Iodine Monoacetate for Efficient Oxyiodinations of Alkenes and Alkynes
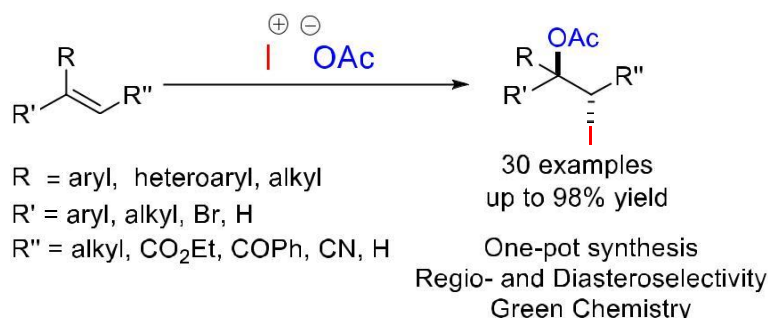
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R = aryl, heteroaryl, alkyl
R' = aryl, alkyl, Br, H
R'' = alkyl, CO$_2$Et, COPh, CN, H

30 examples
up to 98% yield

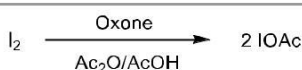One-pot synthesis
Regio- and Diasteroselectivity
Green Chemistry

Abstract A novel and inexpensive, environmentally friendly method for the preparation of iodine monoacetate is presented using iodine and Oxone in acetic acid/acetic anhydride. The reagent is used in a highly efficient approach for the regio- and diastereoselective iodoacetoxylation of alkenes and alkynes in a simple one-pot process.

Key words alkenes, alkynes, iodine, iodine(I)acetate, oxyiodination

Iodine monoacetate is an important reagent for the functionalisation of alkenes, alkynes and ketones.[1] It has been reported to be easily accessible from an equimolar mixture of silver acetate and iodine[2] and higher homologues of the reagent have been made from silver carboxylates and iodine for the synthesis of aliphatic esters.[3] However, iodine monoacetate has not yet been isolated and has only been characterised by ^{1}H NMR[4] and spectrophotometrically.[5] As silver acetate is an expensive reagent, there are alternative ways of generating iodine monoacetate. It can be prepared from very toxic mercuric acetate,[6] lead tetraacetate,[7] peracetic acid[8] or (diacetoxy-iodo)benzene[4] by reaction with iodine.

Herein, we report a novel method for the synthesis of iodine monoacetate using elemental iodine and Oxone in combination with acetic anhydride and acetic acid (Scheme 1).
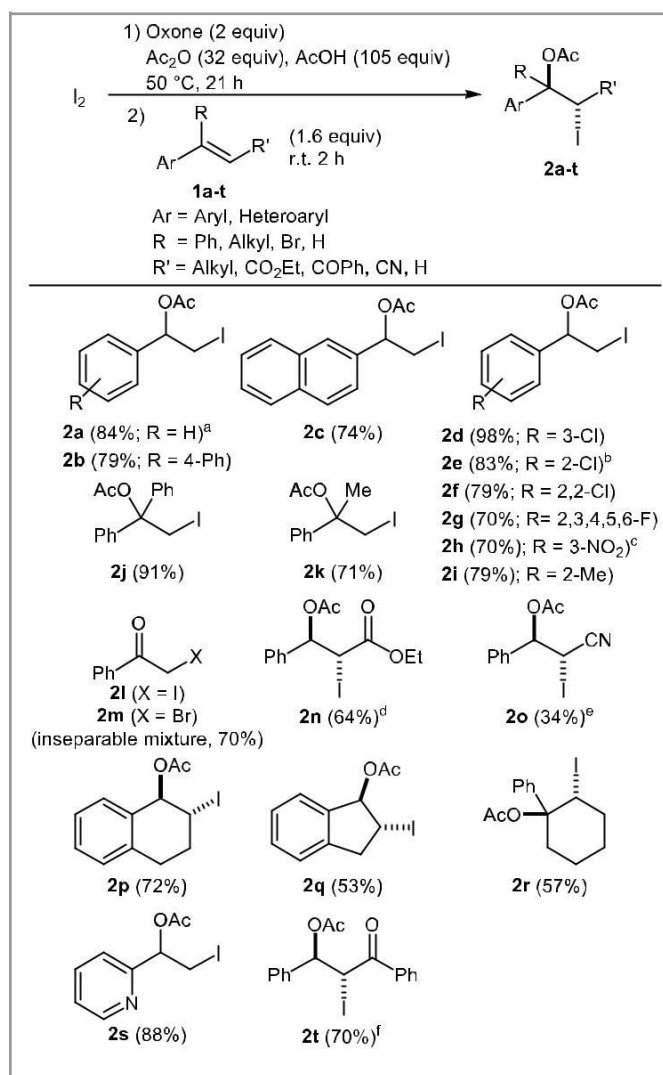
I$_2$ $\xrightarrow[\text{Ac}_2\text{O/AcOH}]{\text{Oxone}}$ 2 IOAc

Scheme 1 Formation of iodine monoacetate using iodine and Oxone.

