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A Protocol To Generate Phthaloyl Peroxide in Flow for the Hydroxylation of Arenes

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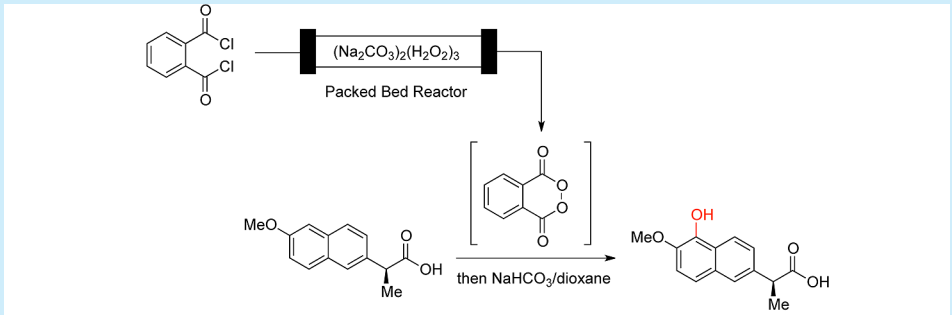
Supporting Information



- No isolation or purification of phthaloyl peroxide required
- Phthaloyl peroxide is generated within minutes from phthaloyl chloride and sodium percarbonate

ABSTRACT: A flow protocol for the generation of phthaloyl peroxide has been developed. This process directly yields phthaloyl peroxide in high purity (>95%) and can be used to bypass the need to isolate and recrystallize phthaloyl peroxide, improving upon earlier batch procedures. The flow protocol for the formation of phthaloyl peroxide can be combined with arene hydroxylation reactions and provides a method for the consumption of peroxide as it is generated to minimize the accumulation of large quantities of peroxide.

Phenols are found in all areas of chemical industry including pharmaceuticals, agrochemicals, and materials. While there are diverse approaches for the synthesis of phenols, there are no broadly applicable methods for directly accessing phenols from arenes. Peroxides have been extensively studied as oxidants for the conversion of arenes to phenols and successfully employed when used in combination with strong acids.[1] These additives are required to both activate the peroxides and deactivate the resulting phenolic compounds, preventing a secondary oxidation reaction. The reagent phthlaloyl peroxide (**1**) alone converts aryl C−H bonds into C−O bonds.[2] The reaction proceeds in good yields and avoids overoxidation. As the oxidant does not require additional catalysts or additives, the procedure is straightforward. Importantly, phthaloyl peroxide (**1**) selectively reacts with arenes while possessing little to no observable reactivity toward a large number of functional groups including those that are typically susceptible to oxidation.

However, the use of stoichiometric amounts of peroxides for oxidative transformations has potential safety drawbacks due to the high energetics of peroxide containing compounds. As a result, we report herein the development of a protocol for the formation of phthaloyl peroxide in flow to circumvent the discrete formation and isolation of large quantities of pure phthaloyl peroxide. The formation of phthaloyl peroxide in flow allows for the direct reaction of phthaloyl peroxide solutions and the immediate consumption of the reagent as it is formed, minimizing the accumulation of peroxide.

The yield of phthaloyl peroxide (**1**) prepared in batch is highly dependent on the rate of stirring and amount of water present (see Supporting Information). On larger scales the efficiency of mixing heterogeneous reactions necessitates longer reaction times. Additionally, a final precipitation is required to access pure material, removing unreacted phthaloyl chloride and phthalic anhydride formed as a byproduct (Figure 1).

In order to avoid working with (and storage of) large quantities of phthaloyl peroxide (**1**), we developed a straightforward method to generate phthaloyl peroxide cleanly in flow. This method when combined with reactions in batch allows for the hydroxylation of a wide array of arenes without isolating phthaloyl peroxide (**1**).

