinyl-phenylmethanone, (eluent: Et_2O)
^{1}H-NMR ($CDCl_3$): 3.13-3.35 (m, 4H, 2CH_2-4), 3.60-3.84 (m, 4H, 2CH_2-3), 5.97 (s, 2H, 2CH-1), 6.30-6.48 (m, 2H), 6.75-6.89 (m, 6H), 7.26-7.50 (m, 2H), 7.68-7.80 (m, 10H), 8.57 (s,1H,NH); ^{13}C-NMR ($CDCl_3$): 24.15 (2CH_2-4), 40.58 (CH-1), 42.70 (2CH_2-3), 52.16 (CH-1), 106.30, 120.18, 123.70, 124.80, 125.14, 126.30, 126.80, 127.80, 128.50, 129.50, 131.20, 132.60, 138.80, 139.15, 141.60, 169.15 (CO), 171.12 (CO): $C_{36}H_{31}N_3O_2$ (537.65): calcd. C 80.42, H 5.81, N 7.82; found C 80.23, H 6.03, N 7.65.

11d: **ethyl 1-[5-(2-ethyloxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolinyl)-1*H*-2-pyrrolyl]-6,7-dimethoxy- 1,2,3,4-tetrahydro-2-isoquinolinecarboxylate,** (eluent: mixture p.ether/ether – 1/3)
^{1}H-NMR ([D6]DMSO): 1.28 (t, 3H, J=7, CH_3), 1.30 (t, 3H, J=7, CH_3), 2.56-2.71 (m, 2H), 2.77-2.87 (m, 2H), 3.18-3.36 (m, 4H), 3.81 (s, 6H, 2MeO), 3.87 (s, 6H, 2MeO), 4.09-

4.24 (m, 4H, $2CH_2$), 5.41 (d, 2H, J=2), 6.20 (s, 2H, 2CH-1), 6.63 (s, 2H), 6.69 (s, 2H), 9.14 (s, 1H, NH); ^{13}C-NMR ($CDCl_3$): 14.65 ($2CH_3$), 28.08 (2C-4), 37.48 (C-1), 38.42 (2C-3), 51.73 (C-1), 55.79 (2MeO), 56.00 (2MeO), 61.57 ($2CH_2$), 107.25, 111.08, 125.45, 126.93, 147.14, 147.99 (CO), 155.48 (CO) - $C_{32}H_{39}N_3O_8$ (593.67): calcd. C 64.74, H 6.62, N 7.08; found C 64.93, H 6.78, N 7.03.

13a: **1-[1-(2-thienyl)-1,2,3,4-tetrahydro-2-isoquinolinyl]-1-ethanone**, (eluent: Et_2O)
^{1}H-NMR ([D6]DMSO): 2.23 (s, 3H, CH_3), 3.00 (t, 2H, J=7, CH_2-4), 3.82 (t, 2H, J=5, CH_2-3), 6.82-6.92 (m, 2H), 7.03 (t, 1H, J=5), 7.17 (s, 1H), 7.32 (s, 4H); ^{13}C-NMR ($CDCl_3$): 21.65 (CH_3), 21.79 (C-4), 36.41 (C-1), 40.46 (C-3), 125.19, 125.47, 126.14, 126.27, 126.63, 127.24, 127.73, 128.61, 129.15, 133.83, 134.75, 134.87, 135.15, 146.04, 168.84 (CO) - $C_{15}H_{15}NOS$ (257.35): calcd. C 70.01, H 5.87, N 5.44; found C 70.20, H 5.93, N 5.30.

13b: **ethyl 1-(2-thienyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate**, (eluent: mixture p.ether/ether – 4/1)
^{1}H-NMR ($CDCl_3$): 1.37 (t, 3H, J=7, CH_3), 2.72-3.05 (m, 2H, CH_2-4), 3.10-3.55 (m, 2H, CH_2-3), 4.27 (q, 2H, J=7, CH_2), 6.62 (s, 1H, CH-1), 6.83 (d, 1H, J=2), 6.95 (t, 1H, J=5), 7.25 (s, 4H), 7.32 (s, 1H); ^{13}C-NMR ($CDCl_3$): 14.17 (CH_3), 25.70 (C-4), 45.60 (C-1), 47.20 (C-3), 64.60 (CH_2), 119.70, 125.16, 127.20, 130.40, 131.50, 132.60, 134.15, 149.70, 156.18 (CO) - $C_{16}H_{17}NO_2S$ (287.38): calcd. C 66.87, H 5.96, N 4.87; found C 66.95, H 6.07, N 4.70.

14b: **ethyl 1-[5-(2-ethyloxycarbonyl-1,2,3,4-tetrahydro-1-isoquinolinyl)-2-thienyl]- 1,2,3,4-tetrahydro-2-isoquinolinecarboxylate**, (eluent: mixture p. ether / ether – 4/1)
^{1}H-NMR ($CDCl_3$) δ: 1.35 (t, 6H, J=6, $2CH_3$), 2.75-3.07 (m, 4H, $2CH_2$-4), 3.12-3.50 (m, 4H, $2CH_2$-3), 4.25 (q, 4H, J=6, $2CH_2$), 6.60 (s, 2H, 2CH-1), 7.22 (s, 8H), 7.35(s, 2H); ^{13}C-NMR ($CDCl_3$) δ: 15.00 ($2CH_3$), 24.30 (2C-4), 45.60 (C-1), 47.80 (2C-3), 56.20 (C-1), 65.18 ($2CH_2$), 118.70, 128.90, 129.70, 130.40, 131.20, 132.40, 133.50, 134.20, 138.60, 143.20, 157.60 (CO), 159.80 (CO) - $C_{28}H_{30}N_2O_4S$ (490.61): calcd. C 68.55, H 6.16, N 5.71; found C 68.70, H 6.25, N 5.79.

16: **ethyl 1-(2-pyrazinyl)-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate**, (eluent: mixture p.ether/ether – 2/1)
^{1}H-NMR ($CDCl_3$) δ: 1.30 (t, 3H, J=7, CH_3), 2.82-3.08 (m, 2H, CH_2-4), 3.52-3.62 (m, 2H, CH_2-3), 4.24 (q, 2H, J=7, CH_2), 6.42 (s, 1H, CH-1), 7.12-7.45 (m, 4H), 8.57 (s, 2H), 8.80 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 14.60 (CH_3), 25.60 (C-4), 50.60 (C-3), 60.55 (C-1), 64.15 (CH_2), 128.16, 129.30, 130.60, 137.50, 138.40, 140.25, 142.17, 150.12, 152.60 (CO), 156.20 - $C_{16}H_{17}N_3O_2$ (283.32): calcd. C 67.83, H 6.05, N 14.83; found C 67.95, H 6.30, N 14.70.

Acknowledgements

We acknowledge financial support from the Fund for Scientific Research of the University of Plovdiv.

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