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Simple and Practical Procedure for the Preparation of Benzofurazan-N-oxides in the Presence of Cyclodextrin in Neutral Condition

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Abstract: A simple and practical procedure for the aqueous-phase preparation of benzofurazan-N-oxides has been developed in the presence of cyclodextrin at room temperature in neutral condition for the first time. Organic solvent can be precluded for the application of cyclodextrin, which can be recovered and reused in subsequent reactions without loss of activity. The reaction mechanism was studied based on the complexation of cyclodextrin and o-nitroaniline, which was proved by ^{1}H NMR and IR spectroscopy.

Keywords: Benzofurazan-N-oxides, cyclodextrin, green chemistry, neutral condition, o-nitroaniline

Benzofurazan-N-oxides (BFOs), are considered as some of the most important drug reagents[1] as well as intermediates, especially for the sythesis of quinoxaline compounds.[2] BFOs are also widely used in the areas of analytical chemistry,[3a,3b,3d] military,[3c] agriculture,[2d,2e] biology,[2d,2e] and materials.[3e]

The formal synthetic method of BFO is oxidation of o-diphenol, which has poor yield, because of the difficult formation of the quinone oxime intermediate. Recently, a new method was developped to achieve the target, which is oxidation of o-nitroaniline with sodium hypochlorite.[4]

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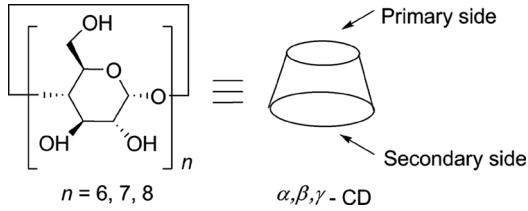
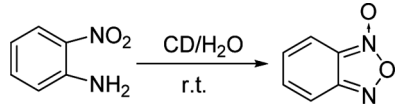


Chart 1. Structures of cyclodextrins.

Though different approaches have been reported, there are various limitations such as the use of strong basic conditions, elevated temperatures, long reaction times, and hazardous organic solvents.

In our efforts to develop a biomimetic approach through supramolecular catalysis, now we report a simple and practical method of the synthesis of BFO from o-nitroaniline in neutral condition in the presence of β-cyclodextrin. Organic reactions in aqueous media have recently become a topic of focus in organic synthesis because they overcome the harmful effects of organic solvents and are environmentally benign.[5] These aqueous reactions can be made more sophisticated if they are performed under supramolecular catalysis. Cyclodextrins (CDs), which are cyclic oligosaccharides (Chart 1), have generated interest as enzyme models because of their ability to bind substrates selectively and catalyze chemical reactions by supramolecular catalysis, involving the reversible formation of host–guest complexes with the substrates by noncovalent bonding, as seen in enzyme complexation processes.[6] Because complexation depends on the size, shape, and hydrophobicity of the guest molecule, CDs have been utilized for biomimetic modeling of the synthesis in water.[7] β-CD was chosen because it is easily accessible and the least expensive among the CDs.

The reaction was carried out by the in situ formation of the complex of CD and o-nitroaniline in water followed by the addition of sodium hypochlorite. It was stirred for 20 min at room temperature to give BFO in a good yield (Scheme 1). The reaction proceeded smoothly without heating. CDs were recovered by filtration and reused for five consecutive runs in this reaction without basically no change in the



Scheme 1. Synthesis of benzofuran-N-oxides from o-nitroaniline in the presence of cyclodextrin.

yield and purity. The product was characterized by ^{1}H NMR, IR, and elemental analysis and was compared with the known compounds[4] by thin-layer chromatography (TLC).

In the absence of CDs, the reaction does take place but the yield was poor (less than 20%) and overoxidation by-product was observed. We tried α-CD (56%), β-CD (85%), γ-CD (93%), hydroxypropyl β-CD (47%), and sulfonebutyl β-CD (61%) to find a suitable catalyst, but only β-CD and γ-CD, produced a favorable yield, possibly because of the suitable size of cavity of β-CD and γ-CD as well as the stenosis cavity of α-CD and the hindering of β-CD derivatives. Inclusion complexation takes place in situ during the reaction, and the complexes have been isolated and characterized by ^{1}H NMR and IR studies.

The inclusion complex of cyclodextrin and o-nitroaniline in the CD-catalyzed reactions in water has been presumed based on the following evidence: the fact that the yield was so poor in the absence of CDs and that o-nitroaniline is almost insoluble in water at room temperature. We deduced that CDs play the part of phase-transfer catalyst to bring o-nitroaniline into an aqueous phase. Besides, perhaps by forming an H-bond to stabilize the intermediate, the overoxdition could decrease dramatically. The cavity of CD is also a proper shield for the active phenyl to exclude the side reaction.

Evidence for this mechanistic approach was deduced from ^{1}H NMR and IR spectroscopy. A comparison of the ^{1}H NMR spectra (D_2O) of β-CD and β-CD-o-troaniline complex was undertaken. There was a clear upfield shift of H1 (0.137 ppm), H2 (0.156 ppm), H3 (0.164 ppm), H4 (0.164 ppm), H5 (0.149 ppm), and H6 (0.092 ppm) protons of β-CD in the β-CD-o-nitroaniline complex as compared to β-CD, indicating the formation of an inclusion complex of o-nitroaniline with β-CD.[8]

A comparison of the Fourier transform (FT)-IR spectra of o-nitroaniline, β-CD, the solid inclusion complex, and the physical mixture of o-nitroaniline and β-CD was also undertaken. In the physical mixture, stretching vibration of hydroxyl group appeared in the region of 3355 cm^{-1}, whereas in the solid inclusion complex, the peak shifted to 3407 cm^{-1} and became much wider, which might be related to the inclusion complexation between β-CD and o-nitroaniline.[9]

Based on the spectra studies, we deduce the mechanism as shown in Chart 2.

