L. Paolo, P. Martínez Fornaso, E. Elhalem, M. Julieta Comin, L. Gandolfi Donadío, A. Bellomo. High-Throughput Experimentation (HTE) Applied to the Synthesis of API Impurities: A Case Study in Oxidative Decarboxylation of Aryl Acetic Acids. Eur. J. Org. Chem. 2024, 27, e202400720. https://doi.org/10.1002/ejoc.202400720

High-Throughput Experimentation (HTE) Applied to the Synthesis of API Impurities: A Case Study in Oxidative Decarboxylation of Aryl Acetic Acids

Luciano Paolo,[a] Patricio Martínez Fornaso,[a] Eleonora Elhalem,[a][b] María Julieta Comin,[a][b] Lucía Gandolfi Donadío[a][b]* and Ana Bellomo[a][b]*

[a] L. Paolo, P. Martínez Fornaso, E. Elhalem, M. -J. Comin, L. Gandolfi Donadío, A. Bellomo
Departamento de Ingredientes Activos y Biorrefinerías,
Instituto Nacional de Tecnología Industrial (INTI),
Buenos Aires, Argentina
E-mail: lgandolfii@inti.gob.ar; abellomo@inti.gob.ar

[b] E. Elhalem, M. -J. Comin, L. Gandolfi Donadío, A. Bellomo
Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET)
Buenos Aires, Argentina

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Abstract: High-throughput experimentation (HTE) has dramatically impacted experimental reaction development by enabling the rapid exploration of a diverse set of reaction conditions. During the past few decades, HTE has evolved as a tool to expedite reaction discovery and optimization. This work details the application of HTE to synthesize impurities of active pharmaceutical ingredients (APIs) with ketone/aldehyde functionality, specially focusing on ibuprofen impurity E. Initial experiments using $K_2S_2O_8$ as oxidant yielded moderate results. Subsequent HTE screens identified cerium ammonium nitrate (CAN) and $RuCl_3$-$NaIO_4$ as new effective decarboxylative oxidants, with $RuCl_3$-$NaIO_4$ in the presence of tetrabutylammonium bromide (TBAB) achieving the highest yield of 65%. This optimized method was successfully applied to synthesize ibuprofen impurity E on a gram scale. Additionally, the applicability of these methods to obtain other API related substances, such as naproxen impurity L and ketoprofen impurity A, was demonstrated. This research highlights the potential of HTE to streamline the synthesis of API impurities, making them widely accessible for pharmaceutical development purposes.

Introduction

High-throughput experimentation (HTE) is a technique that enables the rapid and efficient scientific exploration of diverse chemical spaces and reaction conditions involving lab automation and effective experimental design while ensuring consistent data.[1] HTE allows the parallel execution of large numbers of experiments in arrays using multi-well plates. One attractive feature of this technology is the miniaturization of experiments to conserve material, typically ranging from 2.5–10 µmol substrate per reaction.[2]

These tools and techniques were developed in the field of biology in the 1950s[1f] and have matured to the point that experiments are now routinely executed for high throughput screening in 3456-well microtiter plates.[3] In contrast, when employed in chemical research, HTE is frequently used to optimize reaction conditions for single or multiple target compounds to effect a specific transformation.[4]

In recent years, HTE has emerged as a valuable tool for the pharmaceutical industry at various stages of drug discovery and development. In 2017[4b] and more recently in 2023[5], Shevlin et al. from Merck Research Laboratories reported several applications of HTE, covering from the optimization of individual steps in a total synthesis and the discovery of novel methodologies, to the identification of salts of organic molecules.

There are several advantages associated with HTE use, including shorter development times, the possibility to conduct more experiments with limited valuable materials, parallel evaluation of different substrates and the simultaneous exploration of numerous parameters. Despite this, chemical HTE is primarily practiced by major pharmaceutical companies[6] while its adoption in academic settings remains uncommon.[7]

To achieve the challenging current goals of R&D laboratories, HTE emerges as a powerful enabling technology to conduct chemical exploration. As part of our ongoing efforts to establish new technological capabilities, we have recently set up a small HTE facility with the aim of speeding up process reaction discovery and synthetic development.

