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Piecing together the puzzle: understanding a mild, metal free reduction method for the large scale synthesis of hydrazines

Duncan L. Browne *, Ian R. Baxendale, Steven V. Ley

Innovative Technology Centre, Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom

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Dedicated to Professor Stork on the occasion of his 90th birthday

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ABSTRACT

A key intermediate for the synthesis of hydrazines via a mild, metal free reduction of diazonium salts has been isolated and characterized by X-ray analysis. The presence of this intermediate is general, as demonstrated by the preparation of a number of analogues. A discussion of the mechanism and potential benefits of such a process are also described.

1. Introduction

Of the top 200 selling pharmaceuticals in recent years, 20% of the five-membered heterocyclic ring systems present are pyrazoles or indoles (Fig. 1).[1] These motifs are usually derived from mono-substituted hydrazines either by condensation with 1,3-dicarbonyls (or equivalent surrogates) to provide pyrazoles, or by a Fischer indole synthesis employing the appropriate aldehyde or ketone (Fig. 1). Such synthesis methods are, however, not without inherent problems, including relatively poor control over regioselectivity. The requirement for the use of strong acid catalysis and forcing reaction conditions is also of note particularly for the Fischer indole process. Perhaps most importantly however, access to hydrazines is problematic. These issues have provided organic

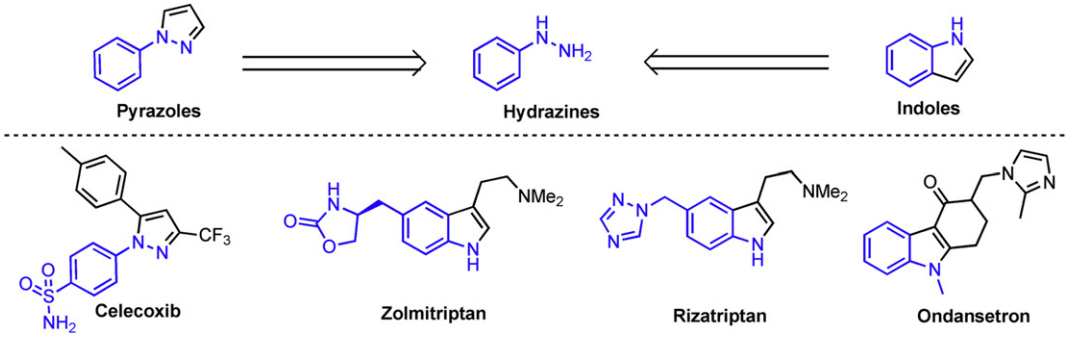

Fig. 1. Exemplary applications of hydrazines to pharmaceutical molecules.

* Corresponding author. Tel.: +44 (0)1223 336402; fax: +44 (0)1223 336442; e-mail address: db543@cam.ac.uk (D.L. Browne).

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chemists with an intriguing problem for many years and one in which ingenious solutions are still being reported today. The quest to synthesise indoles selectively under mild conditions from readily available starting materials is an important area of research.[2,3] Despite the many solutions put forward for this problem, industrial scale processes for the production of indoles most often employ the Fischer approach, indicative that it is still the most reliable and easily applicable method on large scale.[4] With this in mind it follows that another key line of research, which would benefit the production of indoles (specifically the Fischer indole process) is that of a general method for the preparation of hydrazines. Here we provide a brief overview of the recent and most common methods for the preparation of hydrazines. This is then followed by details of some intriguing but somewhat conflicting literature concerning the reduction of diazonium salts by vitamin C to yield hydrazines. We then discuss our own findings in an effort to clarify this conundrum, which is followed by a brief contextual discussion.

2. A brief overview of the synthesis of hydrazines

The synthesis of hydrazines can be classified into two subgroups (Fig. 2). (1) Forging a C–N bond between an activated aryl group (usually a C–X bond, where X is a halogen) and hydrazine; (2) formation of an N–N bond, most typically by the formation and subsequent reduction of a diazonium salt.

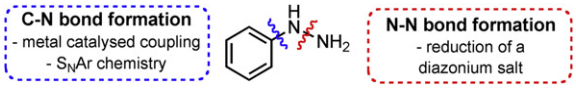
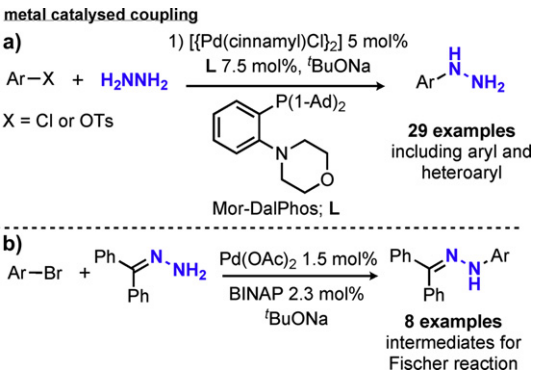


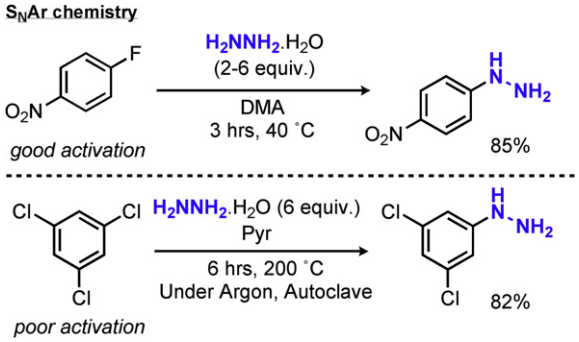
Fig. 2. Possible approaches for the preparation of hydrazines.