Reactions performed in flow offer several advantages over reactions in batch, including a small apparatus footprint and increased safety.[6] Batch reactions optimized on bench scale can be "scaled-out" when attempting to meet high demand while with flow scale up is more transferable.[7] Reactions in flow also circumvent exposure of toxic,[8] air sensitive,[9] or inherently unstable materials[10] simplifying chemical processes. Relevant to our efforts several oxidation reactions have been successfully performed in flow improving upon their batch counterparts.[11] Notably, aerobic oxidation of Grignard reagents has been

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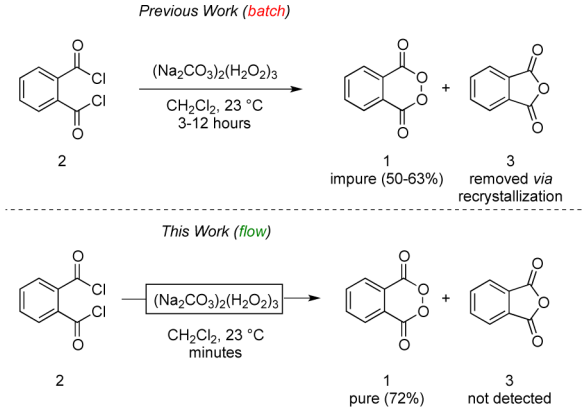
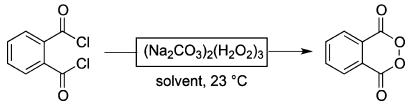


Figure 1. Preparation of phthaloyl peroxide in batch and flow.

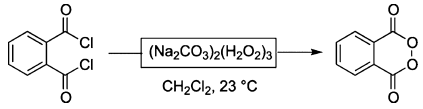
Table 1. Solvent Screening for the Synthesis of Phthaloyl Peroxide from Phthaloyl Chloride Using a Packed Bed Reactor with Sodium Percarbonate[a]



entry	solvent[b]	conversion (%)[c]
1.	ethyl acetate	68
2.	acetone	76
3.	trifluorotoluene	>95
4.	dichloroethane	>95
5.	methylene chloride	>95

[a]Reactions conducted with a 167 μL/min flow rate (t_r = 11 min) using a 40 psi BPR. [b]ACS reagent grade solvent. [c]Determined by NMR.

Table 2. Optimization of the Synthesis of Phthaloyl Peroxide from Phthaloyl Chloride in Flow[a]



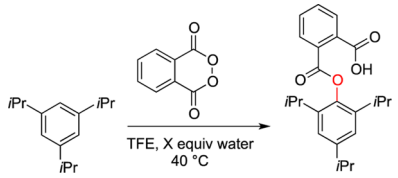
entry	flow rate (μL min^{-1})	CH_2Cl_2	BPR (psi)	conversion (%)[b]	yield (%)[c]
1.	50	anhydrous	40	>95	61
2.	167	anhydrous	40	>95	71
3.	334	anhydrous	40	>95	72
4.	167	anhydrous	none	>95	66
5.	167	wet	40	>95	47
6.	167	reagent grade[d]	40	>95	57

[a]Flow rate of 50 μL/min, t_r = 37 min; flow rate of 167 μL/min, t_r = 11 min; flow rate of 334 μL/min, t_r = 5.5 min. [b]Determined by NMR. [c]Isolated yield. [d]ACS reagent grade.

developed in continuous flow providing access to phenolic compounds.[12]

We envisioned the construction of a packed bed reactor containing solid sodium percarbonate to be the key component to our reaction protocol.[13] Fine mesh sodium percarbonate increased mixing and was found to be required for full conversion. The use of mesh sieves to control the particle size in the packed bed reactor proved important.[14] Particles smaller than the frit porosity tended to clog the packed bed reactor, and the uniformity of particle size of sodium percarbonate increased reproducibility. This procedure uses sodium percarbonate as an in-line reagent, and the contents of the packed bed reactor are ultimately consumed. After a short induction (a volume corresponding to twice the volume of the packed bed reactor) yields were found to fluctuate by 4% over 72 min (using a flow rate of 167 μL/min). For complete instructions for constructing the packed bed reactor with sodium percarbonate please refer to the associated Supporting Information.

Table 3. Effect of Water on the Oxidation of Triisopropylbenzene by Phthaloyl Peroxide[a]



entry	equiv water	conversion (%)[b]
1.	0	94
2.	1	90
3.	2	94
4.	8	94
5.	16	90
6.	32	73
7.	64	59
8.	128	12

[a]Reactions carried out using the existing batch procedure.[2] [b]Determined by NMR.

