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Synthesis of a Monomer for Two-Dimensional Polymerization under Technically Feasible Conditions

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This work is dedicated to Prof. François Diederich on his retirement

The synthesis of a promising 2D polymer uses the double decker rotor-shaped monomer **1**, *containing three anthracene moieties. To accelerate the development of the field of 2D polymers, this monomer was selected for scale-up that would allow its synthesis to be performed on the kg scale under technical conditions. This goal was achieved in collaboration with Polymaterials AG, Kaufbeuren, Germany. Not only was the synthetic route shortened but each and every aspect of the remaining steps was streamlined so as to render them applicable to technical conditions. This involved the entire sequence to be adapted to metal instead of glass reactors and to a number of safety and toxicity concerns. Additionally, not only the utilization of the reactors had to meet strict efficiency requirements but also the work-up procedures had to be facile. The whole sequence was then tested for feasibility under realistic conditions at Polymaterials AG. While this test afforded 130 g of monomer* **1**, *it has the clear potential for the kg scale supposed the safety equipment for the hydrogen evolution for the conversion of compound* **2a** *to* **3** *is available.*

Keywords: *2D polymer, monomer, technical scale synthesis, scale-up, anthracene dimerization*

Introduction

Two dimensional (2D) polymers are a new class of sheet-like polymers, the structure of which is regularly tiled with topologically planar repeat units in x,y-direction (Figure 1).[1] *Following a visionary article by Diederich in Nature 1994 on hypothetical carbon-based, two-dimensional networks,*[2,3] *a variety of representatives could recently be synthesized.*[4,5] *Typically, monomers in a two-dimensionally pre-ordered state are connected by an external photochemical stimulus. The pre-ordering of monomers has so far been achieved in layered single crystals*[6,7] *and in monolayers at an air/water interface.*[8] *Because of the mildness with which 2D polymers can be synthesized and because of their highly porous, mechanically rather robust, long-range ordered molecular structure, a variety of interesting applications is foreseen. For example, 2D polymers are potentially attractive as membranes for water desalination and ultra-efficient gas separation but also as nm-thin insulating layers and ultra-sensitive pressure sensors. Thus, there is a clear need for helping 2D polymers to step out from the research laboratory, in which the corresponding monomers currently cannot be synthesized beyond a few tens of grams in select cases, and to develop them as materials available on the technical scale. While some of the monomers are unlikely to ever be available on a kg scale, others appear to have the potential for that. This particularly concerns monomer* **1**, *which under typical research lab conditions has been synthesized repeatedly and by different people on up to the 30 g-scale (Figure 1). This monomer was therefore our first choice for entering into a collaboration with the company Polymaterials AG to explore technical scale feasibility. We here report on the successful synthesis of monomer* **1** *under technical conditions.*