In conclusion, our methodology provides a method for the conversion of o-nitroaniline to benzofurazan-N-oxides under neutral and mild conditions, and the reaction can be carried out easily at room temperature by recycling cyclodextrin. We also suggest the mechanism of reaction through the study of ^{1}H NMR and FT-IR spectra: cyclodextrins not only play the part of phase-transfer catalyst but also protect the intermediate of the reaction from overoxidation by H-bonding and with the cavity.

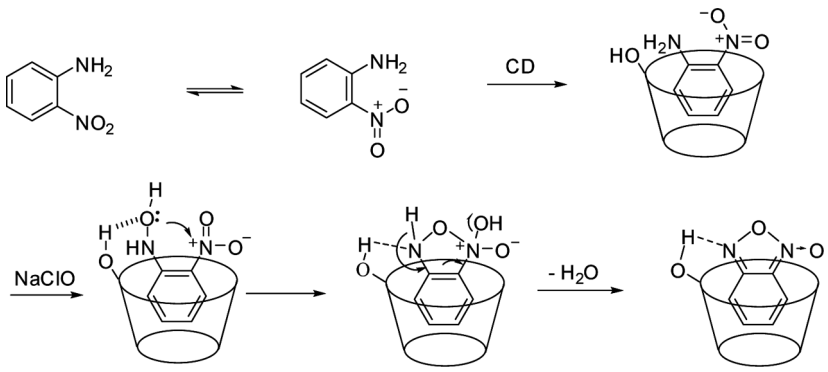


Chart 2. Deduced mechanism from o-nitroaniline to benzofuran-N-oxides in the presence of cyclodextrin.

EXPERIMENTAL

General

Sodium hypochlorite and o-nitroaniline were purchased from Country Medicine Reagent Co., China. Cyclodextrins were purchased from Guangdong Yunan Chemical Reagent Co. and recrystallized three times from distilled water before application. Hydroxypropyl β-CD was purchased from Shandong ZiBo Xinda Chemical Reagent Co. Sulfonebutyl β-CD was a gift from Dr. Shen Jian.

^{1}H NMR and ^{13}C NMR spectra were performed at 400-MHz on a Bruker Avance 400-MHz NMR. IR spectra were performed on an Avatar 370 FT-IR spectrometer. Elemental analysis were performed on a Vario El III, Elmentar Co. Thin-layer chromatographic (TLC) analysis was performed on glass plates precoated with silica gel F254 obtained from Qingdao Haiyang Chem, China.

Synthesis of Benzofurazan-N-oxides

β-CD (1.05 mmol) was dissolved in water at 60°C (15 mL), and a clear solution was formed. o-Nitroaniline (1 mmol) dissolved in methanol (0.5 mL) was added dropwise and stirred for half an hour until the inclusion was formed. Then, aqueous sodium hypochlorite (4 mmol) was added, and the mixture was stirred at room temperature until the reaction was complete (as monitored by TLC). The mixture was extracted with ethyl acetate (20 ml × 3), and the extract was filtered. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under

reduced pressure, and the resulting product was further purified by column chromatography using ethylacetate–petroleum ether(v:v = 5:1) as eluent.

Benzofurazan-N-oxides: yellow powder, mp = 67–68°C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (2H, s, Ar-H), 7.46 (2H, s, Ar-H); IR νmax (KBr) (cm^{-1}): 3443, 2925, 2363, 1616, 1589, 1539, 1485, 1424, 1125, 1016, 893, 835, 750, 671, 572. Anal. calcd. for $C_6H_4N_2O_2$: C, 52.94; H, 2.94; N, 20.59. Found: C, 52.56; H, 2.99; N, 20.52.

Preparation of Inclusion of o-Nitroaniline and β-CD

β-CD (1.05 mmol) was dissolved in water at 60°C (15 mL), and a clear solution was formed. o-Nitroaniline (1 mmol) dissolved in methanol (0.5 mL) was added dropwise and stirred for half an hour until precipitation appeared. The precipitate was collected by filtration under reduced pressure, washed with water, and dried.

Inclusion of o-nitroaniline and β-CD: yellow powder.^{1}H NMR (300 MHz, D_2O): δ 8.05 (1H, d, Ar-H), 7.44 (1H, t, Ar-H), 6.98 (1H, d, Ar-H), 6.74 (1H, t, Ar-H), 5.07 (1H, s, CD-H1), 3.96 (1H, t, CD-H5), 3.84 (1H, s, CD-H6), 3.69 (1H, s, CD-H2), 3.67 (1H, s, CD-H3), 3.61 (1H, s, CD-H4); IR_{max}(KBr) (cm^{-1}): 3408, 2927, 1627, 1572, 1510, 1436, 1257, 1155, 1079, 1029, 943, 867, 750, 703, 580, 529.

Preparation of Physical Mixture of o-Nitroaniline and β-CD

To do FT-IR, a physical mixture of o-nitroaniline and β-CD was needed. o-Nitroaniline (1 mmol) and β-CD (1.05 mmol) need to be ground with KBr separately, well mixed, and then extruded to avoid the inclusion of guest and host molecule during the grinding procedure.[7,10]

Physical mixture of o-nitroaniline and β-CD: grey powder, IR_{max}(KBr) (cm^{-1}): 3355, 2927, 1628, 1570, 1508, 1429, 1348, 1255, 1156, 1081, 1031, 942, 851, 745, 701, 579, 527.

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