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Production of Biomass-Derived *p*-Hydroxybenzamide: Synthesis of *p*-Aminophenol and Paracetamol

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As we work to transition the modern society that is based on non-renewable chemical feedstocks to a post-modern society built around renewable sources of energy, fuels, and chemicals, there is a need to identify the renewable resources and processes for converting them to platform chemicals. Herein, we explore a strategy for utilizing the *p*-hydroxybenzoate in biomass feedstocks (e.g., poplar and palm trees) and converting it into a portfolio of commodity chemicals. The targeted bio-derived product in the first processing stage is *p*-hydroxybenzamide produced from *p*-hydroxybenzoate esters found in the plant. In the second stage a continuous reaction process converts the *p*-hydroxybenzamide to *p*-aminophenol via the Hofmann rearrangement and recovers the unreacted *p*-hydroxybenzamide. In the third stage the *p*-aminophenol can be acetylated to form paracetamol, which is readily isolated by liquid/liquid extraction at >95% purity and an overall *p*-hydroxybenzamide-to-paracetamol process yield of ~90%. We explore how utilization of protecting groups alters the challenges in this process and expands the portfolio of possible products to include *p*-(methoxymethoxy)aniline and *N*-acetyl-*p*-(methoxymethoxy)aniline. These target compounds could become value-added renewably-sourced platform chemicals that could be used to produce biodegradable plastics, pigments, and pharmaceuticals.

Introduction

Paracetamol (*N*-acetoxy-*p*-aminophenol) is a popular aid in dealing with aches and pains. It is one of the most abundantly produced pharmaceuticals in the world, valued at ~130 million USD in 2022 (~8,000 USD/ metric ton) with an annual global consumption of ~16,250 metric tons and projected to increase at a compound annual growth rate (CAGR) of 4.2% (*1*). Several different synthetic routes have been developed to produce paracetamol (*2*), Figures 1 and 2, including a route developed to utilize depolymerized lignin as the biomass source (*3*). The precursor to paracetamol in most synthetic routes is *p*-aminophenol, which itself has an estimated global market of ~700 million tons valued at 1.4 billion USD in 2022 (~2,000 USD/ metric ton) and projected to increase at a CAGR of 4% to 1.7 billion USD in 2027 (*4*).

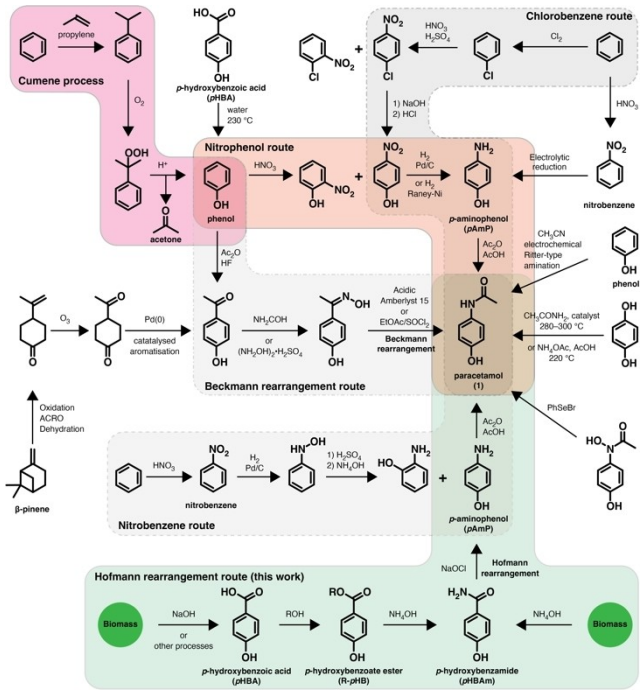

Figure 1. Synthetic routes to produce paracetamol. The common source of paracetamol is petroleum-derived benzene. Various synthetic routes were developed to produce paracetamol using scalable and high-yielding reactions. In this work, paracetamol is produced from biomass.

Utilizing biomass-derived chemicals to synthesize either paracetamol or *p*-aminophenol requires the separation of the target compounds from a complex mixture of coproducts.

