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

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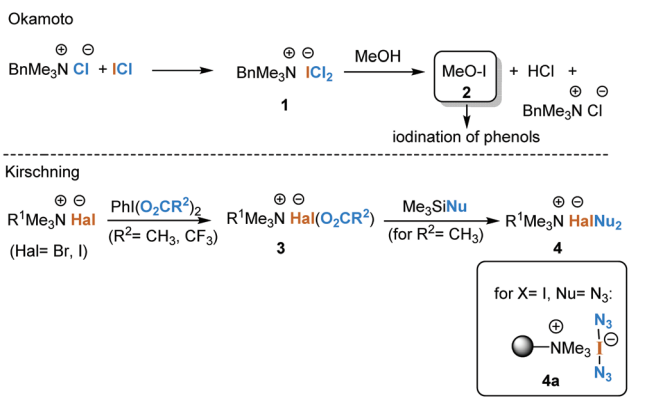
The oxidative oligoazidation of phenols and ketones using iodine azide (IN_3) provided by its release from an ion exchange resin is reported. Preliminary mechanistic studies indicate a previously unknown reactivity of iodine azide toward phenols and ketones.

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_2O_2 [1] 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.[2] Okamoto and collaborators reported a dichloroiodate(I) agent **1** formed from ICl and benzyltrimethylammonium chloride that allows *ortho*-iodination of phenols under mild conditions.[3] 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 **2**.

We reported on the synthesis of electrophilic halonium reagents **3** that are structurally related to **1**. These are obtained by iodine(III)-mediated oxidation of organic ammonium bromides or iodides.[4] The resulting acylated haloate(I) complexes **3**[5] can be further diversified by ligand exchange using silylated nucleophiles yielding ate(I) anions **4**. They have been used in a variety of reactions[6] including activation of thioglycosides[7] and dithioacetals[8] and as cooxidants for TEMPO-mediated oxidations.[9] Chemically, these haloate(I) anions **3** [$Br(OAc)_2^-$, $I(OAc)_2^-$, $I(O_2CCF_3)_2^-$, $I(N_3)_2^-$] behave like Br-OAc, I-OAc, I-OTf and I-N_3.[10] A practical advantage is that the starting ammonium 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.[11] 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.[12]

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.*[3] and haloate(I) reagents producible by iodine(III) oxidation of halide anions.

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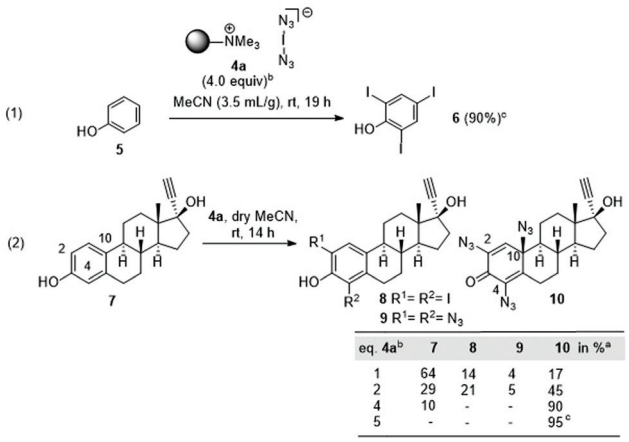
Results and discussion

Exposing phenol **5** to the functionalised polymer **4a** resulted in 2,4,6-triiodophenol (**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.

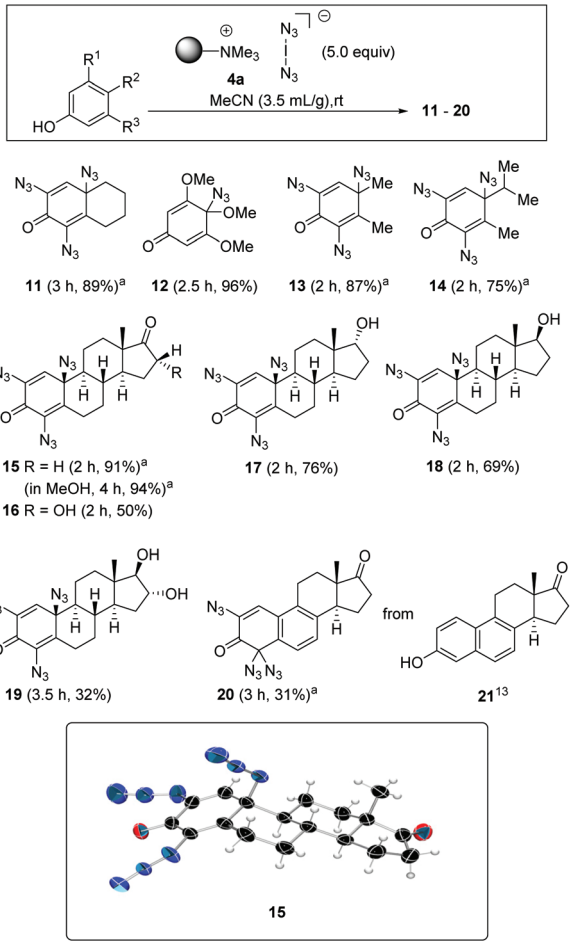
The conversions of several phenols to azides **10–15** consistently proceeded with excellent yields (Scheme 3). A brief investigation of the influence of the solvent showed that methanol can be used in addition to acetonitrile, an observation that fits the results of Okamoto *et al.*,[3] so it can be 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 arene 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,[13] shows diverse biological activities, including antiseborrheic, 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 ^{1}H-NMR spectroscopy (Scheme 4). However, because the reaction pro-



