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Short Note

2,4,6-Trichloro-cyclohexa-2,5-dienone

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Abstract: A continuous flow process was optimised for the perchlorination of *p*-cresol to the corresponding 2,4,6-trichloro-cyclohexa-2,5-dienone derivative employing trichloroisocyanuric acid as a green and safer-to-handle chlorinating agent. The system could furnish 200 g of pure material within 5 h of operation (throughput = 40 g h^{-1}). The compound was easily isolated by filtration and obtained in 95% purity as determined by GC analysis; it could be further purified by crystallisation from a 20:1 Hexane/AcOEt mixture left at −20 °C overnight. The resultant product was characterised by ^{1}H & ^{13}C NMR, MS, IR analyses, with melting point and X-ray single-crystal data being obtained, confirming the structure.

Keywords: perchlorination; flow chemistry chlorinating agent; trichloroisocyanuric acid; X-ray structure; scale-up

1. Introduction

2,4,6-trichloro-cyclohexa-2,5-dienone derivatives have been studied as insecticides and chemotherapeutics (Figure 1) [1–4]. These derivatives have also been used as mild active chlorinating agents for selective *para*-chlorination of phenols, achieving over 95% selectivity [5,6]. We also anticipated that they may hold promise as mild chlorination sources in several new reactions such as organocatalytic and photochemical halogenations. However, there availability is currently limited and thus restricts their wider evaluation and application.

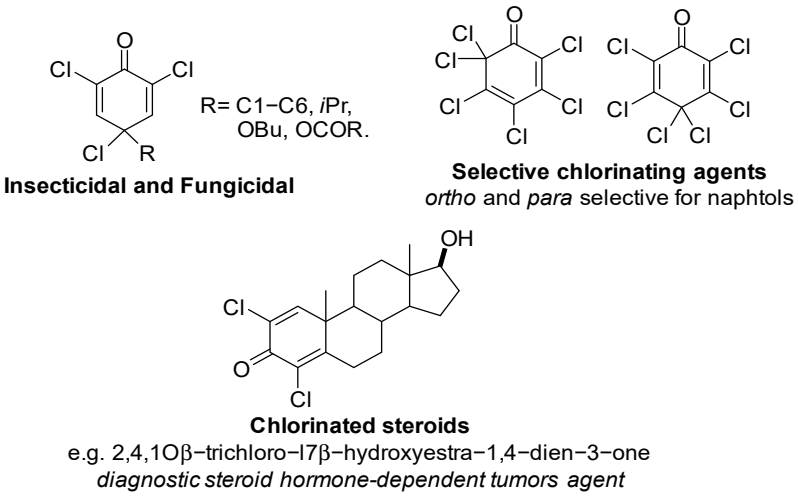

Figure 1. Examples of biological active 2,4,6-trichloro-cyclohexa-2,5-dienone derivatives.

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Various preparative procedures have been investigated for their preparation which consist of perchlorinating phenolic rings utilizing either elemental chlorine or other strong chlorinating agents such as *N*-chlorimides [7–9]. In 1883, Benedikt and Schmidt first reported perchlorination employing chlorine gas as the oxidising agent [10]. In 1959, Mukawa et al. isolated a dienone-estradiol by employing a combination of surfuryl chloride and acetic anhydride; the same group subsequently investigated the alternative usage of trichloroisocyanuric acid (TCCA) [3,11,12]. Later, in 1993, Jacquesy et al. reported the selective *ipso*-chlorination of phenols by employing antimony pentachloride [13]. More recent methodologies have also been reported which utilise sodium hypochlorite pentahydrate, 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), and NaCl/Oxone [14–17].