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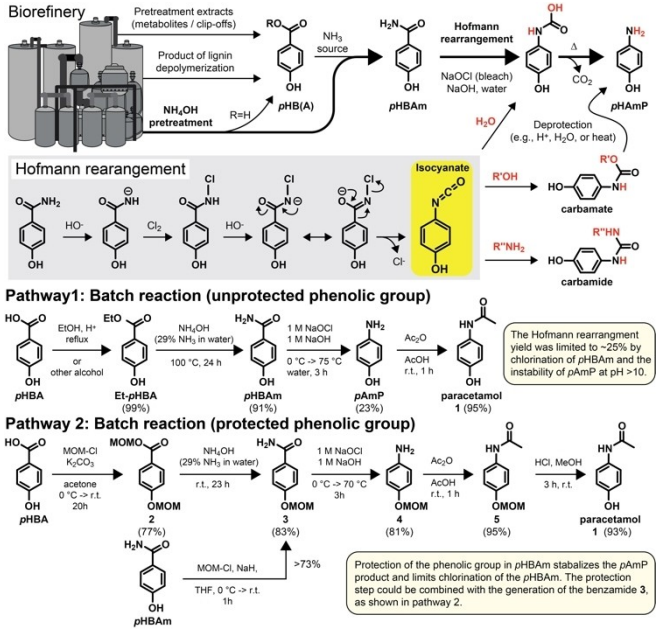

Figure 2. Various biorefinery designs can produce *p*HBA (R = H) and *p*HB esters that can be converted to *p*HBAm, or, as shown here, *p*HBAm can be produced in a single step from the *p*HB esters in biomass. These products could be converted to *p*HBAm and through to *p*-aminophenol via the Hofmann rearrangement. Alternative products could be targeted by *in situ* trapping of the isocyanate intermediate with alcohols or amines. In this work we explore two synthetic routes to produce paracetamol from *p*HBA. **Pathway 1**: A four-step process to convert *p*HBA to paracetamol via the Hofmann rearrangement. **Pathway 2**: A five-step process that uses a phenolic protecting group (methoxymethyl ether or MOM) to stabilize the *p*-aminophenol intermediate. An alternative in pathway 2 involves the direct protection of the phenolic group of *p*HBAm, removing one step in the pathway.

Several of the synthetic routes to paracetamol developed for non-renewable chemical feedstocks are adaptable to production from renewable sources (Figure 1), albeit after one or more high-energy processes and purification operations (e.g., production of benzene from ethanol via acetylene, phenol from lignin, or acetophenone from lignin) (*5*). A viable robust process for the sustainable production of paracetamol from lignocellulosic biomass would use water as the primary solvent and green organic solvents where required (e.g., purification steps using liquid/liquid extraction). The chemical precursor to paracetamol should be produced and isolated from the lignocellulosic biomass using technologies proven to be scalable and generally viewed as economically viable for high production volumes of low-value fuels. The purification of the products should utilize low-cost processes (e.g., counter-current extraction, crystallization, and distillation for low-boiling-point products). One possible precursor chemical that meets these criteria is *p*-hydroxybenzoic acid (*p*HBA). In four steps (1) *p*HBA may be esterified, (2) converted to *p*-hydroxybenzamide (*p*HBAm), (3) transformed into *p*-aminophenol (*p*AmP) via the Hofmann rearrangement, and (4) acetylated to paracetamol.

In some plant species, *p*HBA is available from *p*-hydroxybenzoate (*p*HB) esters in soluble metabolites and it is an intermediate in microbial degradation of phenolic compounds (*6*). Additionally, *p*HBA prominently acylates the sidechain γ-hydroxy groups of lignin (primarily on syringyl units) of clades of angiosperms from the Family Salicaceae that includes *Salix* and *Populus*, e.g., willow, poplar, aspen, and cottonwood (*7*), the Family Arecaceae, including coconut, carnauba, date, and oil palms (*8*), in *Aralia cordata* in the Asterid clade (*9*), and in the seagrass *Posidonia oceanica* in the monocot Family Posidoniaceae (*10*). *p*HBA can be produced from alkaline or acidic hydrolysis of the *p*HB esters in these common plant species and, depending on the species and tissue type, accounts for upwards of 1.5 wt% of extracted woody biomass, e.g., 0.2–1.0 wt% of dried poplar wood (*11*) and 1.0–1.5 wt% of the empty fruit bunches (EFB) from oil palm (*12*).

