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EFFECTIVE PROMOTION OF BEIRUT REACTION BY β-CYCLODEXTRIN IN WATER

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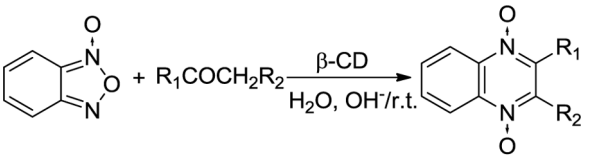
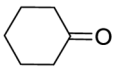
GRAPHICAL ABSTRACT



1: R_1=H, R_2=CH_3
2: R_1=H, R_2=CH_2CH_3
3: R_1=CH_3, R_2=$(CH_2)_3CH_3$

4: 

5: R_1=CH_3, R_2=$COCH_3$

Abstract *A mild and highly efficient, environmentally friendly procedure has been developed for the conversion from benzofurazan-N-oxides to quinoxaline di-N-oxides in the presence of β-cyclodextrin in water at room temperature with excellent yields. The application of cyclodextrin precludes the use of organic solvent, and the catalyst can be recovered and reused in subsequent reactions with the same catalytic activity. Herein, the Beirut reaction is carried out in the medium of water for the first time. The reaction mechanism was proposed based on the inclusion complexation of β-cyclodextrin with benzofurazan-N-oxides which was confirmed by ^1H NMR, ultraviolet/visible spectrum, and infrared spectroscopy.*

Keywords Benzofurazan-N-oxides; catalysis; cyclodextrin; green chemistry; quinoxaline di-N-oxides; water

INTRODUCTION

The compounds of quinoxaline di-N-oxide (QXO) have been widely used as important drugs for sterilization and growth-promotion of animals. QXO also has pharmacological properties that make them usable as intermediates for producing

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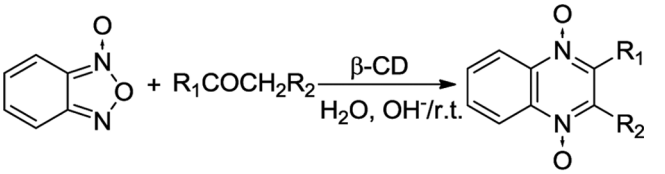
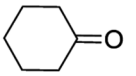
plant-protection agents.[1] Previous methods of synthesis of QXO involve the oxidation of quinoxaline with poor yields and present great trouble in separation.[2] To solve the problem, an efficient and straightforward synthetic path, the Beirut reaction, from benzofurazan-N-oxides (BFO) to QXO was developed. It was generally carried out in organic solvents in the presence of amines, which were used as the catalysts.[3] However, this method needs a long time (overnight), and the application of organic solvent would also cause environmental problems. Also, when BFO is mixed with reducing amine, an explosion might happen because of the high energy of the BFO molecule.[4] These reactions were unsuccessful in water alone[5] because of the poor solubility and inert nature of BFO. Furthermore, much by-product is generated and therefore the yield is poor.

We have explored Beirut reactions using water as the reaction medium at room temperature. The best choice appeared to be through supramolecular catalysis involving cyclodextrins (CDs), with water as solvent, because such reactions do not generate toxic waste products. Thus, an attractive procedure for the synthesis of QXO from BFO, different from the classical approach, was developed for the first time under supramolecular catalysis in water in the presence of β-CD at room temperature (Scheme 1).

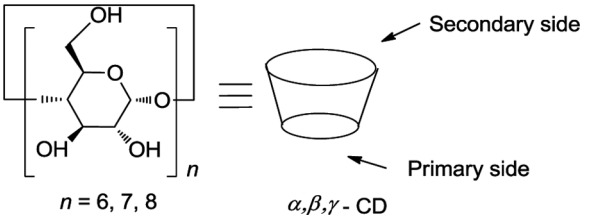
Because green chemistry is becoming a central issue in both academic and industrial research in the 21st century,[6] the integration of catalysis with facile catalyst separation and recycling should be a primary focus of future research activities. The toxic and volatile nature of organic solvents widely used in organic synthesis also has posed a serious threat to the environment. Water is considered as an ideal solvent because it is safe, economical, and environmentally benign.[7] Room-temperature synthesis of the target molecule is also of particular interest for the concern of saving energy.

CDs, cyclic oligosaccharides commonly composed of six, seven, or eight D-glucopyranosyl units connected by α-(1,4)-glycosidic linkages, have the ability to form inclusion complexes with a wide range of substrates in aqueous solution for their particular structures (Scheme 2). Complexation depends on the size, shape,



1: R_1=H, R_2=CH_3
2: R_1=H, R_2=CH_2CH_3
3: R_1=CH_3, R_2=$(CH_2)_3CH_3$
4: 
5: R_1=CH_3, R_2=$COCH_3$

Scheme 1. Beirut reaction in the presence of β-cyclodextrin in water.



