The Mitsunobu 1-*O*-esterification of 1-hydroxy-3-phenyl-1*H*-quinoxalin-2-one 4-oxide

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1-Hydroxy-2-oxo-3-phenyl-1,2-dihydroquinoxaline 4-oxide under conditions of the Mitsunobu reaction reacts with alcohols giving the corresponding esters at the hydroxy group in position 1. Other representatives of hydroxamic acids such as 1,4-dihydroxyperhydroquinoxaline-2,3-dione and 1,4-dihydroxy-3,3,6,6-tetramethylpiperazine-2,5-dione undergo destruction under these conditions.

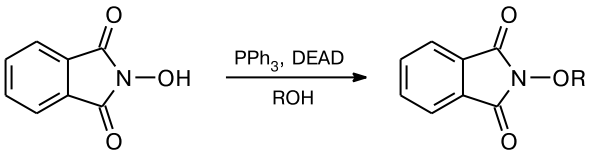
Key words: hydroxamic acids, esterification, the Mitsunobu reaction, quinoxalinones, piperazinediones.

The Mitsunobu reaction discovered in 1967 is widely used in organic synthesis as an efficient instrument for preparing *O*- and *N*-alkylated compounds.[1,2] In the key step of the reaction, the hydroxy group of an alcohol by the action of the system of reagents triphenylphosphine—diethyl azodicarboxylate (DEAD) is transformed into a good leaving group, which is able to be replaced by a wide number of nucleophiles (Scheme 1).

Earlier,[3] we studied methods for modification of heterocyclic hydroxamic acid, in particular, preparation of their *O*-esters. As a rule, *O*-esters are synthesized by alkylation of hydroxamic acids with alkyl halides. However, consideration of a possibility of broadening of a number of alkylating agents due to the involvement into this process of alcohols (including sterically hindered and/or chiral ones) by the Mitsunobu method was of a certain interest.

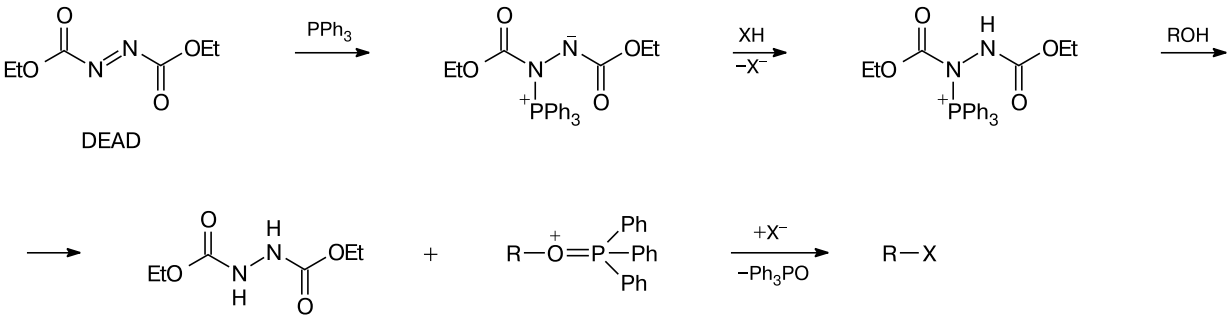
In the literature, the Mitsunobu reaction with *N*-hydroxysuccinimide is described, which similarly to hydroxamic acids contains the CO—NOH group (Scheme 2)[2,4—6] and gives the corresponding *O*-esters, though, in the case of alcohols of a complex structure,[7] problems with the synthesis of desired products were found.

Scheme 2



Only several examples of intramolecular arylation of hydroxamic acids or their esters containing hydroxy group

Scheme 1



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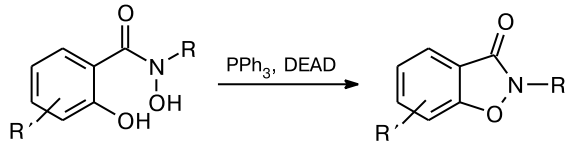
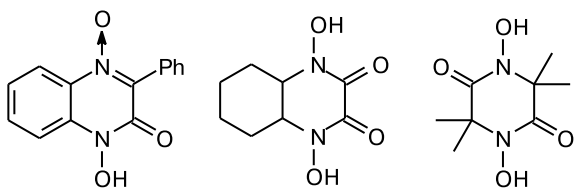
at the carbon atom in the presence of the Mitsunobu reagents are known, which can proceed either at the oxygen atom for *N*-esters[8] (Scheme 3) or at the nitrogen atom for *O*-esters.[9] Examples of the intermolecular Mitsunobu reaction for hydroxamic acids with alcohols, in contrast to *N*-hydroxysuccinimide, are not known.

