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M. X. Zhang, P. F. Pagoria, R. T. Homles, O. E. Alawode, N. B. Zuckerman

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Mao-Xi Zhang*, Philip. F. Pagoria, Robert T. Holmes, Olajide, E. Alawode, and Nathanael B. Zuckerman

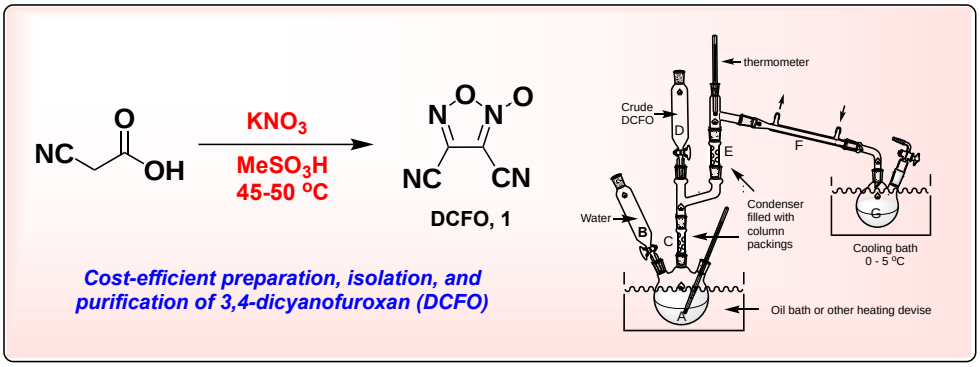
†Lawrence Livermore National Laboratory, 7000 East Ave,
Livermore, California 94550, United States

Cost-efficient and Scalable Nitration of Cyanoacetic Acid with Potassium Nitrate in Methanesulfonic Acid Gives Pure 3,4-Dicyanofuroxan Following Modified Steam Distillation Methodologies

Mao-Xi Zhang*, Philip. F. Pagoria, Robert T. Holmes, Olajide, E. Alawode, and Nathanael B. Zuckerman

Lawrence Livermore National Laboratory, 7000 East Ave, Livermore, California 94550, United States.
email: zhang27@llnl.gov

ABSTRACT



Two issues exist in the preparation of 3,4-dicyanofuroxan (**1**, DCFO) by a nitration of cyanoacetic acid (CAA) with 100% of HNO_3 in trifluoroacetic acid (TFA) or in H_2SO_4/CH_2Cl_2: (1) the cost of 100% of HNO_3 and (2) the isolation and purification of the product. In this paper, we report a cost-efficient nitration methodology by replacing 100% of HNO_3 with KNO_3 in methanesulfonic acid (MSA). The methodology includes adding KNO_3 and CAA portionwise to the solution of MSA at 45-50 ºC and keeping total nitrating time < 90 mins; purifying the product using our newly developed Water-Co-Distilling process or Modified Steam Distillation at atmosphere pressure. The methodology, in general, provided DCFO in 50-60% of yield with >99% of purity as identified by NMR and GC-MS.

Key words: 3,4-dicyanofuroxan, furoxan, nitration, steam distillation

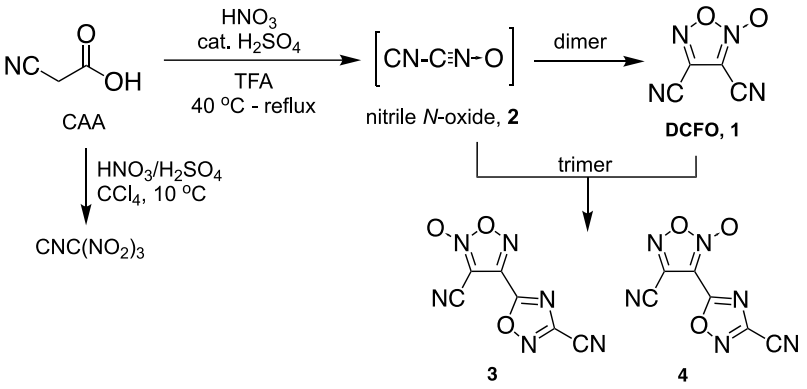
INTRODUCTION

In recent decades, 3,4-dicyanofuroxan or 3,4-dicyano-1,2,5-oxadiazole-2-oxide (**1**, DCFO) has attracted more attention in various research fields, such as in energetic material research, biochemical drug discovery, and academic study. Furoxan ring or 1,2,5-oxadiazole-2-oxide is energetic component, holding heat of formation of 198-226 kJ/mol,[1] having served as building blocks in various energetic material synthesis.[1-11] The heterocyclic unit is also a good resource of nitrogen monoxide (NO) in biological activities. This discovery indicates that furoxan may become a key component in drug discovery and development.[12-14] and Furthermore, cyano (-CN) on furoxan can be converted to various functional groups through a general functional transportation such as to tetrazole, amidoxime,[15, 16] furazan or 1,2,5-oxadiazole,[17] and so on.