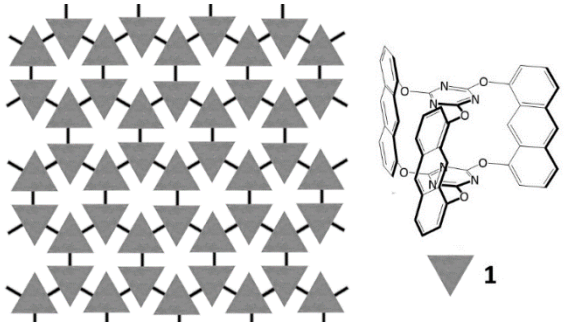
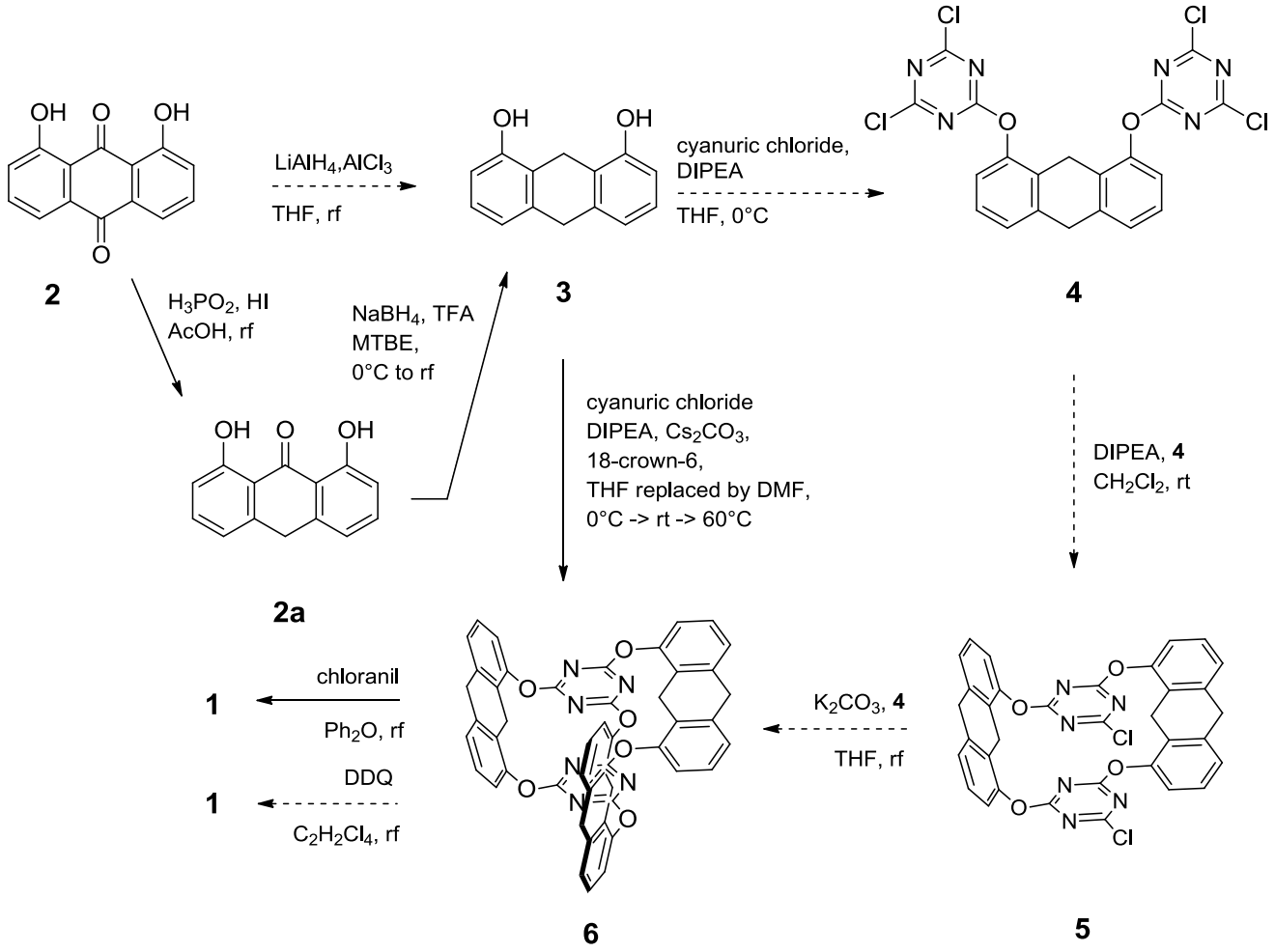


Figure 1. *Sketch of a 2D polymer with its long-range ordered covalent structure and chemical structure of monomer* **1** *used for two-dimensional polymerization in layered single crystals by photochemically triggered [4+4]-cycloaddition between neighboring anthracene units.*