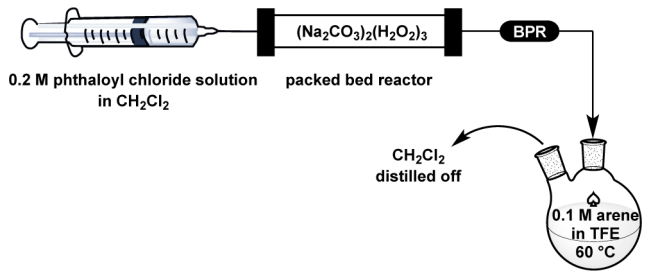


Figure 2. Schematic for the combination of flow and batch reactions using phthaloyl peroxide.

The polar aprotic solvents ethyl acetate and acetone afforded moderate conversion of phthaloyl chloride (Table 1). However, in addition to incomplete conversion the use of these solvents led to the formation of phthalic anhydride in variable amounts. Halogenated solvents proved optimal with clean conversion and no detectable amounts of phthalic anhydride. Ultimately methylene chloride was selected due to its volatility allowing it to be selectively removed by distillation out of batch reactors.

While variable flow rates provide uniformly high conversion the isolated yields of peroxide were best achieved using higher flow rates (Table 2). Unabated, carbon dioxide generated from the reaction of HCl with sodium carbonate propelled material through the reactor at rates faster than selected. Therefore, the feed emanating from the end of the packed bed reactor was affixed with a back-pressure regulator (BPR) to allow constant velocity through the reactor. In addition to providing consistency, an increase in yield was observed after employing a BPR (Table 2, entry 4).

Water-saturated methylene chloride can extract six times the amount of hydrogen peroxide from sodium percarbonate than anhydrous methylene chloride.[15] Consequently, we found that

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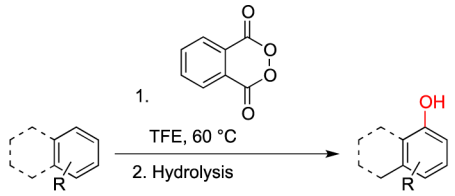

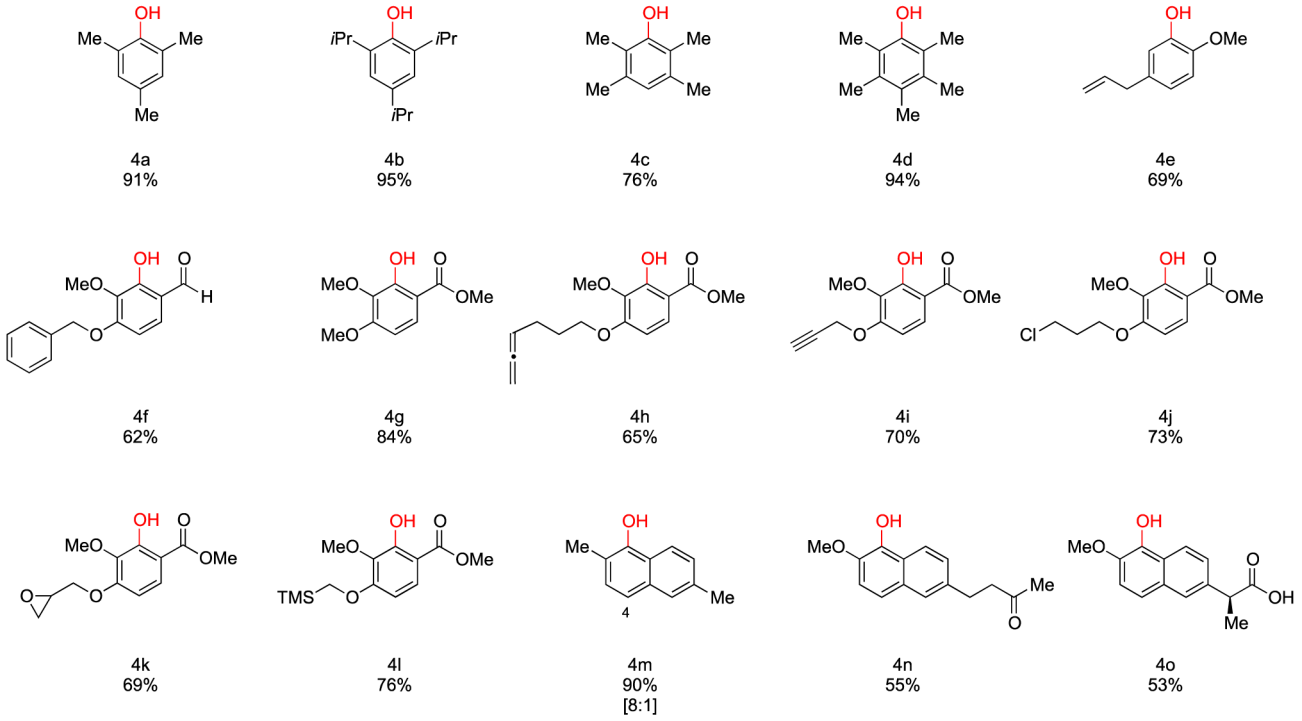

Figure 3. Batch arene hydroxylation by phthaloyl peroxide (**1**) generated in flow.

