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

A R T I C L E   I N F O

Article history:
Received 8 August 2011
Received in revised form 29 September 2011
Accepted 30 September 2011
Available online 12 October 2011

Keywords:
Hydrazines
Vitamin C
Ascorbic acid
Diazonium salts
X-ray

A B S T R A C T

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.

A R T I C L E   B O D Y

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). 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

---

* Corresponding author. Tel.: +44 (0)1223 336402; fax: +44 (0)1223 336442; e-mail address: db543@cam.ac.uk (D.L. Browne).
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.9 With this in mind it follows that another key line of research is the discovery of new biologically active entities. However, given that available starting materials is an important area of research.2,3

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.7,3

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.

2. A brief overview of the synthesis of hydrazines

The synthesis of hydrazines can be classified into two subgroups (Fig. 2). (1) Forgining 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.

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 derive 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 benzophenonehydrazine or other protected hydrazines (b, Scheme 1).5

Interestingly, a Sandmeyer type reaction using hydrazine as the nucleophile is reported not to be successful.6 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 aryl diazonium 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 iso-
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 (1H 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). This method offers a significant improvement over an alternative SnCl2 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 (Scheme 4). 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.

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 material that displayed an identical 1H 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 1H NMR spectrum was comparable to that of the 4-chloro adduct 5b (Table 1). This material was also successfully converted to the corresponding hydrazine 3f in 74% yield (Scheme 5). The bromoaduct 5d was crystallized and analysed by X-ray diffraction (Scheme 6). 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). 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 BF4 diazonium salt.
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

<table>
<thead>
<tr>
<th>Chemical Shift (ppm)</th>
<th>H1</th>
<th>H2</th>
<th>H3</th>
<th>H4</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Cl (ref 14)</td>
<td>4.18</td>
<td>4.60</td>
<td>4.86</td>
<td>5.71</td>
</tr>
<tr>
<td>4-Cl</td>
<td>4.17</td>
<td>4.60</td>
<td>4.87</td>
<td>5.69</td>
</tr>
<tr>
<td>4-NO2 (ref 14)</td>
<td>4.19</td>
<td>4.62</td>
<td>4.88</td>
<td>5.72</td>
</tr>
<tr>
<td>4-NO2</td>
<td>4.19</td>
<td>4.61</td>
<td>4.88</td>
<td>5.71</td>
</tr>
<tr>
<td>4-Br</td>
<td>4.18</td>
<td>4.60</td>
<td>4.87</td>
<td>5.69</td>
</tr>
<tr>
<td>3,5-diCl</td>
<td>4.17</td>
<td>4.60</td>
<td>4.87</td>
<td>5.67</td>
</tr>
<tr>
<td>4-MeO</td>
<td>4.17</td>
<td>4.60</td>
<td>4.86</td>
<td>5.68</td>
</tr>
</tbody>
</table>
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 1H NMR and 13C NMR data of 1a could conceivably fit both structures 1a and 5d (same number of hydrogens; in similar environments, same number of CH₂, CH₃, CH₂ present in both structures), two other pieces of data aided with the assignment. The presence of three exchangeable signals in the 1H 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).

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 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 O₂ 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 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 6](image-url)

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

![Scheme 7](image-url)

**Scheme 7.** Chemical shift of exchangeable protons.

![Scheme 8](image-url)

**Scheme 8.** Infrared spectroscopy data.

![Scheme 9](image-url)

**Scheme 9.** Postulated mechanism of reduction process.
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.

5. Contextual discussion

An analogy of the described pathway can be made to the Japp–Klingemann reaction. This process features the treatment of a mono-substituted 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 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 dicarboxylic 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
The use of a three-input microfluidic chip allowed for a 100 min synthesis run, whereby the tetrafluoroborate diazonium 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. One could imagine diverting a stream of 1a into a variety of other processes, further details of this shall be reported in due course.

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

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 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.

Acknowledgements

We are grateful to Dr. John Davies for conducting X-ray analysis. The authors would like to thank the BP 1702 Chemistry Professorship (S.V.L.), the Royal Society (I.R.B.) and the EPSRC (D.L.B.) for financial support.

Supplementary data

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


15. File reference CCDC 837617.

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.


21. The three-input microfluidic chip was supplied by Uniqsis: http://www.uniqsis.com/.