There are several methods for the preparation of DCFO,[18, 19] in which the most practical and scalable method is by nitrating cyanoacetic acid (CAA) with 100% of HNO_3 in trifluoroacetic acid (TFA) or in

H_2SO_4/CH_2Cl_2.[20] Parker et al. reported that the nitration of CAA with 100% of HNO_3 in the presence of catalytic amount of H_2SO_4 at 40 °C gave DCFO in 38% of isolated yield. Increasing the nitration temperature to 70-72 °C at refluxing, the yield of DCFO was reported in 62% together with byproducts, 3-cyano-4-(3-cyano-1,2,4-oxadiazol-5-yl)-1,2,5-oxadiazole-2-oxide (**3**) in 17% and 4-cyano-3-(3-cyano-1,2,4-oxadiazol-5-yl)-1,2,5-oxadiazole-2-oxide (**4**) in 21%, according to HPLC analysis. However at low nitration temperature and high concentration of H_2SO_4, trinitroacetonitrile was obtained as major product (Scheme 1).

Scheme 1



The formation of byproducts, **3**, **4**, and $CNC(NO_2)_3$ is likely a spontaneous and unavoidable process and the yield of DCFO is depended on nitrating conditions, such as temperature, acid concentration, and solvents. In CH_2Cl_2 and at refluxing temperature (37 - 40 °C) the nitration of CAA with 100% of HNO_3 in H_2SO_4 gave DCFO in 60-80% of yield according to chromatographic analysis. Here, the nitration was preferred in 100% of HNO_3 since lower the concentration of HNO_3 lower the yield of DCFO. Jesse et al. reported that when 70% of HNO_3 was used, the yield of DCFO was significantly decreased. Therefore, 100% of HNO_3 is essential in the successful nitration of CAA to DCFO, but handle and storage are difficult and also is cost.

The isolation and purification of DCFO is other issue in the nitration methodologies. Parker et. al. reported that DCFO was purified by recrystallization from CCl_4 or by sublimation. The recrystallization method indeed provides pure DCFO but loses too much product in mother liquor because it requires more solvent to achieve a reasonable purity of the product. Sublimation is also a way to purify the product, but it requires high vacuum and is only available for small-scale purification. Furthermore, DCFO is volatile, readily hydrolyzed on silica gel (*vide infra*). Therefore, silica gel column chromatography is not a good option in purifying DCFO, especially in large-scale preparation. Except Parker's report, all yield of DCFO reported in literature was based on chromatographic analysis. In this paper, we report a cost-efficient and scalable nitration of cyanoacetic acid (CAA) to DCFO with KNO_3 in methanesulfonic acid (MSA) and introduce water Co-Distilling process and Modified Steam Distillation methodology for the isolation and purification of DCFO in small- and large-scale preparation .

RESULTS AND DISCUSSION

Nitration of cyanoacetic acid to DCFO with KNO_3 in $MeSO_3H$

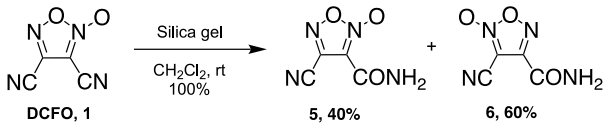
Chemically, the nitration of cyanoacetic acid (CAA) with HNO_3 or with KNO_3 in acidic conditions to 2,3-dicyanofuroxan (DCFO, **1**) is the same, but the nitration with KNO_3 brings a different nitrating environment. As mentioned above the formation of DCFO critically depends on nitrating conditions; therefore, a close look at the chemistry of KNO_3 in the nitration process was underway. In our earlier research we dissolved 12.0 g of KNO_3 in 30 ml of H_2SO_4 at room temperature and added the solution dropwise to the mixture of CAA (5.0 g) in 40 ml of refluxing CH_2Cl_2. This nitration gave DCFO in 53% of yield according to GC-MS analysis (Table 1, entry 1). The yield was encouraged, but the downside was that the addition of KNO_3/H_2SO_4 to the mixture of CAA in CH_2Cl_2 causing precipitating and foaming even though the amount of H_2SO_4 used was much more than that used in the similar nitration with 100% of HNO_3. It is suggested that this nitration process is not suitable for large-scale preparation.