Results and Discussion

Monomer **1** *can not only be obtained according to the published procedure*[9] *but was also found to be accessible in two steps by a reduction of* **2** *or* **2a** *to 1,8-dihydroxyanthracene using* $NaBH_4$ *in MeOH and a one pot assembly of this product with cyanuric chloride analogous to the conversion* **3** *to* **6**. *This shortcut, while feasible on the labscale, was not used for the technical scale as the intermediate 1,8-dihydroxyanthracene is highly reactive and degrades quickly. With only one trial run possible on the technical scale, it was considered safer to go for the more reliable and predictable, albeit longer route. Thus the synthesis developed by Kory was improved and adapted to technical conditions. A major point we concentrated on was the relatively high number of steps the published synthesis of monomer* **1**[9] *involves (Scheme 1). It was investigated whether it can be brought down from five to three steps by developing a direct route from the dihydroxy compound* **3** *to monomer precursor* **6**. *The second point then concerned technical feasibility of each step of the shortened sequence* **2**-**3**-**6**-**1**. *This involved (a) the large quantities of partially reactive Al-salts generated in the reduction of the quinone* **2** *to dihydroxide* **3**, *(b) the choice of solvent for the key assembly step, in which three equivalents of compound* **3** *are reacted with two equivalents of cyanuric chloride and (c) the oxidation of compound* **6** *to the target monomer* **1**. *This had to be performed without 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) as this reagent can give rise to formation of hydrogencyanide, which for safety reasons is unacceptable on a technical scale. These points will be explained in the following.*



Scheme 1. *Original procedure for the synthesis of* **1** *(dashed arrows) and the implemented changes (solid arrows).*

The first step of the envisaged technical scale synthesis therefore involves the reduction of anthraquinone **2** *to compound* **3**. *There are a number of literature reports on the conversion of* **2** *to* **3** *or similar compounds without the use of protecting groups. They often employ either $LiAlH_4$ and $AlCl_3$ or Zn under basic conditions.*[9,10] *All these procedures have the common drawback of a demanding work-up which is due to the large amounts of insoluble salts that form and that clog filters quickly. Already when performing the conversion of* **2** *to* **3** *with $LiAlH_4$ and $AlCl_3$ under lab conditions starting from 28 g of* **2**, *roughly 100 g of aluminum salts formed that needed to be removed from approximately 20 g of product. This could obviously not be tolerated under technical conditions. Furthermore, the formation of 1,8-dihydroxyanthracene as a side product in varying amounts was observed, which also needed to be taken care of.*

Alternative procedures such as reductions with H_2 (as gas and polymethylhydrosiloxane using Pd/C, $PdCl_2$ and $FeCl_3$), Raney nickel, $NaBH_4$, BH_3, $NaBH_3CN$, HI or Wolf-Kishner-reduction yielded at most partially reduced species. Therefore, it was decided to test the detour through intermediate **2a**. *Although this increased the number of steps from three to four the handling and work-up for the sequence* **2**-**2a**-**3** *appeared feasible under technical conditions. The reduction of* **2** *to* **2a** *employing in situ generated HI*[11] *proved to be simple and afforded pure* **2a** *in 81% yield. As in the original procedure, the subsequent reduction of* **2a** *to* **3** *using $NaBH_4$ and trifluoroacetic acid (TFA) also affords 1,8-dihydroxyanthracene as a side product. The ratio between the desired compound* **3** *and the anthracene impurity heavily depends on the reaction conditions (Table 1, Supporting Information) and was therefore thoroughly investigated. The use of a carboxylic acid*[12] *was necessary to obtain* **3** *in good yields and TFA was found most effective at suppressing anthracene formation. In the extreme case, when TFA was used as the solvent at most traces of 1,8-dihydroxyanthracene were observed. While this was obviously attractive, the quenching of $NaBH_4$ caused by the TFA became so fast that most of the hydride was destroyed by the acid before it could reduce the carbonyl function. In this situation, it was decided to find an optimum balance between the opposing effects by using a solvent. Ethers were found suitable for that purpose, whereby for safety considerations the initially used diethyl ether was replaced by methyl(tert.-butyl) ether (MTBE). The hydrogen gas that formed during quenching of the reaction mixture posed yet another safety concern. While hydrogen evolution can easily be dealt with in an industrial context, the necessary equipment was not installed in the current case. Rather this step was outsourced to Taros Chemicals, Dortmund, who performed the step in a series of smaller portions.*

