Reactions of 3-hydroxy-1,2-dihydroquinazolin-4-ones with acid chlorides

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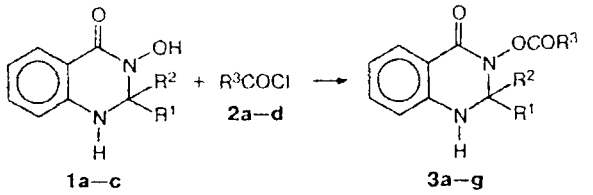
The reactions of 3-hydroxy-1,2-dihydroquinazolin-4-ones with acid chlorides can afford compounds of different types. The structures of the products depend on the type of acid chloride used and on the nature of the substituent at position 2 of the 3-hydroxy-1,2-dihydroquinazolin-4-one.

Key words: 3-hydroxy-1,2-dihydroquinazolin-4-ones, 3-acyloxy-1,2-dihydroquinazolin-4-ones, 3-hydroxyquinazolin-4-ones, quinazolin-4-ones, acylation, dehydration.

In the expectation that acid chlorides would acylate 3-hydroxy-1,2-dihydroquinazolin-4-ones (HDHQs) at the N(1) atom and/or at the O atom of the hydroxyl group to form previously unknown derivatives, we studied the reactions of HDHQs with a number of aliphatic and aromatic acid chlorides as well as with alkyl chloroformates and phosgene.

We found that in many cases these reactions were not terminated in the stage of formation of primary acylation products and the structures of the resulting compounds are determined by the nature of the substituent at position 2 in HDHQ and by the type of acid chloride used. When HDHQs containing a hydrogen atom at position 2 were acylated with alkyl chloroformate or aromatic or unsaturated aliphatic acid chlorides, monoacylation products were formed in rather high yields (50—90%) regardless of the initial reagent ratio. In this case, only the *N*-hydroxyl group was acylated.



1a—c **3a—g**

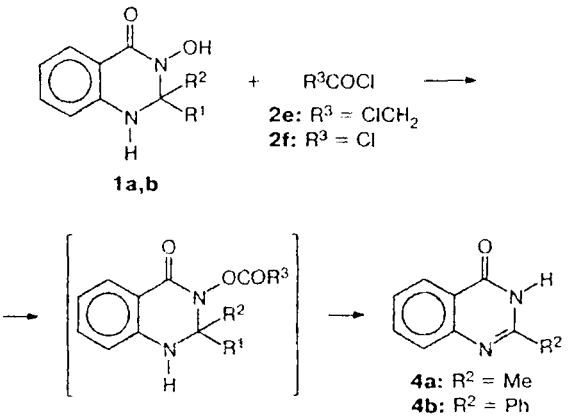
R^1 = H

	R^2	R^3		R^2	R^3
1a	Me		**3a**	Me	Ph
1b	Ph		**3b**	Ph	Me
1c	2-HOC_6H_4		**3c**	Ph	Ph
2a		Ph	**3d**	2-HOC_6H_4	Ph
2b		Me	**3e**	2-HOC_6H_4	4-$O_2NC_6H_4$
2c		4-$O_2NC_6H_4$	**3f**	Ph	MeO
2d		MeO	**3g**	2-HOC_6H_4	MeO

The conclusions about the structures of the resulting compounds were made based on the data of elemental analysis and ^1H NMR spectroscopy as well as by taking into account the negative qualitative test for the hydroxamic group with $FeCl_3$. In the IR spectra of the compounds under study (**3a** and **3c**), the signal of the NH group is observed as a broad band in the region of 3300—3350 cm^{-1}.

The compounds synthesized are high melting crystalline substances (Table 1). These compounds did not undergo further acylation, which is, apparently, due primarily to the steric effect of the substituents at positions 2 and 3 of HDHQ.*

Apparently, the first stage of the reactions of 2-monosubstituted HDHQs with chloroacetyl chloride and phosgene proceeded analogously, but this stage was followed by elimination of the corresponding acids to yield finally products of formal dehydration of the initial HDHQs.



