Oxidative azidations of phenols and ketones using iodine azide after release from an ion exchange resin†

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The oxidative oligoaazidation of phenols and ketones using iodine azide (IN$_3$) provided by its release from an ion exchange resin is reported. Preliminary mechanistic studies indicate a previously unknown reactivity of iodine azide toward phenols and ketones.

Introduction

The iodination of alkenes and aromatics is complicated by the reversibility of this process, which is caused by the formation of HI in the presence of the iodine used. Therefore, ways must be found to remove hydrogen iodide as soon as it has formed in order to achieve the best results. For this purpose HgO, HNO$_3$, HIO$_3$ and H$_2$O$_2$ have been used to oxidise hydrogen iodide. Other ways to achieve efficient iodination of phenols are mixtures consisting of sodium iodide and either tert-butyl hypochlorite or chloramine T. Okamoto and collaborators reported a dichloroiodate( I) agent formed from ICl and benzyltrimethylammonium chloride that allows ortho-iodination of phenols under mild conditions. It proved superior to ICl. It has also been reported that the presence of methanol is beneficial and postulated that the active reagent is methyl hypoiodite.

We reported on the synthesis of electrophilic halonium reagents that are structurally related to 1. These are obtained by iodine(III)-mediated oxidation of organic ammonium bromides or iodides. The resulting acylated haloate(i) complexes can be further diversified by ligand exchange using silylated nucleophiles yielding ate(i) anions. They have been used in a variety of reactions including activation of thioglycosides and dithioacetals and as cooxidants for TEMPO-mediated oxidations. Chemically, these haloate(i) anions [I(OAc)$_2$\(^-\), I(O$_2$CCF$_3$)$_2$\(^-\), I(N$_3$)$_2$\(^-\)] behave like Br-OAc, I-OAc, I-OTf and I-N$_3$. A practical advantage is that the starting amonium halide can be an ion exchange resin (e.g. Amberlyst A-26), so that polymer-bound versions of haloate(i) anions are available. If the nucleophile (Nu) is azide and the halogen atom is iodine, the orange polymer is a stable and safe form of iodine azide. This polymer is in fact non-explosive and can be stored in the dark under an argon atmosphere at \(-15\) °C for several months without loss of activity. We recently showed that this form of iodine azide can also serve as a precursor for azide radicals. The polymeric by-product (ion exchange resin-azide form), which is formed during transformations with 4a, is removed by simple filtration (Scheme 1). The polymer-bound version of reagents 4 can be regenerated by ion exchange with iodide, where PhI(OAc)$_2$ promotes oxidation to 3 (R$_2$ = CH$_3$) and ligand exchange with TMSN$_3$ yields the regenerated polymer.

The close relationship between dichloroiodate(i) 1 and bis-azidoiodate(i) 4a led us to investigate the reactivity of 4a with phenols.

![Scheme 1 Iodination with benzyltrimethylammonium dichloroiodate(i) in methanol according to Okamoto et al. and haloate(i) reagents producible by iodine(III) oxidation of halide anions.](image-url)
Results and discussion

Exposing phenol 5 to the functionalised polymer 4a resulted in 2,4,6-triodophenol (6) in 90% yield (Scheme 2, eqn (1)). This result is consistent with the iodination protocol reported by Okamoto (Scheme 1). However, when extending the protocol to other phenols, we found that this first example is rather an exception. In a second series of experiments, ethinylestradiol (7) was selected as the phenolic substrate, which led to an unexpected result, the formation of three estradiol derivatives 8–10 (eqn (2)). While the formation of diiodide 8 was expected, the formation of bis- and trisazido adducts 9 and 10 revealed a new chemistry of iodine azide. By increasing the equivalents of 4a, it could be determined that first the iodination product 8 is formed, followed by phenol 9. Finally dienone 10 with three azido groups becomes the only product, if a sufficient amount of reagent is used.

Next, this unprecedented reaction was extended to other phenols to afford azides 11–20. The structure including the configuration of the newly formed stereogenic center in 15 (formed from estrone) was unequivocally confirmed by X-ray crystallographic analysis. In view of the structural and stereochemical similarity of the starting steroids (estradiol, estrone and estriol), it can be assumed that the four products 16–19 all have the β-oriented azide substituent at C-10 as determined for 15. The chemical shift δ for H1 at 6.53–6.57 ppm was used as a diagnostic feature for this purpose.