The raw product obtained from Taros Chemicals contained approximately 25% 1,8-dihydroxyanthracene, more than expected from the experience in our laboratories. As Taros could not share the procedures of the reduction, the cause for the increased side product is uncertain. From our own experiments factors that lead to more 1,8-dihydroxyanthracene are mostly incorrect addition order of the reagents, insufficient temperature control or too little TFA as seen in Table 1 (Supporting Information). This impurity could nevertheless easily be removed by selective oxidation.For that purpose the product mixture was taken up in aqueous NaOH and a stream of air was bubbled through

for a few hours as described previously.[9] Improvements on the workup procedure were necessary, as filtration of the basic gel-like substance that formed takes up to 2 h on the lab scale. With the experience from other filtrations within this work, the same filtration could take up to 36 h on the technical scale. It was found that after acidification the desired pure product **3** *could instead be extracted from the insoluble, oxidized 1,8-dihydroxyanthracene that had formed during the oxidation. The yield of compound* **3** *on the technical scale amounted to 27% which was far lower than the yields of 80% on the lab scale. It is anticipated that further improvements, discussed in the outlook, could be achieved at this step.*

Preparation and cleaning of a reactor are main cost factors of any technical scale synthesis. Thus, keeping the number of steps as low as possible had high priority. Considering the rather different reactivities of cyanuric chloride towards sequential nucleophilic displacement,[13] it was deemed possible to convert compound **3** *to* **6** *via the intermediates* **4** *and* **5** *in a one pot reaction. The role of DIPEA is not fully understood but it was found that it accelerates particularly the conversion from* **3** *to* **4** *by as much as a factor of 8, while it seems to suppress conversion* **5** *to* **6**. *An overall optimum was achieved around 1.5 equivalents. Further, K_2CO_3 has to be substituted by Cs_2CO_3, probably for its better solubility in organic solvents. The crown ether (18-crown-6) was suspected to have a positive effect on the reaction time and was thus used in the technical synthesis. After substitution of THF by DMF, however, a new investigation showed no acceleration anymore. A condition for the direct assembly of* **3** *to* **6** *was also to find a solvent that dissolves all intermediates sufficiently well to allow the reaction to progress reliably. The initial choice of THF while yielding the desired product* **6** *on the lab scale required rather different reaction times varying from 6 h to 26 h, with the conversion from* **5** *to* **6** *as the unpredictable step. The improved stirring on the technical scale with helically shaped mechanical stirrers did not lead to shorter reaction times as anticipated, instead the conversion on the technical scale was found to be even slower. At this point it was clear that further optimization was required for conditions robust enough to be scaled up to the range of kilograms. Since the insolubility of not only the intermediate* **5** *but also the base K_2CO_3 was assumed to lead to the long reaction times, the solvent DMF was examined and found to be a suitable substitute for THF. This substitution resulted in a reaction course, which not only was fully reproducible but also accelerated to the degree that product* **6** *was obtainable in 10 h in a yield of 21.2%. This yield is relatively low since the solvent was changed during reaction on the technical scale resulting in a work-up that with current knowledge is not necessary. Further testing showed, that DMF can be used as a solvent for the entire one pot synthesis of* **6** *from* **3** *although a possible side reaction between cyanuric chloride and DMF[14] can partially degrade the cyanuric chloride. Two solutions to suppress this degradation were found, leading to roughly similar quantities of* **6**. *It is possible to add the cyanuric chloride last, to the already deprotonated* **3** *and reduce the reaction time at low temperatures or alternatively use a low quantity of THF for the conversion* **3** *to* **4** *and then dilute by a factor of 4 with DMF to reach the standard concentrations. These changes allowed to isolate* **6** *on up to 100 mg scales with a yield of 48%.*

