Organic & Biomolecular Chemistry

COMMUNICATION

Hypoiodous acid initiated rearrangement of tertiary propargylic alcohols to α-iodoenones†

Wesley J. Moran* and Arantxa Rodríguez*

In the presence of an oxidant, sodium iodide is converted into hypoiodous acid which effects the rearrangement of tertiary propargylic alcohols to α-iodoenones in good yields.

Polyvalent iodine species are mild and selective reagents that have attracted significant attention in organic synthesis because of their range of useful reactivity, low toxicity, and ease of use and handling.[1] The majority of research has concentrated on the use of iodine(III) and iodine(V) compounds, however very recently iodite(I) and iodite(III) species have emerged as useful oxidants in a handful of reactions.[2]

Substituted propargylic alcohols are readily prepared from aldehydes/ketones and terminal alkynes and serve as versatile synthetic intermediates.[3] They have been utilized as starting materials in a variety of processes including polyvalent iodine mediated transformations such as the NIS mediated rearrangement/iodination of acyclic tertiary propargylic alcohols (*e.g.* **1**),[4] and the polymer supported iodobenzene diacetate mediated ring expansion/iodination of 1-alkynylcycloalkanols (*e.g.* **2a**) to β-iodoenones **3** (Scheme 1).[5] Both of these reactions involve carbonyl formation as the driving force in 1,2-rearrangement processes.

Bovonsombat and McNelis showed that the three tertiary propargylic alcohols **2a–c** could be rearranged to α-iodoenones **4a–c** in moderate yields using one equivalent of NIS and 0.1 equivalents of Koser's reagent (PhI(OH)OTs) in methanol (Scheme 2).[6] Little preference for either alkene isomer was observed. Intriguingly, under these conditions the oxygen is the migrating group. Zhang and co-workers reported a related gold-catalyzed rearrangement of propargylic acetates to α-iodoenones.[7]

As part of a wider program to investigate the reactivity of polyvalent iodine species, we were interested in developing rearrangements of tertiary propargylic alcohols such as **2** utilizing hypoiodite species. It is known that treating iodide with oxidants can lead to the formation of hypoiodous acid (or iodic
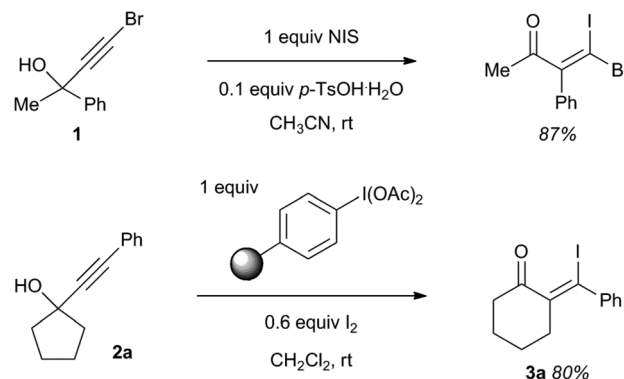
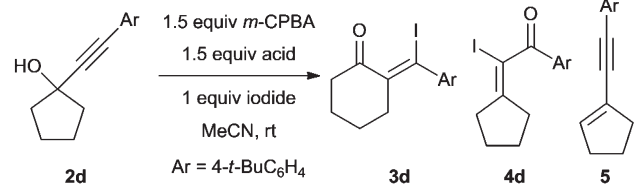**Scheme 1** Polyvalent iodine mediated rearrangements of tertiary propargylic alcohols.
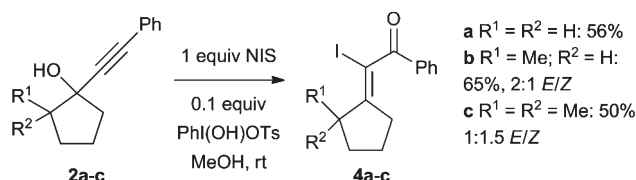
Scheme 2 NIS mediated rearrangement.

acid), however its reactivity has been little studied.[2] At the start of our investigation with cyclic tertiary propargylic alcohols **2**, four possible outcomes were identified: (i) no reaction; (ii) rearrangement with ring expansion; (iii) rearrangement without ring expansion; or (iv) a new reaction.