1a,b

* Interestingly, treatment of compound **3g** with benzoyl chloride resulted in the replacement of the methoxycarbonyl group by the benzoyl fragment to form compound **3d**.

3g + PhCOCl → **3d**

The latter compound did not enter into the analogous reaction or into the subsequent acylation with chloroacetyl chloride or with phosgene.

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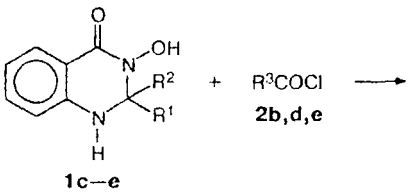
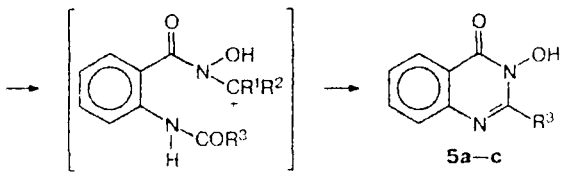
Table 1. 3-Acyloxy-1,2-dihydroquinazolin-4-ones **3a—g**

Compound	M.p. /°C	Found / Calculated (%) C	H	Molecular formula	^{1}H NMR (DMSO-d_6), δ, *J*/Hz
3a	149—150	68.05 68.08	4.86 5.00	$C_{16}H_{14}N_2O_3$	1.45 (d, 3 H, Me, *J* = 8); 5.38 (q, 1 H, H(2), *J* = 8); 6.71 (d, 2 H, *J* = 10); 7.38 (t, 1 H, *J* = 10); 7.62 (m, 4 H); 7.75 (m, 1 H); 8.08 (d, 2 H, *J* = 10)
3b	152—153	67.97 68.01	4.89 5.00	$C_{16}H_{14}N_2O_3$	1.93 (s, 3 H, Me); 6.15 (s, 1 H, H(2)); 6.80 (d, 2 H, *J* = 10); 7.30—7.50 (m, 6 H); 7.62 (s, 2 H)
3c	193—195[3]	73.03 73.24	4.74 4.68	$C_{21}H_{16}N_2O_3$	6.33 (s, 1 H, H(2)); 6.85 (m, 2H); 7.30—7.80 (m, 13 H)
3d	194—196	70.07 70.00	4.48 4.48	$C_{21}H_{16}N_2O_4$	6.65 (s, 1 H, H(2)); 6.85 (t, 4 H, *J* = 10); 7.18 (t, 1 H, *J* = 10); 7.40 (t, 1 H, *J* = 10); 7.53 (s, 3 H); 7.60—7.80 (m, 5 H); 9.94 (br.s, 1 H, OH)
3e	184—185	62.09 62.22	3.75 3.73	$C_{21}H_{15}N_3O_6$	6.65 (s, 1 H, H(2)); 6.81 (m, 4 H); 7.20 (t, 1 H, *J* = 10); 7.40 (m, 1 H); 7.50—7.70 (m, 3 H); 8.03 (d, 2 H, *J* = 10); 8.35 (d, 2 H, *J* = 10); 9.95 (br.s, 1 H, OH)
3f	143—144	64.09 64.42	5.07 4.73	$C_{16}H_{14}N_2O_4$	3.75 (s, 3 H, OMe); 6.21 (s, 1 H, H(2)); 6.72 (d, 2 H, *J* = 10); 7.49 (s, 4 H); 7.58 (s, 2 H); 7.72 (s, 2 H)
3g	174—176	61.07 61.14	4.47 4.49	$C_{16}H_{14}N_2O_5$	3.75 (s, 3 H, OMe); 6.48 (s, 1 H, H(2)); 6.70 (m, 5 H); 7.19 (m, 1 H); 7.35 (m, 1 H); 7.49 (s, 1 H); 7.68 (d, 1 H, *J* = 10); 9.98 (br.s, 1 H, OH)

The second stage of these reactions was, apparently, favored by the presence of relatively strong electron-withdrawing substituents in the residue of the acid.