Finally, the dehydrogenation of the direct monomer precursor **6** *to the monomer* **1** *was improved. This oxidation had originally been performed using DDQ in $C_2H_2Cl_4$. Due to the potential release of HCN when DDQ is brought into contact with water, the oxidation reagent was changed to chloranil, as described in a patent.[15] While DDQ is more reactive, converting 50% of acetate protected* **3** *to its anthracene analogue within 2 h at room temperature, chloranil yields only traces of the product under the same conditions. Apart from the reagent, also the solvent tetrachloroethane, which is highly carcinogenic, was substituted by diphenylether. The lower reactivity of chloranil then turned out to be no issue since the reaction has to be performed anyway at the solvents boiling point (258°C) due to the insolubility of* **6**. *Under these modified conditions and after hot filtration and recrystallization in diphenylether, the target compound* **1** *was obtained in a yield of 52% and a good purity as shown by ^{1}H-NMR spectroscopy. This yield is again below the reported 98% however the previous report included neither a recrystallization or an analysis of purity. The 98% refer to the collected solid by filtration. The solubility of* **1** *is extremely low. While this is a desired property under the aspect of crystallization, it is a drawback in terms of analysis because only very select solvents can be used. Eventually, the ^{1}H NMR spectrum of monomer* **1** *had to be recorded in propylene carbonate, a high boiling solvent which is not commercially available in deuterated form.*

Intermediate **2a** *is also commercially available under tradenames such as Dithranol and Anthralin, which is an option to shorten the synthesis even further.*

Finally, we compare the currently available procedures namely the original lab-scale synthesis,[9] the new lab-scale synthesis and its scale-up to technical scale, both reported here. The key data are collected in Table S2. Ignoring the oxidation step due to the difference in purification, the synthesis by Kory yields premonomer **6** *with 49% while the new lab scale synthesis performed under technical aspects yields up to 35%. The yield of the same process under technical conditions cannot be given currently because of the unnecessary workup during the assembly of premonomer* **6**, *which in retrospect caused unexpectable losses. The concentrations could be increased with the new procedure both on the lab and the technical scale compared to the original procedure by factors of up to 50 while the reaction time for the entire synthesis was reduced from 7 d to 1 d.*

Conclusions and Outlook

The production of a monomer for a two-dimensional polymerization in the single crystal under technical conditions was accomplished. The challenges of converting the lab scale procedures to the technical scale, namely a better reduction system to ease work-up of **3**, *a good solvent system for the conversion of* **3** *to* **6** *and suitable oxidation reagent to obtain* **1**, *could be overcome. Due to toxicity and safety aspects the scale-up of the original synthesis would not have been possible. As the current protocol was executed, 130 g of product were obtained. Repeating the same protocol with the current knowledge will produce compound* **1** *on the kg-scale. Future improvements to the synthesis are expected mostly in the reduction and the key assembly step. For the reduction a main challenge remains the formation of H_2 gas during workup. Employing lower quantities of $NaBH_4$ or (better) using other reduction agents should be further investigated. Alternatively, if a special hydrogenation reactor is available, reactions employing high H_2 pressures (exceeding 1 bar) should be investigated. This might furnish a clean reduction of compound* **2** *to* **3**. *For the one pot assembly step further experiments with other high polarity solvents should be carried out to increase the yield. The conversion of single crystals of monomer* **1** *to its 2D polymer proceeds with virtually 100% conversion but requires at least one further recrystallization step using 2-cyanopyridine as the solvent. On the basis of the reported synthesis the properties of the 2D polymer derived from* **1** *can now be broadly explored by us and others.*

