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Cong-Shan Zhong, Jian-Lan Cui, Si-Yuan Yu, Xiao Wang, Ning Wang

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Graphical Abstract

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A green and practical reduction of N-(4-chlorophenyl)-2-nitroaniline and its derivatives to corresponding N-substituted-benzene-1,2-diamines using thiourea dioxide

Cong-Shan Zhong, Jian-Lan Cui*, Si-Yuan Yu, Xiao Wang, Ning Wang

School of Chemical Engineering and Technology, North University of China, Taiyuan 030051, China

ARTICLE, INFO * Corresponding author. Tel.: +86-155-132-94306; fax: +86-155-132-94306; e-mail:414559203@qq.com

Article history: Received Received in revised form Accepted Available online A new effective approach for synthesizing diverse N-substituted-benzene-1,2-diamines is reported. The treatment of N-substituted-2-nitroanilines with thiourea dioxide in the presence of sodium hydroxide efficiently formed the corresponding N-substituted-benzene-1,2-diamines, including N-(4-chlorophenyl)benzene-1,2-diamine with a good yield of 94%. The by-product is environmentally-friendly urea and is easy to separate from the product by filtration procedure that enhances the convenience of the approach.

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1. Introduction

There is considerable interest in N-substituted-benzene-1,2-diamine derivatives due to their effective bioactivities. The diphenylamine group is an important group of organic chemistry and can be found in pharmaceutical synthesis intermediate. For example, as one of the most important categories of N-substituted-benzene-1,2-diamine derivatives, N-(4-chlorophenyl)benzene-1,2-diamine has been intensively employed as intermediate in clofazimine (CFZ) synthesis worldwide (the synthetic route of CFZ is shown in Scheme 1). CFZ is an important antimycobacterial agent recommended by the World Health Organization (WHO) as a first-line drug to treat leprosy and second-line drug to treat Multidrug-Resistant tuberculosis (MDR-TB).¹ At present, millions of people still suffer from refractory TB every year, which threaten the global progress towards the the targets of The WHO's End TB Strategy.² Therefore, both the clinical use and the synthesis of CFZ are extensively attracting more and more attention.³

In particular, the early studies on the synthesis of N-(4-chlorophenyl)benzene-1,2-diamine (4a), an important intermediate of CFZ, mainly focused on the traditional reducing agents, such as iron powder,⁴ zinc powder,⁵ and stannous chloride.⁶ Although these methods are effective, a large amount of metal residues will be produced, which poses a serious threat to the environment. Additionally, the crude product is easy to be oxidized into brown solid during the complicated post-treatment process. It is necessary to design a green and effective reaction route for reducing N-substituted-2-nitroanilines into the corresponding diamines. It is the first proposed green approach to synthesize 4a and N-substituted-benzene-1,2-diamine derivatives using thiourea dioxide (TDO) as a reducing agent, which will significantly improve the synthesis efficiency of CFZ.



Scheme 1. Synthesis of CFZ. Reagents and conditions: (i) Et_3N , solvent free, 140 °C, 9 h; (ii) Fe/NH₄Cl or Zn/CH₃COOH; (iii) FeCl₃·6H₂O, HCl; rt, 10h; (iv) dioxane, reflux, 6 h.

As a powerful reducing agent, TDO can reduce a variety of compounds such as metal ions,⁷ ketones⁸ and aldehydes,⁹ and it is currently used in the bleaching process of wool in the textile industry. The stability of TDO [(NH₂)₂CSO₂] in alkaline solution is significantly lower than that in neutral or acid conditions. Because a large amount of OH⁻ in alkaline solution acts as a good nucleophilic agent to attack the carbon center, resulting in the breaking of C-S bond and the formation of urea residue and sulfoxylate. As a strong reducing agent, sulfoxylate can reduce the aromatic nitro groups into the corresponding amino groups.¹⁰ Scheme 2 shows the proposed reduction mechanism. TDO is much cleaner and safer than traditional reducing agents and the

$$3(NH_{2})_{2}CSO_{2} + 6OH^{-} \longrightarrow 3(NH_{2})_{2}CO + 3H_{2}O + 3SO_{2}^{2-}$$
(1)
$$3SO_{2}^{2-} + \bigcup_{H} NO_{2} \longrightarrow 3SO_{3}^{2-} + \bigcup_{H} NH_{2} \longrightarrow H^{-} R (2)$$