Many lignocellulose deconstruction processes cleave the *p*HB ester bond linking *p*HBA to the cell wall and, in some cases, the process will convert the lignin and some of the metabolites to *p*HBA (*5, 13*). In 2022 the global market for *p*HBA was ~42,500 tons, valued at 66–85 million USD (~2,000 USD/metric ton) (*14*). It would take ten biorefineries processing 1,000 tons/day of poplar wood with a *p*HBA level of 1.2 wt% to meet the 2022 global demand. Sustainable biorefinery design models indicate that, for viable replacement of petroleum-derived liquid fuels, there would need to be a network of smaller biorefineries feeding larger hub refineries to upconvert the products. Ideally the smaller refineries would be able to utilize similar processes to reduce the cost of design and construction. However, there is something of a mismatch between the global market size of commodity chemicals and the scale at which biomass needs to be processed in large scale biorefineries. Identifying higher-value products with larger global markets (*e.g.*, *p*-aminophenol and paracetamol) that can be produced from *p*HBA or, ideally, more directly from biomass-derived *p*HBs, would enable more biorefinery clones to feed a larger hub, not saturate the global *p*HBA market, and reduce the mismatch in processing scales. If the biorefineries were designed to utilize more than the cell-wall-bound *p*HBA and could instead, or additionally, use catalytic lignin depolymerization to convert a portion of the lignin to *p*HBA (*5, 13*), then it would be even more important to develop alternative product streams for *p*HBA.

Result and Discussion

Production of *p*-Hydroxybenzoic Acid

*p*HBA can be produced by cleaving it from the *p*HB esters in lignin or whole-cell-wall (WCW) biomass using mild alkaline treatment, *e.g.*, 0.2 M NaOH at 25 °C, Table 1, Figure 1 (*7a, 8a*). To isolate the liberated *p*HBA, the treatment liquor must be separated from the solids, either before or after acidification to pH ~1. Acidification of the aqueous solution causes some solubilized sugars and phenolics to precipitate, possibly requiring a second separation step. Once the supernatant is acidified, the *p*HBA can be isolated either by concentration of the aqueous solution and crystallization or through liquid/liquid extraction using an organic solvent such as ethyl acetate

Table 1. Production of *p*HBA and *p*HBAm from debarked poplar wood and oil palm EFBs. [*p*HBAm]:[*p*HBA] ratio determined from ^{1}H NMR analysis of the product mixture. *p*HBA was isolated using 0.2 M NaOH to cleave *p*HB esters, followed by an acidic digestion to cleave phenolic glucosides. *p*HBAm was produced from the *p*HB esters in biomass using 29% NH_4OH. The lignin used in this experiment was isolated from poplar using a GVL organosolv fractionation process (*15*).