Methanesulfonic acid (MAS) is a strong acid and also a common solvent in nitration reactions. Considering the solubility of KNO_3 in MSA, we added 9.0 g of KNO_3 slowly to the mixture of CAA in 35 ml of MSA at 45-50 °C in a trial nitration (*This is an exothermic reaction. We believe there should be an initiative time between the nitration of CAA and the decomposition of nitro cyanoacetic acid to nitrile N-oxide (**2**); therefore, at the beginning the addition of KNO_3 must be slow, allowing the nitration and decomposition to occur).* It was found that at the beginning the nitration mixture appeared homogeneous but turned to cloudy when about 80-90% of KNO_3 was added. After the nitration was completed and quenched into ice, the product was extracted with CH_2Cl_2. NMR and TLC indicated that the crude product contained DCFO and several other byproducts. GC-MS analysis showed that the yield of DCFO was about 46% (Table 1, entry 2). The crude product was treated by silica gel column chromatography eluting with CH_2Cl_2:pentane

(3:1). The first eluted compound was DCFO and the second a mixture that contained two known compounds, **3** and **4**, as identified by NMR. Continuously eluting with ethyl acetate : CH_2Cl_2 (1:4), we obtained another two compounds. NMR and HRMS analysis revealed that the first eluted was 3-carbamoyl-4-cyano-1,2,5-oxadiazole 2-oxide (**5**), a known compound. And the second was assigned to be 4-carbamoyl-3-cyano-1,2,5-oxadiazole 2-oxide (**6**), an isomer of **5**. We assume that amides, **5** and **6**, are the hydrolyzed products of DCFO.

To confirm the formation of the byproducts, we added KNO_3 to DCFO in MSA at 45 °C and stirred the mixture at the temperature for 2.0 hrs. NMR and TLC showed that about 20% of DCFO was converted to amides, **5** and **6**. It is clear that the byproducts indeed came from the hydrolysis of DCFO in the nitration conditions. Actually, DCFO can also be hydrolyzed to amides even by standing with silica gel in CH_2Cl_2 at room temperature. In five days 100% of DCFO was converted to amides in nearly 100% of yield (Scheme 2).

Scheme 2



The results indicate that the cyano group on DCFO possesses strong electrophilicity. It could be hydrolyzed and decomposed in many conditions. Therefore, care must be taken to prevent the product from decomposition during the nitration and purification processes.

From the trial experiments and the analysis, we realized that the nitration conditions with KNO_3 in MSA needed to be optimized. Therefore, we conducted a series of research, aimed to find a better nitration conditions for the preparation of DCFO. The results are summarized in Table 1.

The yield of DCFO in Table 1 was determined by GC-MS. The samples for GC-MS analysis were obtained by extraction of aqueous nitration mixture with CH_2Cl_2 (detail procedure, see experimental section). The crude product usually contains DCFO, Trimer **3** and **4** (5-15%) and amide **5** and **6** (0-2%). Because the isolation of **3** and **4** is difficult, so there were no standard samples for GC-MS analysis. The yield of the byproducts was roughly estimated. The yield of amides, **5** and **6,** were obtained by isolation from the extraction of the aqueous nitration mixture after the extraction of CH_2Cl_2 as mentioned above. Usually, the byproducts obtained are quite pure and reported as mixture.

Due to the hydrolysable tendency of DCFO in the nitration process, the total nitrating time was adjusted based on the nitrating process. As shown in Table 1, carrying the same nitration but shortening the total nitration time from 100 min (entry 2) to 60 min (entry 3), the yield of DCFO and amides were not significantly changed. However, keeping the similar nitration time but allowing the nitration mixture to stir overnight, the yield of DCFO was meanly decreased, while the yield of amides, **5** and **6**, were increased undoubtedly (entry 4). According to the experimental results, we suggest that the total nitration time should be equal to or less than 2.0 hrs.

