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Novel oxidative nitrogen to carbon rearrangement found in the conversion of anilines to benzaldoximes by treating with $HCHO/H_2O_2$

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Abstract

Novel rearrangement was found by reacting anilines with $HCHO/H_2O_2$ resulting in the synthesis of various benzaldoximes. The mechanism of the rearrangement is proposed and suggested that the rearrangement might proceed via unstable *N*-phenyloxazirane intermediate followed by the transfer of aryl moiety from nitrogen to carbon atom leading to the formation of benzaldoxime.

Keywords: Rearrangement; Amines; Oxidation; Peroxides; Benzaldoximes

1. Introduction

During the course of our research on the synthesis of heterocyclic compounds, we surprisingly found that anilines were converted into the corresponding benzaldoximes when heated in over-aged 1,4-dioxane (purchased 12 years ago). It prompted us to investigate the actual reactant(s) involved in this novel transformation, although benzaldoximes can be easily synthesized by reacting benzaldehydes with hydroxylamine hydrochloride as described previously.[1–3]

It is known that 1,4-dioxane can induce a chain radical reactions under thermal,[4] chemical oxidation (i.e., NaClO, O_3/H_2O_2),[5,6] photochemical[7–9] or sonolysis[10,11] producing several intermediates including aldehydes (formaldehyde, acetaldehyde and glyoxal), organic acids (formic, methoxyacetic, acetic, glycolic, glyoxylic and oxalic acids) and the mono- and diformate ester of ethylene glycol.[12] In view of the structures of benzaldoximes (**3**) generated from anilines, one can envisage that the formation of these compounds requires a one-carbon source. Hence, it suggested that formaldehyde generated from long stored 1,4-dioxane might be a key one-carbon source involved in the reaction. To mimic the transformation of anilines to benzaldoximes, we have reacted anilines with ethylene glycol or glycerol in the presence of hydrogen peroxide. The results showed that benzaldoximes (**3**) were obtained under these reaction conditions. Finally, we found that compound **3** can also be prepared by reacting anilines with paraformaldehyde followed by the treatment of the products 1,3,5-triphenylhexahydro-*s*-triazines (**2**) with H_2O_2. From these studies, we found a novel oxidative nitrogen-to-carbon rearrangement of the *N*-aryl group in compounds having N–C–C system (Scheme 1). The results of the new synthetic route for benzaldoximes (**3**) are reported herein.

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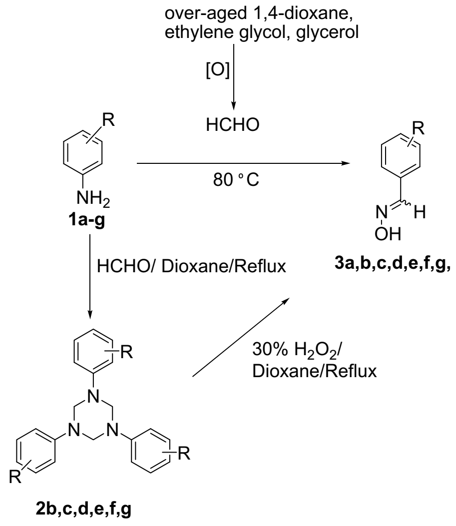


Scheme 1. **a**: R = H; **b**: 2-OMe; **c**: 3-OMe; **d**: 4-OMe; **e**: 2-Me; **f**: 3-Me; **g**: 4-Me.

2. Results and discussion

A mixture of an appropriate aniline (**1a**,**d**) in over-aged 1,4-dioxane was heated at 80 °C. The reaction discontinued after 12 h, but can be re-ignited by adding more 1,4-dioxane. After the removal of solvent, the residue was chromatographed on a silica gel column to give benzaldoximes (**3a**,**d**) as the major products (Scheme 1). However, when the same reactions carried out in the freshly distillated 1,4-dioxane (pretreated with KOH), no reaction was observed even in the presence H_2O_2. This indicated that the reactants (formaldehyde or peroxides) appeared in the over-aged 1,4-dioxane were removed during the pretreatment with KOH and/or distillation processes.