The different steps involved when executing HTE are shown in Figure 1. An iterative process of design, execution, data analysis and hit identification allows a rapid exploration of conditions for reaction optimization. Typically, the hits found in microscale are scaled-up to check for reproducibility.[3e]

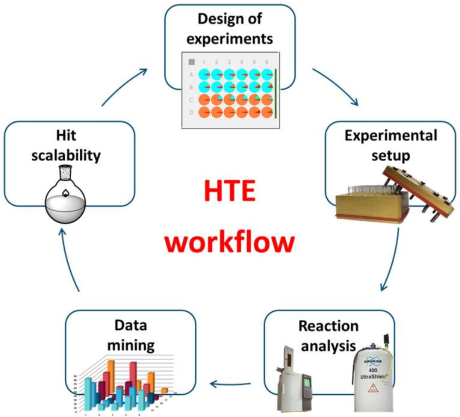


Figure 1. Different steps involved using HTE encompassing a) Design of the experiment array using Library Studio software; b) Set up of the microscale experiment in 8 mm × 30 mm glass vial inserts in metal 24 or 96-well microtiter plates; c) Analysis of vials using TLC, UPLC-MS or GC-MS; d) Data mining to rapidly identify hits; e) Scalability of HTE hits in a synthetically useful scale.

Herein, we outline the synthesis of selected active pharmaceutical ingredients (API) impurities that were developed using a HTE workflow. API impurities may have the potential to affect the quality, safety, and efficacy of pharmaceutical products and therefore, impurity profiling is an essential step during the development of APIs.[8] Regulatory authorities and pharmacopoeias provide guidelines and standards for analyzing these impurities using validated analytical methods.[9] While most of the reference standards used for control of API impurities are commercially available, they are expensive and only accessible in low quantities. To overcome this issue, we decided to use HTE to rapidly identify conditions to synthesize a set of API impurities of selected popular drugs with ketone/aldehyde functionality, derived from the corresponding aryl acetic acid containing drugs. Preliminary results of this work were recently presented.[10]

As a case study, we prepared ibuprofen impurity E (**1**)[11] from ibuprofen using an oxidative decarboxylation strategy employing HTE (Figure 2). This approach aimed to identify scalable and process-friendly conditions for achieving successful production of **1** on a multigram scale.

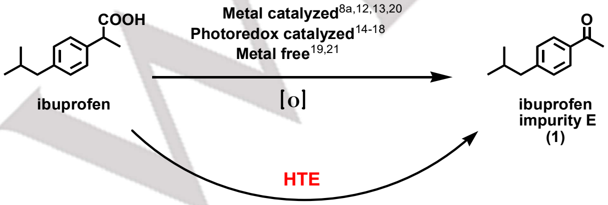


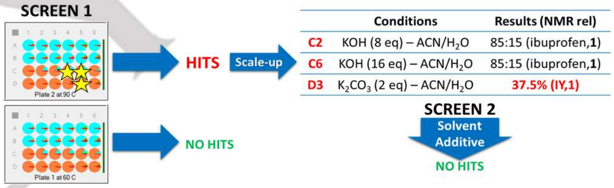
Figure 2. Classical conditions for the synthesis of **1** from ibuprofen and alternative HTE approach.

Results and Discussion

The synthesis of compound **1** from ibuprofen had already been reported using $NaIO_4$ and Mn(III)-catalysis.[12,13] Photolytic decarboxylation approaches[14] were also described using O_2 as the oxidant and HgF_2[15], Cu(II)[16]-Fe(III)-, Ce(III)-[17] and V as catalysts.[18] Metal-free oxidative decarboxylation reactions with $K_2S_2O_8$ were also reported for the synthesis of **1**.[19] Furthermore, aerobic oxidative decarboxylation reactions catalyzed by $FeCl_3$[8a] or $Cu(OAc)_2$[20] at high temperature were described to obtain **1** in moderate yields. More recently, singlet molecular oxygen was reported to achieve the same transformation.[21] Most of these methods generate a large amount of waste and therefore, developing new, widely applicable and effective oxidative decarboxylation methods, particularly in the context of API impurities, is an on-going area of research and of significant practical value.[8a]

We started approaching the synthesis of **1** using the metal free conditions previously reported by Bhat *et al.* in 2017 with 2.0 equiv. $K_2S_2O_8$ in water at 90 °C.[19] In our hands, desired product was obtained although in yields ranging from 30-40% and a complex mixture of by-products was always present.

