Selective monoiodination of aromatic compounds with electrochemically generated I^+ using micromixing†

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Selective monoiodination of aromatic compounds such as dimethoxybenzene has been successfully achieved with I^+, which is generated by anodic oxidation of I_2 in acetonitrile, using micromixing.

Aromatic iodides are important intermediates in the synthesis of functional materials and biologically active compounds.[1] Although various methods for the synthesis of aromatic iodides have been developed so far,[2] iodination of aromatic compounds serves as one of the most straightforward routes to aromatic iodides.[3]

Iodination of aromatic compounds, however, is sometimes problematic because diiodination takes places together with monoiodination, especially in the case of highly reactive aromatic compounds. Selectivity for such competitive consecutive reactions is intrinsically determined by kinetics. However, if the reaction is faster than mixing, simple kinetics based on the homogeneity of the solution does not work. Rys proposed the concept of "disguised chemical selectivity" and pointed out the importance of the way of mixing to control chemical reactions.[4] Thus, we envisioned that the problem of monoiodination/diiodination selectivity can be solved by controlling the way of mixing.

Recently, we have reported that the product selectivity of extremely fast competitive consecutive reactions such as Friedel–Crafts alkylation of highly reactive aromatic compounds with an electrochemically generated highly reactive *N*-acyliminium ion pool[5] was improved significantly by using micromixing.[6] The monoalkylation product was obtained selectively when two reaction components were mixed in 1 : 1 ratio using an multilamination type micromixer (IMM micromixer), whereas a significant amount of dialkylation product was formed in a macro-scale batch process (reaction using a flask with magnetic stirring). The observations indicate that micromixing is quite effective for the improvement of product selectivity of extremely fast reactions using highly reactive reagents.[7]

As to the iodination reagent, we chose to study electrochemically generated "I^+" because this method serves as an environmentally benign industrial process for the synthesis of various aromatic iodides. In this paper, we report that monoiodination of aromatic compounds with electrochemically generated "I^+" took place selectively using a microsystem consisting of a micromixer and a microtube reactor.

Miller and co-workers reported that the electrochemical oxidation of iodine (I_2) in acetonitrile gave CH_3CNI^+ (equivalent of I^+) (eqn (1)) and that this reagent reacted with aromatic compounds to give the corresponding iodinated aromatic compounds (eqn (2)), although CH_3CNI^+ was not well-characterized spectroscopically.[8]

$$1/2\ \ I_2 + CH_3CN \xrightarrow{-e} \text{"}CH_3CN\text{-}I^+\text{"} \tag{1}$$

$$ArH + \text{“}CH_3CN\text{–}I^+\text{”} \rightarrow Ar\text{–}I + CH_3CN + H^+ \tag{2}$$

Romakhin *et al.* also reported that CH_3CNI^+ was obtained as cream-coloured powder by the anodic oxidation of I_2 in CH_3CN.[9] Although they said that the powder did not exhibit IR absorption due to the vibration of the CN triple bond, no other information was available.

It is important to know the nature of the reactive species in order to carry out 1 : 1 mixing strictly using a micromixer. We began our study with characterizing the electrochemically generated reactive iodine species. Following Miller's protocol, "I^+" was generated by the anodic oxidation of I_2 (0.0625 M) in 0.1 M Bu_4NBF_4–CH_3CN at 0 °C. The electrolysis was carried out using a platinum plate anode and a platinum plate cathode under constant current conditions in an H type divided cell. The mixture thus obtained was directly measured by CSI-MS (cold spray ionization mass spectrometry, a variant of electrospray (ESI) MS operating at low temperature, which is quite useful to identify labile reactive species).[10] The signal which could be assigned to CH_3CNI^+ (m/z = 167.9300, Calcd: 167.9305) was observed at 0 °C (Fig. 1). It is interesting to note that $(CH_3CN)_2I^+$ was also observed (m/z = 208.9569, Calcd: 208.9570). The intensity of the peak of $(CH_3CN)_2I^+$ was larger than that of CH_3CNI^+, and the relative intensity depended on the ionization temperature on

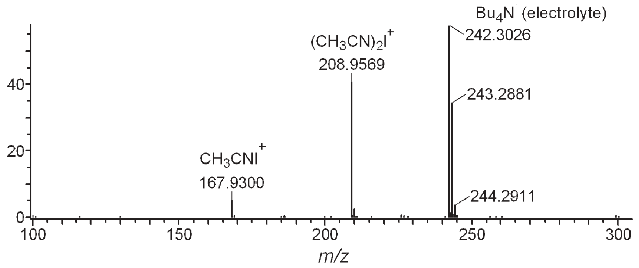

Fig. 1 CSI-MS of electrogenerated I^+ in 0.1 M Bu_4NBF_4–CH_3CN (2.0 F mol^{-1} based on I_2).