Experimental Section

Reagents for the lab scale experiments were purchased from ABCR, Acros, Aldrich and Fluka and used without further purification. Deuterated NMR solvents were purchased from ARMAR and Cambridge Isotope Laboratories. Propylene carbonate, 99% used for the NMR of **1** *was purchased from ABCR. Reagents for the technical scale were purchased from Fischer Scientific, Alfa Aesar, Acros, Fassware Dicke, Fassware Azelis, ABCR, Currenta and Sigma Aldrich.*

^{1}H and ^{13}C NMR spectra were recorded on a 300 MHz Bruker AVANCE spectrometer at 25°C. The doublet solvent signal of propylenecarbonate was chosen as 1.7 ppm. NMR spectra of compound **2a**, **3** *and* **6** *are in accordance with previous reports.[9,16] All intermediate spectra were taken from lab scale samples although NMR spectra were also recorded from technical scale products. Those, however, were often not as highly resolved and contained traces of solvents.*

For the washing steps the total amount of solvent is given, which was divided into several portions as indicated. If not noted differently, reactions were performed under ambient atmosphere.

*Compound **2a***

A 80 L enamel reactor was charged with acetic acid (25 L) and KI (0.46 kg, 2.77 mol, 0.13 eq) was added while stirring. After 15 minutes I_2 (0.703 kg, 2.77 mol, 0.13 eq) was added to the homogenous solution. After another 15 minutes starting material **2** *(5 kg, 20.82 mol, 1eq) was added and rinsed with acetic acid (2.5 L). The temperature was increased over the course of 2h to 80°C. Then hypophosphorous acid (3.3 L, 31.75 mol, 1.53 eq, 50% w/w in H_2O) was added carefully over 3.5h, keeping the reaction temperature below 85°C. Then the temperature was increased to 115°C for 1.5 h. After 3.5 h at reflux the reactor was cooled down to 49°C for 11.5 h and the solids were collected. The reactor and solids were rinsed out and washed twice with water (10 L). Drying in vacuum at 70°C overnight yielded 3.823 kg (81%) product.*

^{1}H NMR (300 MHz, DMSO): 12.09 (s, 2H); 7.61 (t, J = 7.9 Hz, 2H); 7.04 (dd, J = 7.7, 1.2 Hz, 2H); 6.91 (dd, J = 8.4, 1.1 Hz, 2H); 4.48 (s, 2H).

*Compound **3***

The contractor TAROS converted 3.823 kg compound **2a** *to 3 kg compound* **3** *containing 25% anthracene impurity. TAROS could not share the precise conditions of the reduction, thus in the following a laboratory procedure is given. The oxidative purification of* **3**, *to remove said anthracene impurity, is given on the large scale again.*

$NaBH_4$ (33 g, 0.87 mol, 4.6 eq) was suspended in MTBE (600 mL) at -15°C in a 3 L round bottom flask equipped with a thermometer, magnetic stirring bar and 2 condensers stacked on top of each other. TFA (77 mL, 1 mol, 5.26 eq) was slowly added over 1 h keeping the temperature of the suspension below -10°C. Compound **2a** *(43 g, 0.19 mol, 1 eq) was added. After 3.5 h between -15°C to -10°C the cooling bath was removed allowing the reaction to warm. Upon reaching around 10°C the reaction heated up very quickly to boiling temperature (caution!). Once the vigorous reaction subsided the temperature was kept at reflux by a heating bath for a further 30 minutes. Then the solvent was removed under reduced pressure and the residual solid was quenched with 700 mL water and ice. Concentrated HCl was added until the suspension remained slightly acidic. The suspension was stirred for 30 minutes, filtered off and the solids were washed with 200 mL water. The solid contained 7% anthracene impurity according to NMR. Oxidative purification yielded 32.35 g (80%) product* **3**.