Regarding C–N bond formation, Lundgren and Stradiotto recently reported the first palladium mediated cross coupling reaction between aryl chlorides or tosylates and hydrazine (a, Scheme 1).[5] The key to the success of this reaction was the choice of ligand; Mor-DalPhos. This method is a significant advance for organometallic chemistry and may find potential application as an aid for the discovery of new biologically active entities. However, given that the reaction was conducted in a glovebox and the reported scales were relatively small this method appears to be unsuitable for industrial scale processes at this time. Notably the authors also report problems associated with the isolation and storage of some hydrazines and hence derivatise some of their products as hydrazones. This capricious nature of storing and handling some hydrazines is consistent throughout the literature. Indeed, other reports concerning metal catalysed cross coupling have embraced this instability by demonstrating the process with benzophenonehydrazone or other protected hydrazines (b, Scheme 1).[6]



Scheme 1. Palladium cross coupling approach to hydrazines and hydrazones.

Alternatively, aromatic nucleophilic substitution reactions represent an already established industrial process method for securing large quantities of aryl hydrazines via a C–N bond forming event (Scheme 2).[7] As is intrinsic to an aromatic nucleophilic substitution process the substrate scope is limited to the presence of electron withdrawing functional groups in the *ortho* or *para* position. When other non-ideal activating units are present, or suitable activating groups are mislocated (i.e., in the *meta* position) the reaction can still proceed but only at elevated temperatures. This can be particularly hazardous due to the explosive nature of hydrazine.



Scheme 2. Aromatic substitution approaches to hydrazines.

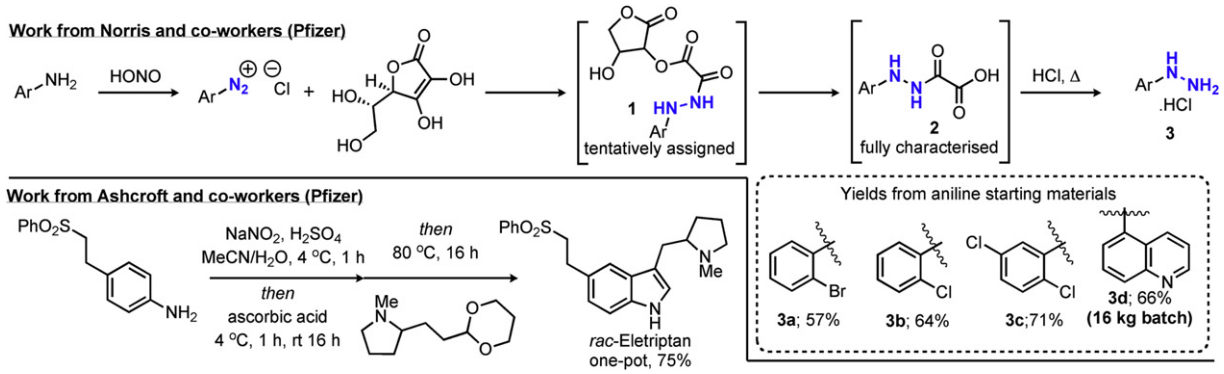
Interestingly, a Sandmeyer type reaction using hydrazine as the nucleophile is reported not to be successful.[8] Instead of the desired C–N bond formation, disproportionation is observed leading to a mixture of phenylazide, ammonia, aniline and hydrazoic acid.

Strategic approaches to the synthesis of the N–N bond are few, however, by far the most common method is the reduction of the corresponding diazonium salt. Most typically this reduction is achieved using sodium sulfite or tin(II) chloride (recently the use of sodium metabisulfite for the synthesis of zolmitriptan has been reported).[9] Indeed, preparation of hydrazines by this general route is the most prevalent in process patents for the synthesis of biologically active molecules.[4]

Ongoing synthesis efforts in our laboratory have examined the generation and use of reactive diazonium salts in situ employing continuous flow technologies.[10] Consequently, a report on the reduction of aryldiazonium salts by ascorbic acid caught our attention. This process represents a mild, scalable technique for the preparation of hydrazines. The use of anilines, which are widely available, is also an attractive facet of such an approach. Moreover, employment of a natural organic reductant; ascorbic acid, adds to the appeal from an environmental and safety standpoint. The process was also one we felt could be adapted to flow chemistry conditions.[11]

3. Existing literature on the reduction of diazonium salts by ascorbic acid

Originally reported by Norris et al. in 2010, treatment of in situ generated diazonium chlorides with ascorbic acid provides materials, which were successfully converted to the corresponding hydrazines by heating in acid.[12] The initial report details the reduction of four different diazonium salts, one of which, a quinoline derivative, was reported on 16 kg scale thus demonstrating that the method offers both the potential to be applied to a range of substrates and can be used for process scale production (Scheme 3). A further benefit of this process is the intermediacy of a stable isolable hydrazine equivalent **2**, which breaks down to provide hydrazine upon treatment with acid (i.e., under conditions typically required for the Fischer indole synthesis or pyrazole formation).