Scheme 3



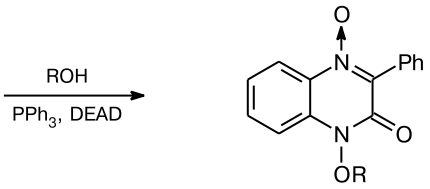
R = Pr^i, Bu^t, Ph, *cyclo*-C_6H_{11}
Rr = H, Me, CHO, NO_2, NHAc

In the present work, we for the first time studied a behavior of hydroxamic acids (HA) **1—3** of heterocyclic series (see Refs 3 and 10—12) under conditions of the Mitsunobu reaction. 1-Hydroxy-2-oxo-3-phenyl-1,2-dihydroquinoxaline 4-oxide (**1**) was chosen as the model compound, which was used for the selection of the ratio and the order of addition of reagents, the temperature and the reaction time (Scheme 4). Butan-1-ol was used as a model primary alcohol. The results obtained are presented in Table 1.



1 **2** **3**

Scheme 4



R = Bu^n (**a**), Pr^i (**b**), Bu^t (**c**), Bn (**d**), menthyl (**e**)

As one can see from Table 1 (entry *1*), when ratio of reagents is equimolar, the formation of ester **4a** is not observed for 1 day at room temperature. In this case, the starting HA **1** was recovered from the reaction mixture virtually quantitatively. When the reaction time was increased to 5.5 days, the conversion of HA reached 72% (entry *2*), however, the yield of the desired ester of HA was only 20%. The change in the ratio of reagents in favor of alcohol, DEAD, and PPh_3 (entry *3*), apparently, accelerates the formation of the target product (the yield increases to 40%) in higher degree than the side processes

Table 1. Alkylation of hydroxamic acids (HA) **1—3** with alcohols by the Mitsunobu reaction

Entry[a]	ROH	HA	Ratio[b]	*t*/h	Method[c]	Yield of ester	Conversion of HA
						%	
1	Bu^nOH	**1**	1 : 1 : 1 : 1	24	*A*	0	0
2	Bu^nOH	**1**	1 : 1 : 1 : 1	132	*A*	20	72
3	Bu^nOH	**1**	1.22 : 2 : 2 : 2	132	*A*	40	55
4	Bu^nOH	**1**	1 : 4 : 4 : 4	132	*A*	45	100
5	Bu^nOH	**1**	1 : 2 : 2 : 2	3.5	*A*	42	80
6	Bu^nOH	**1**	1 : 4 : 4 : 4	3.5	*A*	32	100
7	Bu^nOH	**1**	1 : 2 : 2 : 2	3.5	*B*	57	80
8	Bu^nOH	**1**	1 : 3 : 3 : 3	3.5	*B*	98	100
9	Pr^iOH	**1**	1 : 3 : 3 : 3	3.5	*B*	38	100
10	Bu^tOH	**1**	1 : 3 : 3 : 3	3.5	*B*	10	88
11	BnOH	**1**	1 : 3 : 3 : 3	3.5	*B*	16	100
12	(–)-Menthol	**1**	1 : 3 : 3 : 3	3.5	*B*	25	100
13	Bu^nOH	**2**	1 : 6 : 6 : 6	3.5	*B*	0	100
14	(–)-Menthol	**2**	1 : 6 : 6 : 6	3.5	*B*	0	100
15	Bu^nOH	**3**	1 : 6 : 6 : 6	3.5	*B*	0	100

[a] Experiments *1—4* were carried out at ~20 °C, *5—15* under reflux.
[b] HA : alcohol : PPh_3 : DEAD.
[c] *A*: HA, alcohol, PPh_3, THF were mixed under argon, a solution of DEAD in THF was added dropwise with stirring; *B*: alcohol, PPh_3, THF were mixed, a solution of HA and DEAD in THF was added dropwise with stirring for 1 h (for compound **2**, in THF+DMF).

(conversion of HA is 55%). Further increase in amount of reagents (entry *4*) does not lead to noticeable increase in the yield of the ester, however, it gives an opportunity to reach 100% degree of conversion of HA owing to the side processes. It can be suggested that a cleavage of the weak N—O bond in HA takes place in the presence of PPh_3 with the formation of $Ph_3P{=}O$. Carrying out the reaction at elevated temperature (entry *5*) with 2 equiv. of reagents leads to 80% conversion of HA and virtually does not change the yield of the ester. An increase in the amounts of reagents (entry *6*) causes a complete conversion of HA and a decrease in the yield of the ester to 32%. Thus, it is clear that HA under the reaction conditions decomposes before entering of the reaction with alcohol and should be added gradually. In fact, when the order of addition of reagents is reversed (entries *7* and *8*), virtually quantitative conversion of HA into the corresponding ester **4a** can be reached.