eq. 4a[b]	7	8	9	10 in %[a]
1	64	14	4	17
2	29	21	5	45
4	10	-	-	90
5	-	-	-	95[c]

Scheme 2 Iodination of phenol **5** and ethinylestradiol **7** with functionalised polymer **4a** (the configuration at C-10 in **10** was related to that found in **15** by X-ray crystallographic analysis). [a]Ratios determined by ^{1}H NMR spectroscopic analysis, [b]equivalents refer to theoretical presence of ion exchange sites reported by the vendor, [c]isolated yields are given; the presence of blue LED light did in principal not lead to altered results.



Scheme 3 Azidation of phenols and formation of **11–20** (isolated yields are given; in some cases, the lower yield could be due to the phenol being bound to the cation exchange resin; the configuration at C-10 in **16–19** are proposed based on X-ray crystallographic analysis of **15**: C = black, N = blue, O = red). [a]The characterization of the new azides was accompanied by IR spectroscopy. However, we encountered difficulties in the preparation of mass spectra for a few oligoazides.

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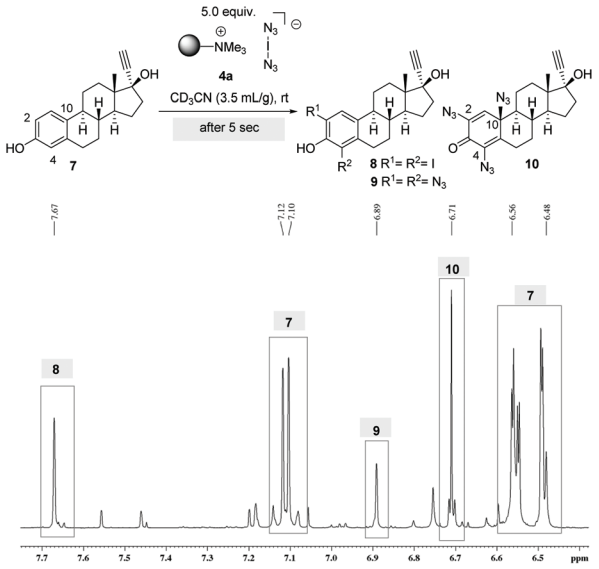
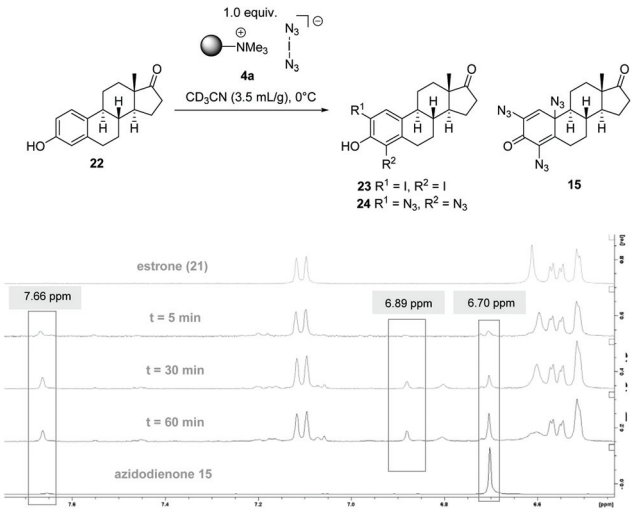


Scheme 4 Reaction tracking of ethinylestradiol (**7**) with **4a** by ^{1}H NMR spectroscopic analysis.

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.

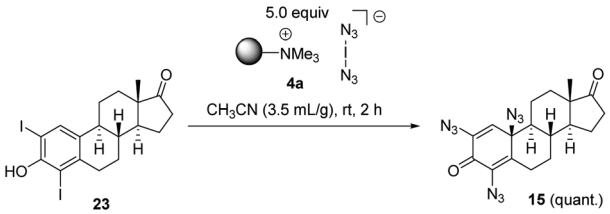


Scheme 5 Reaction monitoring of estrone (**22**) with **4a** by ^{1}H-NMR spectroscopic analysis; samples were taken according to given times (bisazide **24** could not be isolated, but the signal at δ = 6.7 ppm was assigned to bisazide **24** by comparison with the corresponding signal at δ = 6.89 ppm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