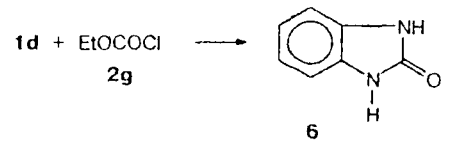
The reactions of acid chlorides with 2,2-dialkyl-substituted or 2-monoaryl-substituted HDHQs whose aryl groups contain an electron-withdrawing substituent followed a different pathway. Apparently, the presence of such a substituent in HDHQ promotes the cleavage of the C—N bond and makes possible the electrophilic attack on the N(1) atom (*cf.* Ref. 1). Subsequent recyclization with the participation of the carbon atom of the carbonyl group afforded 2-substituted 3-hydroxyquinazolin-4-ones. In this case, the R^3 fragment, which was initially a component of the acid chloride used, became a substituent at position 2 of compounds **5a—c**.



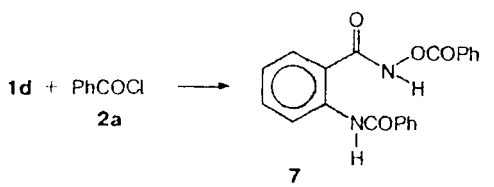


	R^1	R^2		R^3
1c	H	2-HOC_6H_4	**5a**	Me
1d	Me	Me	**5b**	$ClCH_2$
1e	Me	$Me_2C(OH)CH_2$	**5c**	MeO

The reactions of 2,2-disubstituted HDHQs with alkyl chloroformate gave different results. Thus, the reaction of methyl chloroformate (**2d**) with 2-methyl-2-(2-hydroxy-2-methylpropyl)-HDHQ proceeded according to the above-described scheme to form product **5c**, while the reaction of 2,2-dimethyl-HDHQ with ethyl chloroformate (**2g**) afforded a product of deeper conversion, *viz.*, benzimidazolone (**6**), in a similar yield (63—64%).



The possibilities of the reactions of HDHQs with acid chlorides are not limited to the formation of products of types **3—6**. Actually, the reaction of 2,2-dimethyl-HDHQ with benzoyl chloride afforded the dibenzoyl derivative of *o*-aminobenzohydroxamic acid (**7**) in ~60% yield (with respect to the benzoyl chloride



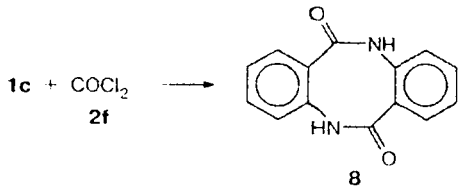


Table 2. The effect of the substituents in 2-R^1-2-R^2-3-hydroxy-1,2-dihydroquinazolin-4-ones and in R^3COCl on the character of the products formed in their reactions

R^1	R^2	R^3	Reaction product	Yield[a] (%)
H	Me	Ph	**3a**	49
H	Ph	Me	**3b**	54
H	Ph	Ph	**3c**	90
H	2-HOC_6H_4	Ph	**3d**	81
H	2-HOC_6H_4	4-$O_2NC_6H_4$	**3e**	85
H	Ph	MeO	**3f**	76
H	2-HOC_6H_4	MeO	**3g**	82
H	Me	$ClCH_2$	**4a**	29
H	Ph	$ClCH_2$	**4b**	78
H	Ph	Cl	**4b**	67[b]
Me	Me	Me	**5a**	38
Me	$MeC(OH)CH_2$	$ClCH_2$	**5b**	62
H	2-HOC_6H_4	$ClCH_2$	**5b**	56
Me	$MeC(OH)CH_2$	MeO	**5c**	63
Me	Me	EtO	**6**	64
Me	Me	Ph	**7**	58[c]
H	2-HOC_6H_4	Cl	**8**	76 (32[d])

[a] The yield of the product obtained according to the known procedure.
[b] See the Experimental section.
[c] The yield with respect to the BzCl used.
[d] From **1d** (see the Experimental section).

used), while treatment of 2-(2-hydroxyphenyl)-HDHQ with phosgene yielded dianthranilide (**8**).