To find a way to reproduce benzaldoximes (**3**) directly from anilines was necessary since we have limited amount of over-aged 1,4-dioxane. One can anticipate that the conversion of anilines to benzaldoximes required one carbon source, such as formaldehyde. Many studies have been reported concerning the production of formaldehyde from polyhydroxy compounds. For example, polyhydroxylated alcohols (i.e., glycerol) and vicinal diols (i.e., ethylene glycol) were oxidized by microsomes isolated from rat liver to formaldehyde together with an aldehyde with less carbon atoms. The reaction was catalyzed in the presence of H_2O_2 and iron.[13–15] These studies demonstrated that H_2O_2 play an important role in the overall pathway for oxidizing ethylene glycol or glycerol to formaldehyde. To mimic the generation of formaldehyde in a biological system, we treated anisidines (**1b**,**c**,**d**) and toluidines (**1e**–**g**) with ethylene glycol or glycerol with 30% H_2O_2 in the freshly distillated 1,4-dioxane. We were able to isolate benzaldoximes (**3b**–**g**) in moderate yields from these experiments (Table 1). In general, the amount of benzaldoximes (**3**) generated from the reaction of ethylene glycol or glycerol/H_2O_2 has no significant difference. It demonstrates that both agents can liberate formaldehyde upon treatment with H_2O_2. To understand that 1,4-dioxane is not involved in the reaction under the applied reaction conditions, we used toluene as the solvent instead of 1,4-dioxane, similar results were observed. It should be noted that the known benzaldoximes (**3**) were isolated as mixture of *E*/*Z* diastereomers, which were determined by ^1H NMR spectrophotometric analysis. It revealed that the *E*/*Z* ratio of benzaldoximes (**3b**–**g**) synthesized by all three methods were almost identical (Table 2).

The reaction of anilines with formaldehyde is of greater interest. Giumanini and Verardo[16,17] reported that reacting anilines with paraformaldehyde afforded 1,3,5-triphenylperhydro-*s*-triazines (**2**, Scheme 1) in toluene under reflux. Triazines **2** may be the key intermediate for constructing benzaldoximes (**3**). To study the conversion of anilines to benzaldoximes in a stepwise manner, we prepared triazines by reacting anilines (**1a**–**g**) with paraformaldehyde

Table 1
Reaction of anilines (**1b**–**g**) with ethylene glycol or glycerol/H_2O_2 in freshly distillated 1,4-dioxane, reaction conditions and yields of compound **3**

Reactant-1[a]	Reactant-2[b]	Solvent (mL) dioxane	30% H_2O_2 (mL)	Reaction time (days)	Product (yield, %)	*E*/*Z* ratio	mp (°C)/Reference
							Compound **3**
1b	A[c]	100	10	3	**3b** (9.2)	100:18	**3b** (83–84)[26]
	B[d]	100	10	4	**3b** (6.6)	100:18	
1c	A	100	10	2	**3c** (33)	100:40	**3c** (43–44)[27]
	B	100	10	4	**3c** (29)	100:40	
1d	A	20	2	1	**3d** (27.8)	100:29	**3d** (73–75)[28]
	B	20	2	3	**3d** (31.2)	100:29	
1e	A	60	10	3	**3e** (25.1)	100:40	**3e** (52–54)[29]
	B	60	6	3	**3e** (27.6)	100:40	
1f	A	20	4	2	**3f** (16.3)	100:38	**3f** (oil)[30]
	B	60	6	3	**3f** (19.9)	100:38	
1g	A	20	4	1	**3g** (31.1)	100:33	**3g** (50–51)[31]
	B	60	6	1	**3g** (43.9)	100:33	

[a] Reactant-1 (1 equiv).
[b] Reactant-2 (4 equiv).
[c] A = Ethylene glycol.
[d] B = Glycerol.

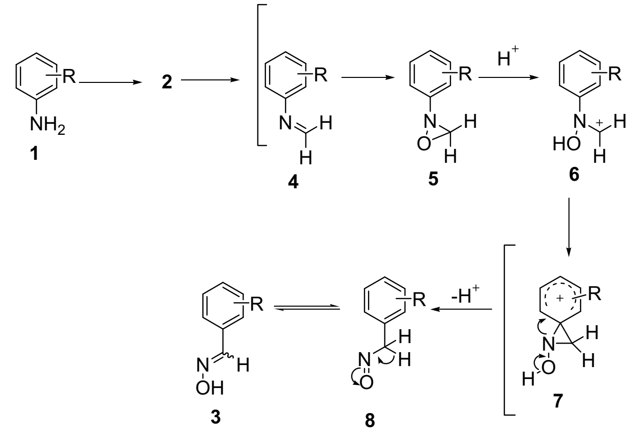
Table 2
Reaction of anilines (**1b**–**g**) (1 equiv), with paraformaldehyde (1.2 equiv)/H_2O_2 in freshly distilled 1,4-dioxane: reaction conditions and yields of compound **3**