Our research group is interested in developing efficient environmentally friendly continuous processes. We have significant experience using the readily available, low-cost, and easy-to-handle reagent, TCCA, which is a potential alternative to other more toxic and unstable chlorinating agents. Furthermore, its active chlorine content of 91.5% per molecule makes TCCA a fantastic candidate for developing atom-economic processes [18,19]. The apolar characteristics inherited by the three chlorine atoms allows TCCA to be highly soluble in most common organic solvents such as ethyl acetate, methanol, acetone, and toluene, whereas its by-product (cyanuric acid) has a much lower solubility and can often be filtered following precipitation from the mixtures.

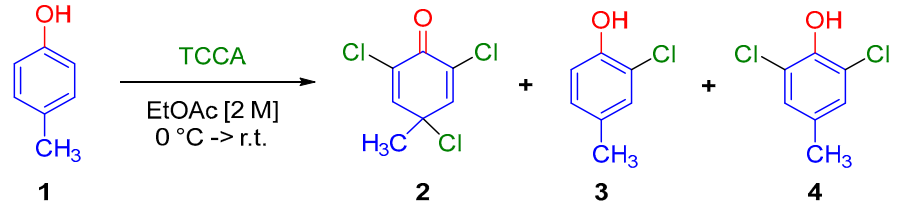
Since the beginning of this century, chemists around the world have been searching for new processing methodologies and tools to perform synthetic organic chemistry more efficiently. Flow chemistry is one of the tools that has been achieving much attention across the various hierarchies of the chemical manufacturing industry [20–23]. Performing chemical transformations through flow streams allows for increased heat and mass transfer as well as a reduced risk of dangerous reactant accumulation during process scale-ups. Better control of critical process parameters such as temperature and reaction times generates improved reaction profiles and as such has found good uptake in the processing of pharmaceutical active ingredients (APIs) in compliance with current Good Manufacturing Practice (cGMP) legislation [24].

Combining our interests in TCCA as a chlorinating agent and flow chemistry as a synthesis tool, we report the first continuous flow perchlorination of *p*-cresol employing TCCA as the chlorinating agent.

2. Results

As a preliminary investigation, we decided to evaluate the batch reaction condition for the perchlorination of *p*-cresol (**1**) (Table 1). Our exploratory experiments were performed by adding TCCA portion-wise at 0 °C to a 2 M solution of **1** in ethyl acetate (10 mmol scale). An increasing quantity of TCCA was investigated to evaluate the best conditions under which to realise complete conversion to the desired 4-methyl-2,4,6-trichloro-cyclohexa-2,5-dienone (**2**). As shown in Table 1, when 2 or 2.2 equivalents of TCCA (6 or 6.6 mole equivalent electrophilic chlorine) were employed, perchlorination occurred only partially, and if extended reaction times of more than 30 min were used, de-chlorination with the resultant formation of 3 and 4 was encountered (Entries 1–4). Increasing the equivalents of TCCA to 2.5 afforded the highest conversions of **2** and reduced undesired impurities (**3** and **4**) (Entry 5). Further increasing TCCA did not improve the conversion (Entry 6). It should be noted that each process needed to be carefully cooled at the start as a strong exothermic process was associated with chlorination, which unchecked gave rise to a 30–38 °C temperature increase. In addition, perchlorination produced copious amounts of white cyanuric acid precipitate which were almost completely insoluble in the EtOAc solvent system.

Table 1. Screening of reaction conditions to perform efficient perchlorination of *p*-cresol (**1**).