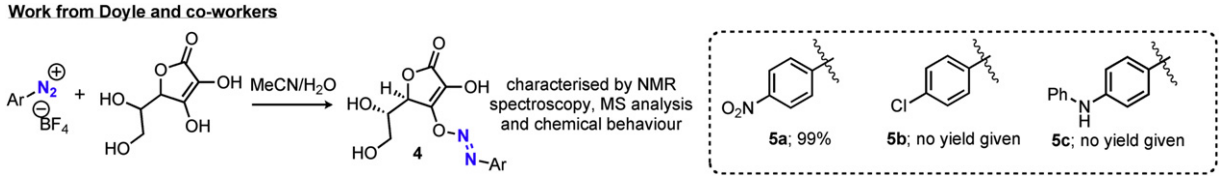
Scheme 3. Use of ascorbic acid for the preparation of pharmaceutical reagents.[12,13]

Despite the clear fact that the overall process described works successfully, mechanistically it appears less well understood. Whilst sufficient data is presented for the diagnosis and characterization of the isolated oxamic acid materials **2**, the corresponding key ascorbic acid/diazonium adduct precursor to this (**1**), perhaps crucial to understanding the process mechanistically, is only tentatively assigned and characterized (^{1}H NMR data only, provided for a single example). Further adding to the utility of this reduction process, Ashcroft et al. (also of Pfizer) have recently described an improved synthesis of Eletriptan, an indole based 5-HT agonist used for the treatment of migraines (Scheme 3).[13] This next generation synthesis route makes use of a Fischer indole reaction whereby the requisite hydrazine is synthesized via an ascorbic acid mediated reduction of a diazonium salt. The reduction method offers a significant improvement over an alternative $SnCl_2$ mediated process (reported as 83% and 13%, respectively, for the reduction steps). Notably in this report, there is no mention of the vitamin C/diazonium adduct intermediate **1**.

Delving a little deeper into the literature we uncovered a seemingly related publication from Doyle et al., which describes the reaction of aryldiazonium salts and vitamin C. However, in this case the isolated products are characterized as diazoether adducts (**4**, Scheme 4).[14] This adduct is not the same as that described by Norris et al. (cf. **1** and **4**). Whereas the Norris intermediate (**1**) is characterized as already having undergone a skeletal rearrangement and reduction of the N–N multiple bonds, the diazoether structure (**4**) is merely an adduct between the two starting materials. Whether these diazoether intermediates (**4**) could be transformed into the corresponding hydrazines was not reported. These contradictory results prompted us to further investigate the reaction to gain insight into this very promising process.

material that displayed an identical ^{1}H NMR spectrum to that reported by Doyle for this process (**5b**, Scheme 5). Intriguingly, when this material was subjected to treatment with 6 M hydrochloric acid, in an analogous method to that reported by Norris et al. for their oxamic acids (**2**), the corresponding hydrazine **3e** was obtained. The yields for this sequence are unoptimised.

The formation of hydrazine **3e** from intermediate **5b** led us to the conclusion that the intermediates present in both of the reported reactions are either identical or members of a common reaction pathway towards hydrazines. Employing one of a small selection of stable tetrafluoroboratediazoniumsalts, which are commercially available, an alternative ascorbic acid adduct was obtained from 4-bromobenzenediazonium tetrafluoroborate. In this case the adduct **5d** was obtained in excellent yield and the ^{1}H NMR spectrum was comparable to that of the 4-chloro adduct **5b** (see Table 1). This material was also successfully converted to the corresponding hydrazine **3f** in 74% yield (Scheme 5). The bromoadduct **5d** was crystallised and analyzed by X-ray diffraction (Scheme 6).[15] Importantly, this result indicates that the identity of the isolable intermediate from the reaction of ascorbic acid and 4-bromobenzenediazonium tetrafluoroborate is actually that proposed by Norris et al. (**1a**) rather than a diazoether structure (**5d**).[16] With regard to the stability of this intermediate, it appears unsurprisingly acid sensitive, this may explain the difficulty in characterization witnessed by Norris et al.. Efforts to repeat the process of Norris et al. at low pH did not provide a clean sample but a mixture attributable to both intermediates described in their paper (**1** and **2**, Scheme 3). This is further supported by Doyle's observation that intermediate **5b** undergoes degradation; we also observed the same behaviour with a sample of our intermediate adduct **5b** prepared via the neutral BF_4 diazonium salt

