Transition-metal-free decarboxylative bromination of aromatic carboxylic acids

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Methods for the conversion of aliphatic acids to alkyl halides have progressed significantly over the past century, however, the analogous decarboxylative bromination of aromatic acids has remained a longstanding challenge. The development of efficient methods for the synthesis of aryl bromides is of great importance as they are versatile reagents in synthesis and are present in many functional molecules. Herein we report a transition metal-free decarboxylative bromination of aromatic acids. The reaction is applicable to many electron-rich aromatic and heteroaromatic acids which have previously proved poor substrates for Hunsdiecker-type reactions. In addition, our preliminary mechanistic study suggests that radical intermediates are not involved in this reaction, which is in contrast to classical Hunsdiecker-type reactivity. Overall, the process demonstrates a useful method for producing valuable reagents from inexpensive and abundant starting materials.

Introduction

Aryl bromides are the substrate of choice when performing transition metal-catalysed cross-coupling reactions1 or preparing Grignard and organolithium reagents.2 They are also used in a variety of other transformations, such as nucleophilic substitution and HalEx reactions,3 and are the core structures in many natural products and dyes.4 Consequently, developing efficient methods for the synthesis of aryl bromides remains an important objective.5 The ability to directly substitute a carboxyl group with a bromo group has interested the synthetic community for many years. This transformation was first demonstrated by Borodine over a century ago, but came to bear the name “The Hunsdiecker Reaction” during the 1940’s and is now a fundamental reaction in organic synthesis.6 The reaction involves the mixing of an aliphatic carboxylic acid with bromine in the presence of a silver salt to produce the desired alkyl halide. Various developments in this area were made during the latter half of the 20th century,6,7 however, the applicability of all these methods was limited due to the requirement of stoichiometric transition metal salts and/or poor generality. It is only recently that significant progress has been made in the decarboxylative bromination of aliphatic acids (Scheme 1A).

Results and discussion

We have recently reported a transition-metal-free decarboxylative iodination of aromatic acids.14 The success of this procedure lies in the ability to prepare a variety of aryl iodides, simply by heating a benzoic acid in the presence of I2. We therefore questioned whether a similarly efficient and low-cost decarboxylative bromination could be developed. We began...
our investigation by exposing the benzoic acid 1a to our previous conditions, but switching the halogen source from I$_2$ to Br$_2$ (Table 1). Unfortunately, this resulted in the undesired formation of the brominated acid 1a’ and dibrominated product 2a’ and none of the desired product 2a (Table 1, entry 1). This reactivity is comparable with the aromatic Hunsdiecker reaction shown in Scheme 2 and demonstrates the challenges for achieving a selective bromination. By lowering the equivalents of Br$_2$ the selectivity could be improved, however, a large amount of the brominated acid 2a’ was still produced (entry 2). We then investigated less electrophilic bromine sources, such as NBS (N-bromosuccinimide) and DBH (1,3-dibromo-5,5-dimethylhydantoin), however a mixture of products was still obtained and the desired product was formed in low yield (entries 3 and 4). We then turned to the use of tribromide reagents as bromine sources for this transformation. Although pyridinium tribromide performed poorly in this reaction (entry 5), we found that tetraalkyl ammonium tribromide salts, N(Me$_4$)Br$_3$ and N(Bu$_4$)Br$_3$, displayed good reactivity and high selectivity for the desired decarboxylative bromination (entries 6 and 7). N(Bu$_4$)Br$_3$ was chosen as the brominating reagent of choice, allowing the product to be isolated in 90% yield. Further control experiments revealed that the reaction does not proceed in the absence of a base (entry 8), but that performing the reaction in the dark or adding one equivalent of water had little effect on the reaction (entries 9 and 10).