The ^1H NMR spectrum of a solution of compound **8** in DMSO is rather complex, which is, apparently, due to the inversion of the eight-membered ring or to tautomerism.

Previously,[2] it was demonstrated that compound **7** can be converted into **6**. In addition, we found that compound **3g** can be converted into **8** upon heating in the presence of catalytic amounts of sulfuric acid:

$$\mathbf{3g} \xrightarrow[\Delta]{H^+} \mathbf{8}.$$

Hence, it is reasonable to suppose that compounds **4**—**8** are products of subsequent conversions of primary products of acylation of HDHQs at the N(1) atom and at the O atom of the hydroxyl group. In our opinion, the above-considered examples rather convincingly demonstrate the effect of substituents in HDHQs on the direction of their conversions. This can be clearly seen from Table 2.

Experimental

The ^1H NMR spectra were recorded on a Bruker AM-300 instrument in DMSO-d_6. The melting points were determined on a Kofler stage. The IR spectra were obtained on a UR-20 instrument in KBr pellets. The mass spectrum was measured on a Kratos MS-30 instrument with direct introduction of the sample into the ion source (EI, 70 eV). The starting HDHQs were prepared according to known procedures.[4]

Reactions of HDHQ with acid chlorides (general procedure). 3-Acyloxy-1,2-dihydroquinazolin-4-ones (3a—g). Py (1 mmol, 0.09 mL) and then an acid chloride (1 mmol) were added to the corresponding HDHQ (1 mmol) dissolved in 1,4-dioxane (3 mL). The reaction mixture was stirred at ~20 °C for 1 h, the solvent was evaporated, and the residue was recrystallized from a water—EtOH mixture. The yields and characteristics of the products are given in Tables 1 and 2.

2-Methylquinazolin-4-one (4a) was prepared from 2-methyl-HDHQ and $ClCH_2COCl$ according to the general procedure. M.p. 228—230 °C (*cf.* Ref. 5: m.p. 232 °C). ^1H NMR, δ: 2.62 (s, 3 H, Me); 7.61 (t, 1 H, J = 12 Hz); 7.78 (d, 1 H, J = 12 Hz); 7.90—8.00 (m, 2 H); 8.15 (d, 1 H, J = 12 Hz).

2-Phenylquinazolin-4-one (4b). *A.* 2-Phenylquinazolin-4-one was prepared from 2-phenyl-HDHQ and $ClCH_2COCl$ according to the general procedure. M.p. 239—240 °C (*cf.* Ref. 6: m.p. 240 °C). ^1H NMR, δ: 7.55 (m, 4 H); 7.75 (d, 1 H, J = 12 Hz); 7.85 (t, 1 H, J = 12 Hz); 8.18 (m, 3 H).

B. Py (0.15 mL) was added to a solution of 2-phenyl-HDHQ (0.2 g, 0.8 mmol) in anhydrous MeCN (3 mL). The reaction mixture was cooled to ~0 °C and a 50% $COCl_2$ solution in CCl_4 (0.16 mL) was added. After 1 h, the solvent was evaporated and the residue was washed with water and recrystallized from a 40% aqueous solution of EtOH. M.p. 239—240 °C.

3-Hydroxy-2-methylquinazolin-4-one (5a) was prepared from 2,2-dimethyl-HDHQ and MeCOCl according to the general procedure. M.p. 212—214 °C (*cf.* Ref. 7: m.p. 214 °C). ^1H NMR, δ: 2.51 (s, 3 H, Me); 7.50 (t, 1 H, J = 10 Hz); 7.62 (d, 1 H, J = 10 Hz); 7.78 (t, 1 H, J = 10 Hz); 8.15 (d, 1 H, J = 10 Hz); 11.63 (br.s, 1 H, NOH).