Nitrile group is usually instable in nitration conditions especially at elevated nitration temperature. Concerning the stability of CAA in methanesulfonic acid, we changed the nitration procedure by adding CAA in portionwise to the nitration mixture other than in one portion at the beginning of the reaction (entry 5). In the nitration process, the yield of DCFO usually increased 5-10%. It indicates that CAA may undergo certain chemical exchanges before being nitrated to nitrile *N*-oxide (**2**). Increasing the volume of MSA (entry 6) improves the solubility of KNO_3 in MSA, but slightly reduces the yield of DCFO due mainly to the increasing the difficulty of the isolation processes. Except these, prolonging nitration time (entry 7), rising equivalents of KNO_3 to CAA from 1.5:1 to 2.5:1 (entry 8), or replacing KNO_3 with $LiNO_3$(entry 9) did not improve the yield of DCFO.

The results in Table 1 show that KNO_3 can be an alternative nitrating reagent in replacement of 100% of HNO_3 in the nitration of cyanoacetic acid (CAA) to 3,4-dicyanofuroxan (DCFO) in methanesulfonic acid. In the nitration process, the ratio of CAA to KNO_3, the concentration of KNO_3 in MSA, and the counter metal of nitrate would not significantly affect the product output. However, shortening exposure of CAA in MSA would increase the yield of DCFO. Based on the analysis, we scaled up the preparation of DCFO by using 1.5 equivalents of KNO_3, adding CAA with KNO_3 portionwise at the same time, and controlling the nitration time in 90 min. Thus, 100 g of CAA was added in five portions to the nitration mixture during the addition of KNO_3 in 700 ml of MSA in the period of 60 min. at 45-50 °C. After stirring for further 30 min at the temperature, the reaction mixture was quenched into ice-water and the product was extracted with CH_2Cl_2. GC-MS analysis revealed that the purity of the crude DCFO was 84%. Using our developed isolation and purification methodologies, we obtained DCFO in 58% of yield with the purity of > 99% according to TLC, GC-MS, and NMR analysis.

The isolation and purification of DCFO has been the issue for a long time in the nitration of CAA with HNO_3 in acidic conditions. We have tried to purify the product by such as silica gel column chromatography, sublimation, and recrystallization from various solvents, but received little progress.

DCFO, 1

Table 1, Nitration of CAA with metal nitrate in $MeSO_3H$.

	CAA (mol)	KNO_3 (mol)	$LiNO_3$ (mol)	MSA (ml)	Time [a] (min)	Method[b]	**1** % [c]	**5**+**6** %[d]
1	0.06	0.12		*e*	60	1	53	*f*
2	0.06	0.09		35	100	1	46	5.3
3	0.06	0.09		40	60	1	50	8.4
4	0.06	0.09		40	*g*	1	20	16.6
5	0.06	0.09		40	90	2	56	6.2
6	0.06	0.09		55	90	2	52	4.4
7	0.06	0.12		40	120	2	58	6.0
8	0.06	0.15		50	120	2	56	7.3
9	0.06		0.12	40	60	2	58	4.9
10	1.18	1.78		700	90	2	64(58)[h]	3.8

a, total nitrating time, ± 5 min. It includes the time for the addition of KNO_3 and the time after the addition. *b*, Method 1: add CAA in one portion to the reaction mixture at the beginning of the nitration; Method 2: add CAA in portionwise while adding KNO_3. *c*, the yield of DCFO was determined based on GC-MS analysis using pure DCFO as reference. *d*, isolated yield. *e*, 30 ml of H_2SO_4 and 40 ml of CH_2Cl_2. *f*, nearly no amides were found in the ethyl acetate extraction. *g*, at 45-50 °C for 60 min and at 25 °C for 14 hrs. *h*, the number in parathesis is isolated yield using modified steam distillation methodology (*vide infra*).

After many trials, we modified steam distillation concept by distilling crude product with water at atmosphere pressure (we also call it as Water-co-Distilling process). In typical process, the crude product and water were distilled through a short distillation column (about five inches long) under atmosphere pressure and collected the pure product in an ice-water bath. Usually, 5-10 ml of water could carry 1.0 g of DCFO; for example, to purify 10 g of crude product, 150 ml of water is added and distilled in 10-15 min. Usually, the product is precipitated in cool water, which can be collected by filtration, but the best by extraction with CH_2Cl_2 and dried over $MgSO_4$ to remove water contaminate. This method usually provides DCFO in the purity of >99% as identified by GC-MS, TLC, and NMR. But the drawback is part of DCFO was hydrolyzed to amide **5** and **6** during the distillation. The percentage of DCFO hydrolyzed depends on the impurities in the crude product. We found that if the crude DCFO was received after the recrystallization from CCl_4, about 10-15% of DCFO was converted to amides. However, if the crude product was obtained from the extraction from aqueous-quenched nitration mixture and trace of acid was existed, DCFO could be completely hydrolyzed. Using buffer solution at pH = 7.0 would not prevent DCFO from hydrolyzing. The distillation with heptane (98 °C), pure DCFO was received with no hydrolyzing, but 100 ml of heptane could only carry out about 1.0 g of DCFO. Obviously, this is not a practical isolation methodology. Water-co-Distilling process is a simple and convenient methodology for the purification of DCFO in small scale preparation and is probably more effective than silica gel column chromatography, but for large scale preparation the method has limitations and risks.