Scheme 2. Structures of cyclodextrins.

and hydrophobicity of the guest molecule. This property has led to their wide applications as enzyme mimics and catalysts.[8] They promote reactions by supramolecular catalysis involving reversible formation of host–guest complexes by noncovalent bonding as observed in enzymes.

In general, the reaction was carried out by the in situ formation of the β-CD complex of BFO in water followed by the addition of the nucleophile, which was then stirred at room temperature for a short time to give the corresponding QXO with impressive yields (Table 1).

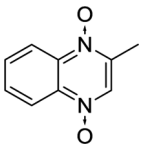
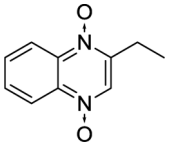
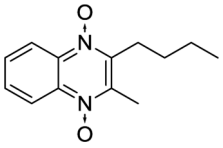
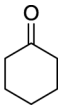
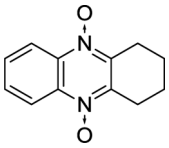
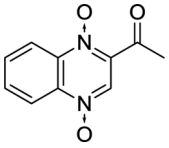
The reaction went smoothly at room temperature and was monitored by thin-layer chromatography (TLC). All the products were characterized by ^{1}H NMR, infrared (IR), mass spectroscopy, elemental analysis, and otherwise compared with the known compounds.[3] In the absence of β-CD, the reaction did take place with a poor yield (less than 40%). β-CD can be recycled and reused without loss of the catalytic activity. The complex inclusion takes place in situ during the process, and the complex has been isolated and characterized by ^{1}H NMR and IR studies.

During the reaction, a homogeneous solution was formed. In the absence of β-CD, the reaction mixture was suspended in liquid. This indicates that β-CD and BFO may form an inclusion complex. The fact that the yields were so poor in the absence of β-CD and also that BFO is insoluble in water shows the primary role that CD plays: the solubilization of BFO through β-CD in water. The inclusion complex of β-CD and BFO in these β-CD-catalyzed reactions in water has been postulated and confirmed by spectroscopic evidence as follows: Evidence to this mechanistic approach was deduced from ^{1}H NMR, ultraviolet/visible (UV-vis) spectrum, and IR spectroscopy. A comparison of the ^{1}H NMR spectra (D_2O) of β-CD and β-CD-BFO complex was undertaken (Table 2). It could be seen that there is a clear upfield shift of H-5 (0.010 ppm) protons of β-CD in the β-CD-BFO complex as compared to β-CD, indicating the formation of an inclusion complex of BFO with β-CD.[9] Based on the ^{1}H NMR results, it could be seen BFO and β-CD might form some kind of complex (Fig. 1).

The complex stoichiometry of BFO/β-CD was confirmed by UV spectroscopy using Job's plot method. The experimental curve (Fig. 2), describing the interactions between BFO and β-CD in the aqueous solution, goes through a maximum at a molar fraction of 0.5, which indicates that the complex stoichiometries of BFO/β-CD in aqueous solution are 1:1.[10] The intermolecular interactions between BFO (guest) and β-CD (host) in water can be represented as follows: $G + H = G \cdot H$.

Moreover, a comparison of the Fourier transform (FT)–IR spectra of BFO, β-CD, the solid inclusion complex, and the physical mixture of BFO/β-CD was also

Table 1. Beirut reaction in the presence of β-cyclodextrin

Entry	Substrate	Product[a]	Time (min)	Conv. (%)[b]	Isolated yields (%)
1	CH_3CH_2CHO		25	99	75
2	$CH_3CH_2CH_2CHO$		35	93	62
3	$CH_3CO(CH_2)_4CH_3$		40	95	67
4			45	84	71
5	$CH_3COCH_2COCH_3$		20	82	61

[a]All the products were characterized by ^{1}H NMR, IR, or elemental analysis.
[b]The product purity without isolation as detected by HPLC.

undertaken (Table 3). In the physical mixture of BFO/CD, N→O stretching absorption in the region 1429 cm^{-1} disappeared in the solid inclusion complex, which proved hydrogen bonding was formed to weaken the N→O bond. In the physical

Table 2. Comparison of the inclusion of CD/BFO and CD

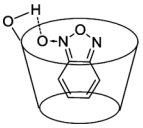
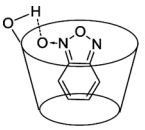
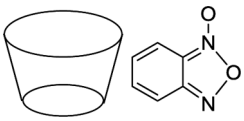
Inclusion of CD/BFO	CD
	