Scheme 2. Proposed reduction mechanism between TDO and N-substituted-2-nitroanilines in alkaline solutions.

reduction reaction produces non-toxic wastes, such as sodium sulfite and urea.¹¹ More importantly, the approach also has the advantages of convenient operation and simple post-processing mode, and is very suitable for industrial production.

2. Results and discussion

Initially, the reaction conditions were optimized by using N-(4-chlorophenyl)-2-nitroaniline (3a) as a model compound and TDO as a reducing agent. The effects of molar ratio, alkali and solvent were investigated and the results are summarized in Table 1. In theory, the molar ratio of 3a, TDO and NaOH was 1: 3: 6 according to the proposed reduction mechanism mentioned above. But the actual dosage of the reagents was greater than the theoretical value in the experiment.

Relying on obtained results, the influence of different ratios of 3a, TDO and NaOH were explored in EtOH-H₂O (v/v, 1/3) (Table 1, Entries 1–9). In the presence of 1 equiv. of 3a, the synthesis of compound 3a to 4a was investigated with the number of equivalents of TDO and NaOH changing, and the yield of 4a increased as the amount of TDO increased from 3 to 5 equiv. No substantial improvement in the yield was observed with a further increase in TDO. In these reactions, TDO was added in batches to the mixture within 15 minutes. Meanwhile, a good yield of 92% could be obtained too when thiourea dioxide was added to the mixture slowly over 2 h (Table 1, entry 7). As a result, the optimal ratio of TDO to 3a was 5: 1 and the yields from 87 to 94% can be afforded. The effect of the amount of NaOH on the reaction was also studied. An increase in yield was observed when the amount of NaOH increased from 5 to 10 equiv. The molar ratio was 1: 5: 10 and a satisfactory yield of 94% was obtained by using the mixed solvent of EtOH and H₂O (v/v, 1/3) (Table 1, entry 6).

Additionally, the effects of alkali other than NaOH in the reaction mixture had not been investigated. It was speculated that the decomposition of thiourea dioxide is related to the strength of alkalinity. The stronger the alkalinity, the stronger the promoting effect on the decomposition of thiourea dioxide. Interested in this idea, the effect of TDO on the reduction of aromatic nitro compounds in the presence of different alkalis was studied. Therefore, KOH, Na₂CO₃, K₂CO₃, NaHCO₃ and NaAc were used in the reaction with a mixed solvent of EtOH and H₂O (Entries 10-14). Among them, in the presence of weak alkali NaHCO₃, a yield of 57% was obtained. Moreover, when NaAc was used in the reaction, no product was obtained. Na₂CO₃ and K₂CO₃ could help increase the yields to 86% and 87%. As expected, strong base NaOH and KOH had the more positive effect on this reduction reaction after comparison in yield. As a result, NaOH, which was cheaper and more commonly used, was more suitable in this reaction than KOH.

Owing to the poor solubility of **3a** in water and the solubility of TDO in organic solvents, the reduction reaction would not actually take place in pure water or in pure organic solvents. For this reason the reduction reactions were carried out in a mixture of water and organic solvents. Next, Entries 15–18 showed that the reduction reaction of **3a** with TDO did not occur in the presence of NaOH and mixed solvents such as THF-H₂O and CH₃CN-H₂O. However, using EtOH, MeOH and DMF with H₂O



