

HETEROCYCLES, Vol. 71, No. 2, 2007, pp. 269 - 280. © The Japan Institute of Heterocyclic Chemistry
Received, 28th September, 2006, Accepted, 28th December, 2006, Published online, 29th December, 2006. COM-06-10899

THE STUDY OF CYCLIZATION OF *N*-ACYLPHENACYL ANTHRANILATES WITH AMMONIUM SALTS UNDER VARIOUS CONDITIONS

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Abstract – *N*-Acylphenacyl anthranilates were heated with ammonium salts in organic acid or NMP, and formation of various heterocyclic compounds was observed. Reaction results are strongly influenced by reaction conditions. The most interesting are imidazole derivatives with various anelated rings.

INTRODUCTION

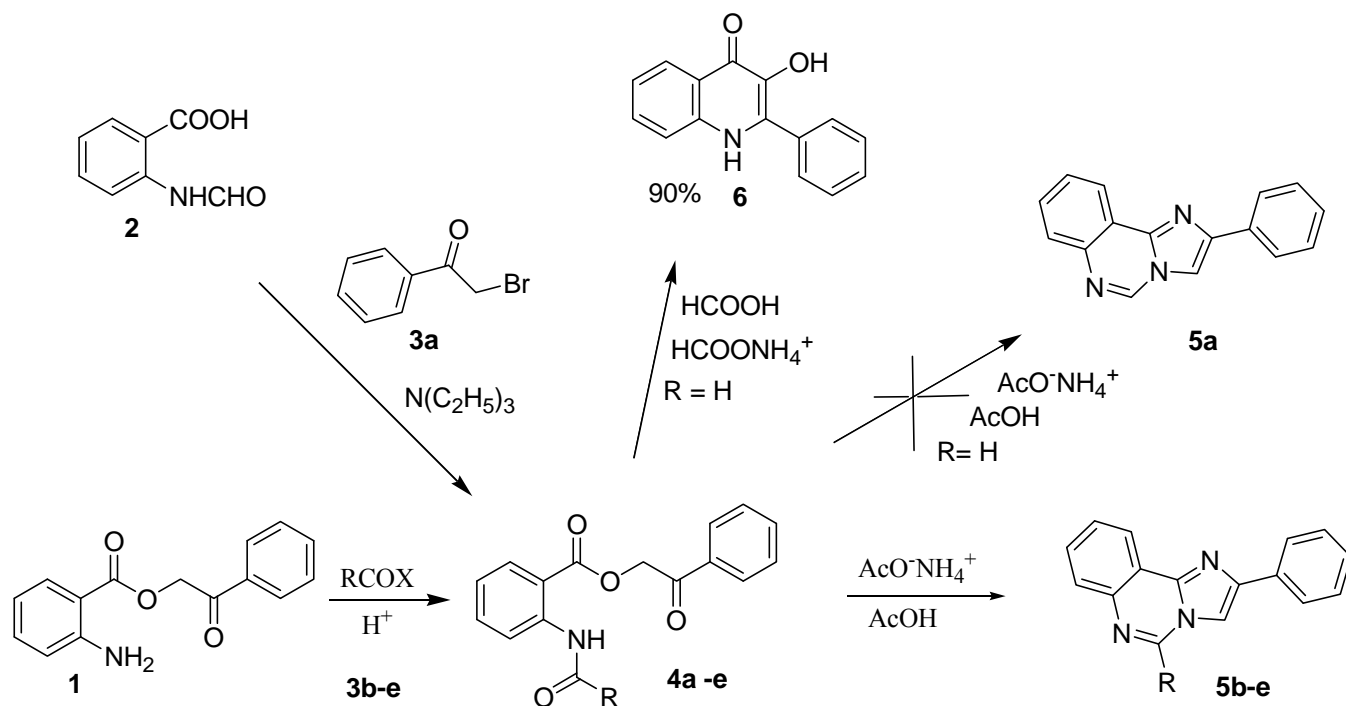
3-Amino-2-phenyl-4(*IH*)-quinolinone derivatives exhibit very interesting biological activities. The simplest way for preparation of these compounds is cyclization of 2'-amino-2,4-diphenyl oxazoles or *N*-phenacyl anthranilamides.¹ In contrast, phenacyl anthranilates, *N*-phenacyl anthranilamides are sometimes hardly available. It was proved that some oxazole derivative can also serve as an alternative starting material.¹ For this reason, 2'-amino-2,4-diphenyl oxazole derivatives synthesis was studied.

RESULTS AND DISCUSSION

Preparation of 2,4-disubstituted oxazole and imidazole derivatives by reaction of esters of 2-hydroxyketones with ammonium acetate in acetic acid was described a long time ago.²

Unfortunately this reaction fails in the case of phenacyl anthranilate, and 2-hydroxymethyl-4-oxo-2-phenyl-1,2,3,4-tetrahydroquinazoline derivatives are prepared in this way.³ For this reason, the behavior of various *N*-acylphenacyl anthranilates at similar conditions was tested. The cyclization did not go in a way that we expected, and various heterocyclic compounds were prepared depending on reaction conditions.

Formyl derivative (**4a**) was prepared by a reaction of salt formyl anthranilic acid (**2**) with phenacyl bromide (**3a**) (Scheme 1). The remaining acyl derivatives (**4b-e**) were prepared from phenacyl anthranilate (**1**) by acylation, acyl chloride or acetic anhydride (Ac₂O) with catalysis by *p*-toluenesulfonic acid (*p*-TsOH), in high yield.



	R	X	cmpd.	yield (%)
a	H		4a	69%
b	CH ₃	OAc	4b	97%
c	CH(CH ₃) ₂	Cl	4c	96%
d	(CH ₂) ₁₄ CH ₃	Cl	4d	93%
e	Ph	Cl	4e	84%

cmpd.	yields (%)		
	A	B	C
5b	21	18	16
5c	68	24	45
5d	51	14	25
5e	10	15	33

Scheme 1

The melting of these acyl anthranilates (**4**) with ammonium acetate and acetic acid in ratio 1 g acetic acid and 1 g ammonium acetate to 1 mmol of phenacyl ester was tested at the beginning.