Status: yellow-white powder ^{1}H NMR (300 MHz, D_2O): δ 4.954 (d, H-1), 3.835 (t, H-5), 3.734 (d, H-6), 3.549 (d, H-2), 3.510 (t, H-3), 3.454 (d, H-4)	Status: white powder ^{1}H NMR (300 MHz, D_2O): δ 4.958 (d, H-1), 3.845 (t, H-5), 3.734 (d, H-6), 3.553 (d, H-2), 3.514 (t, H-3), 3.458 (d, H-4)

Table 3. Comparison of the inclusion of CD/BFO and the physical mixture of CD/BFO

Inclusion of CD/BFO	Physical mixture of CD/BFO
	
Status: yellow-white powder IR v max (KBr, cm^{-1}): 3410, 2927, 1618, 1590, 1539, 1487, 1414, 1334, 1244, 1156, 1080, 1030, 943, 704, 577.	Status: yellow powder IR v max (KBr, cm^{-1}): 3443, 2925, 2363, 1616, 1589, 1539, 1485, 1424, 1125, 1016, 893, 835, 750, 671, 572.

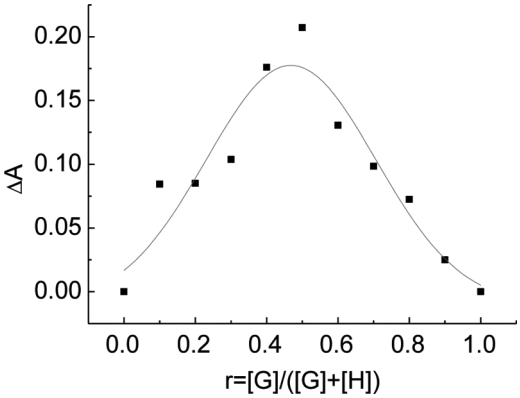


Figure 1. Job's curve of the inclusion complex of BFO/β-CD in the aqueous solution.

mixture, stretching vibration of the hydroxyl group became much wider in the solid inclusion complex, which might be related to the inclusion between β-CD and BFO. We can deduce that BFO is included in the cavity of β-CD.[11] It appears that β-CD not only solubilizes BFO but also forms a β-CD-BFO complex through H bonding, which may weaken the rigidity of the ring of BFO. Covalence effect, just as the role enzymes play, may happen to result in the reaction.

The fact that these yields were less in presence of α-CD as the catalyst may be due to the unsuitable cavity of α-CD for BFO.[12] Besides, β-CD was chosen as the preferred catalyst because it is inexpensive and easily accessible.

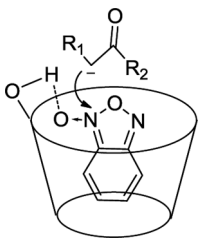


Figure 2. Possible mechanism of the Beirut reaction in the presence of β-cyclodextrin.

In conclusion, our methodology provides a new method for Beirut reaction from BFO to QXO using water as the medium. The reaction proceeds under mild conditions with a good yield and can be carried out easily at room temperature with recycling of β-CD. Since we have reported the green syntheis of BFO,[13] our approach here may provide a new way to produce highly pure and directly used drugs without further purification.

EXPERIMENTAL

Chemicals and solvents were either purchased or purified by standard techniques. β-CD was purchased from Guangdong Yunan Chemical Reagent Co. Ltd. and recrystallized twice from distilled water before application.

Melting points were recorded on a digital melting-point apparatus (WRS-1B) and are uncorrected. An IR spectrum was recorded on an Avatar 370 FI-IR spectrophotometer. ^{1}H NMR spectra was recorded on a Bruker Avance III–300 and Bruker Avance III–400 using dimethylsulfoxide (DMSO) or D_2O as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS; the coupling constants J are given in hertz. UV/vis spectra were recorded at room temperature with a TU-1800 pc UV/vis spectrophotometer. TLC analysis was performed on glass plates precoated with silica gel F254 obtained from Qingdao Haiyang Chemicals, China. High-performance liquid chromatography (HPLC) analysis was performed on a Shimadzu LC-10AT HPLC with a Shimadzu SPD-10A UV-vis detector (detection wavelength = 260 nm), and the mobile phase was selected as a mixture of methanol and water ($V_{methanol}/V_{H2O} = 70/30$) with a 1.0 ml/min flow rate.

Preparation of BFO: General Procedure

To a mixture of o-nitro aniline (10 g), 95% ethanol (50 mL), and KOH (3 g), 8% sodium hypochlorite (25 ml) was added slowly while stirring. The mixture was stirred at room temperature for 2.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, water (20 ml) was added, and a great deal of precipitation appeared. The precipitate was collected by filtration under reduced pressure. The crude product was further purified by recrystallization ($V_{methanol}/V_{H2O} = 4/1$) to provide the pure product in about 90% yields (characterized by ^{1}H NMR, IR, and elemental analysis).

