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Simplified synthesis of aryliodonium ylides by a one-pot procedure

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ABSTRACT

A simplified synthesis of iodonium ylides was developed by the one-pot synthesis of phenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide as a model system. Such ylides are excellent precursors for nucleophilic no-carrier-added ^{18}F-fluorination of even non-activated arenes. The suitability of the one-pot method is exemplified for several electron rich iodonium ylides. Further, the syntheses of 2-, 3- and 4-bromophenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide, and 4-iodophenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide, two novel precursors for 4-[^{18}F]fluoro-1-halobenzene, are reported.

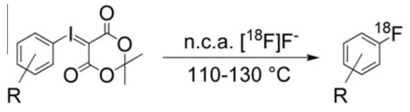
The use of iodonium ylides as precursors for labelling reactions with fluorine-18 has recently been described (Scheme 1).[1] Similar to the use of well-known iodonium salts as precursors,[2–4] even electron rich fluoroarenes can be prepared with aryl iodonium ylides starting from nucleophilic no-carrier-added (n.c.a.) [^{18}F]fluoride. In contrast to the reaction using iodonium salts that using iodonium ylides is claimed to be regiospecific.[1] This uncommon preparation of fluoroarenes is beneficial to the field of fluorine-18 chemistry since the production of electron-rich fluoroarenes would otherwise need electrophilic fluorination agents which require the addition of fluorine-19 as carrier. This results in poor molar activities of the final labelled products.[3,4]

Iodonium ylides are a subclass of zwitterionic iodonium compounds in which a carbon with carbanionic character is present.[5] The carbanionic carbon has to carry strong electron withdrawing groups, such as carbonyl-, ester or amide groups.[5,6] Most iodonium ylides are unstable and decompose at room temperature within hours, while the iodonium ylides formed from Meldrum's acid are comparatively stable. This makes them attractive candidates for use as labelling precursors of [^{18}F]fluoroarenes. Although the existence of the carbon–iodine double bond of ylides is questionable, it is a common practice to draw iodonium ylides as neutral structures.[5] Several resonance structures for phenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide **1** are depicted in Scheme 2 indicating the zwitterionic character of iodonium ylides.

Iodonium ylides are favourably prepared by the reaction of active methylene compounds with diacetoxyiodoarenes under basic conditions, as shown for the reaction between diacetoxyiodobenzene (**2**) and Meldrum's acid (**3**) in Scheme 3.[6] Dichloromethane,[7] mixtures of water and alcohol[8] or acetonitrile[9] are reported as suitable solvents while Na_2CO_3 and KOH are commonly used as bases. Since the two-step methods described so far cause problems with the isolation and purification in case of more complex diacetoxyiodoarenes the procedure here avoids this by using a one-pot reaction.

It is known that bisacyloxyiodoarenes as well as a number of other iodine-III species (**4**) form corresponding iodosoarenes under basic conditions (Scheme 4).[10] Thus, the reaction shown in Scheme 3 is presumably a reaction between Meldrum's acid and iodosobenzene (**5**). This assumption is also in agreement with the results obtained by Goudreau et al. who observed no difference when iodosobenzene was used as aryliodine-III precursor instead of diacetoxyiodobenzene.[7] This means that the reaction should in principal also be possible starting from alternative iodine-III precursors.

In order to simplify the preparation procedure for the synthesis of iodonium ylides, (with regard to those ylides of more complex aryliodides) the possibility of a one pot procedure was investigated. First the iodonium ylide **1** was prepared by several known



Scheme 1. Radiofluorination of iodonium ylides.[1]

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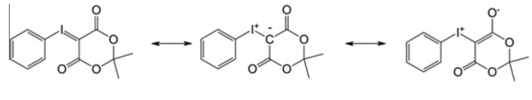
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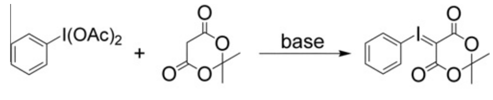
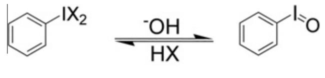
Scheme 2. Resonance structures of phenyliodonium ylide **1**.



2 **3** **1**

Scheme 3. Synthesis of iodonium ylide **1**.



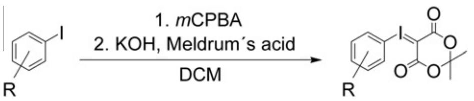
4 **5**

Scheme 4. Equilibrium between the phenyliodosobase and its salts ($X = RCO_2^-, Cl^-$).[10]

modifications (base, solvent) of the method according to Scheme 3 starting from compound **2** and Meldrum's acid. Here, the best results were obtained with the procedure by Goudreau et al.[7] delivering **1** in 31% yield. The yield obtained, however, was lower than reported which was also observed in the following reactions (see below). This is probably due to slight differences in the isolation of the only moderately stable product. However, since the isolation of the products here was always performed by the same protocol, the results obtained are considered to be comparable.