In the event, alcohol **2d** was treated with *m*-CPBA, *p*-toluenesulfonic acid and sodium iodide in acetonitrile at room temperature (Table 1, entry 1). Perhaps unsurprisingly, the strong acid led to dehydration of the starting material and enyne **5** was isolated in 83% yield. Presumably, the alkene was not epoxidised as the *m*-CPBA had been used up in oxidising the iodide. Changing the acid to trifluoroacetic acid also led to isolation of enyne **5** in 80% yield (entry 2). With acetic acid, rearrangement occurred, without ring expansion, to provide α-iodoenone **4d** but in only 9% yield (entry 3).[8] Changing to trichloroacetic acid, the α-iodoenone **4d** was formed in 50% yield (entry 4). Exchanging sodium iodide for tetrabutylammonium iodide led to a similar

Department of Chemical and Biological Sciences, University of Huddersfield, Huddersfield HD1 3DH, UK. E-mail: w.j.moran@hud.ac.uk, a.r.menendez@hud.ac.uk; Fax: +44 (0)1484 472182; Tel: +44 (0)1484 473741
†Electronic supplementary information (ESI) available: General experimental methods, compound characterisation data, copies of NMR spectra. See DOI: 10.1039/c2ob26360b

Table 1 Hypoiodite initiated rearrangement

| Entry	Acid	Iodide	Yield^a (%)
1	4-Toluenesulfonic acid monohydrate	NaI	83 (**5**)
2	Trifluoroacetic acid	NaI	80 (**5**)
3	Acetic acid	NaI	9^b (**4d**)
4	Trichloroacetic acid	NaI	50^b (**4d**)
5	Trichloroacetic acid	Bu$_4$NI	50^b (**4d**)
6	Trichloroacetic acid	NaI	75^c (**4d**)
7	—	NaI	8^b (**4d**)

^{a} Yield of pure isolated product. ^{b} Yield determined by ^{1}H NMR analysis. ^{c} 3 equiv. of *m*-CPBA used.

yield of product however the ^{1}H NMR spectrum of the crude reaction mixture was noticeably messier, therefore the use of sodium iodide was preferred (entry 5). The amount of oxidant was increased to three equivalents and 75% of the α-iodoenone **3** was isolated (entry 6). The reaction was carried out without the acid which led to product formation, however in just 8% yield (entry 7). None of the ring expanded product **3d** was evident in any of these reactions. Trichloroacetic acid is envisaged to have just the right acidity to lead to formation of **4** without causing formation of enyne **5**. The use of hydrogen peroxide in place of *m*-CPBA led to no reaction.

With the optimized conditions in hand, the scope of the rearrangement process was investigated (Scheme 3).‡ Varying the aromatic substituent had no adverse effect on the reaction outcome and the α-iodoenones were formed in good yields. Increasing the size of the ring to six, seven and eight membered and using open chain substrates also led to efficient rearrangements in all cases studied. Unsymmetrical substrate **2p** (R^1 = Me, R^2 = Et) underwent rearrangement to provide **4p** as a 1 : 1 mixture of separable *E* and *Z* alkene isomers, whereas **2q** (R^1 = Me, R^2 = *t*-Bu) rearranged stereoselectively to **4q** (only the *E* isomer could be identified by NMR analysis of the crude reaction mixture).[9] These results can be rationalised by consideration of the steric interactions. In the former case, methyl and ethyl are of similar size whereas a *tert*-butyl group is much larger than a methyl substituent. The phenyl ketone group can rotate out of the plane of the alkene leaving more space for the *tert*-butyl. However, this result is surprising considering the NIS-mediated rearrangement of **2c** to **4c** only gave a 1 : 1.5 *E/Z* ratio (*vide supra*).

The use of alkyl substituted alkynes led to very low conversions (<10%) to the α-iodoenones. Whereas secondary propargyl alcohols failed to rearrange at all under these conditions.

