



An unexpected copper catalyzed 'reduction' of an arylazide to amine through the formation of a nitrene intermediate



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ABSTRACT

Azido nitrobenzoxadiazole (NBD) was observed to undergo a 'reduction' reaction in the absence of an obvious reducing agent, leading to amine formation. In the presence of an excess amount of DMSO, a sulfoxide conjugate was also formed. The ratio of these two products was both temperature- and solvent-dependent, with the addition of water significantly enhancing the ratio of the 'reduction' product. Two intermediates of the azido-NBD reaction in DMSO were trapped and characterized by low-temperature EPR spectroscopy. One was an organic free radical ($S=1/2$) and another was a triplet nitrene ($S=1$) species. A mechanism was proposed based on the characterized free radical and triplet intermediates.

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1. Introduction

Azido compounds are versatile molecules. They are being used extensively in both organic reactions and chemical biology. For example, the 'click' reaction between an azido group and an alkyne,¹ including the copper catalyzed and copper-free 'click' reactions,² are becoming a very important approach to DNA,³ protein,⁴ and glycan labeling⁵ among other applications. The azido group is known to undergo a variety of useful reactions, including the Schmidt reaction, the Curtius reaction, and other important ring-formation or ring-expansion reactions.⁶ Reduction of azides is not only a very efficient method for the preparation of amines,⁷ amides, and sulfonamides,⁸ but also a new approach for the quantitative fluorescence detection of hydrogen sulfide in aqueous solutions.⁹ Azido compounds are known to fragment under light and/or at elevated temperature and to generate nitrenes,¹⁰ which can undergo an insertion reaction with alkenes, yielding aziridines.¹¹ Transition

metals such as copper were also observed to facilitate the fragmentation.¹² Understandably, reduction of the azido group normally requires a reducing agent. However, herein we report a case where azido-NBD was 'reduced' to its corresponding amine in the absence of an obvious reducing agent. Copper was observed to catalyze the reaction. Electron paramagnetic resonance (EPR) studies were also performed to gain initial insight into the reaction process.

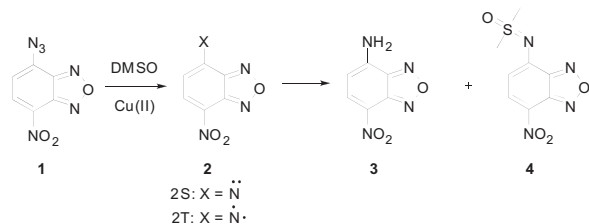
2. Results and discussion

In our effort aimed at modifying the fluorescent dye nitrobenzoxadiazole (NBD), we synthesized azido-NBD (**1**) and conducted copper-mediated Huisgen cycloaddition at room temperature in a mixed solvent of water, DMF, and *tert*-butanol. Instead of the anticipated [2+3] cycloaddition product, we observed the formation of the 'reduction' product, amino-NBD (**3**) in 61% yield, although the reaction contained no obvious reducing agent. In the absence of any reducing agent, reduction of the azido group is nearly impossible unless the reaction went through a very reactive intermediate(s), which could 'rob' electrons or hydrogen atoms from otherwise 'inert' compounds. The formation of a nitrene intermediate (compound **2**)

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can explain the product observed in this study. Specifically, nitrene formation followed by hydrogen abstraction would explain the formation of amino-NBD (**3**, Scheme 1). However, such fragmentations normally require either light or heat.¹³ To the best of our knowledge, room temperature azidoarene fragmentation in the absence of irradiation to the extent that a side product is readily isolated in high yield is considered unusual.



Scheme 1. The copper catalyzed NBD–nitrene reaction in DMSO.

In order to eliminate the possibility that DMF was functioning as the reducing agent, we conducted the reaction using DMSO as the solvent. Interestingly, DMSO adduct **4** was obtained in addition to the reduction product **3**. The nitrene intermediate formed by the fragmentation of an acyl azide group (e.g., Boc-N₃) has been observed to undergo a transfer reaction leading to conjugation with sulfoxides and sulfides,¹⁴ but the aromatic nitrene transfer reaction has not yet been reported. This reaction could provide an alternative approach for the synthesis of the sulfoximines, which are very important intermediates in medicinal chemistry.¹⁵ This could also offer the possibility of fluorescent labeling of the sulfoxide group.

To achieve a further understanding of this unique reaction, a series of experiments were performed to study how several factors affect the reaction outcome. The reaction was carried out at both room and elevated temperatures (80 °C), with or without a transition metal ion (Cu(I), Cu(II), Ag(I), Fe(II), or Fe(III)) as the catalyst. The effects of EDTA, shielding the reaction from any light, and added H₂O were also examined. ¹H NMR spectroscopy was used to monitor the reaction progress. The results of the reactions under different conditions are listed in Table 1.