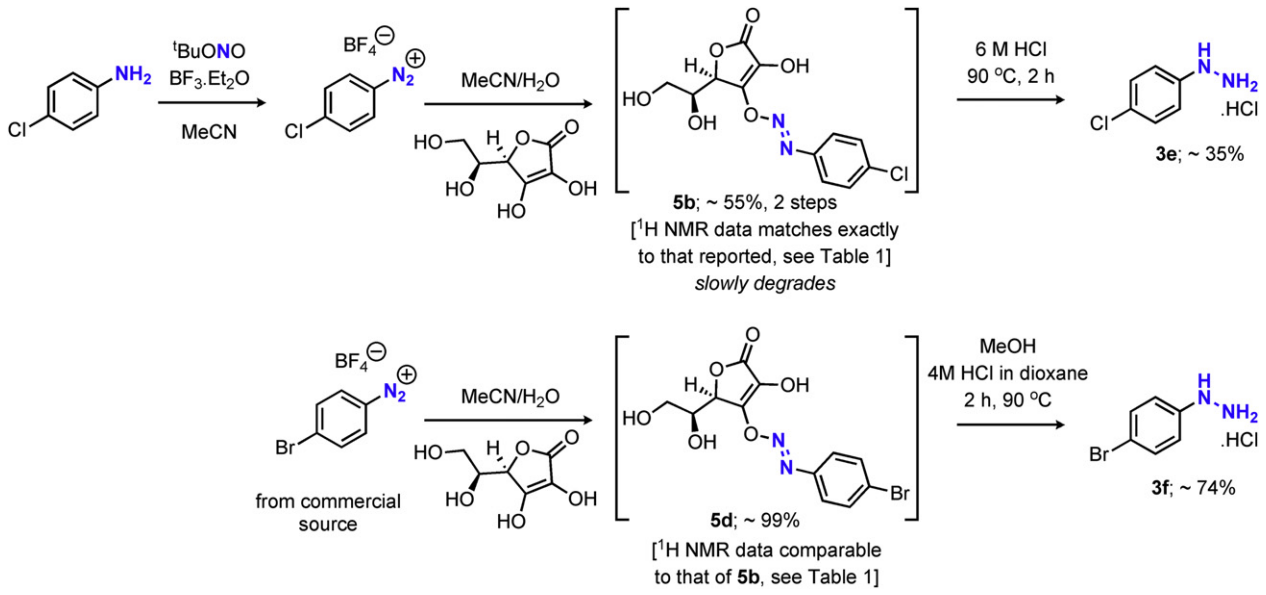


Scheme 4. Reported synthesis of diazoethers from ascorbic acid and diazonium tetrafluoroborate salts.[14]

4. Results and discussion

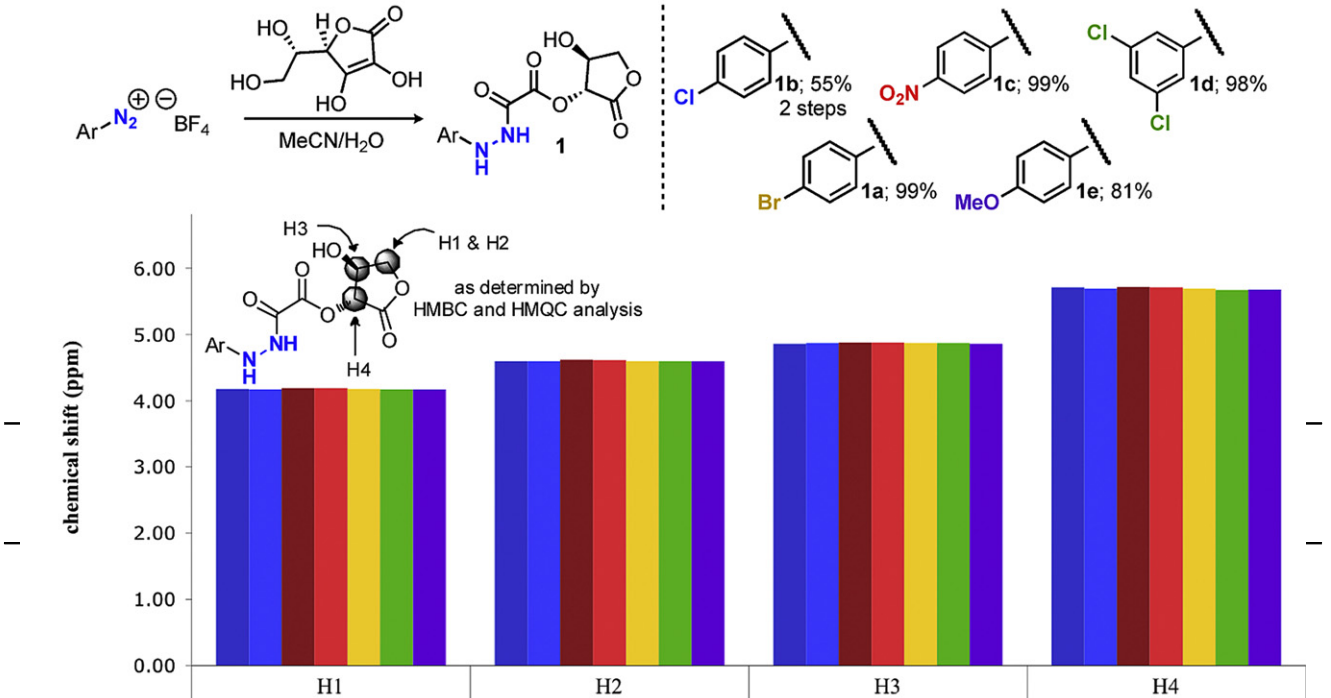
Notable differences of the two reported methods comprise the nature of the counterion of the diazonium salt and the pH of the reaction conditions. We initially therefore set out to determine, which of these factors may affect the outcome of the reaction. Treatment of 4-chlorobenzenediazonium tetrafluoroborate with ascorbic acid in a mixture of acetonitrile and water provided in which some minor degradation was observed over a 3-day period.