To optimize this condition, we started HTE exploration by setting up 48 reactions using $K_2S_2O_8$ as oxidant.[22] Initially, we investigated the influence of base considering Tanner's report on the mechanism of this oxidant to promote decarboxylation reactions[23]. Additionally, we studied solvent and temperature effect on reaction performance. The screening involved 7 inorganic bases at different loadings using water and a mixture of acetonitrile/water as solvent system at 60 °C and 90 °C (Figure 3, Screen 1, see SI for experimental details).



	Conditions	Results (NMR rel)
C2	KOH (8 eq) – ACN/H_2O	85:15 (ibuprofen,**1**)
C6	KOH (16 eq) – ACN/H_2O	85:15 (ibuprofen,**1**)
D3	K_2CO_3 (2 eq) – ACN/H_2O	37.5% (IY,1)

Figure 3. Screen 1 involved the optimization of categorical and continuous reaction parameters using $K_2S_2O_8$ as oxidant. Rows A and B, H_2O (blue); Rows C and D, ACN/H_2O (9:1) (orange). Plate 1 was run at 60 °C and plate 2 at 90 °C. Screen 2 was based on solvent/additive effect.

Selection of solvents for this screen was made considering that common single-phase solvent systems used in the literature for metal-free decarboxylative transformations with peroxodisulfate salts usually involves the combination of water with a polar solvent such as acetonitrile.[24] The two temperatures screened were selected based on previous reports for oxidative decarboxylation.[25] As shown in Figure 3, all vials were qualitative analyzed by TLC and three experiments were identified as potential hits (vials C4, C5 and D5) and subsequently scaled-up. Results obtained at 0.25 mmol scale showed that using K_2CO_3 (2 equiv.) in ACN/H_2O (9:1) at 90 °C yielded the best performance, despite achieving a moderate yield of 37.5%.

To optimize this result, a second HTE screen was launched focusing on more solvents and additive effects (Screen 2, see SI for experimental details). Thus, 48 new reactions were explored focusing on 6 different solvent systems at 60 °C and 90 °C. We also introduced a catalytic amount of Ag(I) in some vials to mitigate the relatively high oxidation potential of aryl acetic acid inspired by recent report on the use of a silver salt for decarboxylative hydroxylation of carboxylic acids.[26] Unfortunately, no hits arose from this screen.

Despite extensive HTE research, we could not improve the yield obtained in the initial experiments using $K_2S_2O_8$ as oxidant to convert ibuprofen into impurity **1**, so we decided to evaluate alternative oxidants.

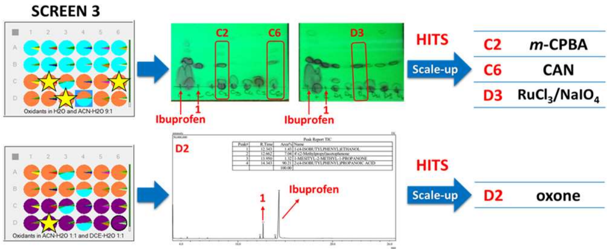
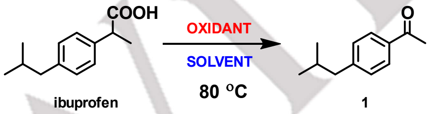


Figure 4. Screen 3: 2 well plates set-up for oxidant screening in 4 solvents. TLC displayed depicts some the promising vials identified for scaling-up. GC-MS analysis of vial D2 shows starting material (ibuprofen) and desired compound (**1**).

To incorporate a broad spectrum of oxidants, the new HTE design involved accessible cerium salts (ex. cerium ammonium nitrate: CAN), periodate containing systems ($RuCl_3$-$NaIO_4$), hypervalent iodine reagents such as PIDA (phenyliodine(III) diacetate)[27] as well as metal oxidants (ex. MnO_2, $KMnO_4$), among others. We performed 48 chemistry experiments using 12 different oxidizing agents and 4 solvent systems using K_2CO_3 as base at 80 °C (Figure 4, Screen 3, see SI for experimental details).

TLC analysis of each reaction vial showed 4 promising oxidants (*m*-CPBA, CAN, $RuCl_3$-$NaIO_4$ and oxone) so they were further analyzed by ^1H NMR for accurate conversion evaluation. These 4 hits were scaled up (0.5 mmol scale) to check reproducibility and the results obtained are shown in Table 1.