Run	Biomass type	T (°C)	Reaction Time (h)	0.2 M NaOH (mL)	Mass (g)	*p*HBA (wt%)	[*p*HBAm]:[*p*HBA]
Oil Palm EFB	WCW	25[2]	24	10.0	1.75	1.4	0:100
NM6 poplar	WCW	25[2]	24	10.0	5.0	0.5	0:100
NM6 poplar	lignin	25[2]	24	10.0	5.0	4.5	0:100
Run	Biomass type	T (°C)	Reaction Time (h)	15.35 M (29%) NH_4OH (mL)	Mass (g)	*p*HBAm (wt%)	[*p*HBAm]:[*p*HBA]
Oil Palm EFB	WCW	140	24	10.0	0.50	1.2	99:1
NM6 poplar	WCW	140[2]	24	10.0	0.50	0.5	99:1
NM6 poplar	lignin	140[2]	24	10.0	0.20	3.1	99:1
NM6 poplar	lignin	140[2]	24	10.0	0.10		98:2
NM6 poplar	lignin	130[2]	24	10.0	0.10		94:6
NM6 poplar	lignin	120[2]	24	10.0	0.10		67:33
NM6 poplar	lignin	100[1]	24	10.0	0.10		50:50
NM6 poplar	lignin	80[1]	24	10.0	0.10		43:57
NM6 poplar	lignin	60[2]	24	10.0	0.10		23:77
NM6 poplar	lignin	60[1]	24	10.0	0.10		30:70
NM6 poplar	lignin	40[1]	24	10.0	0.10		13:87
NM6 poplar	lignin	25[2]	24	10.0	0.10		11:89
NM6 poplar	lignin	25[1]	24	10.0	0.10		15:85

(EtOAc). Removal of the organic solvent and recrystallization from water results in a pure (>95% by NMR analysis) off-white *p*HBA powder.

Production of *p*-Hydroxybenzamide

Direct conversion of *p*HBA to *p*HBAm requires overcoming the acid/base interaction between ammonia and the carboxylic acid (*p*HBA). Converting *p*HBA to a *p*HB ester (*e.g.*, methyl *p*-hydroxybenzoate or, more ideally, the natural lignin-*p*HB esters in biomass) removes the acid-base interaction and allows for the formation of *p*HBAm using aqueous ammonium hydroxide (e.g., 29% NH_4OH) at 100–140 °C. Direct amidation of *p*-hydroxybenzoic acid does not occur in aqueous ammonia under these conditions.

Treating isolated lignin or whole biomass with aqueous NH_4OH liberates a mixture of *p*HBAm and *p*HBA from the lignin-bound *p*HB esters (Figure 1). At low temperatures, *p*HBA (the free acid) predominates whereas at higher reaction temperatures (*e.g.*, 140 °C) the ester is converted to the amide with up to an impressive 99% selectivity, Table 1, thereby providing a more direct 1-step route into the Hofmann rearrangement. The yield of either the *p*HBA or *p*HBAm is dependent on the feedstock, with the yields from 0.2 M NaOH hydrolysis at 25 °C closely matching those obtained from 29% NH_4OH at 140 °C, Table 1. This is demonstrated here (Table 1) with NM6 poplar, a *Populus maximowiczii* × *nigra* hybrid. *p*HBAm was produced in 3.1 wt% yield from a lignin isolated via a γ-valerolactone (GVL) process (*15*), or in 0.5 wt% yield from whole biomass. We also used empty fruit bunches (EFBs) from oil palm as a biomass feedstock, isolating 1.4 wt% *p*HBA (free acid) or 1.2 wt% *p*HBAm (amide).

Producing *p*-Aminophenol from *p*-Hydroxybenzamide

The Hofmann rearrangement converts primary amides into primary amines (*16*) with a hypohalite, which may or may not be formed *in situ*, Figure 2. The rearrangement proceeds through an isocyanate (−NCO) intermediate, which is then hydrolyzed to the corresponding primary amine and carbon dioxide. The isocyanate intermediate is often trapped by the solvent (e.g., water, MeOH, or *t*BuOH) to form a carbamate (e.g., RNH-CO_2H, RNH-CO_2Me, or R-NH-Boc, respectively), which may be isolated or deprotected to the primary amine product. Alternatively, in the presence of an amine, the isocyanate traps to form the carbamide product.

The Hofmann rearrangement has been the subject of extensive mechanistic studies over the years. There are three components that fluctuate between reaction conditions: 1) The oxidant, e.g., hypohalite (hypochlorite or hypobromite), mercuric bromide (*17*), iodine(III) reagents (*18*), lead tetraacetate (*19*), methoxyhypobromite (MeOBr) (*20*), benzyltrimethylammonium tribromide (*21*), and *N*-succinimides (i.e., NBS, NCS, or NIS) (*22*); 2) The base used to deprotonate the *N*-halocarbamide (or

other carbamide) intermediate is usually sodium hydroxide or potassium hydroxide under aqueous conditions or DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in organic solvents; and 3) The solvent (water, alcohols, amines, aprotic organic solvent or a combination). The reaction yield of the Hofmann rearrangement varies depending on the reagents and amide substrate; however, the reaction conditions can often be optimized to give near-quantitative yields of the primary amine.

