Ethyl Acetate as a Pro-Reducing Agent in an One-Pot Reductive Deamination of Nitroanilines

Valeriy A. Bacherikov, May-Jane Wang, Shu-Yun Cheng, Ching-Huang Chen, Kuo-Tung Chen,[1] and Tsann-Long Su*

Laboratory of Bioorganic Chemistry, Institute of Biomedical Sciences, Academia Sinica, Taipei 115, Taiwan

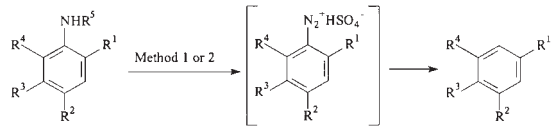
[1]Department of Medicinal Chemistry, College of Pharmacy, Taipei Medical University, Taipei 110, Taiwan

Received September 25, 2003; E-mail: tlsu@ibms.sinica.edu.tw

The one-pot reductive deamination of mono or dinitro substituted anilines to the corresponding nitrobenzenes by using ethyl acetate or ethanol was compared. It revealed that ethyl acetate is more suitable for the reductive deamination of mononitroanilines, while ethanol is more appropriate for dinitroanilines.

The replacement of a diazonium group by hydrogen (hydrodediazoniation) via a reduction process has been widely utilized as an indirect method for removing an amino group from the aromatic ring.[1] The reductive deamination involves a completeness of diazoniation, followed with reduction. The proposed mechanism of reductive deamination by forming a radical intermediate[2] was further confirmed later by Wassmundt et al.[3] The first step of reductive deamination involves the formation of diazonium salt, which can be readily generated by treating amine with sodium nitrite in mineral acid,[1] liquid nitrogen dioxide,[4] and other agents.[5,6] The second step, hydrodediazoniation, can be furnished by using common reducing agents such as alcohols,[1] hypophosphorous acid,[1] DMF,[5] and other.[7,8]

During the course of our research, we synthesized 3,5-dinitrophenol (**2a**) as an intermediate for constructing biological active compounds. Compound **2a** was synthesized from *s*-trinitrobenzene under drastic conditions ($AlCl_3$/120 °C).[9] To avoid using explosive *s*-trinitrobenzene, we prepared **2a** from 5-acetoxy-2-acetylamino-1,3-dinitrobenzene (**1a**) by following a previously described method with modification (Scheme 1).[10] Compound **1a** was hydrolyzed by conc. H_2SO_4 to give the intermediate 4-amino-3,5-dinitrophenol (**1b**), which was not isolated, and subsequently reacted with $NaNO_2$ in boiling EtOH for 3–5 h to yield the desired phenol **2a**. However, the intermediate **1b** was poorly soluble in the reaction medium and required a long refluxing time (ca. 3–5 h) to complete the reaction. To improve the solubility of **1b**, EtOAc was added to the reaction mixture. Under such conditions the reaction went smoothly and finished within a short period of time (ca. 0.5 h). Based on this finding, we were able to directly convert **1a** into **2a** in good yield (74%) in a one-pot reaction in a 20% H_2SO_4 solution by using EtOAc instead of EtOH. The result indicated that EtOAc can be a useful agent for hydrodeamination. This prompted us to study the reductive deamination of various nitro-substituted anilines by our new method (20% H_2SO_4/$NaNO_2$/EtOAc, Method 1) and compared that with a similar procedure previously developed by Paré et al.[11] (i.e., conc. H_2SO_4/$NaNO_2$/EtOH, Method 2) for the dediazonization of 4-methyl-2,6-dinitroaniline (**1c**).