To avoid the hydrolysis of DCFO in large scale purification, we improved the distillation device by inserting a distillation column C between flask A and distillation head and adding crude product from the top

of the head into the flowing steam. The Modified Steam Distillation device is depicted in Figure 1.

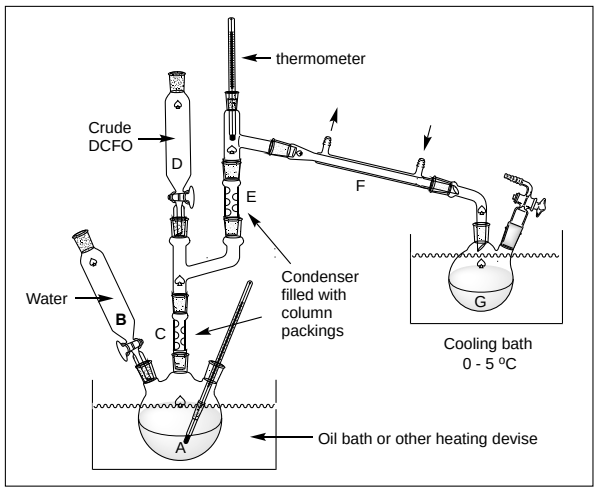


Figure 1. Modified Steam Distillation device for the isolation and purification of DCFO

In the Modified Steam Distillation setup, the sample was not added to flask A, but from the top of a distillation column C. The purpose of Column C is to stop the crude product falling into flask A so as to reduce the time of DCFO contacting with acidic water. Under perfect conditions, DCFO should be carried out before reaching to flask A. Therefore, the length of distillation column C can be adjusted based on the rate of crude DCFO addition. Part E is another distillation column, which is used to separate DCFO from trimers, **3** and **4**. Usually, a 4-5 inches long distillation column is enough to remove the trimers completely. The distillated product and water are primarily cooled on condenser F and further cooled in flask G in ice-water bath. In general nitration process, the crude DCFO usually appears as an oil. However, it may turn to solid when stand at room temperature overnight. If this happens, added 1 ml of CH_2Cl_2 per 10 g of the sample and warmed up to 40 °C to give an oil. This oily crude DCFO can be loaded to addition funnel D and would not be solidified during the distillation. In this distillation process, 1.0 g of DCFO requires 10-15 ml of water.

The general procedure: water was added to flask A and also to addition funnel B if more water is needed. The flask A was heated in an oil bath or other heating device to reflux at atmosphere pressure, and the water was collected in receiver flask G in the rate of 4-6 ml/min. When the steam was stable, crude DCFO was added from addition funnel D dropwise, adjusting the addition rate so that non or small amount of DCFO allowed to enter flask A (if oil is seen in flask A, meaning the addition is too fast). Usually, 50 g of the crude product is distilled in 90 min. After the distillation was finished, the pure DCFO was extracted with CH_2Cl_2 and dried with $MgSO_4$. The product can also be collected by filtration, but it usually contains water and could not be dried completely by suction since DCFO is volatile. In addition, the solubility of DCFO in water at 0-5 °C is about 1.0 g/100 ml. For distillation of 50 g of the crude product, usually use 350-450 ml of water, indicating that without extraction with CH_2Cl_2, about 5-10% of material could be lost in the water. In perfect conditions, the modified steam distillation could recover up to 95% of the product. The purity of the product obtained from the methodology was >99% according to GC-MS, TLC and NMR.