*Oxidative purification of compound **3***

An 80 L enamel reactor was charged with water (15.3 L) and bubbling of air through the reaction was started. Methanol (1.26 L) and NaOH 40% (aq) (6.2 kg, 62 mol) were added slowly, keeping the temperature below 30°C. Impure compound **3** *(from TAROS, 2.96 kg) was added and rinsed with water (0.5 L). TLCs showed the blue anthracene spot to disappear after 6.5 h. Water (3 kg) was added followed by concentrated HCl (5.95 kg, 60 mol) in portions of 250 mL over 2h to keep the temperature below 27°C. A pH value of less than 1 was reached. The solid was collected, washed with water (75 L) and extracted with MeOH (20 L). Portions of 10 L MeOH were added four times to facilitate filtration and extract more product. Evaporation of the MeOH under reduced pressure and extracting the obtained solid with EtOAc (50 L) yielded after concentration and drying 0.97 kg (27%) pure compound* **3**.

^{1}H NMR (300 MHz, DMSO): 9.41 (s, 2H); 6.97 (t, J = 7.7 Hz, 2H); 6.79 – 6.63 (m, 4H); 3.83 (d, J = 2.4 Hz, 1H); 3.72 (d, J = 2.3 Hz, 1H).

*Compound **6** under technical conditions*

Dry THF (12.6 L) was cooled to -5°C in a 70 L Hastalloy reactor equipped with a helical stirrer. Cyanuric chloride (552.3 g, 3 mol, 2.06 eq) dissolved in dry THF (1.87 L) was added and rinsed with THF (330 mL). Cs_2CO_3 (1.186 kg, 3.6 mol, 2.5 eq) was added as a solid and the stirring speed was chosen such that the suspension just did not splash around. DIPEA (293.6 g, 2.27 mol, 1.57 eq) was added followed by a solution of 18-crown-6 (96.01 g, 0.36 mol, 0.25 eq) in THF (173 mL) and rinsed with THF (160 mL). Compound **3** *(307.75 g, 1.45 mol, 1 eq) was added as a solution in dry THF (470 mL) and rinsed with THF (160 mL). TLC after 2 h showed full conversion of compound* **3** *to intermediate* **4**. *A solution of compound* **3** *(615.2 g, 2.90 mol, 2eq) in THF (1.21 L) was added and rinsed with THF (160 mL). Cs_2CO_3 (1185 g, 3.6 mol, 2.5 eq) was added followed by a solution of 18-crown-6 (96.2 g, 0.36 mol, 0.25 eq) in THF (160 mL) and rinsed with THF (155 mL). The temperature was increased to 40°C over 1 h. The white suspension was stirred at 40°C for 2 h after which a TLC showed consumption of intermediate* **4** *and formation of intermediate* **5**. *The temperature was increased to reflux over 1 h. A TLC after 4 h showed incomplete conversion of intermediate* **5** *to compound* **6**. *The suspension was diluted with THF (25 L) and after refluxing for another 6 h was cooled to room temperature. A TLC showed still incomplete conversion and the temperature was increased again to reflux for 8 h before cooling down and work-up by filtration. The THF solution was concentrated and dried yielding 1320 g brown residue. The collected solid was washed 4 times with water (7 L), suspended in 0.5 M HCl (6 L) stirred for 30 minutes, filtered off and washed again twice with water (5 L) and then twice with methanol (6 L). Drying at 60°C in vacuum yielded 253.6 g.*

^{1}H-NMR spectroscopy showed incomplete conversion from **5** *to* **6** *in the collected solid and residual* **3** *in the brown THF residue. The compounds were stored for 5 months covered from light under N_2 in a fridge at 10°C.*

Then the brown THF residue (1302 g) was dissolved in dry DMF (21 L) in a 80 L enamel reactor equipped with a impeller stirrer and reflux condenser. The collected solid (253 g) and Cs_2CO_3 (3 kg, 9.2 mol) were added. The temperature was increased to 70°C for 30 min and then kept for 6 h. TLC showed complete conversion of intermediate **5** *to compound* **6**. *The suspension was cooled to room temperature and 4 M HCl (6.6 L) was added. The solids were filtered off, washed with water (5 L), suspended in 2 M HCl (18 L) and stirred for 1.5 h. The solids were collected by filtration, washed 5 times with water (2 L), twice with methanol (5 L) and once with acetone (5 L). Drying at 50°C under reduced pressure yielded 242 g (21.2%) compound* **6**.