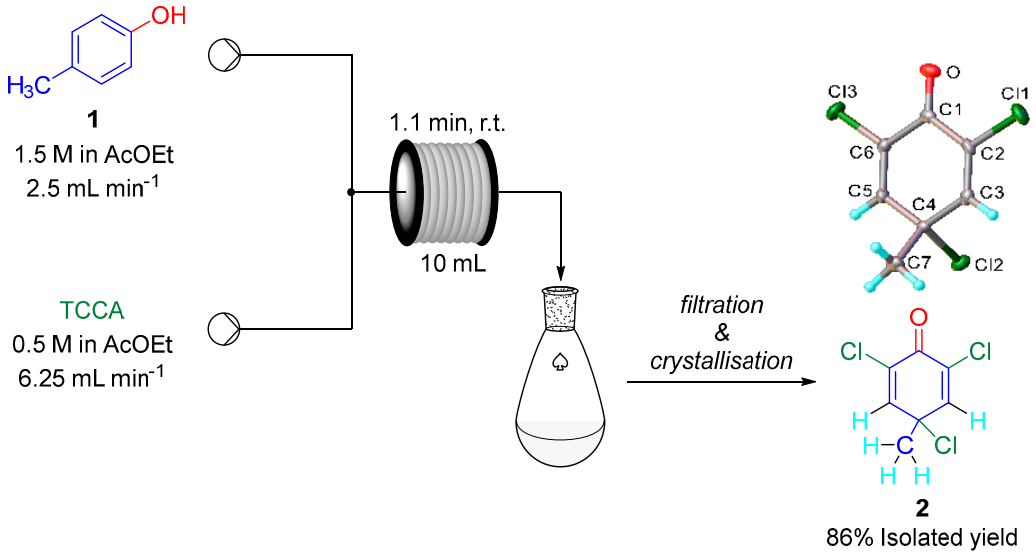
1 **2** **3** **4**

Entry [1]	TCCA (equiv.)	Residence Time (min)	2	3	4
1	2	20	57.7	42.3	-
2	2	30	75.0	25.0	-
3	2	60	67.0	20.9	11.9
4	2.2	30	75.0	25.0	-
5	2.5	30	84.9	9.4	5.7
6	2.7	30	83.7	16.3	-

[1] The experiments were carried out on a 10 mmol scale.

Having outlined a set of viable reaction conditions, we decided to convert the sequence to a flow system capable of continuously chlorinating p-cresol (**1**), taking into account the biphasic nature of the reaction and the notable exotherm. Many techniques have been implemented to avoid solid accumulation when dealing with slurry in flow processes [25–29]. High flow rates and ultrasonic radiation have been employed many times, and these can be easily adopted in a chemistry laboratory [30–35]. Furthermore, due to the high surface area of a coiled tubular flow reactor, the heat generated from the TCCA addition could be easily dissipated without the need of excessive external cooling of the reaction stream. Finally, the improved mixing process, created by the turbulent flow in the reactor, should lead to improved control and therefore an improved selectivity reaction.

Based upon our initial batch reaction conditions, and following some scoping runs pertaining to solubility limits and precipitation (avoidance of reactor blockage), we determined the following optimised procedure. A 1.5 M stock solution of p-cresol (**1**) in EtOAc was merged with a flow stream comprising a 0.5 M solution of TCCA in the same solvent (Scheme 1, Figure 2). A Y-shaped PEEK thru mixer (1/4-28 Y mixer 0.020 in thru) was used to blend the two streams. The unified stream was subsequently directed through a 10 mL PTFE coil (1.5 mm I.D.) placed in an ultrasonic bath (Ultrawave 50–60 Hz) maintained at 25 °C (Scheme 1, Figure 2). The exiting reaction mixture (69 s residence time) was collected for 5 h in a Schott bottle and then filtered over celite. We tested the reaction mixture upon directly exiting the reactor and again sampled after standing for 1, 3, and 5 h, but this showed no change in composition (GC peak area of 94.6% for **2**, 4.5% for **3,** and 0.9% for **4**). After filtration and solvent evaporation, an orange liquid was obtained that on standing crystallised. The final product **2** could be obtained in pure form by recrystallisation (hexane/EtOAc 20:1) isolated in an 86% (204 g) yield (throughput = 40 g h^{-1}). The flow system proved robust, enabling repeated runs to be performed at different scales, and thus fresh material could be generated on demand in a very simple set up.



Scheme 1. Setup employed for the preparation of **2** under flow conditions.

Figure 2. A photo of the setup employed for the perchlorination of *p*-cresol to **2**.