The selected conditions were used by us for the study of behavior of various alcohols and hydroxamic acids. Thus, it was shown (entries *8—12*) that the model HA **1** reacts with primary aliphatic (98%), benzylic (16%), secondary (38 and 25%), and even tertiary (10%) alcohols to form the corresponding esters **4a—e**.

The other HA under study, *viz.*, 1,4-dihydroxyperhydroquinoxaline-2,3-dione (**2**) and 1,4-dihydroxy-3,3,6,6-tetramethylpiperazine-2,5-dione (**3**), do not give target diesters under similar conditions (entries *13—15*) despite of their complete conversion. The starting alcohol was quantitatively recovered from the reaction of HA **2** with (–)-menthol, whereas TLC method (a comparison with the authentic sample) showed formation of $Ph_3P{=}O$, which confirmed our suggestion on the side process involving the cleavage of the N—O bond in HA with triphenylphosphine. The difference in behavior of HA **2** and **3** from **1**, apparently, is caused by their lower OH-acidity, which is a principal factor for successful proceeding of the Mitsunobu reaction (see review 2).

In conclusion, we for the first time synthesized esters of HA **1** with primary, benzylic, secondary, and even tertiary alcohols under conditions of the Mitsunobu reaction, which allows one to increase a variety of derivatives of quinoxaline series.

Experimental

Melting points of the synthesized compounds were determined on a Boetius heating stage (Kofler apparatus). IR spectra were recorded on a Bruker Vektor 22 spectrometer in KBr pellets (the concentration was 0.25%, $l = 1$ mm). ^{1}H NMR spectra were recorded on a Bruker WP-200-SY (200.13 MHz), Bruker AC-200 (200.13 MHz), and Bruker AM-400 (400.13 MHz) spectrometers, $CDCl_3$ was used as the solvent, the signal of the residual protons of the deuterated solvent was used as the reference. Elemental analysis of new compounds was performed in the Laboratory of Microanalysis of the N. N. Vorozhtsov Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences. High-resolution mass spectra of compound **4e** was recorded on a Finnigan MAT 8200 mass spectrometer.

Reaction progress was monitored by TLC on Silufol UV-254 plates, hexane—EtOAc from 5 : 2 was used as the eluent. Visualization was made in aqueous $KMnO_4$ or under the UV light. Solvents were distilled before use. Commercial reagents were used as purchased.

1-Butoxy-3-phenyl-1*H*-quinoxalin-2-one 4-oxide (4a). Method *A*. Diethyl azodicarboxylate (0.310 mL, 2 mmol) in THF (2 mL) was added to a mixture of 1-hydroxy-3-phenyl-1*H*-quinoxalin-2-one 4-oxide (**1**) (0.508 g, 2 mmol), Ph_3P (0.524 g, 2 mmol), and Bu^nOH (0.185 mL, 2 mmol) in THF (8 mL) under argon for 1 h. The reaction mixture was kept for 132 h at ~20 °C, treated with 10% aq. NaOH (10 mL), extracted with EtOAc (3×10 mL). The aqueous layer was acidified with aq. HCl to pH = 2, and HA **1** was filtered off (0.15 g, 72% conversion). Organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. From the residue thus obtained, compound **4a** (0.13 g, 20%) was isolated by column chromatography (SiO_2, hexane—EtOAc (5 : 2) as the eluent).

Method *B*. Diethyl azodicarboxylate (0.522 g, 3 mmol) in THF (2 mL) and compound **1** (0.25 g, 1 mmol) in THF (2 mL) were added simultaneously with the use of two syringes to a solution of Ph_3P (0.786 g, 3 mmol) and Bu^nOH (0.278 mL, 3 mmol) in THF (6 mL) under argon for 1 h. The mixture was refluxed for 3.5 h, cooled to ~20 °C, treated with 10% aq. NaOH (10 mL), and extracted with EtOAc (3×10 mL). The organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated. From the residue thus obtained, compound **4a** (0.305 g, 98%) was isolated by column chromatography (SiO_2, hexane—EtOAc (5 : 2) as the eluent), m.p. 122—125 °C. Found (%): C, 69.37; H, 5.91; N, 8.84. $C_{18}H_{18}N_2O_3$. Calculated (%): C, 69.66; H, 5.85; N, 9.03. ^{1}H NMR ($CDCl_3$), δ: 1.01 (t, 3 H, CH_3, J = 7.0 Hz); 1.48—1.69 (m, 2 H, $C\underline{H}_2CH_3$); 1.80—1.97 (m, 2 H, $OCH_2C\underline{H}_2$); 4.33 (t, 2 H, OCH_2, J = 6.5 Hz); 7.34—7.90 (m, 8 H, H arom.); 8.46 (dd, 1 H, CH arom., J = 8.3 Hz, J = 1.1 Hz). IR, ν/cm^{-1}: 1657 (C=O), 2868—3245 (C—H).