CONCLUSION

A cost-efficient and scalable nitration methodology was developed for the preparation of 3,4-dicyanofuroxan (**1**, DCFO) by nitrating cyanoacetic acid (CAA) with KNO_3 in methanesulfonic acid (MSA) at 45-50 °C. The nitration conditions were optimized through a series of research. Due to the nature of the chemistry, the yield of DCFO from the nitration was about 50-60% similar to those obtained from other nitration methodologies. The advantage of the methodology is the nitration can be achieved by using KNO_3 instead of 100% HNO_3 and the preparation can be scaled up to several hundred grams. But the drawback is that the heterogeneous nitration could make temperature control difficult in kilograms scale synthesis. Water-co-Distilling process is effective and convenient method for the isolation and purification of DCFO in less than 20 g of the product when the crude product is pre-purified by recrystallization from CCl_4, free from acidic contaminants. And Modified Steam Distillation process are suitable for small- and large-scale purification and pre-purified process is not required.

Experimental Section

All reagents were purchased from commercial suppliers and used without further purification. GC-MS was recorded on Agilent 5975C MS Spectrometer equipped with inert XL EI/CI MSD through a 7890 Gas Chromatography system. Proton and C-13 NMR spectra were acquired on either a Bruker 500 MHz spectrometer (500 and 150 MHz, respectively) or an Anasazi Instruments Eft-90 MHz spectrometer with Varian magnet (90 and 22.5 MHz, respectively). Proton and C-13 NMR chemical shifts were reported relative to the residual solvent as internal standard, such as, DMSO-d_6 (2.50 ppm for proton and 39.5 ppm for C-13). Melting point was recorded on OptiMelt Automatic Melting Point System with heating rate at 2.0 °C. IR spectra were collected using Bruker Alpha ZnSe ATR FTIR as neat solids.

*Hydrolysis of DCFO on silica gel in CH_2Cl_2 to 3-carbamoyl-4-cyano-1,2,5-oxadiazole 2-oxide (**5**) and 4-carbamoyl-3-cyano-1,2,5-oxadiazole 2-oxide (**6**)*

DCFO (1.0 g, 7.3 mmol) and silica gel (230-400 mesh for column chromatography, 2.0 g) were mixed in 10 ml of CH2Cl2. The mixture was caped and allowed to stand on bench at room temperature for 5 days. TLC analysis showed that 100% of DCFO was consumed to give two compounds with Rf = 0.7 and 0.4, CH_2Cl_2:ethyl acetate, 2:1. The compounds were isolated by a silica gel column chromatography, eluting with CH_2Cl_2:ethyl acetate, 3:1 to give **5** and **6**. Amide **5**, pale yellow solid, 0.63 g (56%), m.p. 171.8 °C [lit.186 °C]. ^{1}H NMR (acetone-d_6): δ 7.87 (sb, 1H), 7.55 (sb, 1H); ^{13}C NMR (acetone-d_6): δ 153.7, 134.7, 110.6, 107.2. IR (powder): 3396, 3153, 1681, 1597, 1468, 1374, 1136, 1020, 774, 698, 642 cm^{-1}. HRMS: m/z = 109.9996 [M-$CONH_2$], corresponding to compound **5**: $C_4H_2N_4O_3$, calculated: 109.9996 [M-$CONH_2$]. Amide **6**, pale yellow solid, 0.46g (41%), m.p. 179.7 °C. ^{1}H NMR (acetone-d_6): δ 8.10 (sb, 1H), 7.73 (sb, 1H); ^{13}C NMR (acetone-d_6): δ 156.1, 151.1, 105.4, 97.1. IR (powder): 3390, 3218, 2259, 1702, 1620, 1605, 1487, 1381, 1066, 1031, 837, 755, 676 cm^{-1}.HRMS: m/z = 109.9995 [M-$CONH_2$], corresponding to compound **6**: $C_4H_2N_4O_3$, calculated: 109.9996 [M-$CONH_2$].

The nitration of cyanoacetic acid with KNO_3 in H_2SO_4/CH_2Cl_2

To a 250 ml of three necked round bottom flask equipped with magnetic stir bar, thermometer, and a condenser with a liquid addition funnel was added cyanoacetic acid (5.0 g, 0.06 mol) and 40 ml of CH_2Cl_2. The mixture was heated to reflux (~ 37 °C) and the solution of KNO_3 (12.0 g, 0.12 mol) in 30 ml of H_2SO_4 was added from the top of condenser dropwise. *The addition should be slow at the beginning since a lot of solid was floating on the top of the liquid and foaming.* About 50% of the solution was added, foaming was reduced, but precipitate appeared and coated around the wall of the flask. After the addition was completed (31 min), the nitration mixture was refluxed for further 30 min. The reaction mixture was cooled to room temperature and quenched into 120 g of ice and the product was extracted with CH_2Cl_2 (3X30 ml), washed with brine (2X20 ml) and dried over MgSO4. Removal of solvent gave an oily crude product. 2.88g. GC-MS analysis showed that the purity of the crude product was 73% (estimated yield, 53%). The crude product was purified by modified steam distillation (Figure 1) to give 1.73 g pure DCFO. The isolated yield was 47%.