Anilines	Solvent (mL) dioxane	30% H_2O_2 (mL)	Reaction time (h)	Product (yield %)	*E*/*Z* ratio
1b	70	2	3	**3b** (35.3)	100:18
1c	60	2	3	**3c** (21)	100:40
1d	50	2	2.5	**3d** (55.1)	100:29
1e	60	2	2.5	**3e** (46)	100:40
1f	60	2	3	**3f** (28)	100:38
1g	60	2	2.5	**3g** (61.2)	100:33

(1.2 equiv) by following the method described previously.[16,17] In some cases, we were able to isolate the triazine derivatives (**2a**,**d**,**g**) as crystal form, which were further treated with H_2O_2 in the freshly distillated 1,4-dioxane to give benzaldoximes (**3a**,**d**,**g**). The overall yields of **3a**,**d**,**g** were better when the intermediate triazines (**2a**,**d**,**g**) were not isolated and directly treated with H_2O_2. Thus, the desired benzaldoximes (**3b**–**g**) were prepared in better yields in comparison with what were obtained from other synthetic routes by treating anilines (**1b**–**g**) with paraformaldehyde, followed by direct reacting with H_2O_2 (Table 2).

The Stieglitz rearrangement has been widely studied. Compounds involved in this carbon-to-nitrogen rearrangement usually consist of an 'Ar-C–N' skeleton. Hoffmann et al. reported that the Stieglitz rearrangement of tritylamines, benzhydrylamines and benzyl amines can be induced by *p*-nitrobenzensulfonyl peroxide or *N*-(arylsulfonoxy)amine.[18,19] They postulated a mechanism for the rearrangement and demonstrated that the aryl migration from carbon to nitrogen atom is concerted with the loss of the arylsulfonate leaving group to form arylenamines.

As previously described, benzaldoximes (**3**) can be prepared by heating anilines in old-aged 1,4-dioxane, formaldehyde or with triazines **2** in the presence of H_2O_2 possibly via an aryl migration. Early reports by Emmons[20] and others showed that triazines **2** were unstable and can be thematically convert into Schiff base **4** bearing an 'Ar-N–C' back bone. Thus, a plausible reaction mechanism for the synthesis of compounds **3** is proposed as shown in Scheme 2. The initiate intermediate of the reaction would be the Schiff bases (**4**), which may be delivered from triazines **2** upon heating. Early studies showed that Schiff base can be oxidized by peracetic acid to oxazirane (**5**) in a similar manner as of oxidation of alkenes to epoxides.[19,20] The triazine or Schiff base is possibly transformed into oxaziranes (**5**) upon treatment with hydrogen peroxide. Since the commercially available hydrogen peroxide (30%) is acidic in nature, under such reaction conditions, oxaziranes (**5**) are subsequently converted into the unstable intermediates **6**, which lead to the formation of the transition state **7**. This proposed structure illustrates that the *N*-aryl moiety preferentially migrates to the positively charged primary carbon, leading to the formation of intermediates **8**, which are further converted into benzaldoximes (**3**).



Scheme 2. The proposed mechanism for the rearrangement of aryl group in phenyloxaziranes.

3. Conclusion

In the current study, we surprisingly found an alternative synthetic route for benzaldoximes (**3**) by the reaction of anilines with paraformaldehyde/H_2O_2 or triazine/H_2O_2. These were obtained in moderate yields in a mixture of diastereomeric *E*/*Z* isomers with a ratio of about 100:30 in most cases. It indicated that the method lacks stereo-selectivity for the formation of *E*/*Z* isomers. However, we found a novel oxidative nitrogen-to-carbon rearrangement in oxaziranes (**5**), from which benzaldoximes (**3**) were prepared.