The conversions of several phenols to azides 10–15 consistently proceeded with excellent yields (Scheme 3). A brief investigation of the influence of the solvent showed that methanol can be used in addition to acetonitrile, an observation that fits the results of Okamoto et al., so it can be assumed that hypoiodite 2 is also formed as a reactive intermediate in this case. A similar yield was found for azidodienone 15 with extended reaction time. Interestingly, the use of an arenne with three methoxy groups gave the para-substituted mono-azidodienone 12 in a remarkable yield of 96%. The steroidal hormone equilenin (21), first isolated from the urine of pregnant mares, shows diverse biological activities, including antiseborrhic, lipid metabolism regulating or neurological disorders treating properties. The conversion to azide 20 is synthetically useful as it reveals a new protocol for derivatizations of this type of steroids. Remarkably, we found that the aromatic B ring remained intact in the presence of iodine azide.

To gain a mechanistic insight into the stepwise formation of azidodienone 10, the reaction was monitored in an NMR tube. For this purpose we performed the conversion of ethinylestradiol (7) with 5.0 equiv. of 4a in deuterated acetonitrile and collected a sample directly after setting up the reaction. After only five seconds the formation of diiodide 8 (δ = 7.67 ppm) and the formation of bis- (δ = 6.89 ppm) and trisazides (δ = 6.71 ppm) 9 and 10 could be detected by 1H-NMR spectroscopy (Scheme 4). However, because the reaction pro-
ceeded very rapidly, this experiment did not provide clear evidence on the time course of the formation of individual intermediates and on the question of whether mechanistically parallel pathways to the iodides and azides might exist. We were able to isolate and characterize all products 8–10.

To collect further information on azidodienone formation and possible precursor iodides, we repeated the reaction tracking for the reaction of estrone (22), whose structure was clearly secured by X-ray analysis, with only 1.0 equiv. of 4a in deuterated acetonitrile at 0 °C and collected samples over a period of 1 h (Scheme 5). This experiment proceeded analogous to that for phenol 7, but it allowed the observation of the time course of the formation of intermediates.

To collect evidence that azidodienone formation occurs via the initial electrophilic iodination of ortho positions, we independently prepared diiodide 22 (see ESI†) which quantitatively yielded the expected trisazido adduct 15 under our standard conditions (Scheme 6).

After only five minutes, the appearance of a strong signal at δ = 7.66 ppm was detected, which is characteristic of diiodide 23 (Scheme 5). Next, after 30 minutes, a signal at δ = 6.89 ppm is clearly visible, which is characteristic of bisazido adduct 24. From these findings, it can be concluded that diiodide 23 (δ = 7.66 ppm) must most likely be a precursor for bisazido product 24 and the latter for azidodienone 15.

These analytical studies allow us to propose a possible mechanism for the formation of azidodienone 15 from estrone (22, Scheme 7). After electrophilic iodination of both ortho positions, which provides diiodide 23, we propose an activation of the phenolic position by iodine azide, which gives hypoiodite 26. Next, the nucleophilic addition of azide leads to the formation of dienone 27, which after iodonium migration can form a new hypoiodite 28. Aromatization could be the driving force for this step. After this sequence, azide is introduced two more times, the last addition is facilitated by the strong electrophilic character of dienone 25.

Scheme 4 Reaction tracking of ethinylestradiol (7) with 4a by 1H NMR spectroscopic analysis.

Scheme 5 Reaction monitoring of estrone (22) with 4a by 1H-NMR spectroscopic analysis; samples were taken according to given times (bisazide 24 could not be isolated, but the signal at δ = 6.7 ppm was assigned to bisazide 24 by comparison with the corresponding signal at δ = 6.89 ppm for bisazide 9 in Scheme 4).

Scheme 6 Synthesis of azidodienone 15 starting from diiodide 23.

Scheme 7 Postulated mechanism for oligoazide formation.
Conclusions

In summary, we have uncovered a new reactivity of iodine azide toward phenols and ketones, which is initiated by the release of this highly reactive agent from an ion-exchange resin into the organic solution. Mechanistically, we propose the formation of hypoi-dite intermediates as a key step in achieving oxidative azidation of phenols and ketones.\textsuperscript{15} We believe that the extension of the synthetic potential of iodine azide under safe conditions will open new amination pathways for pharmaceutically relevant phenols.

Conflicts of interest

There are no conflicts to declare.

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