1-Isopropoxy-3-phenyl-1*H*-quinoxalin-2-one 4-oxide (4b) was obtained similarly (method *B*), the yield was 0.113 g (38%), m.p. 146—149 °C. Found (%): C, 68.65; H, 5.67; N, 9.22. $C_{17}H_{16}N_2O_3$. Calculated (%): C, 68.68; H, 5.38; N, 9.43. ^{1}H NMR ($CDCl_3$), δ: 1.43 (d, 6 H, 2 CH_3, J = 6.24 Hz); 4.95 (t, 1 H, CH, J = 6.24 Hz); 7.36—7.56, 7.65—7.74, 7.79—7.88 (all m, 8 H, CH arom.); 8.46 (dd, 1 H, CH arom., J = 8.19 Hz, J = 0.8 Hz). IR, ν/cm^{-1}: 1664 (C=O), 2863.0—3100.0 (C—H).

1-*tert*-Butoxy-3-phenyl-1-quinoxalin-2-one 4-oxide (4c) was synthesized similarly (method *B*), the yield was 0.031 g (10%), m.p. 170—174 °C. Found (%): C, 69.71; H, 6.00; N, 8.93. $C_{18}H_{18}N_2O_3$. Calculated (%): C, 69.67; H, 5.80; N, 9.03. ^{1}H NMR ($CDCl_3$), δ: 1.51 (s, 9 H, Bu^t); 7.33—7.56, 7.60—7.75, 7.78—7.87 (all m, 8 H, CH arom.); 8.46 (dd, 1 H, CH arom., J = 7.59 Hz, J = 0.8 Hz). IR, ν/cm^{-1}: 1656 (C=O), 2850.9—3090.2 (C—H). The aqueous layer, obtained after treatment of the reaction mixture with 10% aq. NaOH and extraction with EtOAc, was acidified to pH = 2, the precipitated unreacted HA **1** was filtered off and dried to give compound **4c** (0.22 g, 88% conversion).

1-Benzyloxy-3-phenyl-1*H*-quinoxalin-2-one 4-oxide (4d) was obtained similarly (method *B*), the yield was 0.054 g (16%), m.p. 172—175 °C. Found (%): C, 73.46; H, 5.12; N, 7.73. $C_{21}H_{16}N_2O_3$. Calculated (%): C, 73.25; H, 4.65; N, 8.14. ^{1}H NMR ($CDCl_3$), δ: 5.35 (s, 2 H, CH_2); 7.37—7.45, 7.45—7.72, 7.81—7.89 (all m, 13 H, CH arom.); 8.45 (dd, 1 H, CH arom., J = 7.2 Hz, J = 0.8 Hz). IR, ν/cm^{-1}: 1666.6 (C=O), 2853.0—3091.0 (C—H).

1-(2-Isopropyl-5-methylcyclohexyloxy)-3-phenyl-1*H*-quinoxalin-2-one 4-oxide (4e) was obtained similarly (method *B*), the yield was 0.099 g (25%), m.p. 27—35 °C. ^{1}H NMR ($CDCl_3$), δ: 0.82 (d, 3 H, CH_3, J = 7.0 Hz); 0.92 (dd, 6 H, $CH(C\underline{H}_3)_2$, J = 7.0 Hz, J = 4.9 Hz); 1.00—2.30 (m, 8 H, $C\underline{H}(CH_3)_2$, CH, cyclohexane); 3.45 (m, 1 H, CH, cyclohexane); 5.47 (m, 1 H, OCH); 6.30—7.55, 7.65—7.90 (all m, 8 H, CH arom.); 8.46 (dd, 1 H, CH arom., J = 8.46 Hz, J = 1.32 Hz). IR, ν/cm^{-1}: 1667.5 (C=O), 2870.7—2957.0 (C—H). MS, m/z: 392.2104 $[M]^+$. $C_{24}H_{28}N_2O_3$. M_{calc} 392.2100.

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