To select the reaction conditions, we applied the constraint that the main processing solvent needed to be water, as this is both the most environmentally friendly solvent and allowed the process to be integrated with an aqueous fractionation process in our envisioned biorefinery. The choice of base, NaOH over KOH, for these studies was due to its lower cost. In an aqueous system the cheapest oxidant would be NaOCl that, when paired with NaOH as the base, would produce NaCl as a side-product. Under these reaction conditions, the Hofmann rearrangement is an attractive reaction to up-convert renewably-sourced *p*HBAm into higher-value platform chemicals with larger bulk-chemical markets. If these reaction conditions could be tuned to give the near-quantitative yields as has been observed for other compounds, then carbon dioxide, water, and NaCl would be the only byproducts.

To the best of our knowledge, however, there is no literature precedence for the Hofmann reaction from *p*-hydroxybenzamide to *p*-aminophenol. This omission indicated to us that there was something unusual with the standard Hofmann rearrangement conditions or with the product resulting under those conditions; we suspected that the reactivity of *p*-aminophenol under alkaline conditions was the issue. Using a batch reaction design, the yield of the Hofmann rearrangement of *p*HBAm to *p*AmP was limited to ~25%. This limit was independent of the conversion efficiency of *p*HBAm and determined to be limited by the stability of the *p*AmP product in the reaction conditions (2 M NaOH, pH $>$10) and the chlorination *ortho* to the hydroxy group of *p*HBAm by NaOCl (making 3-chloro-4-hydroxybenzamide and 3,5-dichloro-4-hydroxybenzamide), and chlorination *ortho* to both the hydroxy and amino groups of *p*AmP (producing 2,3,5,6-tetrachloro-4-aminophenol). Varying the concentration of NaOCl relative to *p*HBAm, the concentration of NaOH, the reaction temperature, and the reaction time altered the percent conversion, but did not increase the yield of product above ~25%. The formation of the chlorinated phenolic products limits the application of *p*AmP-derived products to those that can tolerate some chlorinated aromatic compounds. We contend that these side-reactions and low yields explain the conspicuous absence in the literature of the Hofmann rearrangement of *p*HBAm.

Protecting Group to Increase Paracetamol Yield

When the phenolic group of *p*HBAm was protected (e.g., as the methoxymethyl (MOM) ether, compound **3** in pathway 2 of Figure 2), then the Hofmann rearrangement quantitatively formed the MOM-protected *p*-aminophenol (**4**) and no chlorination or polymerization products were observed, Figure 2 (Pathway 2). Acetylation of amine **4** followed by acid-catalyzed deprotection of the MOM group on compound **5** generated paracetamol with high overall yields, Figure 2 (Pathway 2). Depending on the importance placed on atom economy, the MOM protection could be performed directly on the *p*HBAm (e.g., using methoxymethyl chloride and sodium hydride) or the *p*HBA could be reacted with two equivalents of methoxymethyl chloride to both protect the phenolic group and form the ester required for the amidation reaction, Figure 2 (Pathway 2). This route produces a secondary target product *p*-(methoxymethoxy)aniline (**4**), which itself is a synthetic building block for the production of pharmaceuticals, dyes, and other value-added products (*23*).