^{1}H NMR (300 MHz, $C_2D_2Cl_4$): 7.33 – 7.22 (m, 12H); 7.03 – 6.96 (m, 6H); 4.27 – 4-02 (m, 4H); 3.76 – 3.58 (m, 3H); 3.38 – 3.20 (m, 3H).

*Compound **6** in DMF*

DIPEA (0.12 mL, 0.69 mmol, 1.5 eq) and Cs_2CO_3 (385 mg, 1.2 mmol, 2.5eq) were added to compound **3** *(100 mg, 0.47 mmol, 1eq) in 6.8 mL dry DMF. The suspension was cooled down to -15°C and cyanuric chloride (195 mg, 1.06 mmol, 2.2 eq) was added. After 8 minutes more compound* **3** *(200 mg, 0.94 mmol, 2 eq) and Cs_2CO_3 (385 mg, 1.2 mmol, 2.5eq) was added and the reaction was warmed up to 60°C. The precipitate was collected by centrifugation after 2 h at 60°C and washed twice with 12 mL 2M HCl, then 12 mL MeOH and twice with 12 mL acetone. Drying yielded 178 mg (48%) of the white product.*

*Compound **1***

A suspension of compound **6** *(241.5 g, 0.307 mol, 1eq) in diphenyl ether (9.95 kg) was degassed at 30°C in a 70 L Hastalloy reactor under nitrogen equipped with a reflux condenser and helical stirrer for 30 minutes by bubbling N_2 through. The glass window of the reactor was covered to protect from light. A suspension of chloranil (260 g, 1.06 mol, 3.44 eq) in diphenyl ether (856 g) in a round bottom flask was degassed by bubbling N_2 for 30 min. The reactor was heated to reflux over 2 h when the chloranil suspension was added and rinsed with diphenyl ether (259 g). The reaction was refluxed for 20 min under N_2 and then cooled to 30°C for 1 h. The solids were collected after 2 h at room temperature by filtration, washed with methanol (2 L) and suspended in methanol (12.5 L). Stirring for 20 min, filtration and drying at 50°C under reduced pressure yielded 634 g product with diphenyl ether incorporated. The product was protected from light whenever possible. Due to shortages in the supply of diphenyl ether only a part of the obtained product could be recrystallized so far.*

Recrystallization of the obtained solid (210 g) in diphenyl ether (12.8 kg) was performed in a 70 L Hastalloy reactor under nitrogen equipped with a reflux condenser, helical stirrer and thermometer connected to a heated pressure filter by a heated tube. The suspension was degassed for 30 minutes at 30°C by bubbling N_2 and then heated to reflux over 4 h. Hot filtration under 2 bar N_2 pressure over 20 min yielded a clear solution that was cooled to 30°C. The crystals that formed after 5 h were collected by filtration, washed twice with methanol (15 L) and once with acetone (2 L). Drying at 50°C under reduced pressure yielded 41.07 g (52%) compound **1** *containing additionally 4% (w/w) diphenylether. ^{1}H NMR (300 MHz, propylene carbonate): 9.15 (s, 3H); 8.45 (d, J = 8.7 Hz, 6H); 8.14 (s, 3H); 7.96 (t, J = 8.0 Hz, 6H); 7.72 (d, J = 7.3 Hz, 6H).*

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author contributions

P.T. performed all experiments on the lab scale and participated in some of the experiments on the technical scale. G. M. helped with the scale-up planning and was responsible for the technical scale operations. A. D. S. initiated the research. P. T. and A. D. S. wrote the manuscript.

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