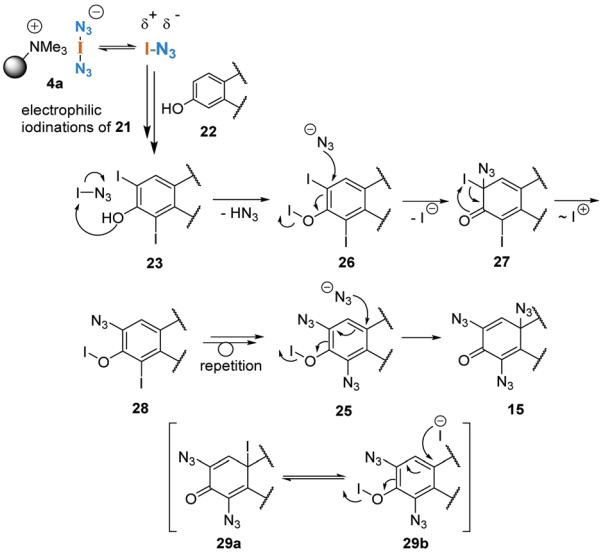
To collect evidence that azidodienone formation occurs *via* the initial electrophilic iodination of *ortho* positions, we independently prepared diiodide **22** (see ESI†) which quantitatively yielded the expected trisazido adduct **15** under our standard conditions (Scheme 6).

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 6 Synthesis of azidodienone **15** starting from diiodide **23**.



Scheme 7 Postulated mechanism for oligoazide formation.

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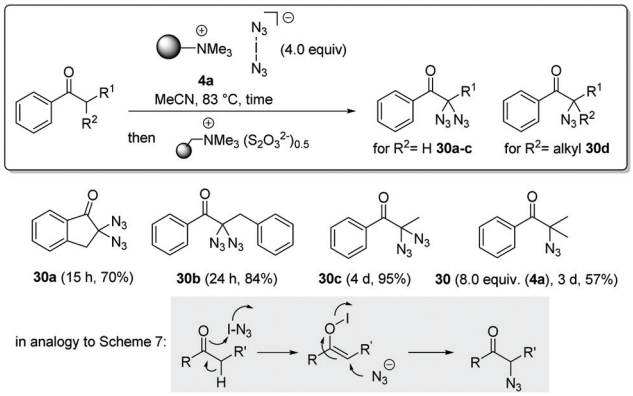

Scheme 8 Azidation of acylarenes (isolated yields are given).

With this mechanistic proposal in hand, we concluded that enols might behave similarly to phenols in the presence of iodoazide. In a first proof of concept study we chose acylarenes as substrates and treated these with an excess of polymer-bound iodine azide **4a** in acetonitrile at 83 °C (Scheme 8). As expected, mono- and diazidations occurred in the α-positions within 15 h to 3 d after treatment and azides **30a–d** were isolated in yields ranging from 57% to 95%. Geminal bisazides can be directly converted into nitrogen-containing heterocycles such as tetrazoles or triazoles, which play an important role in pharmaceutical research.[14] For this protocol, we used a thiosulfate ion exchange resin for reductive workup to remove by-products such as iodine and IN_3, obviating the need for hydrolytic workup. Mechanistically, this oxidation could be initiated by hypoiodite formation, similar to that proposed in Scheme 7 for phenol oxidation.

Experimental section

General procedure for the oxidative azidation of phenols

A mixture of the phenol (0.5 mmol, 1.0 equiv.) and polymer-bound iodine azide (**4a**, 1.19 g, 2.50 mmol, 5.0 equiv. according to theoretical functionalisation) was stirred in absolute MeCN (4.16 mL, 3.5 mL g^{-1} polymer) at ambient temperature under an argon atmosphere. After complete consumption of the reactant as judged by TLC, the reaction was terminated by filtration and the resin was washed with EtOAc and the combined filtrates were concentrated under reduced pressure. E.g., this protocol provided 4-azido-3,4,5-trimethoxycyclohexa-2,5-dien-1-one (**12**) (107.8 mg, 479 μmol; 96% yield) starting from 3,4,5-trimethoxyphenol. **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ [ppm] 5.51 (s, 2H, 2 × C*H*), 3.77 (s, 6H, 3 × C═COCH_3), 3.18 (s, 3H, N_3-COCH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): δ [ppm] 185.5 (q, *C*═O), 165.3 (q, 2 × C=*C*OCH_3), 103.2 (t, 2 × *C*H), 85.2 (q, N_3-*C*OCH_3), 56.5 (p, 2 × C═CO*C*H_3), 53.0 (p, N_3-C*C*H_3); **IR** ν_{max} [cm^{-1}] 2116 $\nu(N_3)$; **ESI-MS** (ESI+) *m*/*z* calculated for $C_9H_{11}N_3O_4Na^+$ $[M + Na]^+$ 248.0647; found 248.0644

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 hypoiodite intermediates as a key step in achieving oxidative azidation of phenols and ketones.[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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