In order to establish if the formation of this reduced diazonium adduct is common for a range of substrates, a number of other intermediates were successfully synthesized and isolated. Comparison of the ^{1}H NMR data corresponding to the γ-lactone portion shows that the formation of the reduced adduct is general (analysis by ^{1}H NMR was more convenient since these materials are not

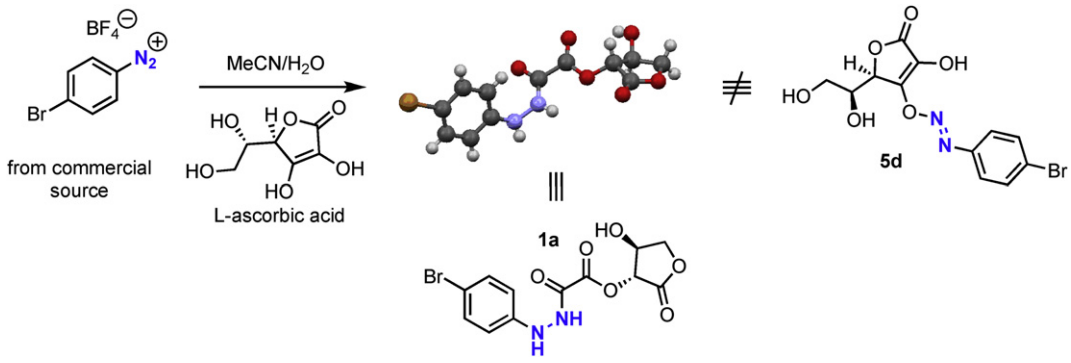


Scheme 5. Synthesis of reported diazoethers and their conversion to hydrazines.

Table 1
Comparison of chemical shift data for key protons taken from a number of diazoniumtetrafluoroborate/ascorbic acid adducts



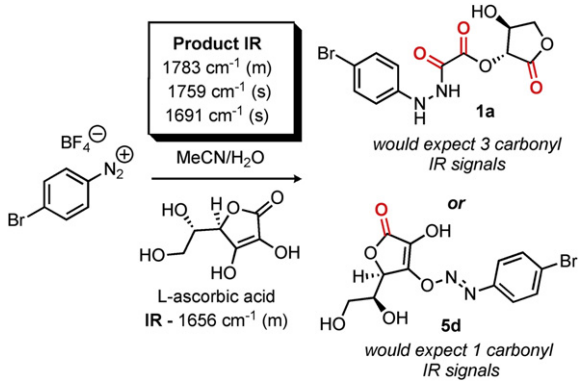
	H1	H2	H3	H4
4-Cl (ref 14)	4.18	4.60	4.86	5.71
4-Cl	4.17	4.60	4.87	5.69
4-NO2 (ref 14)	4.19	4.62	4.88	5.72
4-NO2	4.19	4.61	4.88	5.71
4-Br	4.18	4.60	4.87	5.69
3,5-diCl	4.17	4.60	4.87	5.67
4-MeO	4.17	4.60	4.86	5.68



Scheme 6. X-ray analysis confirms identity of key intermediate.

easily crystallised). As shown in Table 1, the chemical shift of the protons present on the γ-lactone portion of the derived adducts are in excellent accord with those of the structure corroborated by X-ray diffraction. Furthermore, all adducts were successfully converted to hydrazine salts following analysis by NMR spectroscopy, albeit in an unoptimised fashion.

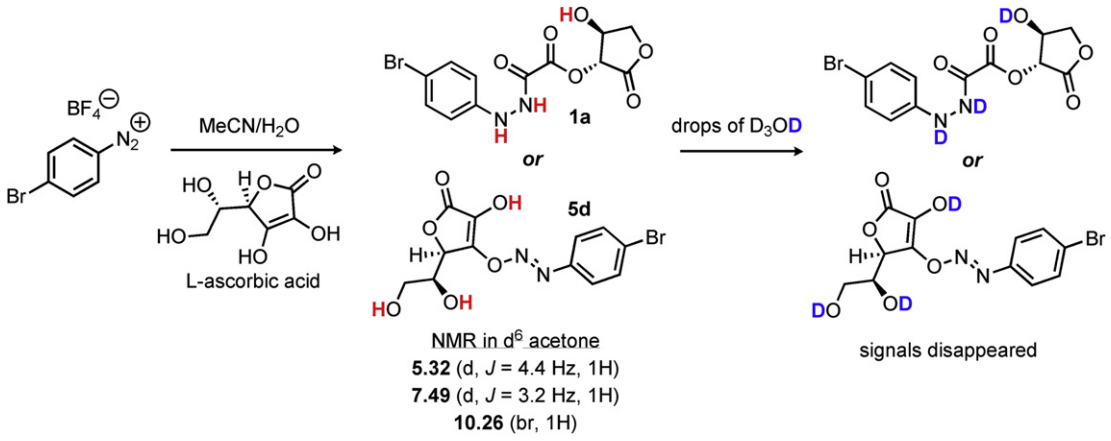
Whilst the ^{1}H NMR and ^{13}C NMR data of **1a** could conceivably fit both structures **1a** and **5d** (same number of hydrogens; in similar environments, same number of CH_0, CH_1, CH_2 present in both structures), two other pieces of data aided with the assignment. The presence of three exchangeable signals in the ^{1}H NMR spectrum of **1a** at markedly different chemical shifts (5.32, 7.49 and 10.26) is likely to be attributable to a structure containing an amide, aniline and alcohol rather than a molecule containing an enol and two closely related alcohols (Scheme 7). The infrared spectrum of product **1a** contains three peaks in the carbonyl stretching frequency region {1783 cm^{-1} (m), 1759 cm^{-1} (s), 1691 cm^{-1} (s)}, congruent with the γ-lactone oxamide structure rather than the ascorbic acid diazoether adduct **5d**. This is further validated by comparison to the infrared spectrum of ascorbic acid, which shows only a single peak in the carbonyl stretching region {1656 cm^{-1} (m)} (Scheme 8).