Beirut Reaction in Presence of β-CD in Water

β-CD (1 mmol) and NaOH (1 g) was dissolved in water (50 mL) and a clear solution was formed. BFO (1 mmol) dissolved in methanol (1 mL) was added dropwise and stirred for half an hour until the inclusion was formed. Then, the carbonyl compound (4 mmol) was added and the mixture was stirred at temperature until the reaction was complete (as monitored by TLC, $V_{ethyl\ acetate}/V_{petroleum} = 5/1$). The mixture was extracted with ethyl acetate (20 ml × 3), and the extract was collected. The organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The product was directly tested by HPLC. The

resulting product can be further purified by column chromatography using a mixture of ethyl acetate and petroleum ($V_{ethyl\ acetate}/V_{petroleum} = 10/1$) as the eluent. After neutralization of the mixture and removal of the water under reduced pressure, β-CD was recovered by filtration with an 85% yield and reused for five consecutive runs in this reaction without change in the yield or purity of the product. The control experiment was carried out at the same conditions except for the addition of β-CD.

Preparation of Inclusion of β-CD/BFO

β-CD (1.05 mmol), and KOH (3 g) was dissolved in water (25 ml), and a clear solution formed. BFO (1 mmol) dissolved in methanol (1 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.

Detection of the Stoichiometries of BFO/β-CD Complex

Two equimolar stock solutions (10^{-3} mol/L), one of BFO (g) and the other of β-CD (h), were prepared. A set of working solutions was then obtained by mixing V_g mL of the stock BFO solution with ($V_t - V_h$) mL of the stock β-CD's solution, where V_t is a fixed total volume and V_g is a variable value (from 0 to 10 mL, $0 \leq V_g \leq V_t$).

Experimental Characterization Data for the Obtained Compounds

BFO. Yellow powder; mp = 66–67 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.69 (2H, s, Ar-H), 7.46 (2H, s, Ar-H); IR ν max (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.

Compound 1. Yellow powder; ^{1}H NMR (400 MHz, DMSO-d_6): 8.80 (1H, s, CH), 8.48–8.42 (2H, q, Ar-H), 7.98–7.89 (2H, m, Ar-H), 3.15 (3H, t, CH_3). Calcd. for $C_9H_8N_2O_2$: C, 61.00; H, 4.55; N, 15.81. Found: C, 60.49; H, 4.80; N, 15.51.

Compound 2. Yellow powder; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.69 (1H, s, CH), 8.49–8.42 (2H, m, Ar-H), 7.97–7.91 (2H, m, Ar-H), 2.90 (2H, q, CH_2), 1.26 (3H, t, CH_3); IR ν max (KBr, cm^{-1}): 3437, 3072, 3021, 2973, 2941, 1636, 1605, 1537, 1501, 1453, 1433, 1367, 1338, 1267, 1241, 1172, 1119, 1096, 1068, 916, 892, 868, 837, 770, 740, 637, 612, 541. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 62.96; H, 5.369; N, 14.65.

Compound 3. White powder; ^{1}H NMR (400 MHz, DMSO-d_6): 8.50–8.46 (2H, m, Ar-H), 7.93–7.88 (2H, m, Ar-H), 3.10–3.05 (2H, t, CH_2), 2.61 (3H, s, CH_3-methy), 1.65–1.55 (2H, m, CH_2), 1.49–1.40 (2H, m, CH_2), 0.96–0.91 (3H, t, CH_3-butyl). Calcd. for $C_{12}H_{12}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.17; H, 6.90; N, 12.01.

Compound 4. Yellow powder; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.43 (2H, d, $J = 3.5$ Hz, Ar-H), 7.88 (2H, d, $J = 3.2$ Hz, Ar-H), 2.93 (4H, s, CH_2), 1.83 (4H, s, CH_2); IR ν max (KBr, cm^{-1}): 3455, 3125, 2943, 2866, 1987, 1953, 1737, 1605, 1516, 1441, 1422, 1400, 1357, 1315, 1277, 1246, 1125, 1089, 1016, 979, 933, 904, 842, 824,

776, 694, 668, 640, 613, 557, 528, 436. Calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.34; H, 5.32; N, 12.90.

Compound 5. Yellow powder; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.51–8.43 (2H, m, Ar-H), 8.04–7.95 (2H, m, Ar-H), 2.66 (3H, s, CH_3), 2.37 (3H, s, CH_3); IR ν max (KBr, cm^{-1}): 3438, 1717, 1635, 1518, 1419, 1333, 1280, 1214, 1098, 1053, 967, 830, 776, 638, 613, 513. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 2.78; N, 12.84. Found: C, 60.35; H, 2.89; N, 12.18.

All compounds were compared with the known (prepared through the formal synthetic method[3]) by TLC (with the same *Rf* values) and HPLC (with the same retention times).

ACKNOWLEDGMENTS

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