CHEMISTRY LETTERS, pp. 1369-1372, 1993.

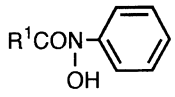
Migration of the Hydroxyl Group of N-Hydroxy-N-phenylamides to the Phenyl Group with Tertiary Phosphines and Tetrachloromethane. A Novel Transhydroxylation Reaction

Yasuo KIKUGAWA* and Kimiyo MITSUI
Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-02

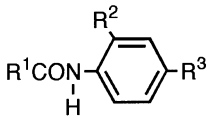
The hydroxyl group of N-hydroxy-N-phenylamides rearranges mainly to the *ortho* position of the N-phenyl ring by the system (*n*-Bu)$_3$P-CCl$_4$-CH$_3$CN; use of less than a stoichiometric amount of (*n*-Bu)$_3$P is effective for this reaction.

During studies on the chemistry of divalent positively charged nitrogen species (imidonium or nitrenium ions),[1] we have undertaken investigation of the reaction of N-hydroxy-N-phenylamides (**1**) with the system tributylphosphine (**9**)-tetrachloromethane-acetonitrile,[2] and found that a hydroxyl group of **1** rearranges mainly to the *ortho* position of the N-phenyl group. This transhydroxylation reaction proceeds in contrast to the principle that the driving force for many reactions involving tertiary phosphines is the formation of the very strong phosphoryl (P=O) bond.[2] Furthermore, use of less than a stoichiometric amount of **9** is effective for transportation of a hydroxyl group.

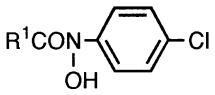
A typical experimental procedure is as follows: tetrachloromethane (0.15 ml, 1.60 mmol) was added with stirring to a mixture of N-hydroxy-N-phenylacetamide (**1a**) (120.9 mg, 0.8 mmol), tributylphosphine (**9**) (0.22 ml, 0.88 mmol), and acetonitrile (4 ml) cooled in an ice bath. The stirring was continued for 1 h with cooling and 40 h at room temperature with protection from moisture, then water (7 ml) was added. The aqueous solution was extracted with ethyl acetate (2 x 20 ml). The combined extracts were washed with brine (20 ml), dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (30 g). First elution with hexane-acetone (3:1) afforded N-(2-chlorophenyl)- and N-(4-chlorophenyl)acetamides (**4a**) (5.8 mg, 4.3%) and (**5a**) (17.4 mg, 12.8%), respectively. Further elution with hexane-acetone (1:1) afforded N-(2-hydroxyphenyl)- and N-(4-hydroxyphenyl)acetamides (**2a**) (91.4 mg, 75.6%) and (**3a**) (8.8 mg, 7.3%), respectively. Several N-hydroxy-N-phenylamides were reacted in this way, and the results are presented in Table 1.



1a $R^1 = CH_3$
1b $R^1 = C_6H_5$
1c $R^1 = C_6H_5CH_2CH_2$
1d $R^1 = Z\text{-}C_6H_5CH{=}CC_6H_5$



2 $R^2 = OH$, $R^3 = H$
3 $R^2 = H$, $R^3 = OH$
4 $R^2 = Cl$, $R^3 = H$
5 $R^2 = H$, $R^3 = Cl$
7 $R^2 = OH$, $R^3 = Cl$
8 $R^2 = R^3 = Cl$



6a and **d**

$(n\text{-}C_4H_9)_3P$
9

Table 1. Reaction of **1** with $(n\text{-Bu})_3P\text{-}CCl_4$[a)]

Compd	Reaction time /h	Product (isolated yield/ %)			
1a	41	**2a** (75.6)	**3a** (7.3)	**4a** (4.3)	**5a** (12.8)
1b	115	**2b** (64.8)	**3b** (6.3)	**4b** (2.5)	**5b** (11.0)
1c	96	**2c** (73.5)	**3c** (5.7)	**4c** (5.5)	**5c** (9.9)
1d	21	**2d** (55.5)	**3d** (8.5)	**4d** (15.9)	**5d** (14.0)

a) All the experiments were performed in CH_3CN at room temperature by using $(n\text{-Bu})_3P$ (1.1 mol equiv.) - CCl_4 (2 mol equiv.). All products were identified by comparison of their melting points and the spectral data with those of authentic samples.