Scheme 8. Infrared spectroscopy data.

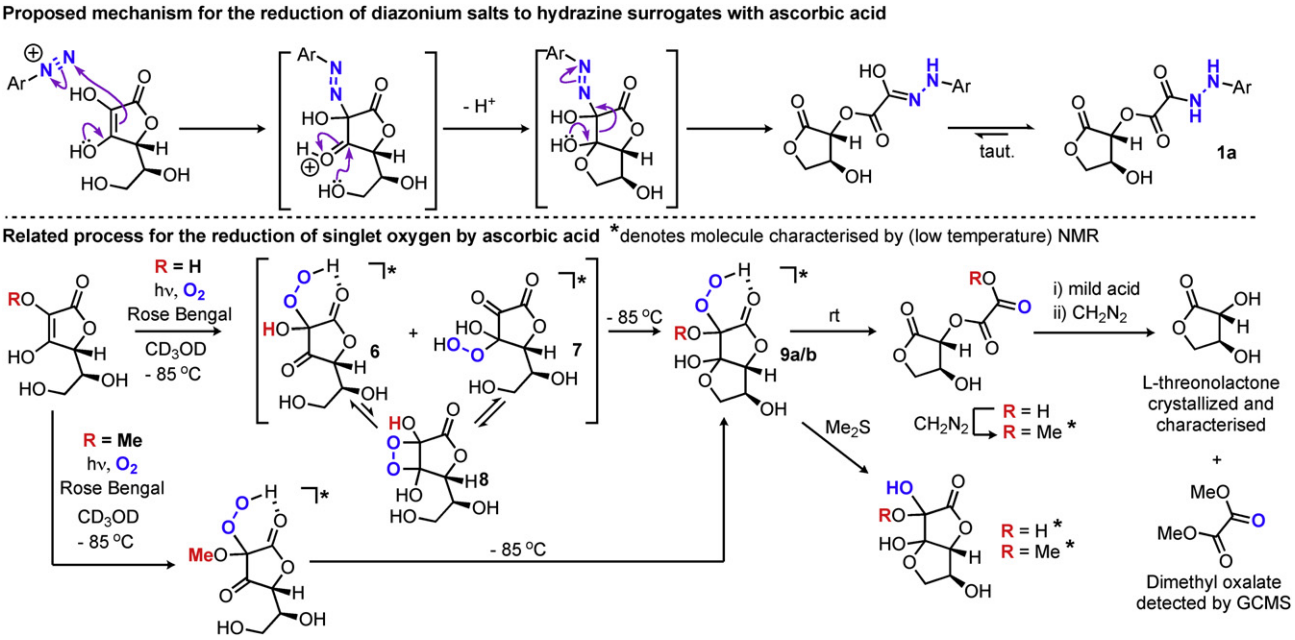
a fashion, which reduces the diazo bond to provide the tautomeric form of the oxamide product (**1a**).[17]

This proposed mechanism is well supported by similar methodology for the reduction of O_2 by ascorbic acid reported by Kwon and Foote in which a number of intermediates in their reduction process were characterized by NMR monitoring.[18] Interestingly, in



Scheme 7. Chemical shift of exchangeable protons.