1a. $R^1 = R^4 = NO_2$, $R^2 = OAc$, $R^3 = H$, $R^5 = Ac$
1b. $R^1 = R^4 = NO_2$, $R^2 = OH$, $R^3 = R^5 = H$
1c. $R^1 = R^4 = NO_2$, $R^2 = Me$, $R^3 = R^5 = H$
1d. $R^1 = R^4 = NO_2$, $R^2 = Me$, $R^3 = H$, $R^5 = Ac$
1e. $R^1 = R^4 = NO_2$, $R^2 = R^3 = R^5 = H$,
1f. $R^1 = OMe$, $R^2 = NO_2$, $R^3 = R^4 = R^5 = H$
1g. $R^1 = OMe$, $R^3 = NO_2$, $R^2 = R^4 = R^5 = H$
1h. $R^1 = Cl$, $R^2 = NO_2$, $R^3 = R^4 = R^5 = H$
1i. $R^1 = Cl$, $R^2 = R^4 = R^5 = H$, $R^3 = NO_2$

2a. $R^1 = R^4 = NO_2$, $R^2 = OH$, $R^3 = H$
2c. $R^1 = R^4 = NO_2$, $R^2 = Me$, $R^3 = H$
2e. $R^1 = R^4 = NO_2$, $R^2 = R^3 = H$
2f. $R^1 = OMe$, $R^2 = NO_2$, $R^3 = R^4 = H$
2g. $R^1 = OMe$, $R^2 = R^4 = H$, $R^3 = NO_2$
2h. $R^1 = Cl$, $R^2 = NO_2$, $R^3 = R^4 = H$
2i. $R^1 = Cl$, $R^2 = R^4 = H$, $R^3 = NO_2$

Scheme 1. Conversion of mono and dinitro substituted anilines to corresponding benzenes.

Aniline derivatives bearing dinitro and mononitro function(s) (**1a–1e** and **1f–1i**, respectively) were used for our studies. In Method 1, the reductive deamination was carried out by adding finely powdered $NaNO_2$ to a mixture of aniline, 20% H_2SO_4 and EtOAc (1:1 v/v) at 50–55 °C (internal temperature) (Method 1). However in Method 2 the pulverized $NaNO_2$ was added portionwise at a rate to keep the internal temperature at 80 °C to a suspension of nitroanilines in a mixture of conc. H_2SO_4 and EtOH. The deaminated products (**2**) were isolated from the organic layer in satisfactory yield either by recrystallization or column chromatography (Table 1).

As shown in Table 1, the deaminated products derived from the mononitro-substituted anilines **1f–1i** were obtained in good-to-high yield by Method 1 depending upon the position of the nitro group to the amino function. The higher yield of the deaminated products was observed from the substituted *meta*-nitroanilines **1g** and **1i** than that from the *para*-nitroanilines, **1f** and **1h**. However, EtOAc was less effective in the reaction of **1h** than other mononitroanilines (**1f**, **1g**, and **1i**). It also revealed that in the reactions of mononitro substituted anilines **1f–i**, a significant substituent effect (methoxy vs chloro) was not observed. Reductive deamination of the dinitro substituted anilines by Method 1 (i.e., **1c** or **1d** → **2c** and **1e** → **2e**) was unexpected in low yield. The amount of **2e** obtained was dependent on the addition rate of $NaNO_2$. In general, a higher yield of the product could be obtained when the internal reaction temperature was kept approximately at 50 °C during the addition of $NaNO_2$. It should be noted here that the reaction proceeded slowly, or afforded a complicated mixture of products when conc. H_2SO_4 was used in Method 1. To prove EtOAc is involved in deamination process, we studied the products formed from this agent under the reaction conditions described above by ^1H NMR spectroscopy method. Thus, EtOAc was treated with 20% H_2SO_4 in the presence of $NaNO_2$ at 50 °C for 10 min, the organic and aqueous layers were separated and then subjected to NMR measurements. Ethanol and acetic acid (each

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Table 1. Hydrodeamination of Various Nitro Substituted Anilines