Continuous-Flow Reaction Design

By transitioning to a continuous-flow reactor (Figure 3), product stability was improved, and side-reactions were suppressed. Tuning the reaction's residence time and the ratio of [NaOCl]:[*p*HBAm] allowed for optimization of the conversion of *p*HBAm by the Hofmann rearrangement and the yield of paracetamol (following acetylation), and minimizing the loss of *p*-aminophenol to degradation, Table 2. To stabilize the product mixture, excess NaOCl was quenched with sodium bisulfite ($NaHSO_3$); similar reagents (e.g., sodium dithionite) could also be used. The resulting aqueous reaction mixture (pH ~6) containing *p*-aminophenol, *p*HBAm, sodium chloride, sodium sulfate, and sodium bisulfite was acidified to pH ~1 with

Table 2. Reagent ratio and product distribution in the continuous synthesis of paracetamol.[1]

	[NaOCl] : [*p*HBAm]	Recovered *p*HBAm (mol%)	Yield paracetamol (mol%)	Product balance *p*HBAm + paracetamol (mol%)
1	5.5	12	47	59
2	3.8	28	53	81
3	3.3	31	50	81
4	2.8	30	57	87
5	1.1	50	41	91

[1] Reaction conditions: Flow rate: 1.5 mL/min of solution A (0.18 M *p*HBAm in 2 M NaOH); 1.5 mL/min of solution B (1.0 M NaOCl in 2 M NaOH); total flow rate of 3 mL/min (solutions A and B); 2 mL sample loop; 40 s residence time; 20 min collection time; 25 °C reaction temperature; quenched the reaction with 2 M $NaHSO_3$ at 0 °C.