Oxone is an inexpensive and environmentally safe oxidant which is known to oxidise iodine salts such as ammonium iodide to iodine(I). This has been explored in the synthesis of α-iodinated ketones[9] or to prepare iodohydrins and iodoesters from alkenes[10] and, in combination with sodium iodide, to make α-aryl ketones from arylalkenes.[11]

We started our investigation to form iodine monoacetate using iodine and Oxone in acetic acid/acetic anhydride. The success of reaction was indicated by a subsequent reaction with styrene (**1a**) as test substrate which reacts in an iodoacetoxylation to **2a**. Best results for the iodoacetoxylation were achieved by treatment of iodine with 2 equivalents of Oxone in a mixture of acetic acid and acetic anhydride at 50 °C for 21 h. After addition of styrene (**1a**) (2 equiv) and 2 h reaction time at room temperature, only the Markovnikov product **2a** was obtained in 84% yield in this one-pot synthesis. Further optimisation experiments such as concentration of the reagents and reaction times are described in the supporting information (Table S1). An iodoacetoxylation in the absence of acetic anhydride did not provide **2a** and with traces of acetic acid in acetic anhydride a much longer reaction time and a higher amount of oxone were necessary, indicating that both, acetic acid and acetic anhydride, are necessary for the success of this reaction. The reaction scope with iodine monoacetate was explored with different arylalkenes (Scheme 2). The phenyl-substituted aromatic ring in **1b** did not affect the yield of **2b** (79%) and also 2-vinylnaphthalene (**1c**) provided **2c** with good yield (74%). A chlorine substituent in 3-position led to an almost quantitative yield of **2d** (98%), whereas substitution in 2-position gave 83% of **2e** together with the corresponding iodohydrin (4%). Furthermore, 2,6-dichlorostyrene (**1f**) gave similar yield (79%). Strong electron withdrawing groups such as fluoro- (**2g**) and nitro substituents (**2h**) reduced the yield to 70%, whereas a methyl substituent did not affect the outcome of the reaction (**2i**, 79%). Afterwards, the effect of substituents in α-position was investigated. A high yield was achieved for the iodoacetoxylation of **1j** with a phenyl substituent in α-position (**2j**, 91%), a methyl substituent gave 71% yield of **2k**. An inseparable mixture of ketones **2l** and **2m** (1.25:1) was obtained using α-bromostyrene as starting material.
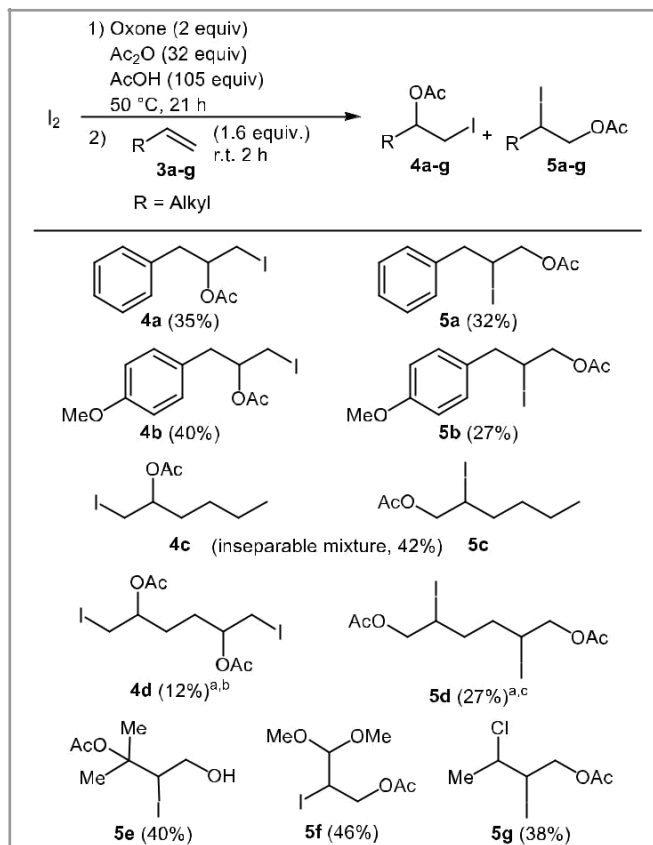
Scheme 2 Substrate scope for the iodoacetoxylation of styrene derivatives (0.5 mmol I$_2$, 1 mmol Oxone, 0.8 mmol alkene in Ac$_2$O (1.5 mL) and AcOH (3.0 mL).

[a] 2.0 equivalents of **1a** were used; [b] The corresponding iodohydrin was isolated in 4% yield; [c] Iodohydrin was isolated in 26% yield; [d] Recovery of 8% starting material [e] 4 Days reaction time; Recovery of 59% starting material; [f] Recovery of 10% starting material.