Table 1. Oxidant scale-up results from the hits obtained in Screen 3.[a]



Entry	Oxidant	Solvent	**1** (IY) [b]
1	*m*-CPBA	ACN/H_2O (9:1)	6%
2	CAN	ACN/H_2O (9:1)	52%
3	$RuCl_3$-$NaIO_4$	ACN/H_2O (9:1)	30%
4	oxone	DCE/H_2O (1:1)	12%

[a] reactions were carried out using ibuprofen (0.5 mmol), oxidant (4 equiv.), K_2CO_3 (2 equiv.), solvent (0.1 M). [b] isolated yield.

We initially attempted the reactions at 60 °C, but only trace amount of product was observed in all cases. Increasing the temperature to 80 °C, to accelerate the decarboxylation step resulted in product formation across all experiments, with CAN and $RuCl_3$-$NaIO_4$ yielding the best results (entries 2 and 3). Having identified two effective oxidants for the desired transformation, we employed HTE to optimize several parameters for each case.

To enhance the yield of ibuprofen impurity E obtained with CAN, we set up 24 new HTE screens using 6 different bases and 4 solvent systems (Screen 4, see SI for experimental details). Two vials from Screen 4 (vial A2: Na_2CO_3 in dioxane/water and vial D5: $KHCO_3$ in acetonitrile/water) showed good TLC and ^1H NMR conversion so they were subjected to scale-up. The desired product was obtained under both conditions as displayed in Table 2 although we could not improve the 52% yield obtained previously with K_2CO_3 as shown in Table 1, entry 2. One contributing factor was the generation of by-product **2** (entries 1-2), which is the corresponding ketone precursor.

Table 2. Scale-up results from selected vials in Screen 4 using CAN as oxidant.[a]

Entry	Solvent	Base	Results (IY) [b]
1	dioxane/H_2O (9:1)	Na_2CO_3	**1** (40%), (22%)
2	ACN/H_2O (9:1)	$KHCO_3$	**1** (31%), **2** (20%)

[a] reactions were carried out using ibuprofen (0.5 mmol), oxidant (4 equiv.), base (2 equiv.), solvent (0.1 M), 80 °C. [b] isolated yield.

Coordination of carboxylic acids with cerium catalysts had already been described by Huang and Xiao in a recent paper[17] while oxidative decarboxylation of electron rich phenyl acetic acids promoted by CAN with nitric acid at high temperature (90 °C) was reported in 1974 affording a mixture of different compounds in low yields.[28] Despite these precedents, to our knowledge, this is the first account on the use of CAN under mild conditions to perform this oxidative decarboxylative transformation.

To improve the generation of **1**, we shifted our focus to utilizing $RuCl_3$-$NaIO_4$, another oxidant identified during our initial HTE exploration (Table 1, entry 3).

Oxidative decarboxylation of diphenylacetic acid using sodium periodate was first published in 2004 and the method was improved years later with the use of $(n\text{-Bu})_4NIO_4$ and Mn(salophen) as catalyst.[12, 13b] However, to date, there have been no reports on the use of $RuCl_3$-$NaIO_4$ for oxidative decarboxylation.

We used HTE and explored the chemical space with $RuCl_3$-$NaIO_4$ to optimize reaction parameters focusing on base and solvent effect. Screen 5 entailed 24 new reactions at 80 °C including 6 bases and 4 solvent mixtures (see SI for experimental details). According to TLC, the best results were obtained in vials A4 (K_3PO_4 in ACN/H_2O 9:1) and B2 ($KHCO_3$ in ACN/H_2O 1:1) so we checked reproducibility at 0.5 mmol scale (Table 3). Conditions described in entry 1 yielded the best results, providing ibuprofen impurity E in an isolated yield of 44%.

Table 3. $RuCl_3$-$NaIO_4$ scale-up results from the hits obtained in Screen 5.[a]

Entry	Base	Solvent	Results (IY)[b]
1	K_3PO_4	ACN/H_2O 9:1	**1** (44%), SM (10%)
2	$KHCO_3$	ACN/H_2O 1:1	**1** (6%), **2** (15%)

[a] reactions were carried out using ibuprofen (0.5 mmol), oxidant (4 equiv.), base (2 equiv.), solvent (0.1 M), 80 °C.