A complicated mixture was received by reaction of a compound (**4a**). When ammonium formate and formic acid were used instead of acetic acid and ammonium acetate, the quinolinone (**6**)⁴ was formed in high yield (Scheme 1). The synthesis of quinolinone (**6**) by cyclization of phenacyl anthranilate (**1**) in PPA with normal heating⁴ or micro wave irradiation⁵ is known.

The compound (**4b**) reacted in a different way. The starting material (**4b**) was not observed after 30 minutes in the melt. The reaction mixture was poured into water and the precipitated solid was filtered off. An amount of the compound was formed in this way, but one was dominant. Dried solid was stirred with acetone and insoluble part was a clean compound, later identified as **5b**. Additional quantity was

isolated by column chromatography from the mother liquor (toluen : EtOAc 1 : 1). No positive influence of longer reaction time on the yield of compound (**5b**) and on the number of impurities was observed. The same conditions were used for the cyclization of compounds (**4a** and **4c-d**). For aliphatic acyl derivatives, the dominant imidazo[1,2-*c*]quinazoline derivatives (**5**) were formed. In this way compounds (**5c** and **5d**) were prepared. The compounds (**5**) were analyzed in detail using two dimensional ^1H , ^{13}C NMR spectra and for compound (**5b**) also ^1H , ^{15}N HMBC spectrum. The ^1H , ^{13}C and ^{15}N chemical shifts are collected in Experimental. The following numbering of atoms was used for this purpose (Figure 1).

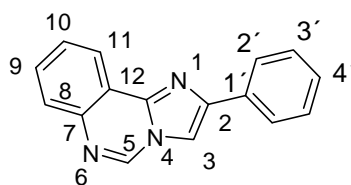


Figure 1

Table 1

Yields of compound (**5**)

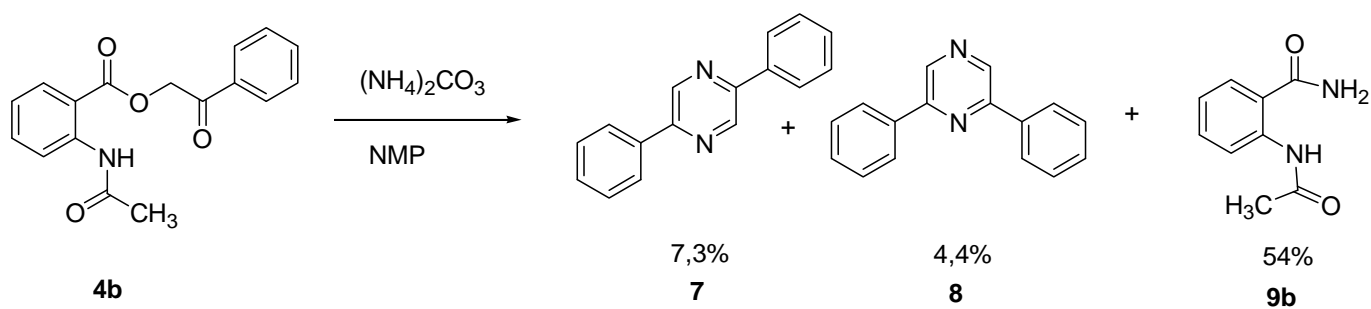
Cmp.	Method A		Method B		Method C		mp (°C)	solvent
	Yield (%)	time (h)	Yield (%)	time (h)	Yield (%)	time (h)		
5b	21	0.5	18	3	16	2	214-216	acetone
5c	68	1	24	5	45	2.5	218-221	MeOH
5d	51	0.5	14	16	25	5	87- 94	MeOH
5e	10*	1	15	3	33	2	145 - 148	MeOH

* yield of compound (**10e**) was 11%

The behavior of derivatives (**4**) in terms of dependence on the temperature and ratio of ammonium acetate and acetic acid was tested, by using three conditions (method A-C). If the amount of ammonium acetate was smaller than described in method A, the reaction was slower and some starting material was present in the reaction mixture after 10 hours of heating. Better results were achieved if the amount of acetic acid was 4 times higher than ammonium acetate and if 1 g of ammonium acetate was used for 1 mmol of acetyl derivative (**4b**) (method B). When the reaction was performed in a glass autoclave at a temperature of 190 °C, the reaction time was shortened and the yield was improved (method C).

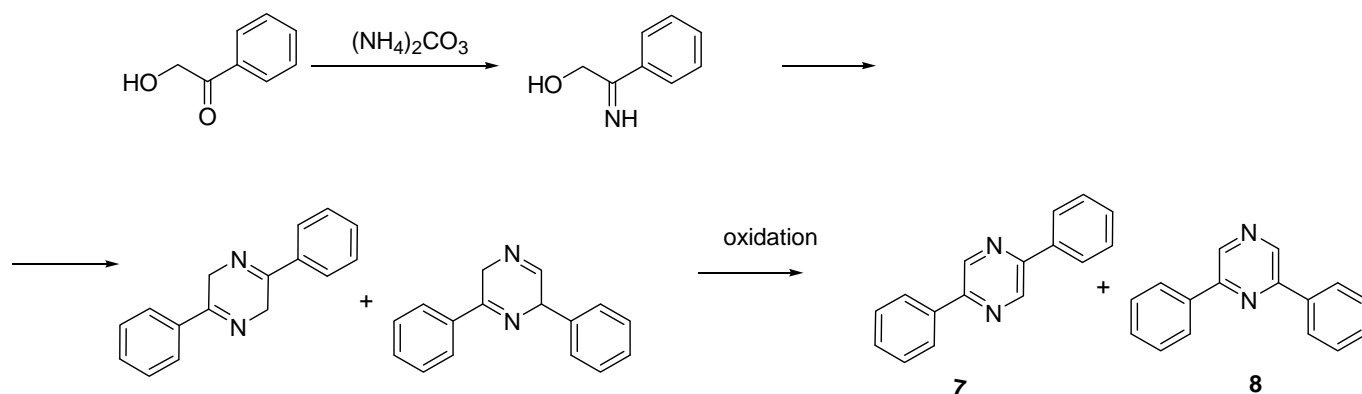
The usage of different ammonium sources and reaction conditions were tested. Inseparable mixtures were mostly received, and positive results were received in only few cases.