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Entry	components	ratio	(1/3)	(h)	%) d				
1	3a/TDO/NaOH	1: 3: 6	EtOH-H ₂ O	2.4	68				
2	3a/TDO/NaOH	1: 3.5: 7	EtOH-H ₂ O	2.4	73				
3	3a/TDO/NaOH	1: 4: 8	EtOH-H ₂ O	2.4	76				
4	3a/TDO/NaOH	1: 5: 5	EtOH-H ₂ O	2.3	87				
5	3a/TDO/NaOH	1: 5: 9	EtOH-H ₂ O	1.8	91				
6	3a/TDO/NaOH	1: 5: 10	EtOH-H ₂ O	1.5	94				
7	3a/TDO/NaOH	1: 5: 10	EtOH-H ₂ O	2.5	92 ^b				
8	3a/TDO/NaOH	1: 6: 12	EtOH-H ₂ O	1.4	93				
9	3a/TDO/NaOH	1: 7: 14	EtOH-H ₂ O	1.4	92				
10	3a/TDO/Na ₂ CO ₃	1: 5: 5	EtOH-H ₂ O	2.5	86				
11	3a /TDO/K ₂ CO ₃	1: 5: 5	EtOH-H ₂ O	2.5	87				
12	3a/TDO/KOH	1: 5: 10	EtOH-H ₂ O	2.3	90				
13	3a/TDO/NaHCO ₃	1: 5: 10	EtOH-H ₂ O	2.6	57				
14	3a/TDO/NaAc	1: 5: 10	EtOH-H ₂ O	-	0				
15	3a/TDO/NaOH	1: 5: 10	DMF-H ₂ O	1.6	85				
16	3a/TDO/NaOH	1: 5: 10	MeOH- H ₂ O	2.3	92				
17	3a/TDO/NaOH	1: 5: 10	CH ₃ CN- H ₂ O	-	0				
18	3a/TDO/NaOH	1: 5: 10	THF-H ₂ O	-	0				

^a Reaction conditions: compound 3a (10 mmol), alkali, solvent (20 mL). 5 equiv. TDO was added in batches within 15 minutes, stirred at 50 °C.

^b Compound **3a** (10 mmol), NaOH (10 equiv.), EtOH-H₂O (20 mL), 5 equiv. TDO was added in batches over 2h, stirred at 50 °C.

^c Volume ratio 1:3.

^d Isolated yield.

as solvents could significantly promote the reduction reaction. The yield of the reaction in DMF-H₂O was medium, and the reaction time in MeOH-H₂O was longer. It could be concluded that EtOH-H₂O (v/v, 1/3) is the best solvent choice. Product **4a** was insoluble in water and slightly soluble in ethanol, while inorganic salts such as the by-product urea was soluble in water but not in ethanol, so when the ratio of water to ethanol was 3: 1, the product could be successfully obtained by reaction and suspended in mixed solvents, which could be filtered easily and enhance the convenience of the treatment. As stated before, when the molar equivalent of **3a**, TDO and NaOH was 1: 5: 10 respectively, the effective reduction of **3a** was the best. Subsequently, **4a** was obtained at 50 °C within 1.5 h and the yield was 94% (Table 1, Entry 6).

Table 2. Traditional reaction condition in the synthesis of 4a



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Entry	components	Molar ratio	remperature (°C)	JOI Time (h)	urnal F 1 ieiu (%) ^a
1 ^b	3a / Fe/NH ₄ Cl	1:4.5:0.2	80	2.5	81
2°	3a/Zn/HAc	1:3.8:0.005	rt	3.5	64
3°	3a/ NaBH ₄ /CuS ₄	1:5:2	rt	1.5	76
4°	3a/ SnCl ₂	1: 5	70	3.5	68

^a Isolated yield.

^b The reaction was conducted in mixed solvent EtOH-H₂O (v/v, 10/1).

^c The reaction was conducted in EtOH.