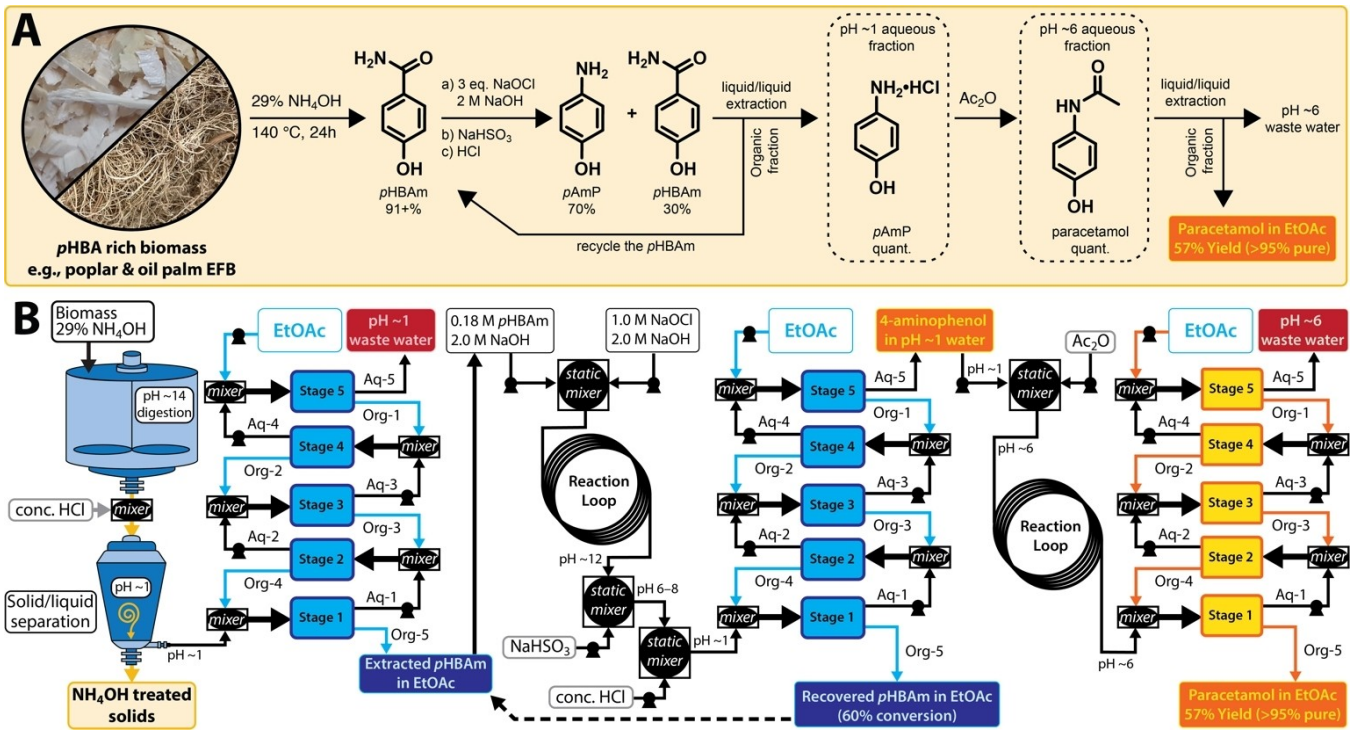

Figure 3. Producing paracetamol from biomass-derived *p*HBAm. (**A**) The process scheme to produce *p*HBAm directly from biomass and convert it to paracetamol in a continuous process by the Hofmann rearrangement to make *p*-aminophenol, liquid/liquid recovery and recycling of the unreacted *p*HBAm, using acetic anhydride to neutralize the acid and acetylate the *p*-aminophenol to form paracetamol, and liquid/liquid extraction to isolate the paracetamol in 41–57% isolated yield. (**B**) The operational flow-scheme used to convert *p*HB esters in biomass to paracetamol.

hydrochloric or sulfuric acid. The unconverted *p*HBAm was recovered by liquid-liquid extraction with ethyl acetate (with or without membrane assistance). The *p*HBAm was extracted into the organic phase whereas the protonated *p*-aminophenol remained in the aqueous phase. The *p*-aminophenol was then acetylated using acetic anhydride (Ac_2O), which also adjusted the solution to pH ~6. Paracetamol was then isolated by liquid-liquid extraction using ethyl acetate (with or without membrane assistance). Removal (with recovery) of the solvent yielded the paracetamol product as a white solid, with yields ranging from 41–57% depending on the [NaOCl]:[*p*HBAm] ratio, Table 2. The crude paracetamol could then be purified further through recrystallization from water or via more extensive purification strategies (e.g., silica gel chromatography) as required for downstream applications.

The continuous flow process shown in Figure 3 used EtOAc as the organic solvent, NaOCl as the oxidant, and the conversion of *p*HBAm to *p*-aminophenol was adjusted to 57%, with recovery of *p*HBAm at 30% (Table 2, entry 4). One of the advantages of this stepwise purification scheme is the ability to recycle the recovered *p*HBAm back through the Hofmann rearrangement reaction, thus increasing the overall conversion of *p*HBAm to *p*-aminophenol. Under these conditions, the overall yield for *p*HBAm to paracetamol becomes ~90%.

Market Size Impact on Hub-to-Depot Biorefinery

Utilizing small ~1,000 metric ton/day biorefineries operating with dilute NH_4OH or mild alkaline pretreatment to co-produce 12 metric tons/day *p*HBA or *p*HBAm from the pretreatment liquor, adds value to the pretreatment process. The conversion of some of the pretreatment liquor's phenolics to *p*-aminophenol and paracetamol expands the size and scale of the product market from ~85 million USD to over 1.5 billion USD. This greatly increases the viability of constructing a network of small 1,000 metric ton/day biorefineries that can feed large biomass conversion hubs further enabling the global transition from petrochemical-sourced fuels and chemicals to processes from renewable, sustainable materials.

Conclusions

Using aqueous ammonia treatment of biomass rich in *p*HB esters provides an opportunity to build a portfolio of co-products (*p*HBA and *p*HBAm) as part of the biorefinery. When the pHBAm is isolated and treated with an oxidant (e.g., NaOCl) an array of products is possible, including high-value large-market commodity chemicals *p*-aminophenol and paracetamol. Using a continuous Hofmann rearrangement process integrated to liquid/liquid extraction, acylation, and a second liquid/liquid extraction, *p*HBAm was converted to high purity paracetamol in ~90% yield. Modifications of this process have the potential to

produce an array of chemical building blocks for the manufacturing materials and chemical products like plastics, surfactants, pigments, and pharmaceuticals.

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Conflict of Interests

We hold a patent on the process (US patent #10286504).

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Biomass · rearrangement · green chemistry · renewable resources · amination

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