If cyclization of compound (**4b**) was done in *N*-methylpyrrolidone (NMP) and ammonium carbonate, a bunch of compounds was formed also, but there were not traces of compound (**5b**), in the reaction mixture. Small amount of compounds (**7** and **8**)^{6,7} and dominant compound (**9b**)⁸ were isolated by column chromatography (Scheme 2).



Scheme 2

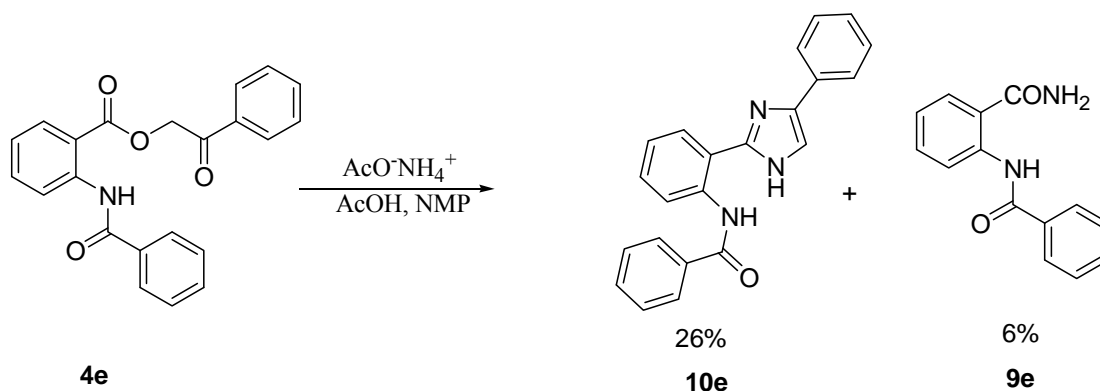
The mechanism of the formation of these compounds starts by the first reaction step - aminolysis of ester bond. Compound (**9b**) and 2-hydroxyacetophenone are formed. The next step is the reaction of 2-hydroxyacetophenone with ammonium, cyclization of imine and final oxidation and formation of pyridazine derivatives (Scheme 3). It is not clear what the oxidation agent is, but the quantity of pyridazine derivatives formed is so small that it could be oxygen from the air or some compound in the reaction mixture.



Scheme 3

If the compound (**4b**) was heated with ammonium acetate in NMP, the reaction mixture was more complex. Compounds (**5b**, **7**, **8** and **9b**) apart from many other different unidentified compounds were found. There was no advantage if different sources of ammonium such as ammonium hydroxide, ammonium chloride, ammonium sulfite, and urea were tested.

Cyclization of compound (**4e**) took a slightly different course. Apart from compound (**5e**), significant amounts of compounds (**10e**) were received (Method A). In the case of the reaction of benzoyl derivative (**4e**) with ammonium acetate, acetic acid and NMP imidazo derivative (**10e**) was dominant. Compound (**9e**)⁹ was isolated also from the reaction mixture. During this reaction formation of compound (**5e**) was not observed (Scheme 4). Milder reaction conditions were also tested, the reaction of compound (**4e**) was done with ammonium acetate in acetic acid and ethanol, the reaction time was longer, compounds (**5e**) were not formed and compounds (**10e** and **9e**) were dominant, but a large amount of unknown compounds were also formed.



Scheme 4

The ^1H and ^{13}C NMR data of compound (**10e**) were measured and analyzed in the same way as those for compounds (**5**). The following numbering of atoms was used for this purpose (Figure 2).

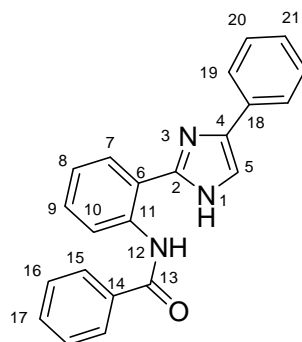
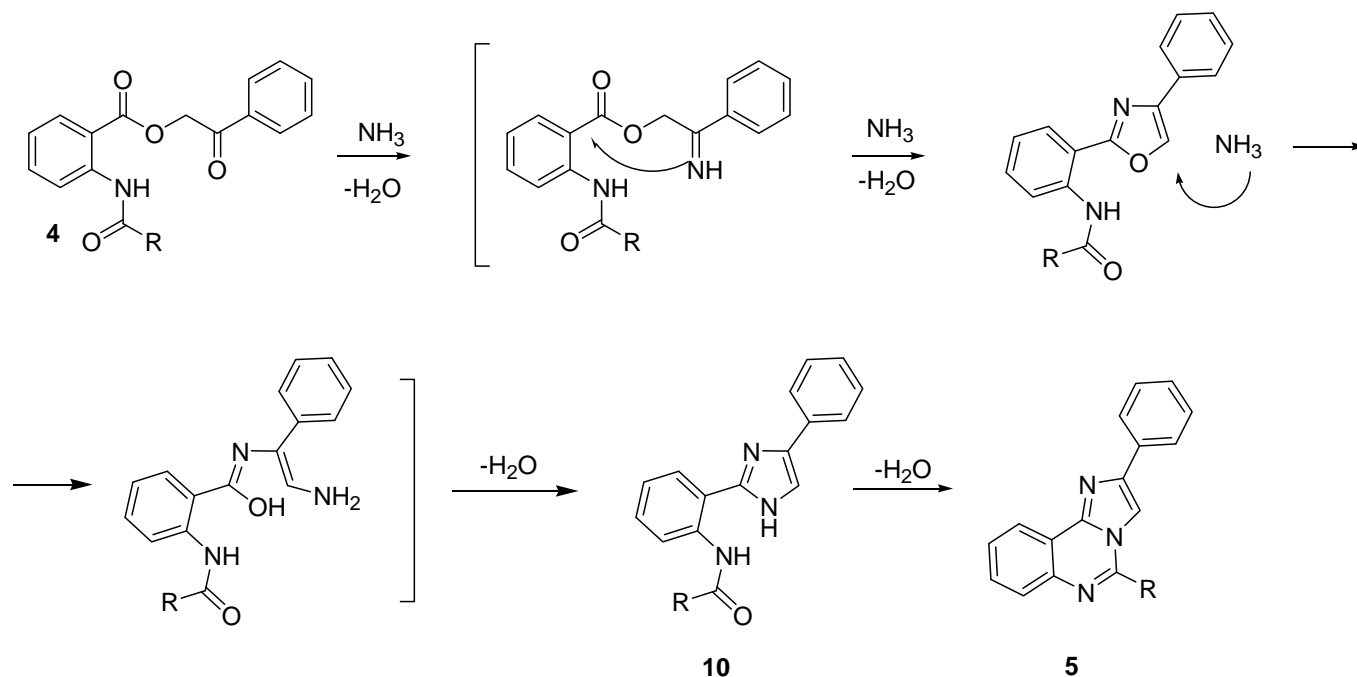