The mechanism of this rearrangement is postulated to proceed through oxidation of the iodide to hypoiodous acid (HOI) which reacts with the alkyne to generate an iodonium cation (Scheme 4). Addition of water, followed by a proton transfer and loss of water
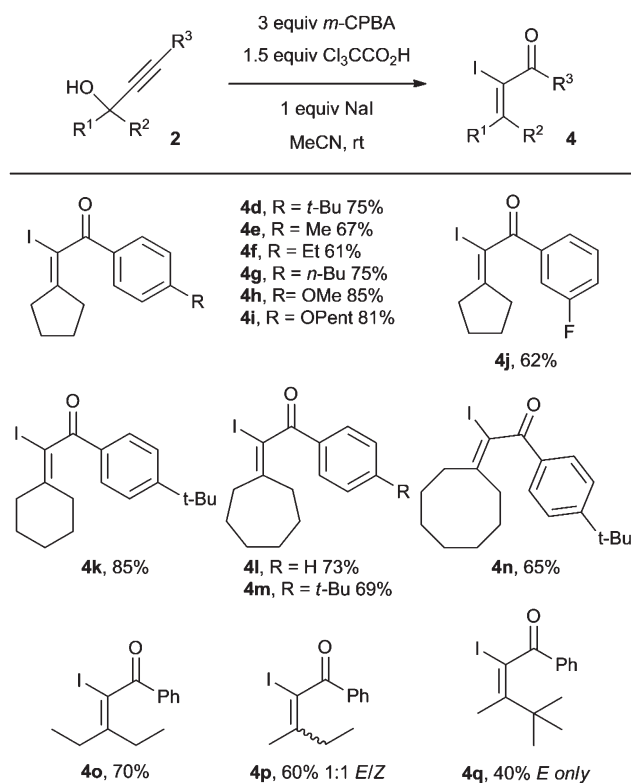
Scheme 3 Scope of rearrangement process.
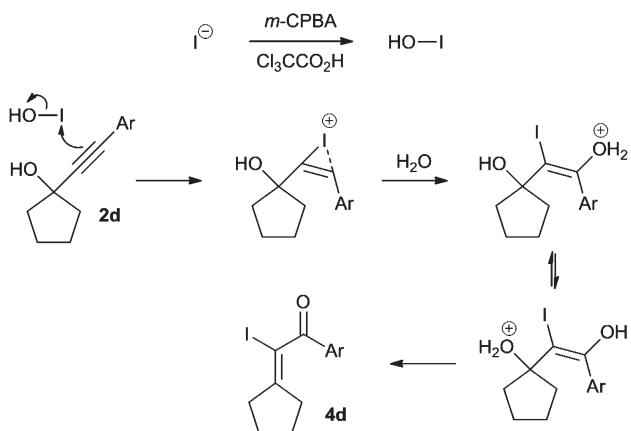
Scheme 4 Postulated hypoiodous acid initiated rearrangement mechanism.

generates the final product **4**. Iodide can also be oxidised to iodic acid (HIO$_3$), and hypoiodous acid can disproportionate into iodic acid and iodine;[10] however, as the final product is an alkenyl iodide, hypoiodous acid is probably the reactive species. Reaction with iodine should lead to formation of ring-expanded product **3**, however this compound is not observed.

In conclusion, we have demonstrated that *in situ* generated hypoiodous acid initiates the rearrangement of tertiary propargylic alcohols to α-iodoenones in good yields. This process is exceptionally simple to carry out and the products are potentially valuable for further synthesis.[11] Related studies are in progress and will be reported in due course.

Notes and references

‡ Typical reaction procedure: Substituted propargylic alcohol **2** (0.21 mmol), *m*-CPBA (109 mg, 0.63 mmol), sodium iodide (31 mg, 0.21 mmol) and trichloroacetic acid (51 mg, 0.31 mmol) were dissolved in acetonitrile (1 mL) at room temperature under a nitrogen atmosphere and stirred overnight. The reaction mixture was quenched with saturated aqueous sodium thiosulfate solution and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous sodium bicarbonate solution, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate) to afford the corresponding α-iodoenone **4**.

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6 P. Bovonsombat and E. McNelis, *Tetrahedron Lett.*, 1993, **34**, 8205.

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8 Compounds **3d** and **4d** are distinguishable by ^{1}H NMR as shown in ref. 4*a* and 5*a*.

9 *E*-isomer assigned with the aid of NOESY experiments; see ESI† for further details.

10 $5HIO \rightarrow HIO_3 + 2I_2 + 2H_2O$.

11 For example, see: E. Negishi, *J. Organomet. Chem.*, 1999, **576**, 179.

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