3. Materials and Methods

All solvents were purchased from Fisher Scientific and used without further purification. The substrates, their precursors, and the reagents were purchased from Fluorochem. ^{1}H-NMR spectra were recorded on Bruker Avance-400 instrument and are reported relative to the residual solvent, $CDCl_3$ (δ 7.26 ppm). ^{13}C-NMR spectra were recorded on the same instruments and are reported relative to $CDCl_3$ (δ 77.16 ppm). Data for the ^{1}H-NMR spectra are reported as follows: chemical shift (δ/ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, s, br = broad singlet, and app. = apparent. Data for the ^{13}C-NMR spectra are reported in terms of chemical shift (δC/ppm). IR spectra were obtained using a Perkin Elmer Spectrum Two UATR Two FT-IR Spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21–70% of tallest signal), or strong (s, >71% of tallest signal).

Low-resolution gas chromatography mass spectrometry (GC-MS) was performed on a Shimadzu QP2010-Ultra equipped with an Rxi-5Sil MS column (0.15 µm × 10 m × 0.15 mm) in EI mode. Reactions were conducted in flow using Vapourtec SF-10 as peristaltic pumps, along with 0.5–1.5 mm PTFE tubing. A PEEK 1/4-28 Y mixer 0.020 in thru was employed.

The entire connector tubing was 1/4″ OD. The ultrasonic cleaning bath employed was an Ultrawave U300H.

For TLC, Sigma Aldrich glass-backed plates were used, and visualisation was performed using UV irradiation and $KMnO_4$ staining. Organic solutions were concentrated under reduced pressure using a Buchi rotary evaporator, and hi-vacuum was achieved using an Edwards RV5 pump and Schlenk line.

The procedure for the continuous perchlorination of *p*-cresol (**1**).

Pumping of the solutions was performed using two independently controlled Vapourtec SF10 Laboratory pumps.

A 1.5 M solution of *p*-cresol in AcOEt (flow rate = 2.5 mL min^{-1}) was merged with a solution 0.5 M of TCCA in AcOEt (flow rate = 6.25 mL min^{-1}) and progressed into a 0.5 mm PTA coil reactor (Volume = 10 mL) placed into an ultrasonic bath maintained at 25 °C. The heterogenous mixture was collected in a Schott bottle for a fixed period. The mixture was filtered through celite, and the solvent was evaporated under vacuum. The orange liquid residue was solubilised in a 20:1 Hexane/AcOEt mixture and left at −20 °C overnight to give an off-white crystalline product.

2,4,6-trichloro-4-methylcyclohexa-2,5-dien-1-one (**2**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 1.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.93, 145.48, 131.18, 60.94, 29.98. FT-IR νmax 3058 (CH, w), 2989 (CH, w), 1681 (C=O, s), 1599 (s), 1446 (m), 1320 (m), 1038 (s), 908 (s), 769 (s), 654 (s). GC-MS Rt 3.77 min, *m*/*z* 176.0 [M-Cl]+. m.p. 110.9–112.8 °C.

X-ray: (CIF: CCDC 2415243): Crystal data for $C_7H_5Cl_3O$ (M = 211.46 g/mol): monoclinic, space group P21. a = 5.3071(5) Å, b = 10.6875(10) Å, c = 7.7006(7) Å. α/°: 90. β/°: 105.038(4). γ/°: 90. Volume/$Å^3$: 421.82(7). Z: 2. ρcalcg/cm^3: 1.665. μ/mm^{-1}: 1.019. F(000): 212.0. Crystal size/mm^3: 0.246 × 0.152 × 0.078. Radiation MoKα: (λ = 0.71073). 2Θ range for data collection/°: 5.478 to 61.044. Index ranges: $-7 \leq h \leq 7$, $-15 \leq k \leq 15$, and $-10 \leq l \leq 10$. Reflections collected: 8893. Independent reflections: 2571 [Rint = 0.0295, Rsigma = 0.0305]. Data/restraints/parameters: 2571/1/120. Goodness-of-fit on F2: 1.063. Final R indexes [$I \geq 2\sigma$ (I)]: R1 = 0.0238 and wR2 = 0.0563. Final R indexes [all data]: R1 = 0.0290 and wR2 = 0.0577. Largest diff. peak/hole/e $Å^{-3}$: 0.29/−0.23. Flack parameter: −0.02(3).