Having demonstrated an efficient transition metal-free decarboxylative bromination, we then turned to exploring the scope of this reaction (Scheme 3). Previously, the decarboxylative bromination of 4-methoxybenzoic acid under Hunsdiecker-type conditions resulted in a mixture of products (Scheme 2), therefore we were impressed to observe the formation of the aryl bromide 2b in high yield and high selectivity. This clearly demonstrates the advantages of our procedure over previous techniques. The desired product, 2c, was not observed when using 3-methoxybenzoic acid, suggesting the position of decarboxylation must be sufficiently nucleophilic for the decarboxylative bromination to occur. Other highly electron-rich substrates (1d–h) could also undergo the desired transformation, including non-ortho-substituted benzoic acids (1b, 1h), which are generally unreactive in transition metal-mediated decarboxylative functionalisations. The procedure can also be applied on a large scale, thus, 5.5 g of the brominated product 2e was prepared using the standard conditions on the bench top at room temperature, without requiring column chromatography. Poly methylated benzoic acids are poorly reactive substrates in transition metal-mediated decarboxylations, but they, and even simple toluic acid, showed good reactivity under our conditions (2f–2i). The procedure could also...
be applied to napthoic acids, despite a slight loss in selectivity (2m, 2n). The position of dibromination is indicated in both Schemes 3 and 4 by a red asterisk. A range of halogenated and trifluoromethylated benzoic acids were successfully decarboxylated, however, the presence of a methoxy group was necessary to maintain efficient reactivity (2o–2y). Benzoic acids that do not bear electron-donating substituents were unreactive under these conditions (2z–2ac). In light of this, we were surprised to observe good reactivity with electron-poor polyfluorinated benzoic acids (2ad–2af). This goes against the general trend of reactivity in this reaction and we are currently investigating the cause of this unique behaviour.

The procedure could also be applied to a range of heteroaromatic acids (Scheme 4). The bromination of heteroaromatic acids is highly limited as elevated temperatures (>160 °C) and stoichiometric transition metals are generally necessary. Our conditions were applicable to indoles (4a), benzothiophenes (4b, 4c) and benzofurans (4d). Unfortunately, under standard reaction conditions benzothiophene-2-carboxylic acid (4e) afforded undesirable levels of dihalogenation. This side-reaction, namely the β-bromination of benzo-fused five-membered heterocycles, is well-known to proceed readily at room-temperature with a variety of brominating agents; thus representing a limitation of our methodology. A range of 5-membered heterocycles (4f–4j) as well as pyridine (4k), chromone (4l) and cinnamic acid (4m) derivatives all underwent the desired decarboxylative bromination selectively.

Having established an efficient protocol for the decarboxylative bromination of aromatic acids, we began a preliminary mechanistic investigation. Our initial experiment involved the use of the oxallyl-substituted benzoic acid 1A as a radical clock (Fig. 1a). The formation of cyclised products, via attack of an aryl radical on the pendent allyl chain of this compound, is an extremely fast process (k = 8 × 109 s⁻¹). Therefore, if cyclised products were to be observed in this reaction a radical mechanism could be suggested. Upon exposing oxallyl-substituted benzoic acid 1A to our standard reaction conditions we only observed the formation of the aryl bromide 2A and none of the

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**Scheme 3** Scope of the decarboxylative bromination of aromatic acids. Reactions carried out on a 0.5 mmol scale. Ratios in brackets indicate mono : dibrominated material by NMR analysis before separation. Asterisk indicates position of dibromination. Isolated as mixture. Room temperature. Yields determined by NMR analysis. 4.0 equiv.

**Scheme 4** Scope of the decarboxylative bromination of heteroaromatic acids. Reactions carried out on a 0.5 mmol scale. Ratios in brackets indicate mono : dibrominated material by NMR analysis before separation. Asterisk indicates position of dibromination. Isolated as mixture. 50 °C.
cycloalkane product. In light of this, we can suggest that either the reaction does not proceed through a radical mechanism or, if radicals are involved, then the rate at which the product is formed from the radical intermediate is an exceptionally fast process. This is an interesting observation as similar experiments that have previously been conducted on Hunsdiecker-type decarboxylations of aliphatic carboxylic acids have strongly supported a radical mechanism.15 Likewise, previous Hunsdiecker-type decarboxylations of aromatic acids have also been proposed to proceed through radical intermediates.15b–15c,18 Overall, although the above result does not definitively rule out a radical mechanism, it calls for a more thorough evaluation of Hunsdiecker-type reactivity.

Our previous work on decarboxylative iodinations established a concerted decarboxylation-iodination process, via a 4-membered transition state, as a possible non-radical pathway for decarboxylative halogenations.24 Following a similar protocol (Fig. 1b), our DFT study found a pathway for decarboxylative bromination proceeding through an analogous concerted decarboxylation-bromination transition state, TS-II. Thus, our current mechanistic hypothesis is as follows: the benzoic acid is initially transformed into the hypobromite species I upon exposure to K$_3$PO$_4$ and N(Bu$_4$)Br$_3$.29 The hypobromite then undergoes decarboxylation via a 4-membered transition state (TS-II), to provide the product 2e with concomitant loss of CO$_2$. The barrier for this transformation was calculated to be 19.2 kcal mol$^{-1}$, which is consistent with a process that proceeds at room temperature.20