4. Experimental

Melting points were determined on a Fargo melting point apparatus and are uncorrected. Column chromatography was carried out on Silica Gel G60 (70–230 mesh, ASTM; Merck and 230–400 mesh, Silicycle Inc.). Thin-layer chromatography was performed on Silica Gel G60 F_{254} (Merck) with short-wavelength UV light for visualization. Elemental analyses were done on a Heraeus CHN–O Rapid instrument. ^1H NMR spectra were recorded on a 600 MHz, Brucker AVANCE 600 DRX and 400 MHz, Brucker Top-Spin spectrometers. The chemical shifts were reported in ppm (δ) relative to TMS.

*4.1. Reaction of anilines (**1a**,**d**) with over-aged 1,4-dioxane*

A mixture of aniline (**1a**, 10 mmol) in over-aged 1,4-dioxane (50 mL) was heated at 80 °C for 5 days. After all aniline was consumed, the reaction mixture was evaporated in vacuo to dryness and the residue was chromatographed on a silica gel column using hexane/EtOAc (100:30 v/v) as the eluent to give known benzaldoxime (**3a**): yield 0.427 g (35%) as an oil.[24,25]

*4.2. 4-Methoxybenzaldoxime (**3d**)*

Compound **3d** was prepared from 4-anisidine (**1d**, 10 mmol) in over-aged 1,4-dioxane (50 mL) by following the same procedure as that for **3a**. Yield 0.805 g (53.3%), mp 73–75 °C (Lit.[28] mp 73–74 °C).

*4.3. General procedure for the synthesis of benzaldoximes (**3b–g**) by the reaction of anilines (**1b–g**) with ethylene glycol or glycerol/H_2O_2*

A mixture of an appropriate anilines (**1b–g**, 1 equiv), ethylene glycol (4 equiv) or glycerol (4 equiv) and 30% H_2O_2(0.5 mL/1 mmol of aniline) in freshly distilled 1,4-dioxane was heated at reflux for an appropriate time as indicated in Table 1. After the reaction is completed, the reaction mixture was evaporated to dryness and the desired product was isolated by column chromatography (SiO_2, hexane/EtOAc, 100:30 v/v). The yields of **3b–g** are shown in Table 1.

*4.4. General procedure for the synthesis of benzaldoximes (**3a,d,g**) by reacting 1,3,5-triphenylperhydro-s-triazines (**2a,d,g**) with H_2O_2*

To a solution of known 1,3,5-triphenylperhydro-*s*-triazine (**2a**, 0.945 g, 3 mmol)[21] in freshly distilled or newly purchased 1,4-dioxane (50 mL) was added dropwise 30% H_2O_2 (1 mL) at room temperature. The mixture was then heated at reflux temperature until all starting material was consumed (2–3 h). The reaction mixture was evaporated to dryness under reduced pressure and the residue was chromatographed on a silica gel column (solvent: $CHCl_3$/MeOH, 100:1 v/v). The fractions containing the main product were combined and evaporated to dryness to yield the corresponding benzaldoximes (**3a**), 0.197 g (54.3%), which is identical with one previously synthesized.

By following the same procedure as that for **3a**, the following compounds were prepared.

*4.5. 4-Methoxybenzaldoxime (**3d**)*

Compound **3d** was prepared from known 1,3,5-tris-(4-methoxyphenyl)[1,3,5]triazine (**2d**, 0.810 g, 2 mmol)[22] and 30% H_2O_2(1 mL). Yield: 0.157 g (51%).

*4.6. 4-Methylbenzaldoxime (**3g**)*

Compound **3g** was Prepared from known 1,3,5-tri-*p*-tolyl-[1,3,5]triazine (**2g**, 0.714 g, 2 mmol)[23] and 30% H_2O_2 (1 mL). Yield: 0.174 g (64.5%).

4.7. General procedure for the reaction of anilines with parafomaldehyde/H_2O_2

A mixture of an appropriate aniline (**1b–g**, 1 equiv) and paraformaldehyde (1.2 equiv) in freshly distilled or newly purchased 1,4-dioxane was heated at reflux temperature until all anilines were consumed. Then reaction mixture cooled to room temperature and then treated with 30% H_2O_2 (0.5 mL/1 mmol of aniline). The resulting mixture was again heated to reflux for 2–3 h. After completion of reaction, the reaction mixture was evaporated to dryness under reduced pressure and the residue was chromatographed on a silica gel column (solvent: $CHCl_3$/MeOH, 100:1 v/v). The fractions containing the main product were combined and evaporated to dryness to yield the corresponding benzaldoximes (**3b–g**). The yields of each product are shown in Table 2.