Figure 2

Isolation of imidazole derivative (**10e**) from the cyclization mixture uphold the mechanism of the cyclization of compounds (**4b-d**). It is probably the reaction step followed by the ring closing and formation of compounds (**5**) (Scheme 5).



Scheme 5

Imidazoquinazolines (**5**) were formed only at higher temperature, in acid conditions.

EXPERIMENTAL

Melting points were measured in the Kofler apparatus and are uncorrected. TLC was performed on Polygram Sil G/UV₂₅₄ with UV light detection and mobil phase n-hexane : ethylacetate 7 : 3. Infrared spectra (KBr disks) were taken with an ATI Unicam Genesis FTIR instrument. MS characterisation was carried out using the DEP-CI-MS-MS (direct exposure probe-chemical ionisation-tandem mass spectrometry) technique with quadrupole ion trap mass analyzer and methane as a CI reagent gas. NMR spectra were measured with a Bruker Avance 300 spectrometer operating at 300 MHz (¹H) and 75 MHz (¹³C) Bruker Avance 500 spectrometer operating at 500.13 MHz (¹H), 125.76 MHz (¹³C) and 50.68 MHz (¹⁵N). The compounds were dissolved in DMSO-*d*₆ and measured at 300 K. Construction of the microwawe reactor was described recently.¹⁰

¹H and ¹³C chemical shifts were referenced to the central signal of the solvent ($\delta = 2.55$ (¹H)). ($\delta = 39.6$ (¹³C)). The ¹⁵N chemical shifts were referred to external neat nitromethane in a co-axial capillary ($\delta = 0.0$). All 2D experiments (gradient-selected (gs)-COSY, gs-HMQC, gs-HMBC) were performed using manufacturer's software. Proton signals were assigned using gs-COSY. Protonated carbons were assigned by gs-HMQC and quaternary carbons gs-HMBC. The ¹⁵N chemical shifts of compound (**5b**) were read from gs-¹H, ¹⁵N-HMBC spectrum

2-Oxo-2-phenylethyl 2-Formylaminobenzoate (**4a**)

Mixture of *N*-formyl anthranilic acid (**2**) (8.26 g, 50 mmol), Et₃N (5.3 g, 7.3 mL, 52.4 mmol), acetone (100 mL) and phenacylbromide (**3a**) (9.95 g, 50 mmol) was stirred at rt for 3 hours. Then acetone was evaporated under *vacuo* and residuum was stirred with water. Precipitated solid was filtered off, and isolated product was crystallized from MeOH. The yield of compound (**4a**) was 9.8 g (69 %), mp 92.5 – 96°C.

Anal. Calcd for C₁₆H₁₃NO₄ C, 67.84; H, 4.63; N, 4.94. Found C, 67.90; H, 4.78; N, 4.41.

Full MS, *m/z* (relative intensity) 284 (2) [M+H]⁺, 312 [M+C₂H₅]⁺, 324 [M+C₃H₅]⁺, 255 [M+H-CHO]⁺, 188, 176, 148 (100) [C₆H₄NHCO(CO)]⁺, 120, 105 [C₆H₅CO]⁺, 91; MS²(284,w3,EV1), *m/z* 265, 255 (100), 225, 197, 148, 133, 120, 105.

¹H NMR (DMSO-*d*₆, 300 MHz) δ 10.59 (1H, s), 8.53 (1H, s), 8.50 (1H, s), 8.11 (1H, dd, *J* = 8.0, 1.2 Hz), 8.03 (2H, d, *J* = 8.0 Hz), 7.77-7.55 (4H, m), 7.28 (1H, ddd, *J* = 7.7, 7.5, 1.1 Hz), 5.81 (2H, s); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 192.5, 165.9, 160.9, 139.1, 134.5, 134.0, 133.7, 130.9, 128.9, 127.8, 123.4, 121.1, 116.2, 67.4.

2-Oxo-2-phenylethyl 2-Acetylaminobenzoate (**4b**)

Phenacyl ester (**1**) (15.8 g, 61.9 mmol) was dissolved in EtOAc (80 mL) and Ac₂O (14.9 g, 146 mmol) and *p*-TsOH (50 mg) were added. The reaction mixture was refluxed with stirring for 4 h. Phenacyl ester (**1**) was not observed on TLC. Compound (**4b**) was filtered off after the cooling. Part of the product was isolated from the mother liquor (2 g). Total yield was 17g (96.6 %), mp 162-163 °C.

Anal. Calcd. for C₁₇H₁₅NO₄ C, 68.68; H, 5.09; N, 4.71. Found C, 68.79; H, 5.23; N, 4.47.

Full MS, *m/z* (relative intensity) 298 (3) [M+H]⁺, 326 [M+C₂H₅]⁺, 338 [M+C₃H₅]⁺, 280 [M+H-H₂O]⁺, 255 [M+H-COCH₃]⁺, 238, 202, 190, 162 (100) [C₆H₄NHCOCH₃(CO)]⁺, 144, 120, 105 [C₆H₅CO]⁺, 91; MS²(298,w3,EV1), *m/z* 255 (100), 224, 197, 175, 162, 133, 120, 105.

¹H NMR (DMSO-*d*₆, 300 MHz) δ 10.45 (1H, s), 8.33 (1H, dd, *J* = 8.4, 0.8 Hz), 8.09-8.01 (3H, m), 7.78-7.55 (4H, m), 7.28 (1H, ddd, *J* = 7.7, 7.5, 1.1 Hz), 5.81 (2H, s), 2.12 (3H, s); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 192.6, 168.5, 166.3, 139.8, 134.2, 134.0, 133.7, 130.7, 128.9, 127.8, 123.0, 121.0, 116.9, 67.3, 24.5.