trace water content in batch reactions was critical to ensure adequate leaching of hydrogen peroxide. The opposite was observed for the synthesis of phthaloyl peroxide in flow: yields increased 24% using anhydrous methylene chloride in place of wet solvent.

While the role of water was well understood in the formation of phthaloyl peroxide (**1**), the presence of water in the course of the hydroxylation was investigated (Table 3). The synergistic effects of water in fluorinated alcohol solvents for an organocatalytic C−H oxidation reaction has been noted.[16] Similarly water has been found to assist the reaction of malonyl peroxides with styrenes and stillbenes.[17] Despite no improvements in the reaction of phthaloyl peroxide with arenes the hydroxylation reaction is tolerant of water; addition of up to 16 equiv of water did not affect the conversion. This further supports our previous observation that the direct use of solvents as supplied from commercial sources is permissible.

The reaction of phthaloyl peroxide with arenes has been optimized using fluorinated alcoholic solvents. The addition of cosolvents typically reduces yields. Reaction of mesitylene with phthaloyl peroxide in a 1:1 solution of methylene chloride/hexafluoroisopropanol (HFIP) resulted, after hydrolysis, in a diminished 56% yield of trimethylphenol as compared to the reaction conducted solely in HFIP generating trimethylphenol in 97% yield. To remove methylene chloride, boiling point measurements and analysis of distillates were conducted in mixtures of methylene chloride and fluorinated alcohol solvents. While methylene chloride and HFIP form an azeotrope, we found that trifluoroethanol (TFE) and methylene chloride do not, allowing the selective removal of methylene chloride. This enabled our reaction design to provide pure phthaloyl peroxide in TFE in analogy to our previous reactions in batch.

Combination of the formation of phthaloyl peroxide in flow with batch reactions was achieved through the setup shown in Figure 2. Using a syringe pump a 0.2 M solution of phthaloyl chloride in methylene chloride is passed through a packed bed reactor with solid sodium percarbonate at a rate of 167 μL/min. This system empties into a two-neck round-bottom flask containing the arene of interest at 0.1 M in TFE heated in an oil bath set to 60 °C. The flask is equipped with a distillation head to permit the continuous distillation of methylene chloride as the phthaloyl peroxide solution adds.

Similar to reactions employing isolated, solid phthaloyl peroxide arenes possessing a variety of functionality are tolerated by this method. Steric encumbrance bears little effect on the reaction (**4a−d**, Figure 3). Groups classically considered labile toward oxidative conditions are left unreacted. Allylic (**4e**), allenic (**4h**), and propargylic (**4i**) groups are not oxidized. Carbonyls derivatives can be hydroxylated with no evidence of Baeyer−Villiger/Dakin oxidations as seen for the syntheses of the phenols **4f** and **4n**.

Molecules possessing more than one benzene ring are selectively oxidized on the most electronically activated ring

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(**4f**). Naphthalene derivatives are hydroxylated in good yield. Trimethylsilyl groups (**4l**) remained intact as well as epoxides (**4k**). Finally, phenols of the nonsteroidal anti-inflammatory drugs (NSAID) nabumetone (**4n**) and naproxen (**4o**) were generated providing potential metabolite standards.

In summary, we have described a method to safely generate phthaloyl peroxide (**1**) in flow and use this procedure, in combination with batch reactions, to hydroxylate arenes. This procedure circumvents the need to isolate solid phthaloyl peroxide. The development of a reaction apparatus allows for the continuous removal of methylene chloride providing solutions of phthaloyl peroxide in TFE, therefore maximizing reactivity.

■ ASSOCIATED CONTENT

Supporting Information

Detailed instructions for assembling the flow apparatus, experimental procedures, and characterization data are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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