Table 1
Product analysis of the NBD–nitrene reaction in DMSO^a

Entry	Catalyst	Other	Solvent	Temp	1	3	4 ^b
1	None	None	DMSO	rt	0.84	0.08	0.08
2	None	None	DMSO	80 °C	0	0.24	0.76
3	CuCl	Dark	DMSO/H ₂ O	rt	0.95	0.05	0
4	None	None	DMSO/H ₂ O	80 °C	0.29	0.55	0.16
5	None	Dark	DMSO	80 °C	0.48	0.18	0.34
6	CuCl ₂	None	DMSO	80 °C	0	0.25	0.75
7	CuCl ₂	Dark	DMSO	80 °C	0	0.26	0.74
8	CuCl	None	DMSO	80 °C	0	0.32	0.68
9	CuCl	Dark	DMSO	80 °C	0	0.39	0.61
10	AgNO ₃	None	DMSO	80 °C	0.11	0.22	0.66
11	AgNO ₃	Dark	DMSO	80 °C	0.55	0.06	0.39
12	CuCl ₂	None	DMSO/H ₂ O	80 °C	0	0.74	0.26
13	CuCl ₂	Dark	DMSO/H ₂ O	80 °C	0	0.64	0.36
14	CuCl	None	DMSO/H ₂ O	80 °C	0	0.74	0.26
15	CuCl	Dark	DMSO/H ₂ O	80 °C	0.07	0.69	0.24
16	AgNO ₃	None	DMSO/H ₂ O	80 °C	0	0.70	0.30
17	AgNO ₃	Dark	DMSO/H ₂ O	80 °C	0.17	0.55	0.26
18	FeCl ₃	None	DMSO/H ₂ O	80 °C	0.29	0.53	0.17
19	FeCl ₂	None	DMSO/H ₂ O	80 °C	0.23	0.66	0.11
20	None	EDTA, Dark	DMSO/H ₂ O	80 °C	0.71	0.19	0.10
21	None	EDTA	DMSO/H ₂ O	80 °C	0	0.76	0.24
22	None	EDTA, Dark	DMSO	80 °C	0.39	0.32	0.29
23	None	EDTA	DMSO	80 °C	0.1	0.47	0.43

^a Unless otherwise indicated, reactions were proceeded for 24 h with 10 mg of **1**, 0.8 mL of DMSO-*d*₆ or DMSO-*d*₆/D₂O 3:1, 20 mmol % of catalyst. 'Dark' refers to protecting from light using foil.

^b Ratio is determined by the crude ¹H NMR spectra.

When comparing reaction outcomes in entries 1 and 5 as well as 3 and 15, one can see that the reaction was temperature-dependent. In DMSO, the reaction gave a 16% conversion at room temperature in 24 h without catalyst (Table 1, entry 1), whereas full conversion was achieved in 24 h at 80 °C (entry 2). It also seems that ordinary room-light makes a difference. For example, at 80 °C the reaction achieved full conversion under light (entry 2), but only about 50% conversion when the reaction was run in the dark (entry 5). Subsequent reactions in the presence of metal ions (entries 10 and 11, 16 and 17) or EDTA (entries 20 and 21, 22 and 23) also indicate room-light affords reaction acceleration. It was found that Cu(II) and Cu(I) (under N₂ atmosphere) seem to facilitate the reaction. Comparing the results from entries 7 and 9 to that of entry 5 in Table 1, one can see that the addition of copper significantly accelerates the reaction (This was also confirmed in Fig. 1b.). In the absence of any metal ions and in the dark, 48% of the starting material remained at the end of the reaction (entry 5), whereas all starting material disappeared when the same reaction was carried out in the presence of Cu(II) (entry 6) or Cu(I) (entry 9). However, addition of either Cu(II) or Cu(I) did not seem to affect the product ratio significantly. For example, Cu(II)-facilitated reactions gave a 3:1 ratio between **4** and **3** independent of whether the reaction was run in the dark. This ratio is the same as the reaction under light and in the absence of any metal ions (entry 2). We also tested the effect of silver ions. It was surprising to find that Ag actually inhibits the reaction. For example, heating **1** at 80 °C in DMSO led to the complete disappearance of the starting material after 24 h. However, the same reaction in the presence of AgNO₃ still had 11% starting material after 24 h. The specific reason for this inhibition is not clear.

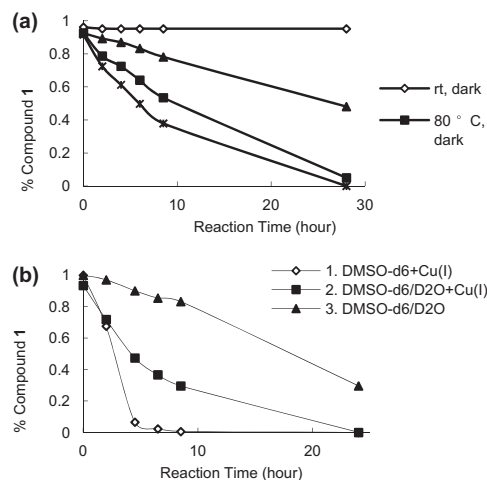


Fig. 1. Time dependent decrease of **1** as a percentage of the initial concentration under different reaction conditions. (a) Reaction was performed in DMSO-*d*₆/D₂O in the presence of Cu(I). (b) Reaction was performed at 80 °C in the dark. DMSO-*d*₆/D₂O ratio was 3:1. Cu(I) was 20 mmol %.

In all the above reactions, the DMSO adduct **4** was the major product. However, upon addition of water, reaction seems to slow down (entry 2 vs 4) leading to the reduction product **3** being the major component. For example, when the reaction was performed in a solvent system of DMSO/H₂O (3:1), the ratio of the two isolated products **3** and **4** was found to be around 3:1, while the reaction in dry DMSO gave a 1:3 ratio. Again, addition of either Cu(I) or Cu(II) accelerated the reaction but did not seem to alter the ratio of the reduction product and the DMSO adduct. For example, in the presence of water, the ratio between **3** and **4** was approximately 3:1 with or without added Cu (at the valence state of I or II) (entries 12 and 14). When carried out in the dark, this ratio decreased slightly.

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