In an attempt to increase the yield of **1** achieved thus far, we were inspired by Akamanchi work on the use of 2-iodoxybenzoic acid in combination with 1 equivalent of tetraethylammonium bromide (TEAB) to generate ketones from acetamides.[29] Following this report, we envisioned incorporating an additive to improve the oxidative decarboxylation performance and screened tetrabutylammonium bromide (TBAB) with $RuCl_3$-$NaIO_4$ and CAN in the presence of 6 bases and 4 solvent systems (Screens 6 and 7, see SI for experimental details). Using TLC and ^1H NMR, we identified 6 vials that were scaled up to 0.5 mmol and the corresponding results are shown in Table 4. The synthesis of the target compound **1** was achieved in all cases with $RuCl_3$-$NaIO_4$-TBAB (entries 1-5) outperforming CAN-TBAB (entry 6). Entries 1, 2 and 4 showed comparable and improved yields. However, no by-product **2** was detected when K_2CO_3 was used (entry 1) and therefore, it was selected as the optimal condition for this transformation.

The system CAN-TBAB also generated compound **1** albeit in low yield (Table 4, entry 6). Notably, a major compound (**3**) identified in this reaction corresponds to ibuprofen impurity J. The non-decarboxylating C-H activation within the alkyl backbone of ibuprofen leading to the formation of compound **3**, depicts a complete change in oxidation regioselectivity. This finding is currently an objective of further research in our lab.

Table 4. Effect of TBAB on $RuCl_3$-$NaIO_4$ and CAN hits at 0.5 mmol scale.

Entry	Oxidant	Solvent	Base	Result (IY)
1	$RuCl_3$-$NaIO_4$ (Screen 6)	ACN/H_2O 9:1	K_2CO_3	**1** (65%)
2			$KHCO_3$	**1** (65%), **2** (1.5%)
3			KOH	**1** (51%), **2** (5%)
4			K_3PO_4	**1** (64%), **2** (3%)
5		DCE/H_2O 1:1	K_2CO_3	**1** (60%)
6	CAN (Screen 7)	ACN/H_2O 9:1	K_2CO_3	**1** (6%), (45%)

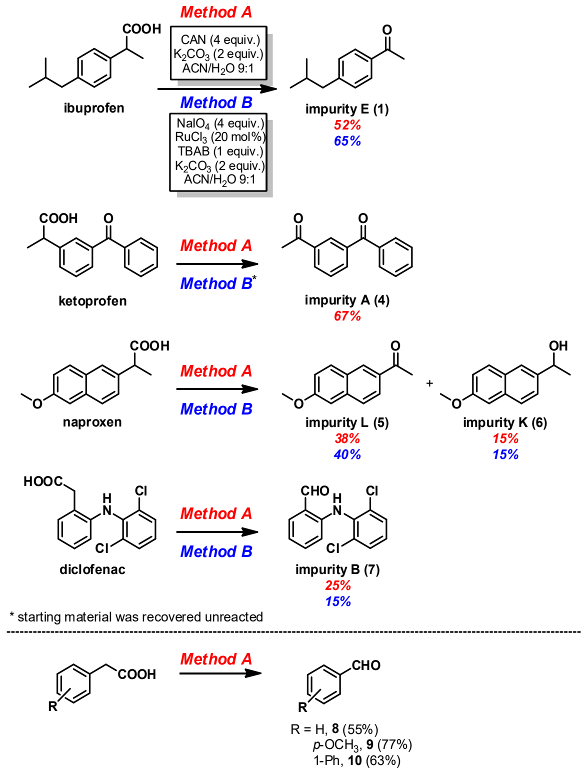
Conditions for $RuCl_3$-$NaIO_4$-TBAB: ibuprofen (0.5 mmol), $NaIO_4$ (4 equiv.), $RuCl_3$ (20 mol%), base (2 equiv.), TBAB (1 equiv.), solvent (0.1 M), 80 °C. Conditions for CAN-TBAB: ibuprofen (0.5 mmol), CAN (4 equiv.), base (2 equiv.), TBAB (1 equiv.), solvent (0.1 M), 80 °C.

In summary, HTE enabled us to discover two new systems capable of performing oxidative decarboxylation from ibuprofen to produce the corresponding impurity E (**1**). Additionally, we identified reaction conditions to increase the original 30% yield obtained when using $RuCl_3$-$NaIO_4$ (Table 1, entry 3) to 65% yield in the presence of TBAB. These two novel synthetic methods offer a valuable tool for the synthesis of ketones and aldehydes from readily available carboxylic acid providing a relevant complement to alternative existing oxidative protocols; utilizing readily available oxidants and requiring no specialized equipment, unlike photocatalytic approaches, and no drastic conditions. The optimized conditions found by HTE in each system for the efficient generation of **1** from ibuprofen are shown in Scheme 1 as “method A” and “method B”.