3-Hydroxy-2-chloromethylquinazolin-4-one (5b) was prepared from 2-methyl-2-(2-hydroxy-2-methylpropyl)-HDHQ and $ClCH_2COCl$ as well as from 2-hydroxyphenyl-HDHQ and $ClCH_2COCl$ according to the general procedure. M.p. 190—192 °C (from an AcOEt—EtOH mixture) (*cf.* Ref. 8: m.p. 210 °C). ^1H NMR, δ: 4.80 (s, 2 H, CH_2); 7.59 (t, 1 H, J = 10 Hz); 7.72 (d, 1 H, J = 10 Hz); 7.85 (t, 1 H, J = 10 Hz); 8.19 (d, 1 H, J = 10 Hz); 12.10 (br.s, 1 H, NOH).

3-Hydroxy-2-methoxyquinazolin-4-one (5c) was prepared from 2-methyl-2-(2-hydroxy-2-methylpropyl)-HDHQ and MeOCOCl according to the general procedure. M.p. 215—217 °C (from water) (*cf.* Ref. 9: m.p. 220 °C). ^1H NMR, δ: 3.72 (s, 3 H, OMe); 7.12 (t, 1 H, J = 10 Hz); 7.60 (t, 1 H, J = 10 Hz); 8.00 (d, 1 H, J = 10 Hz); 8.31 (d, 1 H, J = 10 Hz); 10.80 (br.s, 1 H, NOH).

Benzimidazolone (6) was prepared from 2,2-dimethyl-HDHQ and EtOCOCl according to the general procedure. M.p. 304—306 °C (*cf.* Ref. 8: m.p. 306 °C). ^1H NMR, δ: 6.90 (s, 4 H); 10.50 (s, 2 H).

***N,O*-Dibenzoylanthranilohydroxamic acid (7)** was prepared from 2,2-dimethyl-HDHQ and PhCOCl according to the general procedure. M.p. 164—165 °C (*cf.* Ref. 2: m.p. 169 °C). ^1H NMR, δ: 7.30 (t, 1 H, J = 10 Hz); 7.50—8.00 (m, 10 H); 8.15 (d, 1 H, J = 10 Hz); 8.61 (d, 1 H, J = 10 Hz); 11.65 (s, 1 H).

Dianthranilide (8). *A.* Py (0.15 mL) was added to a solution of 2-(2-hydroxyphenyl)-HDHQ (0.2 g) in anhydrous MeCN (3 mL). The reaction mixture was cooled to ~0 °C and a 50% $COCl_2$ solution in CCl_4 (0.16 mL) was added. After 1 h, the solution was concentrated and the residue was recrystallized from a 40% aqueous solution of EtOH, m.p. 328–

330 °C (*cf.* Ref. 10: m.p. 330 °C). Found (%): C, 70.12; H, 4.42. $C_{14}H_{10}N_2O_2$. Calculated (%): C, 70.58; H, 4.23. ^{1}H NMR, δ: 6.98—7.01 (m, 2 H); 7.47 (t, 1 H, J = 10 Hz); 7.55 (t, 1 H, J = 10 Hz); 7.77—7.89 (m, 2 H); 8.18 (d, 1 H, J = 10 Hz); 8.25 (d, 1 H, J = 10 Hz). MS, m/z (I_{rel} (%)): 239 $[M + 1]^+$ (8), 238 $[M]^+$ (62), 219 (10), 148 (29), 119 (100), 97 (64) (*cf.* Ref. 11).

B. One drop of concentrated H_2SO_4 was added to a solution of compound **3g** (0.2 g) in anhydrous 1,4-dioxane and the reaction mixture was refluxed for 4 h. The solvent was evaporated and the residue was recrystallized from PrⁱOH, m.p. 328—330 °C.

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