2-Oxo-2-phenylethyl 2-*i*-Butyrylamino benzoate (**4c**)

Phenacyl ester (**1**) (10 g, 39.2 mmol) was dissolved in acetone (60 mL) and Et₃N (6.5 mL, 4.54 g, 45 mmol) and *i*-butyryl chloride (4.8 g, 45 mmol) were added. The reaction mixture was refluxed with stirring for 1 h. Phenacyl ester (**1**) was not observed on TLC, the reaction mixture was concentrated under *vacuo* and residuum was stirred with water, precipitated solid was filtered off, and crystallized from acetone. The yield was 12.2 g (95.6 %), mp 92 – 93.5 °C.

Anal. Calcd for C₁₉H₁₉NO₄ C, 70.10; H, 5.89; N, 4.31. Found C, 70.52; H, 6.01; N, 4.66.

Full MS, *m/z* (relative intensity) 326 (5) [M+H]⁺, 354 [M+C₂H₅]⁺, 366 [M+C₃H₅]⁺, 308 [M+H-H₂O]⁺, 255 [M+H-COCH(CH₃)₂]⁺, 230, 218, 190 (100) [C₆H₄NHCOCH(CH₃)₂(CO)]⁺, 172, 160, 146, 120, 105 [C₆H₅CO]⁺, 91; MS²(326,w3,EV1), *m/z* 282, 264, 255 (100), 224, 206, 197, 190, 188, 175, 162, 133, 120.

¹H NMR (DMSO-*d*₆, 300 MHz) δ 10.55 (1H, s), 8.42 (1H, dd, *J* = 8.4, 0.8 Hz), 8.08 (1H, dd, *J* = 8.7, 1.4 Hz), 8.07-8.01 (2H, m), 7.78-7.55 (4H, m), 7.25 (1H, ddd, *J* = 7.8, 7.4, 0.9 Hz), 5.81 (2H, s), 2.60 (1H, m), 1.13 (6H, d, *J* = 6.8 Hz); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 192.5, 175.0, 166.5, 140.2, 134.4, 134.0, 133.6, 130.7, 128.9, 127.8, 122.9, 120.7, 116.4, 67.4, 35.9, 19.1.

2-Oxo-2-phenylethyl 2-Palmitoylamino benzoate (**4d**)

Compound (**4d**) was prepared according to the procedure **4c**. The yield was 93%, mp 62-64 °C (MeOH).

Anal. Calcd. for C₃₁H₄₃NO₄ C, 75.42; H, 8.78; N, 2.84. Was found C, 75.71; H, 9.03; N, 2.59.

Full MS, *m/z* (relative intensity) 494 (20) [M+H]⁺, 522 [M+C₂H₅]⁺, 534 [M+C₃H₅]⁺, 476 [M+H-H₂O]⁺, 416, 398, 386, 359, 358 (100), 356, 342, 329, 312, 297, 255 [M+H-CO(CH₂)₁₄CH₃]⁺, 178, 161, 149, 137, 120, 105 [C₆H₅CO]⁺, 91; MS²(494, w3, EV1), *m/z* 448, 408, 359, 358 (100), 357, 338, 313, 256.

¹H NMR (DMSO-*d*₆, 300 MHz) δ 10.45 (1H, s), 8.39 (1H, dd, *J* = 8.4, 0.8 Hz), 8.09-8.01 (3H, m),

7.78-7.55 (4H, m), 7.25 (1H, ddd, $J = 7.9, 7.5, 1.0$ Hz), 5.81 (2H, s), 2.37 (2H, t, $J = 7.3$ Hz), 1.59 (2H, m), 1.30-1.13 (24H, m), 0.85 (3H, t, $J = 6.9$); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 192.5, 171.3, 166.4, 140.0, 134.3, 134.0, 133.7, 130.7, 128.9, 127.8, 122.9, 120.8, 116.6, 67.3, 37.1, 31.2, 28.9, 28.8, 28.6, 28.4, 24.8, 22.0, 13.8.

2-Oxo-2-phenylethyl 2-Benzoylamino benzoate (**4e**)

Compound (**4e**) was prepared according to the procedure **4c**. The yield was 84 %, mp 163.5 – 166°C.

Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{NO}_4$, 373.38; H, 4.57; N, 3.90. Found C, 73.82; H, 4.94; N, 3.51.

Full MS, m/z (relative intensity) 360 (5) $[\text{M}+\text{H}]^+$, 388 $[\text{M}+\text{C}_2\text{H}_5]^+$, 400 $[\text{M}+\text{C}_3\text{H}_5]^+$, 342 $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$, 282, 264, 252, 237, 224 (100) $[\text{M}+\text{H}-\text{OCH}_2\text{COC}_6\text{H}_5]^+$, 207, 197, 179, 146, 120, 105 $[\text{C}_6\text{H}_5\text{CO}]^+$, 91; $\text{MS}^2(360, \text{w}3, \text{EV}1)$, m/z 237, 224 (100), 207, 196, 179, 146.

^1H NMR (DMSO- d_6 , 300 MHz) δ 11.50 (1H, s), 8.65 (1H, dd, $J = 8.4, 0.8$ Hz), 8.19 (1H, dd, $J = 8.0, 1.4$ Hz), 8.06-8.00 (2H, m), 7.96-7.89 (2H, m), 7.80-7.52 (7H, m), 7.32 (1H, ddd, $J = 7.8, 7.7, 1.1$ Hz), 5.81 (2H, s); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 192.3, 167.0, 164.7, 140.4, 134.7, 134.2, 134.0, 133.6, 132.1, 130.9, 128.9, 127.8, 126.9, 123.4, 120.7, 116.3, 67.6.