To demonstrate the efficacy of method B and to generate enough quantities of **1**, a 0.5-gram scale reaction on ibuprofen was carried out successfully obtaining ibuprofen impurity E (**1**) as a colorless liquid in 65% isolated yield.

To broaden the scope of methods A and B, we focused our attention on other drug molecules that could undergo oxidative decarboxylation to generate the corresponding oxidative dehomologated API impurity.

Scheme 1 shows popular APIs such as naproxen, ketoprofen and diclofenac that smoothly converted into their corresponding impurities[30] under methods A/B. The best isolated yield was obtained in the case of ketoprofen furnishing ketoprofen impurity A (**4**) by method A. Unfortunately, when this API was subjected to method B, starting material was recovered unreacted. In naproxen's case, impurity L (**5**) was obtained in moderated yield using either of the two methodologies. Naproxen impurity K (**6**) was formed as well in 15% isolated yield by both methods. Diclofenac related compound B (**7**) was obtained in low yields with concomitant formation of several by-products using methods A and B. This could be attributed to lactam formation.



Scheme 1. API impurities synthesized using methods A or B developed through HTE. Both methods were run at 80 °C at 0.1 M concentration. Common phenylacetic acids subjected to thermal decarboxylative oxygenation using method A. See SI for experimental details and reaction time for each substrate.

Arylacetic acids, such as phenylacetic acid, *p*-methoxyphenylacetic acid and naphthylacetic acid underwent smooth conversion using method A to render the corresponding aldehyde product (**8-10**) in good yield. This illustrates the potential generality of this new decarboxylative oxygenation methodology. In contrast, method B was ineffective as starting material was recovered unreacted in the case of 1-naphtylacetic acid (**10**) and decomposition was observed with the other tested substrates. Further confirmation will be pursued by subjecting more complex substrates to methods A and B with results to be reported in due course.

Conclusion

In this study, we have demonstrated the utility of High-Throughput Experimentation (HTE) for rapidly and cost-effectively developing new synthetic methodologies. Specifically, HTE was used herein to promptly identify oxidants for the efficient thermal oxidative decarboxylation of arylcarboxylic acids.

After extensive screening, CAN and $RuCl_3$-$NaIO_4$ were identified as leads to successfully generate the decarboxylated products. This finding represents the first report on the use of these oxidants under mild conditions to achieve this transformation.

Further optimization led to the development of methods A and B, which were applied to synthesize keto-related impurities of popular APIs, being crucial substances for impurity profiling during drug development. Notably, the $RuCl_3$-$NaIO_4$ method was well scaled up to synthesize ibuprofen impurity E.

We are currently working on the application of this protocol for late-stage functionalization of medically important drug molecules and gaining insights into the mechanism involved. Accessibility to HTE technology expedited our experimental research and saved valuable time in the process of reaction optimization for the synthesis of API impurities. Dissemination of HTE workflows will pave the way to its implementation among the scientific community.

Supporting Information

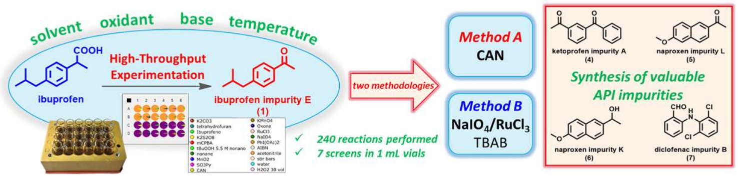
Full experimental procedures, characterization data, and copies of NMR spectra are included. The authors have cited additional references within the Supporting Information.[31-35]

Acknowledgements

LP acknowledges INCALIN/UNSAM for a PhD fellowship, PMF acknowledges INTI for an undergraduate fellowship. LG, EE, MJC and AB acknowledge INTI and CONICET for financial support.

Keywords: API Impurities • Microscale • Oxidative decarboxylation • Parallelization • Screening.

Entry for the Table of Contents



High-throughput experimentation (HTE) was applied to identify new methodologies to achieve oxidative decarboxylation of arylcarboxylic acids in a rapid and cost-effective manner. The two oxidant systems discovered ($RuCl_3$-$NaIO_4$ and CAN) were used to obtain a series of popular API impurities, which are essential for impurity profiling during drug development.

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