Next, the influence of substituents in the β-position was investigated. To our delight, reactions of ethyl cinnamate (**1n**) and cinnamonitrile (**1o**) demonstrated the tolerance of substituents in the β-position to give regio- and diastereoselective iodoacetoxylation providing the *trans*-product **2n** in good yield (64%). However, the cyanide substituent slows down the reaction. After a reaction time of 4 days **2o** was isolated in 34% yield and 59% of **1o** recovered. Additionally, cyclic alkenes such as 1,2-dihydronaphthalene (**1p**), indene (**1q**) or 1-phenyl-1-cyclohexene (**1r**) can be used in this one-pot functionalisation to give reasonable yields of compounds **2p**, **2q** and **2r** (53% to 72%). The heteroaromatic compound 2-vinylpyridine (**1s**) was converted in excellent yield (88%) to **2s** and chalcone (**1t**) gave product **2t** in good yield (70%).

The reactivity of non-conjugated alkenes with iodine monoacetate was explored (Scheme 3). As expected, allylbenzene (**3a**) provided a mixture of regiosiomers and the Markovnikov product **4a** and *anti*-Markovnikov product **5a** were obtained in almost equal

amounts (35% and 32%). A larger excess of Markonvikov product (1.5:1) was obtained with a methoxy substituent in 4-position (**3b**) to give **4b** and **5b** in 40% and 27% yield, respectively. 1-Hexene (**3c**) gave a better regioselectivity and **4c/5c** in 42% combined yield (**4c/5c** = 2:1). Furthermore, 1,5-hexadiene (**3d**) provided diasteromers of product **4d** (12%) and **5d** in addition to a third regioisomer (27% combined yield). Surprisingly, 2-methyl-3-buten-2-ol (**3e**) led to the rearranged product **5e** (40%).[12] Alkenes **3f** and **3g** were functionalised in moderate yields to exclusively **5f** (46%) and **5g** (38%).

Scheme 3 Substrate scope for the iodoacetoxylation of alkyl-substituted alkenes.

[a] 0.8 Equivalents of **3d** were used; [b] Mixture of diasteromers; [c] Mixture of diasteromers of **5d** and a third regioisomer.
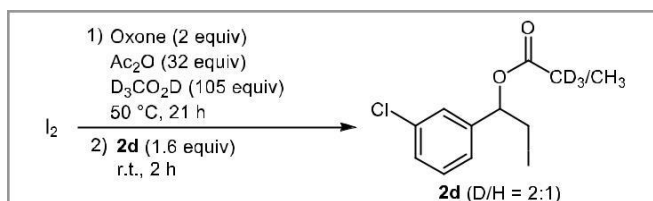
Interestingly, alkynes also reacted smoothly under the same reaction conditions in good yields to the iodoacetoxylated products. A mixture of **7a** and **8a** was obtained by reaction of phenylacetylene (**6a**) in 60% combined yield. **8a** is the result of a second iodoacetoxylation of **7a** followed by ketal cleavage. On the contrary, 1-phenyl-1-propyne (**6b**) led exclusively to product **7b** (71%) and 1-hexyne (**6c**) gave only the diiodoketone **7c** in 73% yield. Compound **6d** did not react in the expected way and the diiodinated product **7d** was obtained (39%) as verified by literature spectra.[13] Additionally, propiophenone (**6e**) could be iodinated in the α-position to give **7e** in good yield (70%). Compound **8e** was obtained as side product in 5% yield.

Table 1 Reaction of iodine monoacetate with other substrates.

Entry	Substrate	Product(s)
1	6a	7a + 8a (inseparable mixture, 60%)
2	6b	7b (71%)
3	6c	7c (73%)
4	6d	7d (39%)
5	6e	7e (70%) + 8e (5%)

[a] BF$_3$·OEt$_2$ (2.4 mmol) was added.

To further verify the existence of iodine monoacetate, acetic acid and acetic anhydride were removed and the remaining oil was examined, which was protected from moisture to prevent decomposition, *via* ^{1}H NMR. A peak at δ_H = 2.19 ppm reveals the formation of iodine monoacetate.[4] To get further insight into the role of acetic acid and acetic anhydride, acetic acid was replaced by deuterated acetic acid-d$_4$ followed by reaction with styrene (Scheme 4). In this case, partial deuteration of product **2a** was observed (D/H = 2:1), which indicates again that both, acetic acid and acetic anhydride, play an important role in the formation of iodine monoacetate.

Scheme 4 Iododeuteroacetoxylation of **1a** in acetic acid-d$_4$.

In conclusion, we have demonstrated a novel and inexpensive, environmentally friendly method for the formation of iodine monoacetate using iodine and Oxone in a mixture of acetic acid and acetic anhydride. The reagent was used in a highly efficient approach for the regio- and diastereoselective iodoacetoxylation of

alkenes and alkynes in a simple one-pot process. Scope and limitation of the method was illustrated with a broad range of alkenes and alkynes. Styrene derivatives gave highest yields, whereas allylic and aliphatic olefins produced regioisomeric mixtures in lower yields. Alkynes led to mono- and diiodinations in comparable yields. Compared to previous procedures, this inexpensive, metal-free and environmentally friendly method provides high yields and mild reaction conditions.

Supporting Information

Yes.

Primary Data

No.

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