5-Substituted-2-phenylimidazo[1,2-*c*]quinazoline (**5**)

Method A

Acyl derivative (**4**) (8 mmol) was heated with mixture AcOH (10 g) and ammonium acetate (10 g) for 30 min under reflux (temperature 130 °C). When the starting material was not observed on TLC (*n*-hexane: EtOAc 7: 3), water (100 mL) was added and solution was neutralized by sodium carbonate to pH 5 to 7 and precipitated product was filtered off. After drying the product was purified by column chromatography in toluene - EtOAc mixture and crystallized.

Method B

Acyl derivative (**4**) (1 mmol) was heated with mixture AcOH (5 g) and ammonium acetate (1.25 g) under the reflux (temperature probably 130 °C). When the starting material was not observed on TLC (*n*-hexane: EtOAc 7: 3), reaction mixture was worked on as in the process A.

Method C

Acyl derivative **4** (1 mmol) was heated with mixture AcOH (5 g) and ammonium acetate (1.25 g) in glass autoclave tube to 190 °C. When the starting material was not observed on TLC (*n*-hexane: EtOAc 7: 3), reaction mixture was worked on as in the process A.

5-Methyl-2-phenylimidazo[1,2-*c*]quinazoline (**5b**)

Results are summarized in Table 1.

Anal. Calcd for C₁₇H₁₃N₃ C, 78.74; H, 5.05; N, 16.20. Found C, 78.39; H, 5.22; N 16.00.

Full MS, *m/z* (relative intensity) 260 (100) [M+H]⁺, 288 [M+C₂H₅]⁺, 300 [M+C₃H₅]⁺; MS²(260,w3,EV1.5), *m/z* 256, 233 (100) [M+H-HCN]⁺, 220, 218, 206, 202, 193, 165, 157, 143, 130, 117, 103.

¹H NMR (DMSO-*d*₆, 500 MHz) δ 8.61 (H-3,1H, s), 8.45 (H-11,1H, d, *J* = 7.7 Hz), 8.11 (H-2',2H, d, *J* = 7.5 Hz), 7.86 (H-8,1H, d, *J* = 7.9 Hz), 7.77 (H-9, 1H, m), 7.72 (H-10, 1H, m), 7.50 (H-3',2H, dd, *J* = 7.7, 7.4 Hz), 7.37 (H-4',1H, dd, *J* = 7.4, 1.7Hz), 2.89 (CH₃,3H, s); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 146.4 (C-5), 143.5 (C-2), 142.5 (C-13), 140.6 (C-7), 133.1 (C-1'), 129.8 (C-9), 128.7 (C-3'), 127.9 (C-4'), 127.4 (C-10), 127.3 (C-8), 125.6 (C-2'), 122.1(C-11), 117.6 (C-12), 109.1 (C-3), 20.8 (CH₃), ¹⁵N NMR (DMSO-D₆, 50.68 MHz) δ -127.1 (N-6, correlations with proton H-8 and protons of methyl group in *gs*-¹H, ¹⁵N-HMBC spectrum), - 141.4 (N-1, correlation with proton H-3 in *gs*-¹H, ¹⁵N-HMBC spectrum), -182.5 (N-4, correlations with proton H-3 and protons of methyl group in *gs*-¹H, ¹⁵N-HMBC spectrum).

5-Isopropyl-2-phenylimidazo[1,2-*c*]quinazoline (**5c**)

Results are summarized in Table 1.

Anal. Calcd for C₁₉H₁₇N₃ C, 79.41; H, 5.96; N, 14.62. Found C, 79.80; H, 6.13; N 14.30.

Full MS, *m/z* (relative intensity) 288 (100) [M+H]⁺, 316 [M+C₂H₅]⁺, 328 [M+C₃H₅]⁺, 259. MS²(288,w3,EV1.5), *m/z* 272 (100), 259, 246, 245 [M+H-CH(CH₃)₂]⁺, 220, 183, 168, 118.

¹H NMR (DMSO-*d*₆, 500 MHz) δ 8.78 (H-3, 1H, s), 8.47 (H-11, 1H, dd, *J* = 7.5, 1.7 Hz), 8.14 (H-2' 2H, dd, *J* = 8.0, 1.3 Hz), 7.89 (H-8 1H, dd, *J* = 7.9, 1.0 Hz), 7.73 (H-9, 1H, ddd, *J* = 7.9, 7.1, 1.7 Hz), 7.67 (H-10 1H, ddd, *J* = 7.7, 7.1, 1.2 Hz), 7.50 (H-3', 2H, dd, *J* = 7.7, 7.3 Hz), 7.37 (H-4', 1H, dd, *J* = 7.5, 1.7Hz), 3.69 (CH, 1H, m), 1.46 ((CH₃)₂ 6H, d, *J* = 6.6 Hz); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 153.2 (C-5), 143.6 (C-2), 142.8 (C-13), 140.4 (C-7), 133.2 (C-1'), 129.9 (C-9), 128.6 (C-3'), 127.9 (C-4'), 127.7 (C-10), 127.6 (C-8), 125.6 (C-2'), 122.1 (C-11), 117.7(C-12), 108.6 (C-3), 31.2 (CH), 19.8 (CH₃)₂.

5-Heptadecyl-2-phenylimidazo[1,2-*c*]quinazoline (**5d**)

Results are summarized in Table 1.

Anal. Calcd for C₃₁H₄₁N₃ C, 81.71; H, 9.07; N, 9.22. Found C, 81.60; H, 9.43; N, 8.88.

Full MS, *m/z* (relative intensity) 456 (100) [M+H]⁺, 484 [M+C₂H₅]⁺, 496 [M+C₃H₅]⁺, 440, 426, 412, 398, 384, 370, 356, 342, 328, 315, 301, 289, 272, 259; MS²(456,w3,EV1.5), *m/z* 454, 440, 426, 412, 398, 384, 370, 356, 342, 328, 314, 300, 286, 272, 258, 246, 234, 220.