The ^{1}H NMR characterisation and indicative IR signals for compound **2** match well with those previously reported via an alternative synthetic procedure [36]. However, the previously determined melting point of 89–90 °C [crystallised from petroleum ether (b.p. 30–60 °C)] [36] did not match our findings of 110.9–112.8 °C [crystallised from 20:1 Hexane:AcOEt]. However, the additional obtained ^{13}C NMR spectra and X-ray single-crystal structure provided further evidence for the authentication of the material obtained.

4. Conclusions

The described procedure is operationally simple and readily scalable, offering easy access to multigram quantities (40 g h^{-1}, 86% isolated yield) of 2,4,6-trichloro-cyclohexa-2,5-dienone (**2**) for the first time in a safe and much improved yield compared to the existing literature [8,37]. We also believe that the general approach should also be readily adaptable to other derivatives.

Supplementary Materials: Supplementary Information including ^{1}H & ^{13}C NMR, IR, and additional X-ray data are provided [38,39].

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References

1. Leftwick, A.P.; Parnell, E.W. New Pesticides Derived from Cyclohexadiene, OA5232A, Application Date 1976, Publication Date 1981. Available online: https://patents.google.com/patent/OA05232A/en?q=(A.P)&inventor=Leftwick,&oq=Leftwick,+A.P (accessed on 14 February 2025).
2. Takegawa, B. Steroid Compound, JPH0267296A. 1988. Available online: https://patents.google.com/patent/JPH0267296A/en?oq=JPH0267296 (accessed on 14 February 2025).
3. Mukawa, F. 10β-Chloro-17β-hydroxyestra-1,4-dien-3-one and its related compounds. *J. Chem. Soc. Perkin Trans. 1* **1988**, 457–460. [CrossRef]
4. Kaiser, K.L.E.; Niculescu, S.P. On the PNN modeling of estrogen receptor binding data for carboxylic acid esters and organochlorine compounds. *Water Qual. Res. J. Can.* **2001**, *36*, 619–630. [CrossRef]
5. Guy, A.; Lemaire, M.; Guetté, J.P. Halogenation regioselective en serie aromatique-II. Chloration des naphtols et de leurs ethers a l'aide de reactifs mettant en jeu des interactions du type donneur-accepteur. *Tetrahedron* **1982**, *38*, 2347–2354. [CrossRef]
6. Mamaghani, M.; Zolfigol, M.A.; Shojaei, M. N-Chloro-2,3,4,4,5,6-hexachlorocyclohexa-2,5-dienylideneamine as a mild and highly regioselective chlorinating reagent. *Synth. Commun.* **2002**, *32*, 735–740. [CrossRef]
7. Fischer, A.; Henderson, G.N. Ipso chlorination of 4-alkylphenols. Formation of 4-alkyl-4-chlorocyclohexa-2,5-dienones. *Can. J. Chem.* **1979**, *57*, 552–557. [CrossRef]
8. Bergquist, K.-E.; Nilsson, A.; Ronlán, A.; Norin, T.; Hjeds, H. Electrophilic Chlorination of 4-Methylphenols with Molecular Chlorine. Synthesis of Dimethoxy Aromatics by Methanolysis of 4-Chloro-4-methylcyclohexa-2,5-dienones. *Acta Chem. Scand.* **1982**, *36*, 675–683. [CrossRef]
9. Antinori, G.; Baciocchi, E.; Illuminati, G. Non-conventional paths in electrophilic aromatic reactions. Part VI. Chlorination of 3,5-dichloro-2,4,6-trimethylanisole and related compounds. *J. Chem. Soc. B Phys. Org.* **1969**, 373–377. [CrossRef]