The nitration of CAA with KNO_3 in MSA: a general procedure

Cyanoacetic acid (5.0 g, 0.06 mol) was added to methanesulfonic acid following method 1 or method 2 procedures as listed in Table 1. The solution was heated to 45 °C in a water bath. Nitrate was added from a solid addition funnel slowly. This is an exothermic reaction. At the beginning, the addition should be slow, allowing the nitration and decomposition to occur. When about 5% of KNO_3 was added, the addition should be paused if the reaction temperature was not increased. Once the reaction spontaneously increased to 48-50 °C, the heating bath temperature was controlled at 35-37 °C and the addition of KNO_3 was resumed. Controlling the nitration temperature at 45-50 °C by adjusting the addition speed. After the addition was finished, the nitration mixture was heated at 45-50 °C for further period of the time. The reaction mixture was then cooled to room temperature and poured into ice-water (usually use 4 times of the volume of MSA) and the product was extracted with CH_2Cl_2 (5X30 ml) and the organic phase was washed with water (3X30 ml) and dried over $MgSO_4$. Removal of the solvent gave the crude product as wet colorless solid. The yield of DCFO was determined by GC-MS and listed in Table 1. The combined aqueous solution was further extracted with ethyl acetate (3X50 ml) and washed with brine (2X30 ml), dried over MgSO4. The solvent was removed on Vacuo and the oily residue was treated with CH_2Cl_2 (5 ml). The precipitate was collected by filtration and washed with CH_2Cl_2 and dried by suction. This usually gave pure amides **5** and **6.** The total yield was also reported in Table 1. Trimers, **3** and **4**, were obtained by a silica gel column chromatography, eluting with CH_2Cl_2:hexane 2:1. In the conditions, DCFO was removed completely, but the trimers could not be further separated. The mixture of trimers was identified by NMR should that the ratio of **3** and **4** was about 5:2 and fully identical to the chemical shift reported in literature.[19]

Preparation of 2,3-dicyanofuroxan from $KNO_3/MeSO_3H$

To a 2L of round bottom flask equipped with mechanic stirrer, thermometer, solid addition funnel, was added 700 ml of methanesulfonic acid (MSA). The solution was stirred in a water bath at 45-50 °C. When the temperature reached to 45 °C, cyanoacetic acid (CAA, 100g, 1.18 mol) was added in 5 portions, each time 20-25g), following by KNO_3 (180g, 1.78 mol) from a solid addition funnel. At beginning, the addition of KNO_3 should be slow. When 2-3 g of KNO_3 was added, the reaction temperature increased from 45 °C to 47 °C. (*If the reaction temperature does not increase, the addition of KNO_3 should be stopped, waiting for few minutes to allow the nitration to occur*). When the reaction temperature spontaneously increased and gases were releasing, the addition of KNO_3 was resumed while the water bath temperature was adjusted to 35-40 °C,

keeping the nitration temperature between 45-50 °C. The addition time was 70 min. After the addition was finished, the mixture was stirred at 45 °C for further 20 min. The reaction mixture was cooled to room temperature and quenched into ice-water (1000 g of ice and 1000 ml of water). The product was extracted with CH_2Cl_2 (5X300 ml), the combined organic phase was washed with water (3X300 ml), and dried over $MgSO_4$. Removal of solvent gave oily crude product. DCFO was purified by modified steam distillation and the product was extracted with CH_2Cl_2 (2X100 ml) and dried over $MgSO_4$. The solvent was removed on *vacuo* at 25 °C to give a colorless solid. The solid was crashed with 50 ml of pentane and collected by filtration, washed with 20 ml of pentane, and dried by suction (usually 5 min.) until no pentane was identified from proton NMR analysis. DCFO was obtained in 46.8g (58%). GC-MS, NMR showed that the purity of the product was >99%.

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INTEREST CONFLICT

No

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