¹H NMR (DMSO-*d*₆, 500 MHz) δ 8.69 (H-3, 1H, s), 8.45 (H-11, 1H, dd, *J* = 7.8, 1.5 Hz), 8.13 (H-2', 2H, dd, *J* = 7.7, 1.3 Hz), 7.88 (H-8, 1H, dd, *J* = 7.9, 1.3 Hz), 7.73 (H-9, 1H, ddd, *J* = 7.6, 7.2, 1.5 Hz), 7.67 (H-10,1H, ddd, *J* = 7.9, 7.1, 1.3 Hz), 7.50 (H-3', 2H, dd, *J* = 7.9, 7.3 Hz), 7.37 (H-4',1H, dd, *J* = 7.4, 1.7Hz), 3.20 (2H, t, *J* = 7.3 Hz), 1.95 (2H, m), 1.48 (2H, m), 1.37 (2H, m), 1.25 (20H, m) (all CH₂), 0.84

(3H, t, $J = 7.0$ Hz); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ 149.1 (C-5), 143.5 (C-2), 142.6 (C-13), 140.5 (C-7), 133.1 (C-1'), 129.9 (C-9), 128.6 (C-10), 128.6 (C-3'), 127.9 (C-8), 127.5 (C-4'), 125.6 (C-2'), 122.1 (C-11), 117.6 (C-12), 108.7 (C-3), 32.9, 31.2, 28.9, 28.6, 28.6, 28.5, 25.1, 22.0 (all CH_2), 13.8 (CH_3).

2,5-Diphenylimidazo[1,2-c]quinazoline (**5e**)

Results are summarized in Table 1.

Anal. Calcd for $\text{C}_{22}\text{H}_{15}\text{N}_3$ C, 82.22; H, 4.70; N, 13.08. Found C, 82.10; H, 4.89; N, 13.20.

Full MS, m/z (relative intensity) 322 (100) $[\text{M}+\text{H}]^+$, 350 $[\text{M}+\text{C}_2\text{H}_5]^+$, 362 $[\text{M}+\text{C}_3\text{H}_5]^+$; $\text{MS}^2(322, w3, \text{EV}1.5)$, m/z 317, 305, 295 (100) $[\text{M}+\text{H}-\text{HCN}]^+$, 266, 244, 235, 217, 205, 190, 165, 139, 116.

^1H NMR (DMSO- d_6 , 500 MHz) δ 8.53 (H-11, 1H, dd, $J = 7.5, 1.5$ Hz), 8.38 (H-3, 1H, s), 8.12 (H-2', 2H, dd, $J = 7.5, 1.4$ Hz), 8.02 (H-2'', 2H, m), 7.97 (H-8, 1H, dd, $J = 7.7, 1.4$ Hz), 7.82-7.64 (H-9, H-10, H-3'', H-4'', 5H, m), 7.45 (H-3', 2H, dd, $J = 7.9, 7.1$ Hz), 7.36 (H-4', 1H, ddd, $J = 7.3, 7.2, 1.1$ Hz); ^{13}C NMR (DMSO- d_6 , 125 MHz) δ 146.5 (C-5), 143.7 (C-2), 143.5 (C-13), 140.7 (C-7), 133.0 (C-1'), 132.9 (C-1''), 130.9 (C-4''), 130.2 (C-9), 128.8 (C-3''), 128.7 (C-2''), 128.6 (C-3'), 128.2 (C-10), 128.0 (C-8), 127.9 (C-4'), 125.9 (C-2'), 122.2 (C-11), 117.8 (C-12), 109.3 (C-3).

3-Hydroxy-2-phenylquinolin-4(1H)-one (**6**)

Formyl phenacyl anthranilate (**4a**) (0.6 g, 2.1 mmol), ammonium formate (2g) and formic acid (20 g) were heated under reflux for 5 h in microwave reactor. Then formyl anthranilate (**4a**) was not observed on TLC, water was added into the reaction mixture and precipitated solid was filtered off, and crystallized from BuOH. The yield of compound (**6**) was 0.45 g (90 %), mp 275-278 °C (lit.,⁴ 278-281 °C).

Cyclization of compound (**4b**) with ammonium carbonate in NMP

Mixture of acetyl derivative (**4b**) (1.15 g, 3.87 mmol) and ammonium carbonate (2.3 g, 23.94 mmol) in NMP (5.5 mL) was heated for 30 min at temperature 140 °C. The starting material was not observed on TLC (*n*-hexane: EtOAc 7 : 3). Then 100 mL of water was added. Solid compound was filtered off and water layer was extracted by EtOAc (5 x 75 mL), organic layer was dried by sodium sulfate and after the filtration EtOAc was evaporated *in vacuo*. The rest was mixed with Et₂O and precipitated solid was filtered off. Together with product from mother liquor was isolated 2-acetylaminobenzamide (**9b**) 340 mg (54%), mp 180 °C (lit.,⁸ mp 180 °C).

Anal. Calcd for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_2$ C, 60.66; H, 5.66; N, 15.72. Found C, 61.00; H, 5.78; N, 16.10.

Full MS, m/z (relative intensity) 179 (2) $[\text{M}+\text{H}]^+$, 207 $[\text{M}+\text{C}_2\text{H}_5]^+$, 219 $[\text{M}+\text{C}_3\text{H}_5]^+$, 162 (100) $[\text{M}+\text{H}-\text{NH}_3]^+$, 144 $[\text{M}+\text{H}-\text{NH}_3-\text{H}_2\text{O}]^+$, 136, 120; $\text{MS}^2(162, w3, \text{EV}1)$, m/z 144 (100), 120, 116, 92, 89, 65.

^1H NMR (DMSO- d_6 , 300 MHz) δ 11.55 (1H, s), 8.42 (1H, d, $J = 8.3$ Hz), 8.22 (1H, s), 7.78 (1H, d, $J =$

7.9, 1.0 Hz), 7.69 (1H, bs), 7.45 (1H, ddd, $J = 7.8, 7.6, 1.1$ Hz), 7.10 (1H, ddd, $J = 7.8, 7.6, 1.0$ Hz), 2.1 (3H, s); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 170.6, 168.0, 139.5, 132.0, 128.4, 122.2, 120.0, 119.7, 24.8.

Mother liquor was evaporated until dryness and divided by column chromatography on silicagel in toluene. 2,5-Diphenylpyrazine (**7**) 74 mg (7.3 %) was isolated, mp 193.5 -194 °C. (lit.,⁶ 195 °C)

Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2$ C, 82.73; H, 5.21; N, 12.06. Found C, 84.20; H, 5.38; N, 12.00.