We further probed the mechanism of this reaction by conducting $^{13}$C/$^{12}$C KIE experiments. Heavy atom isotope effects have been widely used as a means to study decarboxylation events in chemical and enzymatic processes.24 The KIE at the C1 position for decarboxylation processes can be accurately determined at natural abundance by measuring the isotopic composition of the evolved CO$_2$ through mass-spectroscopy technique.22 Unfortunately, with this method no information is gained on the other carbon atoms. Exploiting quantitative $^{13}$C-NMR, Singleton and co-workers have devised a useful procedure for determining intramolecular competitive $^{13}$C/$^{12}$C KIEs at all positions at natural abundance.23 Over the course of the reaction, the starting material is progressively enriched in the slowest reacting isotopologues. By evaluating the isotopic composition in the starting material before and after the reaction the KIEs can be determined. This has proved a powerful tool in elucidating reaction mechanisms and we were eager to test its value on our system. Two independent experiments were performed on 2,6-dimethoxybenzoic acid (1e) under standard reaction conditions at 30 °C for 70 minutes (Fig. 1c). Remarkably, a primary KIE was observed at both C1 and C2 positions: KIEs of 1.014 ± 0.004 and 1.009 ± 0.006 were obtained for C1, while larger KIEs of 1.028 ± 0.004 and 1.025 ± 0.005 were measured for C2. These values are consistent with the proposed pathway in which a concerted decarboxylation-bromination transition state is involved in the product determining step (Fig. 1b). The lower KIE for C1 in comparison to C2 suggests either an early transition state,27 or that another kinetically relevant step is occurring prior to the product determining step.28 Examination of the reaction path by DFT (TS-II to 2e) revealed an early formation of the C1–Br bond, resulting in an “hidden” Wheland intermediate.28 Extrusion of CO$_2$ from this transient species took place late along the reaction coordinates, thus in agreement with the experimental observations.29 To further probe our mechanistic hypothesis, the KIE values for the proposed path were calculated (Fig. 1c). Computed and experimental values were found to be in excellent agreement, lending strong support to the proposed concerted decarboxylation-bromination pathway.

We have conducted a preliminary mechanistic study of the developed decarboxylative bromination of aromatic acids. At present, we have strong evidence that excludes the intermediacy of aryl radicals (Fig. 1a). By measuring the $^{13}$C/$^{12}$C KIEs and performing DFT calculations we identified a concerted decarboxylation-bromination as a possible pathway for this transformation (Fig. 1b and c). This represents an alternative mechanism for Hunsdiecker-type reactivity, as radicals are usually considered key intermediates in similar processes. While further investigations are necessary to better establish the mechanism of this reaction, we believe that these initial studies highlight previously unrealised features of our system. We hope that these results inspire future studies that may greatly impact this and related procedures, and lead to the development of more efficient decarboxylative technologies.

**Conclusions**

Due to slow progress and issues with selectivity, the utility of the aromatic Hunsdiecker reaction has previously failed to be fully...
realised. In this report we have detailed the successful development of a high yielding aromatic Hunsdiecker-type reaction. This has led to the development of a decarboxylative bromination of electron-rich aromatic acids using low-cost and abundant starting materials. The avoidance of transition metals and the ability to scale-up the reaction make the process attractive for its simplicity and low cost. The Hunsdiecker reaction is commonly proposed to proceed via a radical pathway, however, our combined experimental and theoretical mechanistic study has suggested an alternative mechanism that does not involve radical intermediates. These results directly challenge a long-held view of Hunsdiecker-type reactivity. Further studies are necessary, but we hope that future investigations will better elucidate this mechanism. Overall, we believe that this report demonstrates the potential of decarboxylative halogenation as an efficient route to value-added chemical commodities.

Conflicts of interest
There are no conflicts to declare.

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References


16 See ref. 12b, d–f.


25 The signal of C4 and C6 was used as “internal standard” in the determination of the isotopic composition of the starting material before and after the reaction. For further information see ESI† and ref. 23a.

26 Kinetic isotope effects were calculated using ISOEFF98 according to the Bigeleisen equation. (a) V. Anisínov and P. Paneth, J. Math. Chem., 1999, 26, 75–86; (b) V. Anisínov, P. Paneth, ISOEFF98, Lodz, Poland, 1998 Tunnelling correction was applied using Pyquiver according to Bell’s infinite-parabola model. The effect was found to be negligible (c) T. L. Anderson and E. E. Kwan, PyQuiver, 2016; (d) R. P. Bell, Chem. Soc. Rev., 1974, 3, 513–544. For further information see ESI†.


29 See ESI† for further details.