Among phosphorus compounds examined, the reactivity is decreased in the order $(n\text{-Bu})_3P > PhEt_2P > Ph_3P >> (Me_2N)_3P$. For example, use of triphenylphosphine gives **2a** (50.5%), **3a** (15.1%), **4a** (5.5%), and **5a** (7.5%); use of tris(dimethylamino)phosphine gives ambiguous results and **5a** (25.8%) is the only isolable product. Compounds **6a** and **d** which carry a chlorine atom on the *para* position of the phenyl group are more reactive than **1**. Surprisingly, use of less than

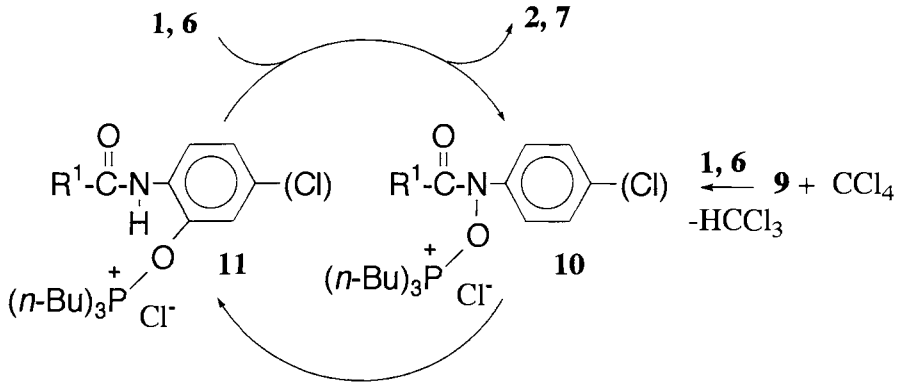
Table 2. Reaction of **6** with $(n\text{-Bu})_3P\text{-}CCl_4$[a)]

Compd	$(n\text{-Bu})_3P$ (equiv.[b)])	CCl_4 (equiv.[b)])	Reaction time/h	Product (isolated yield/%)	
6a	1.1	2	8	**7a** (74.8)	**8a** (8.0)
6a	0.55	1	20	**7a** (76.0)	**8a** (5.5)
6a	0.3	0.6	144	**7a** (33.0)[c)]	**8a** (2.7)
6d	1.1	2	1.5	**7d** (68.6)	**8d** (10.5)
6d	0.55	1	2	**7d** (72.6)	**8d** (9.3)

a) All products gave satisfactory spectral and analytical data. The position of the hydroxyl group of **7d** was determined by comparison with $^1H\text{-}^1H$ 2D NMR spectral datum with that of known **7a**. b) Molar equiv. with respect to **6.** c) Plus 49.5% of **6a**. Yields were determined by ^1H NMR integrals.

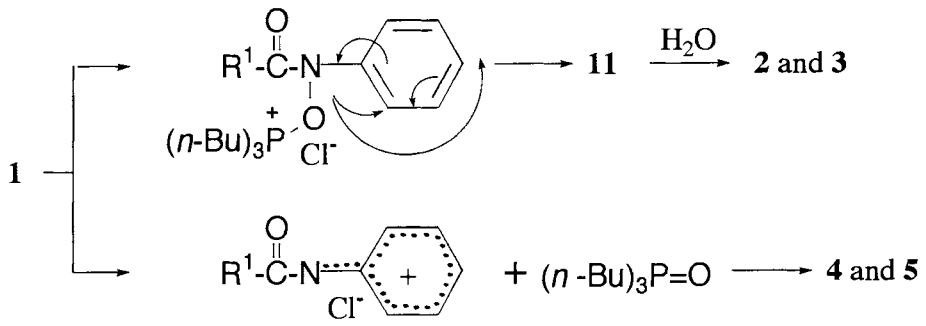
a stoichiometric amount of **9** is effective for the reaction of **6**, although a somewhat longer reaction time is required for completion. The results are presented in Table 2.

Treatment of **6a** in CD_3CN with **9** and tetrachloromethane under the conditions described in Table 2 results in the appearance of two major peaks in the ^{31}P NMR spectrum, an upfield peak at +50.1 ppm coresponding to tributylphosphine oxide, and a downfield peak at +107.2 ppm corresponding to the oxyphosphonium chloride **12**. The latter assignment is consistent with the reported chemical shift of tributyl oxyphosphonium salt (+100.6 ppm).[3] These peaks appear within 15 min after mixing reagents and are still present on standing overnight.