10. Benedikt, R.; Schmidt, M.V. Notizen über Halogenderivate. *Monatshefte Für Chem.* **1983**, *4*, 604–609. [CrossRef]
11. Mukawa, F.; Suzuki, T.; Ishibashi, M.; Yamada, F. Estrogen and androgen receptor binding affinity of 10β-chloro-estrenen derivatives. *J. Steroid Biochem.* **1988**, *31*, 867–870. [CrossRef] [PubMed]
12. Mukawa, F. The anomalous chlorination of estradiol 17β-acetate with isocyanuric chloride. *Tetrahedron Lett.* **1959**, *1*, 17–20. [CrossRef]
13. Ferron, B.; Jacquesy, J.C.; Jouannetaud, M.P.; Karam, O.; Coustard, J.M. Ipso-chlorination of 4-alkylphenols ethers a novel route to 4-chlorocyclohexa-2,5-dienones. *Tetrahedron Lett.* **1993**, *34*, 2949–2952. [CrossRef]
14. Uyanik, M.; Sasakura, N.; Kuwahata, M.; Ejima, Y.; Ishihara, K. Practical oxidative dearomatization of phenols with sodium hypochlorite pentahydrate. *Chem. Lett.* **2015**, *44*, 381–383. [CrossRef]
15. Zhang, Z.; Sun, Q.; Xu, D.; Xia, C.; Sun, W. Direct halogenative dearomatization of 2-naphthols by NXS (X = Cl, Br) in water. *Green Chem.* **2016**, *18*, 5485–5492. [CrossRef]
16. Yin, Q.; Wang, S.G.; Liang, X.W.; Gao, D.W.; Zheng, J.; You, S.L. Organocatalytic asymmetric chlorinative dearomatization of naphthols. *Chem. Sci.* **2015**, *6*, 4179–4183. [CrossRef]
17. Uyanik, M.; Sahara, N.; Ishihara, K. Regioselective Oxidative Chlorination of Arenols Using NaCl and Oxone. *Euro. J. Org. Chem.* **2019**, *2019*, 27–31. [CrossRef]
18. Tilstam, U.; Weinmann, H. Trichloroisocyanuric Acid: A Safe and Efficient Oxidant. *Org. Process Res. Dev.* **2002**, *6*, 384–393. [CrossRef]
19. Gaspa, S.; Carraro, M.; Pisano, L.; Porcheddu, A.; De Luca, L. Trichloroisocyanuric Acid: A Versatile and Efficient Chlorinating and Oxidizing Reagent. *Euro. J. Org. Chem.* **2019**, *2019*, 3544–3552. [CrossRef]
20. Gambacorta, G.; Sharley, J.S.; Baxendale, I.R. A comprehensive review of flow chemistry techniques tailored to the flavours and fragrances industries. *Beilstein J. Org. Chem.* **2021**, *17*, 1181–1312. [CrossRef] [PubMed]
21. Sagmeister, P.; Williams, J.D.; Hone, C.A.; Kappe, C.O. Laboratory of the future: A modular flow platform with multiple integrated PAT tools for multistep reactions. *React. Chem. Eng.* **2019**, *4*, 1571–1578. [CrossRef]
22. Webb, D.; Jamison, T.F. Continuous flow multi-step organic synthesis. *Chem. Sci.* **2010**, *1*, 675–680. [CrossRef]
23. Pastre, J.C.; Browne, D.L.; Ley, S.V. Flow chemistry syntheses of natural products. *Chem. Soc. Rev.* **2013**, *42*, 8849–8869. [CrossRef]
24. Sasaki, T.; Yahata, K.; Isomura, M.; Ohashi, I.; Fukuyama, T.; Miyashita, Y.; Watanabe, Y.; Murai, N.; Matsuda, M.; Kamada, A.; et al. What Does It Take to Develop Structurally Complex Molecules by Total Synthesis? Rapid Process Development and GMP Manufacturing of E7130 Drug Substance for First-in-Human Clinical Study. *Org. Process Res. Dev.* **2024**, *28*, 2077–2089. [CrossRef]