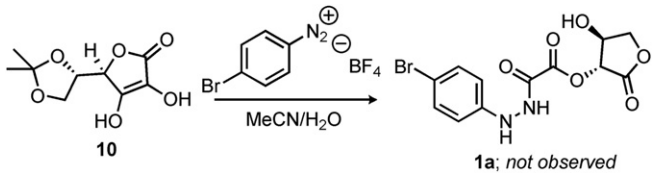
With good evidence that the reduction process provides oxamic esters of threonic acid lactones we began to consider how such a skeletal rearrangement might occur. Our postulated mechanism for its formation is shown in Scheme 9. It starts with the nucleophilic attack through carbon of the 1,3-dicarbonyl motif present in ascorbic acid onto the diazonium salt. The resulting oxonium ion is then trapped as a hemiacetal by an intramolecular cyclisation of the pendant diol moiety. This intermediate subsequently fragments in their studies, the initial formed complex was observed to exist as two regioisomers in which both dicarbonyl compounds **6** and **7** were observed by NMR, whereas the proposed peroxo-bridged intermediate **8** was not observed. It appears that both regioisomers funnel through a thermodynamic equilibrium to be trapped by the pendant diol arm as the bicyclic intermediate **9**. Importantly, the existence of such regioisomers is not observed when the 3-hydroxyl group is replaced with a methylether. Both of the



Scheme 9. Proposed mechanism and rationale.

bicyclic intermediates (OMe and OH) **9a** and **9b** rearrange to provide the threonolactone oxalic acid or ester compounds, which are analogous to ester **1a**.

A brief mechanistic study to demonstrate the importance of the pendant diol chain for the vitamin C reduction process was designed. Treatment of 4-bromobenzenediazonium tetrafluoroborate with L-ascorbic acid acetonide (**10**) under identical conditions to those previously employed, provided an uncharacterisable mixture, which did not contain any of the desired rearranged adduct **1a** (Scheme 10). A skeletal rearrangement/redox pathway involving planar intermediates at the chiral centres can be ruled out based on evidence that the absolute stereochemistry of the starting ascorbic acid is conserved in the product adduct (as shown by X-ray diffraction). Single electron transfer processes are often associated with vitamin C chemistry, however, this type of pathway with diazonium salts is always in conjunction with a metal.[19] Also, given the lack of observed dimers (Ar–Ar coupling) and related radical type byproducts we rule this out as a likely mechanism.

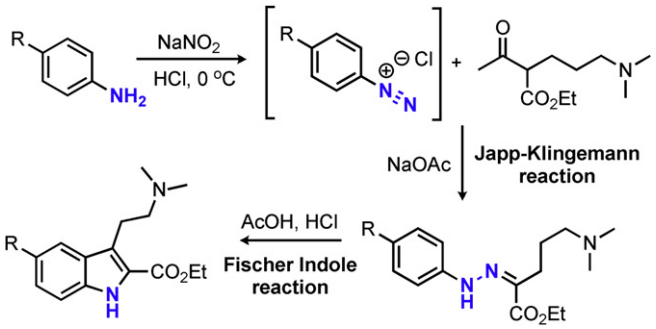


Scheme 10. Pendant diol is key to the reduction process.

5. Contextual discussion

An anology of the described pathway can be made to the Japp–Klingemann reaction. This process features the treatment of a monosubstituted 1,3-dicarbonyl with a diazonium salt in the presence of a base resulting in the formation of a hydrazone (Scheme 11).[20]

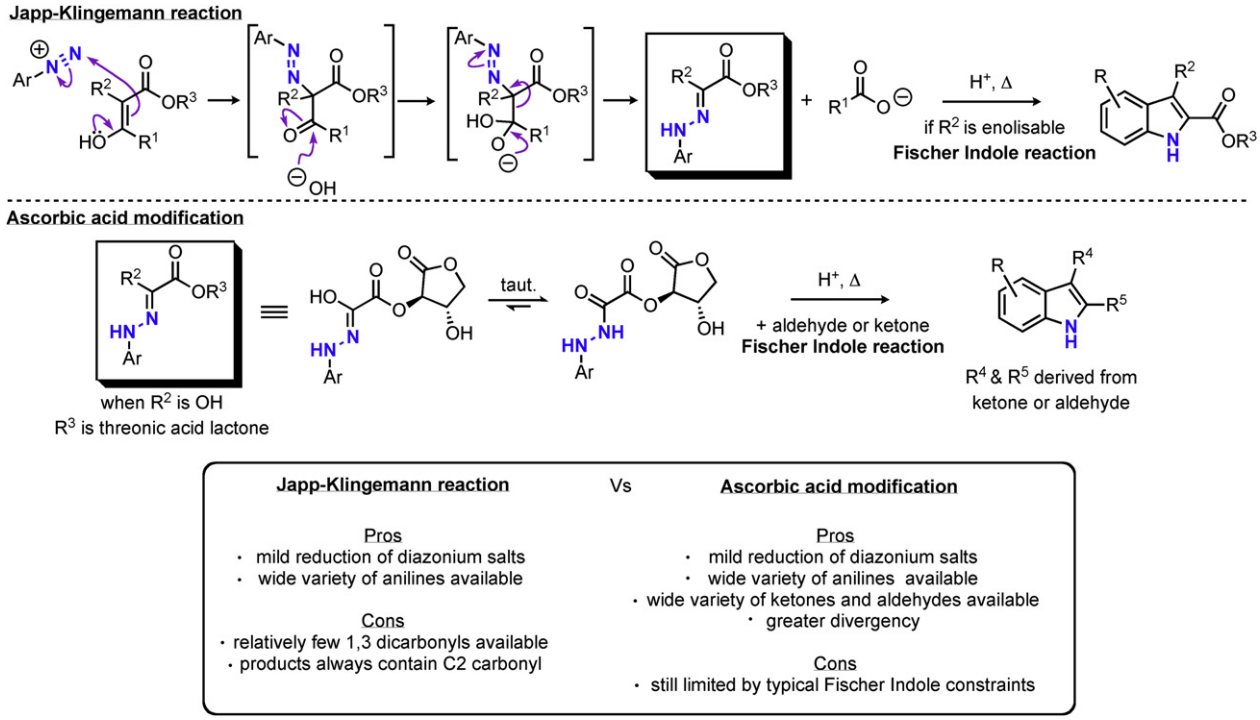
In the Japp–Klingemann reaction the enol of the 1,3-dicarbonyl attacks a diazonium compound via the enol carbon, fragmentation of the thus formed diazodicarbonyl compound is then triggered by an external base, which provides an α-hydrazonyl carbonyl product