Alternatively iodobenzene was first oxidized with *meta*-chloroperoxobenzoic acid (*m*CPBA) in DCM, an oxidation procedure which has been used by Bielawski and Olofsson for the synthesis of iodonium salts,[11] and subsequently a suspension containing Meldrum's acid and KOH was added. Using this procedure product **1** was formed in 36% yield. Obviously *meta*-chlorobenzoate does not have a negative impact on the reaction. Finally, the reaction was also conducted as a two-step one-pot procedure adding KOH and Meldrum's acid directly as solids to previously *m*CPBA-oxidized iodobenzene (Table 1). Here the product was formed in 31% yield proving the possibility of a one pot procedure. In an additional experiment starting from iodosobenzene and Meldrum's acid the desired product was isolated in 30% yield, showing no difference in the reactivity of diacetoxyiodobenzene and iodosobenzene which is consistent with the results of Goudreau et al.[7] discussed above. In general, results of all procedures were comparable under the chosen conditions with the yield of the desired product **1** amounting to 33 ± 3%.

Table 1
Iodonium ylides produced by the one-pot procedure



Entry	R	Yield (%)
1	H	31
2	3-OBn	0
3	4-OBn	44
4	2-OMe	59
5	3-OMe	26
6	4-OMe	35
7	4-Me	20
8	2-Br	29
9	3-Br	13
10	4-Br	28
11	4-I	19

As further examples of the synthesis of more complex iodonium ylides, that is, isomeric iodophenoxyethers, 3-benzyloxy-phenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide and 4-benzyloxy-phenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide were prepared by the one pot procedure (Table 1, entries 2 and 3). While the *para*-derivative was produced in 44% yield it was not possible to isolate the desired product in the case of the *meta*-derivative under the same reaction conditions. However, in the case of the iodonium ylides derived from 2-, 3-, 4-iodoanisole and 4-iodotoluene the one-pot procedure worked quite well (Table 1, entries 4–7). The yield of 2-methoxyphenyl-iodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide amounting to 59 % was surprisingly high. This could be due to an additional stabilization of the iodine-III centre by the neighbouring oxygen. Additionally 2-, 3- and 4-bromophenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide, which are possible precursors for the corresponding [^{18}F]fluorobromobenzenes, were also synthesized by the one-pot procedure (Table 1, entries 8–10). While the yields of the *ortho*- and the *para*-derivatives were in the typical range of about 30% (Table 1, entry 2), the yield of 13% of the *meta*-derivative was noticeably low. This trend was also observed in the case of the anisole derivatives and could explain the problems in the synthesis of 3-benzyloxyphenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide. It seems to be correlated with electronic factors influencing either the oxidation or the stability of the product (or both).

Recently, we reported an improved synthesis of (4-iodophenyl)(aryl)iodonium salts which are precursors, for example, for the versatile intermediate 4-[^{18}F]fluoro-1-iodobenzene.[12] Since 4-iodophenyliodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-di-one]) ylide would be a further promising precursor for 4-[^{18}F]fluoro-1-iodo-benzene, an attempt was made to prepare this compound by the one-pot procedure. The yield of 19% was relatively low (Table 1, entry 11), which is presumably due to the previously reported difficulties in the oxidation of 1,4-diiodobenzene.[11] Thus, it was also tried to couple 4-iodo-1-[hydroxyl(tosyloxy)iodo]benzene, a derivative of Koser's reagent, to Meldrum's acid under conditions similar to those of Goudreau et al.[7] This way, the desired product was achieved in 42% yield, again demonstrating that coupling of various iodine-III precursors is possible in order to obtain iodonium ylides.

In conclusion, the possibility of a one-pot procedure for the synthesis of iodonium ylides was demonstrated. The application to two iodobenzyloxybenzene isomers, however, was only successful in the case of the 4-isomer while the synthesis of the corresponding anisole derivatives was successful for all three isomers. Additionally, the synthesis of the iodonium ylides derived from the *o*-, *m*- and *p*-bromoiodobenzenes, possible precursors for the corresponding [^{18}F]fluorobromobenzenes, was accomplished. Furthermore, the synthesis of 4-iodophenyl-iodonium-(5-[2,2-dimethyl-1,3-dioxane-4,6-dione]) ylide, a promising precursor of 4-[^{18}F]fluoro-1-iodobenzene, was accomplished by two different procedures.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.018.

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