25. Browne, D.L.; Deadman, B.J.; Ashe, R.; Baxendale, I.R.; Ley, S.V. Continuous Flow Processing of Slurries: Evaluation of an Agitated Cell Reactor. *Org. Process Res. Dev.* **2011**, *15*, 693–697. [CrossRef]
26. Deadman, B.J.; Browne, D.L.; Baxendale, I.R.; Ley, S.V. Back Pressure Regulation of Slurry-Forming Reactions in Continuous Flow. *Chem. Eng. Technol.* **2015**, *38*, 259–264. [CrossRef]
27. Sharma, M.K.; Suru, A.; Joshi, A.; Kulkarni, A.A. A Novel Flow Reactor for Handling Suspensions: Hydrodynamics and Performance Evaluation. *Ind. Eng. Chem. Res.* **2020**, *59*, 16462–16472. [CrossRef]
28. Bianchi, P.; Williams, J.D.; Kappe, C.O. Oscillatory flow reactors for synthetic chemistry applications. *J. Flow Chem.* **2020**, *10*, 475–490. [CrossRef]
29. Doyle, B.J.; Gutmann, B.; Bittel, M.; Hubler, T.; Macchi, A.; Roberge, D.M. Handling of Solids and Flow Characterization in a Baffleless Oscillatory Flow Coil Reactor. *Ind. Eng. Chem. Res.* **2020**, *59*, 4007–4019. [CrossRef]
30. Hartman, R.L.; Naber, J.R.; Zaborenko, N.; Buchwald, S.L.; Jensen, K.F. Overcoming the Challenges of Solid Bridging and Constriction during Pd-Catalyzed C−N Bond Formation in Microreactors. *Org. Process Res. Dev.* **2010**, *14*, 1347–1357. [CrossRef]
31. Schoenitz, M.; Grundemann, L.; Augustin, W.; Scholl, S. Fouling in microstructured devices: A review. *Chem. Commun.* **2015**, *51*, 8213–8228. [CrossRef]
32. Wu, K.; Kuhn, S. Strategies for solids handling in microreactors. *Chim. Oggi/Chem. Today* **2014**, *32*, 62–66.
33. Dong, Z.; Zhao, S.; Zhang, Y.; Yao, C.; Yuan, Q.; Chen, G. Mixing and residence time distribution in ultrasonic microreactors. *AIChE J.* **2017**, *63*, 1404–1418. [CrossRef]
34. Rivas, D.F.; Kuhn, S. Synergy of Microfluidics and Ultrasound: Process Intensification Challenges and Opportunities. *Top. Curr. Chem.* **2016**, *374*, 70. [CrossRef] [PubMed]
35. Dong, Z.; Delacour, C.; Carogher, K.M.; Udepurkar, A.P.; Kuhn, S. Continuous ultrasonic reactors: Design, mechanism and application. *Materials* **2020**, *13*, 344. [CrossRef]
36. Chip, G.K.; Grossert, J.S. Aromatic halogenation with titanium (IV) chloride in presence of peroxytrifluoroacetic acid. *Can. J. Chem.* **1972**, *50*, 1233–1240. [CrossRef]
37. Husain, S.; Kifayatullah, M. Phenol-dienone rearrangement in the chlorination of p-cresol with tert-butyl hypochlorite. *Indian J. Chem. Sect. B Org. Chem. Incl. Med. Chem.* **1985**, *24B*, 711–714.
38. Sheldrick, G.M. Crystal structure refinement with SHELXL. *Acta Crystallogr.* **2015**, *71*, 3–8. [CrossRef]
39. Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: A complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42*, 339–341. [CrossRef]