Scheme 11. An example of the Japp–Klingemann reaction.

as shown in Scheme 12. This is analogous to the key fragmentation process proposed for the ascorbic acid mediated process with the exception that the pendant diol behaves as the triggering nucleophile and no external base is required. An attractive facet of the ascorbic acid modified Japp–Klingemann reaction is the potential for divergence when constructing indoles. Typically, the ester hydrazones derived from the traditional method are employed for the synthesis of indoles directly (intercepting the Fischer indole reaction) and therefore the desired indole substituents must be present in the starting dicarbonyl material. However, the ascorbic acid reaction allows for the same mild reduction of diazonium salts whilst offering the full substrate scope, which is usually available for the Fischer indole reaction without synthesizing bespoke 1,3-dicarbonyl motifs (Scheme 12).

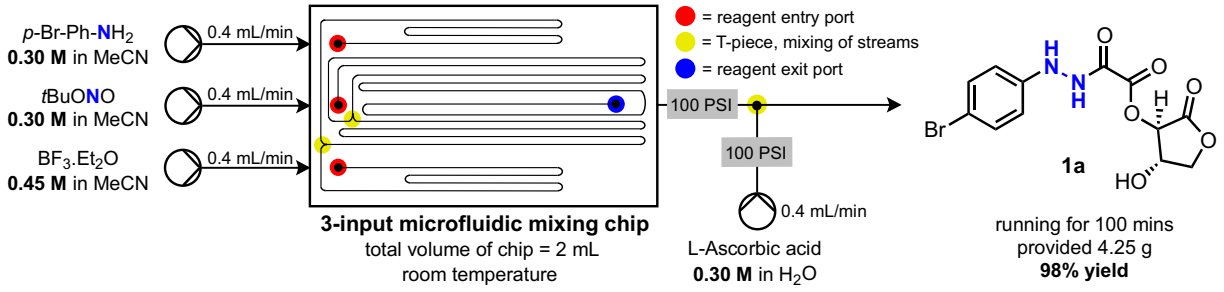
Our original motivation for studying this chemistry was to explore the potential benefits of conducting such a process in continuous flow mode. Clearly the generation and direct consumption of small quantities of diazonium salts in a rapid and environmentally benign manner is an attractive goal. The current described batch process features careful manipulation of temperatures to avoid exothermic phenomena, a consideration that can often be conveniently disregarded in flow mode processes. One example of our investigations towards this end is depicted in Scheme 13. The



Scheme 12. Mechanism of the Japp–Klingemann reaction and its analogy/comparison to the ascorbic acid modification.

use of a three-input microfluidic chip allowed for a 100 min synthesis run, whereby the tetrafluoroboratediazonium salt was generated within the 2 mL chip and quenched with ascorbic acid via a T-piece at the exit of the chip, thus providing essentially quantitative yield of key intermediate **1a**.[21] One could imagine diverting a stream of **1a** into a variety of other processes, further details of this shall be reported in due course.

Japp–Klingemann reaction and the benefits of a divergent strategy from the ascorbic acid modification described. Until clarification aided by the studies described here, there were two conflicting reports concerning this important transformation. This report should serve to provide a good understanding of the process and allow further work to be undertaken on implementing and improving this method.



Scheme 13. Microfluidic chip set-up for continuous production of oxamic intermediates.

6. Conclusions

In conclusion, the synthesis of hydrazines is of paramount importance for the design and production of biologically active molecules. A key intermediate for the synthesis of hydrazines via a mild, metal free reduction of diazonium salts has been isolated and characterized by X-ray analysis. A number of diazonium salts have been reduced by ascorbic acid to provide the same intermediate adducts. Preliminary results confirming the conversion of the isolated intermediates to hydrazines have been reported. The mechanism of this reduction has been likened to that of the

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2011.09.146.

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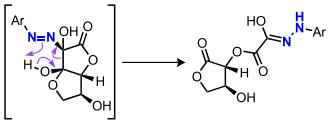
16. Comparison of NMR analysis data of the crude material from which the crystals were grown with that of the crystals following diffraction shows negligible difference.
17. We thank one of the referees for suggesting the possible breakdown of the hemiacetal intermediate via a hetero-eneprocess, which is of course an alternative possibility to the arrows we have drawn.



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20. For an excellent overview of the Japp–Klingemann reaction see: Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; San Diego, Elsevier Academic: 2005.
21. The three-input microfluidic chip was supplied by Uniqsis: http://www.uniqsis.com/.