For the purpose of exploring an optimum approach of the synthesis of 4a, some reactions employing traditional reducing agents to form products were also planned. And the results are listed in Table 2. Fe/NH₄Cl system could be used as a reducing agent to smoothly reduce 3a to 4a in yield of 81%. However, the reaction generated a large amount of iron mud, which contained organic impurities and had the difficulty in handling. When SnCl₂ were selected as reductant, the reduction reaction was conducted at the reflux temperature with a slightly longer time to yield 4a in 68%. When the reduction system of Zn/HAc or NaBH₄/CuSO₄ were selected, the reaction could be carried out at room temperature, but both of them had medium yield in 64% and 76% respectively. The common characteristic of these approaches was the difficulty of product separation from the excess metal residue. It was worth mentioning that, the product could be obtained in good yields by simple filtration by using a new reducing agent thiourea dioxide in the reduction reaction. And this approach was more environmentally friendly and more effective than the above experimental method.

Under the optimal conditions, a series of N-substituted-benzene-1,2-diamine derivatives were synthesized. As shown in Table 3, 1fluoro-2-nitro-benzene was employed as raw material to react with different aromatic anilines, aliphatic amines and imidazole in the presence of triethylamine at 140 °C. And the desired products **3a-j** were obtained. Unfortunately, the meta-substitud nitroaniline were failded to obtained owing to the low activity of 1-Fluoro-3-nitrobenzene during nucleophilic substitution reaction. N-(4-chlorophenyl)-4-nitroaniline (**3k**) also had a poor yield under the same condition.¹² Next, the desired N-substituted-2-nitroaniline derivatives were treated with TDO in the presence of NaOH at 50 °C in EtOH-H₂O (v/v, 1/3). Notably, when the substituted groups were aromatic anilines, the yields of products were good (**4a-4f**, 86%-94%). Aliphatic amines as substituted groups could give moderate yields (**4g-4i**, 55%-74%). However, when 1-(2-nitrophenyl)imidazole (**3j**) and N-(4-chlorophenyl)-4-nitroaniline (**3k**) were used as raw material under the same reduction reaction conditions, only trace amount of product **4j** and **4k** were detected. It was likely that the different solubility of **4j** and **4k** in the reaction system affected the reduction process, and side reactions might occur.

To sum up, this reaction method was more suitable for the synthesis of aromatic anilines substituted derivatives with good yield.



N-substituted-benzene-1,2-diamine

derivatives.^a



^a Reaction conditions: 1 (11 mmol), 2 (16 mmol), Et₃N (5.5 mmol), solvent-free, 140 °C, 9 h; **3a-k** (10 mmol), TDO (50 mmol), NaOH (100 mmol), EtOH-H₂O (20 mL,v/v, 1/3), 50 °C. Yields refer to isolated pure products.

Conclusion

An effective system for the preparation of N-substituted-benzene-1,2-diamine derivatives with green reduction agent TDO in the presence of NaOH was established. In particular, A new effective and useful synthetic reaction of N-(4-chlorophenyl)-2-nitroaniline with TDO was carried out to give N-(4-chlorophenyl) benzene-1,2-diamine in yield of 94% in this study. Compared with earlier methods, this procedure has several advantages including simplicity in experiments and work-up and no generated toxic commercial wastes. Furthermore, This approach only needed simple filtration to give the corresponding diamines due to the poor solubility of the products. There was no doubt that all these advantages were effective improvements to the existing methods for the synthesis of N-substituted-benzene-1,2-diamine derivatives. And further research is also needed for the reduction reactions of various types of nitrobenzene.

The reagent TDO was used as reducing agent for the first time in the synthesis of N-(4-chlorophenyl)benzene-1,2-diamine. Compared with the reducing agents reported in the literature, TDO had the advantages of good stability, low environmental pollution and inexpensive. It would provide a new approach of CFZ's production in laboratory and industry.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Graphical Abstract



- Thiourea dioxide is first used in the reduction of N-substituted-2-nitroanilines
- Thiourea dioxide has the advantages of good stability and inexpensive
- This procedure do not generated toxic commercial wastes
- Simple filtration is needed to give N-(4-chlorophenyl)benzene-1,2-diamine