Starting material	Reaction conditions				Product[c)]	Mp/°C[c)]
	Method 1[a)]		Method 2[b)]			
	Time/h	Yield/%	Time/h	Yield/%		
1a	0.5	60[a)]	1.0	74[a)]	**2a**	121–122 (126[9])
1c	0.3	39[a)]	2.0	78[a)]	**2c**	90–91 (93.5[11])
1d	0.2	38[a)]	8.0	63[a)]	**2c**	
1e	0.2	35[b)]	1.0	64[b)]	**2e**	89–90 (90[12])
1f	0.5	68[b)]	1.0	35[b)]	**2f**	35–36 (39[13])
1g	0.5	82[a)]	1.0	58[a)]	**2g**	53–55 (52[14])
1h	0.5	50[a)]	1.5	43[a)]	**2h**	44–46 (46–48[15])
1i	0.5	87[a)]	3.0	45[a)]	**2i**	84–85 (83.5[16])

Yield obtained from a) 40 mmol and b) 2 mmol scale of the starting material.

about 5%) were detected from their spectra, respectively. Since EtOH is used as a reducing agent for reductive deamination,[1,2] the dediazonization reaction in Method 1 was proceeded even in the presence of 5% of EtOH generated from EtOAc, suggesting that the latter displays not only as a solvent for two-phase reaction, but also as a pro-reducing agent.

Table 1 shows that Method 2 is more favorable for the deamination of dinitro-substituted anilines than that for the mononitroanilines. 3,5-Dinitrophenol (**2a**) was isolated in good yield (78%) derived either from 5-acetoxy-2-acetylamino-1,3-dinitrobenzene (**1a**) or 4-amino-3,5-dinitrophenol (**1b**). Similarly, 3,5-dinitrotoluene (**2c**) was obtained in good yield (63%) directly from *N*-(4-methyl-2,6-dinitrophenyl)acetamide (**1d**). Notably, the deamination of 2,6-dinitroaniline (**1e**) was not complete by both methods either under a prolong reaction time, or by adding an excess of $NaNO_2$ reagent. The starting material, **1e** (5–10%), was recovered after column chromatography. This observation is probably due to the relatively weaker basicity of **1e**, resulting in incompletion of its diazoniation under the reaction conditions in compared with to 4-substituted 2,6-dinitroanilines **1b** and **1c**, which have a methyl or hydroxy functions at the *para* position to the amino group.

The present study on the reductive deamination by Method 2 showed that the result was not as good as that described in the literature.[11] The desired product was always accompanied with by-products, resulting in a lower yield. In spite of the current studies revealing that using EtOH as a reducing agent (Method 2) is preferable for the deamination of 2,5-dinitroanilines, employing EtOAc for deamination (Method 1) provides several advantages: 1) Method 1 is more suitable for the deamination of 3-nitroanilines; 2) Our present studies demonstrated that EtOAc is not only the useful agent for the hydrodediazoniation of mononitro substituted anilines, but also serves as a solvent for a two-phase reaction. That is convenient for isolating the deaminated product, especially for those compounds that are soluble in EtOAc; and 3) Using EtOAc for reductive deamination in Method 1 requires a shorter reaction time and a lower temperature compared with that in Method 2.

Experimental

All structures of compounds in Table 1 were determined by ^{1}H NMR (Brucker AMX-400 spectrometer) and melting points (determined on a Fargo melting points apparatus) were compared with the data, reported in the cited references (Table 1, in the parentheses) and were uncorrected.

General Procedure. Compounds **1a** and **1d** were hydrolyzed with conc. H_2SO_4 to give **1b** and **1e**, respectively. The reaction mixture was diluted with ice to a 20% H_2SO_4 solution and then directly employed for the next reaction. Method 1: Pulverized $NaNO_2$ (100 mmol) was added portionwise to a solution of nitroaniline (40 mmol) in 20% H_2SO_4 and EtOAc (each 100 mL) at a rate to keep the internal temperature at 50–55 °C. After heating for an additional 10 min, the mixture was cooled, diluted, and extracted with EtOAc. The products were isolated and purified by usual procedure. Method 2 was similar to that of Method 1; conc. H_2SO_4/EtOH (1:5 v/v, 6 mL for 1 mmol of starting aniline) was used. The reaction mixture was gently refluxed with $NaNO_2$ (reaction time see in Table 1). The products were isolated and purified by usual procedure.

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