Scheme 1. The Assumed Mechanism.

Although it is premature to discuss the precise mechanism at the present stage, the most plausible reaction route for transhydroxylation is illustrated in Scheme 1. An adduct initially formed by the combination of **9** and tetrachloromethane reacts with **1** or **6** to afford a P-O-N phosphonium chloride **10**. Migration of the oxygen from the nitrogen to the neighboring *ortho* position affords a P-O-C phosphonium chloride **11**, which reacts with **1** or **6** to give the product **2** or **7**, accompanying by regeneration of **10** (as shown in Scheme 1). Formation of tributylphosphine oxide from **10** to a small extent affords an N-acylnitrenium ion, the positive charge of which is dispersed in the *ortho* and *para* positions of the phenyl group, to which a chloride ion attacks



Scheme 2.

intermolecularly to give **4** and **5** in a similar manner described in an aromatic fluorination of N-aryl-N-hydroxyamides with diethylaminosulfur trifluoride.[4] The reaction routes are outlined in Scheme 2. In a previous paper[5] we explained an intramolecular aluminum chloride-mediated migration of a methoxy group from N-methoxy-N-phenylamides to the *ortho* position of the phenyl group by assuming a tight ion pair intermediate. In the present case, concomitant formation of *para* hydroxy compounds suggests that the intermediate should have more dissociated form. According to literatures, N-hydroxybenzamide reacts with triphenyl phosphine under the Mitsunobu conditions[6] to afford phenyl isocyanate, a product of the Lossen rearrangement, and triphenylphosphine oxide;[7] N-hydroxy-N-methylbenzamide is reduced with **9** and diphenyl disulfide to afford N-methylbenzamide and tributylphosphine oxide.[8] As the system tertiary phosphines and tetrachloromethane has been widely utilized for removal of oxygen from O-functional compounds, by forming the strong P=O bond,[2,9] it is worth to note that the phosphorus atom is capable of transferring an oxygen atom without forming the P=O bond.

References

1) R. A. Abramovitch and R. Jeyaraman, "Azides and Nitrenes," ed by E. F. V. Scriven, Academic Press, New York (1984), pp. 297-357; M. Novak, M. Pelecanou, A. K. Roy, A. F. Andronico, F. M. Plourde, T. M. Olefirowicz, and T. J. Curtin, *J. Am. Chem. Soc.*, **106**, 5623 (1984); Y. Kikugawa and M. Kawase, *ibid.*, **106,** 5728 (1984); Y. Kikugawa and M. Shimada, *Chem. Lett.*, **1987**, 1771; T. Sakamoto, I. Hosoda, and Y. Kikugawa, *J. Heterocyclic Chem.*, **25**, 1279 (1988); M. Kawase, T. Kitamura, and Y. Kikugawa, *J. Org. Chem.*, **54,** 3394 (1989); Y. Kikugawa and M. Kawase, *Chem. Lett.*, **1990,** 581.

2) R. Appel and M. Halstenberg, "Organophosphorus Reagents in Organic Synthesis," ed by J. I. G. Cadogan, Academic Press, London (1979), pp. 387-431.

3) D. Camp and I. D. Jenkins, *Aust. J. Chem.*, **45**, 47 (1992).

4) Y. Kikugawa, K. Matsumoto, K. Mitsui, and T. Sakamoto, *J. Chem. Soc., Chem. Commun.*, **1992,** 921.

5) Y. Kikugawa and M. Shimada, *J. Chem. Soc., Chem. Commun.*, **1989**, 1450.

6) O. Mitsunobu, *Synthesis*, **1981**, 1.

7) S. Bittner, S. Grinberg, and I. Kartoon, *Tetrahedron Lett.*, **1974**, 1965.

8) D. H. R. Barton, W. B. Motherwell, E. S. Simon, and S. Z. Zard, *J. Chem. Soc., Perkin I*, **1986,** 2243.

9) J. Emsley and D. Hall, "The Chemistry of Phosphorus," Harper & Row Ltd., London (1976), p. 112.

(Received May 6, 1993)