Full MS, m/z (relative intensity) 233 (100)[$\text{M}+\text{H}$]⁺, 261 [$\text{M}+\text{C}_2\text{H}_5$]⁺, 273 [$\text{M}+\text{C}_3\text{H}_5$]⁺, 204, 179, 158, 130, 102, 91; $\text{MS}^2(233, w3, \text{EV}1.5)$, m/z 206[$\text{M}+\text{H}-\text{HCN}$]⁺, 204, 179, 178, 155, 130, 128, 115, 103 (100).

^1H NMR (DMSO- d_6 , 300 MHz) δ 9.33 (2H, s), 8.20 (4H, dd, $J = 8.4, 1.6$ Hz), 7.63-7.47 (6H, m); ^{13}C NMR (DMSO- d_6 , 75 MHz) δ 149.6, 141.0, 135.6, 129.8, 129.0, 126.5.

The compound 2,6-diphenylpyrazine (**8**) 42 mg (4.4 %) was isolated by column chromatography - eluent toluene : EtOAc 1 : 1., mp 87-89 °C. (lit.,⁷ 87-88°C)

Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_2$ C, 82.73; H, 5.21; N, 12.06. Found C, 82.53; H, 5.28; N, 12.08.

Full MS, m/z (relative intensity) 233 (100)[$\text{M}+\text{H}$]⁺, 261 [$\text{M}+\text{C}_2\text{H}_5$]⁺, 273 [$\text{M}+\text{C}_3\text{H}_5$]⁺, 204, 179, 158, 130, 102, 91; $\text{MS}^2(233, w3, \text{EV}1.5)$, m/z 206 [$\text{M}+\text{H}-\text{HCN}$]⁺, 204, 179, 178, 155, 130, 128 (100), 115, 103.

Cyclization of compound (**4e**) by heating in the presence of ammonium acetate, acetic acid in NMP Mixture of ammonium acetate (3 g), AcOH (3 g) and benzoyl derivative (**4e**) (0.61 g, 2.0 mmol) in *N*-methylpyrrolidone (6 g) was heated by single mode microwave under the reflux for 1 min (energy 100 W). (Starting material was not observed by TLC). Then the reaction mixture was diluted by water and precipitated solid was filtered off at 50 °C. Solid compound was washed by hot water (30 mL), after drying product was crystallized from toluene and *N*-[2-(4-phenyl-*1H*-imidazol-2-yl)phenyl]benzamide (**10e**) was received in yield 176 mg (26 %), mp 252 – 257 °C.

Anal. Calcd for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}$ C, 77.86; H, 5.05; N, 12.38. Found C, 78.05; H, 5.34; N, 11.99.

Full MS, m/z (relative intensity) 340 (100) [$\text{M}+\text{H}$]⁺, 368 [$\text{M}+\text{C}_2\text{H}_5$]⁺, 380 [$\text{M}+\text{C}_3\text{H}_5$]⁺, 322 [$\text{M}+\text{H}-\text{H}_2\text{O}$]⁺, 311, 262, 133, 105, 91; $\text{MS}^2(340, w3, \text{EV}1.0)$, m/z 322, 311, 295, 262.

^1H NMR (DMSO- d_6 , 500 MHz) δ 13.58 (H-12, 1H, s), 13.05 (H-1, 1H, s), 8.85 (H-10, 1H, dd, $J = 8.4, 0.9$ Hz), 8.12 (H-15, 2H, dd, $J = 8.1, 1.3$ Hz), 8.02 (H-7, 1H, dd, $J = 7.9, 1.1$ Hz), 7.90 (H-5, 1H, d, $J = 2.2$ Hz), 7.81 (H-19, 2H, dd, $J = 7.7, 1.4$ Hz), 7.65 (H-17, 1H, dd, $J = 7.7, 1.4$ Hz), 7.55 (H-16, 2H, m), 7.44 (H-9, 1H, m), 7.40 (H-20, 2H, m), 7.29 (H-21, 1H, m), 7.25 (H-15, 1H, m),

^{13}C NMR (DMSO- d_6 , 125 MHz) δ 165.3 (C-13), 145.3(C-2), 140.0 (C-4), 136.7 (C-11) 135.3 (C-14), 133.4 (C-18), 131.8 (C-17), 129.0 (C-9), 128.7 (C-16), 128.4 (C-20), 127.4 (C-15) 126.7 (C-21), 125.7 (C-7), 124.7 (C-19), 123.1 (C-8), 120.0 (C-10), 116.4 (C-6), 114.3 (C-5).

Solid compound was isolated from the water layer after the cooling. Later it was identified as 2-benzoylaminobenzamide (**9e**). Yield was 30 mg (6 %), mp 214 - 215 °C (lit.,⁹ 211 -213°C)

Anal. Calcd for C₁₄H₁₂N₂O₂ C, 69.99; H, 5.03; N, 11.66. Found C, 70.40; H, 5.32; N, 11.20.

Full MS, *m/z* (relative intensity) 241(3) [M+H]⁺, 269 [M+C₂H₅]⁺, 281 [M+C₃H₅]⁺, 224 [M+H-NH₃]⁺, 252 [M+C₂H₅-NH₃]⁺, 264 [M+C₃H₅-NH₃]⁺, 196, 163, 146, 105, 91; MS²(241,w3,EV1.0), *m/z* 239, 223, 196, 179, 163, 146, 137, 118, 105.

¹H NMR (DMSO-*d*₆, 300 MHz) δ 12.95 (1H, s), 8.71 (1H, dd, *J* = 8.4, 0.9 Hz), 8.42 (1H, s), 7.96 (2H, dd, *J* = 7.0, 1.6 Hz), 7.91 (1H, dd, *J* = 7.9, 1.3 Hz), 7.85 (1H, s), 7.66-7.53 (4H, m), 7.18 (1H, ddd, *J* = 7.8, 7.6, 1.1 Hz); ¹³C NMR (DMSO-*d*₆, 75 MHz) δ 171.1, 164.3, 140.0, 134.6, 132.5, 131.9, 128.8, 128.7, 126.9, 122.5, 119.9, 119.1.

ACKNOWLEDGEMENT

We are grateful to the Ministry of Education, Youth and Sport of the Czech Republic, for the grant MSM6198959216.

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