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Supplementary data

Characterization data, a copy of ^{1}H and ^{13}C NMR spectrum of each compound and copy of HMBC spectrum of compound **3a**,**d**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.033.

References and notes

1. Ballini, R.; Barboni, L.; Filippone, P. *Chem. Lett.* **1997**, 475–476.
2. Hajipour, A. R.; Mohammadpoor, B. I.; Nikbaghat, K. I. *Synth. Commun.* **1999**, *29*, 1697–1701.
3. Ren, R. X.; Ou, W. *Tetrahedron Lett.* **2001**, *42*, 8445–8446.
4. Kuchler, L.; Lambert, L. *Z. Physik. Chem. (Leipzig)* **1937**, *B37*, 285.
5. Klecka, G. M.; Gonsoir, S. J. *J. Harzard Mater.* **1986**, *13*, 161–168.
6. Adams, C. D.; Scanlan, P. A.; Secrist, N. D. *Environ. Sci. Technol.* **1994**, *28*, 181–1818.
7. Maurino, V.; Calza, P.; Minero, C.; Pelizzetti, E.; Vincenti, M. *Chemosphere* **1997**, *35*, 2675–2688.
8. Houser, J. J.; Sibbio, B. A. *J. Org. Chem.* **1977**, *42*, 2145–2151.
9. Mazzocchi, P. H.; Bowen, M. W. *J. Org. Chem.* **1975**, *40*, 2689–2690.
10. Beckett, M. A.; Hua, I. *Environ. Sci. Technol.* **2000**, *34*, 3944–3953.
11. Beckett, M. A.; Hua, I. *Water Res.* **2003**, *37*, 2372–2376.
12. Stefan, M. I.; Bolton, J. R. *Environ. Sci. Technol.* **1998**, *32*, 1588–1595.
13. Clejan, L. A.; Cedebaum, A. I. *Arch. Biochem. Biophys.* **1992**, *298*, 105–113.
14. Kukielka, E.; Cedebaum, A. I. *Drug Metab. Dispos.* **1991**, *19*, 1108–1115.
15. Clejan, L. A.; Cedebaum, A. I. *Arch. Biochem. Biophys.* **1991**, *285*, 83–89.
16. Giumanini, A. G.; Verardo, G. *J. f. Prakt. Chem.* **1985**, *327*, 739–748.
17. Giumanini, A. G.; Verardo, G. *J. f. Prakt. Chem.* **1987**, *329*, 1087–1103.
18. Hoffman, R. V.; Poelker, D. J. *J. Org. Chem.* **1979**, *44*, 2364–2369.
19. Hoffmann, R. J.; Kumar, A. *J. Org. Chem.* **1985**, *50*, 1859–1863.
20. Emmons, W. D. *J. Am. Chem. Soc.* **1957**, *79*, 5739–5754.

21. Janowski, W. K.; Prager, R. H.; Smith, J. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, *19*, 3212–3216.
22. Shiozaki, M.; Masuko, H. *Heterocycles* **1984**, *8*, 1727–1728.
23. Eibner, A. *Justus Liebigs Ann. Chem.* **1898**, *302*, 335–370.
24. Berrier, C.; Brahmi, R.; Carreyre, H.; Coustard, J. M.; Jacquesy, J. C.; Violeau, B. *Bull. Soc. Chim. Fr.* **1991**, *5*, 730–737.
25. Beckmann, E. *Chem. Ber.* **1904**, *37*, 3043.
26. Brady, O. L.; Bennett, C. L. *J. Chem. Soc.* **1927**, 894–898.
27. Brady, L.; Goldstein, R. F. *J. Chem. Soc.* **1926**, 1918.
28. Owston, N. A.; Parker, A. J.; Williams, M. J. *Org. Lett.* **2007**, *9*, 73–75.
29. Wuyts, H.; Koeck, H. *Bull. Soc. Chim. Belg.* **1932**, *41*, 196–199.
30. Shoppee, C. W. *J. Chem. Soc.* **1932**, 696–703.
31. Hashem, S.; Hosseini, S. M. *Synlett* **2001**, 99–101.