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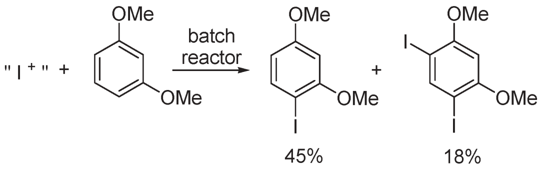
CSI-MS. The amount of CH_3CNI^+ increased at the expense of $(CH_3CN)_2I^+$ at higher ionization temperature. These observations suggested that I^+ is mainly existing as $(CH_3CN)_2I^+$ and CH_3CN is partially liberated to give CH_3CNI^+.[11] To the best of our knowledge, this is the first indication that $(CH_3CN)_2I^+$ is the major reactive species in solution generated by electrochemical oxidation of I_2 in CH_3CN.

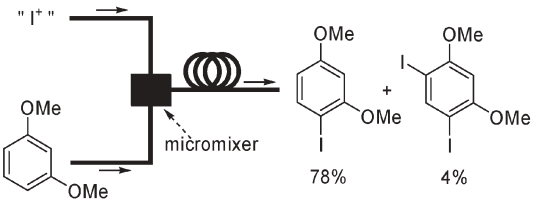
With the reactive iodine species characterized by CSI-MS in hand, we next examined the reaction of 1,3-dimethoxybenzene using a macro-scale batch reactor at 0 °C. The reaction with the "I^+" generated from 0.625 equiv. of I_2 (0.0625 M) in 0.3 M Bu_4NBF_4–CH_3CN with 2.1 F mol^{-1} of electricity based on I_2 gave rise to the formation of the monoiodo compound as a major product (45% yield) (eqn (3)). A significant amount of the diiodo compound, however, was also formed (18% yield). Although roles of the two reactive species (CH_3CNI^+ and $(CH_3CN)_2I^+$) in the iodination are not clear at present, the present observation indicated the effectiveness of these species for the iodination of aromatic compounds.



(3)

Since a monoiodo compound should be less reactive than the parent compound because the iodo group is an electron-withdrawing group, the formation of the diiodo compound can be ascribed to disguised chemical selectivity. Thus, we examined the use of micromixing[12] to solve the diiodination problem.[13,14] The micromixing (flow rate 3.0 mL min^{-1} for each) of 1,3-dimethoxybezene with electrochemically generated "I^+" (generated from 0.625 equiv. of I_2) using a microsystem consisting of an IMM single mixer (channel width 50 μm) and a microtube reactor (ϕ = 500 μm × 2 m) at 0 °C resulted in significant increase of the selectivity (Scheme 1). The monoiodo compound was obtained in 78% yield, whereas the diiodo compound was obtained in only 4% yield. The smaller effect of micromixing in the present reaction in comparison with that observed for the Friedel–Crafts alkylation seems to be attributed to the smaller rate of iodination because CFD (computational fluid dynamics) simulation indicated that the effect of the micromixing on the selectivity increases with the increase in reaction rate.[6b]

The effect of the flow rate on the selectivity was examined, because it is known that the mixing rate strongly depends on the flow rate. The IMM single mixer gave a better mixing performance at larger volume flow rate (greater than a few mL min^{-1}).[15] As shown in Fig. 2, the selectivity of the monoiodo compound decreased dramatically with the decrease in flow rate. This observation indicates that the observed improvement in selectivity is ascribed to the extremely fast mixing.



Scheme 1 Selective monoiodination of 1,3-dimethoxybenene using micromixing.

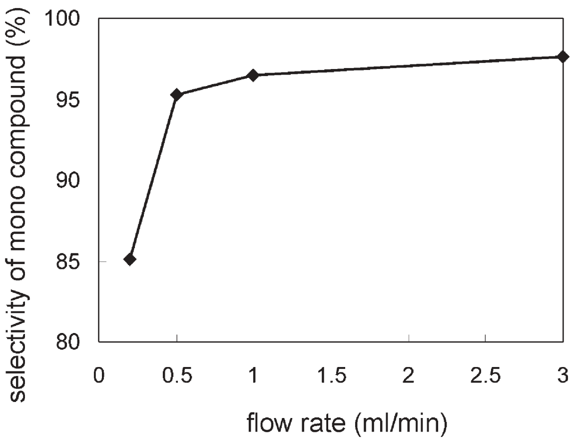
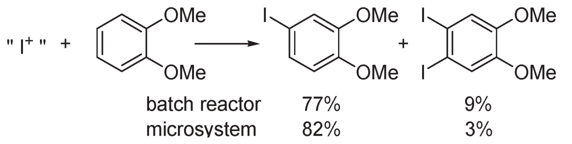


Fig. 2 Effect of flow rate of "I^+" solution on the selectivity of iodination of 1,3-dimethoxybenene (the flow rate of 1,3-dimethoxybenzene solution was adjusted to the same flow rate).

A similar effect of micromixing was observed for the reactions of 1,2- and 1,4-dimethoxybenzene, and 1,3,5-trimethoxybenzene, indicating the generality of the effect of micromixing on the selectivity (eqn (4–6)).



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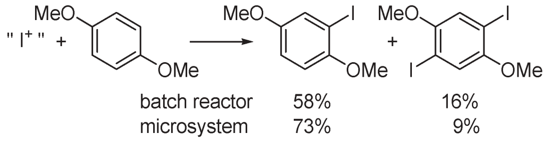

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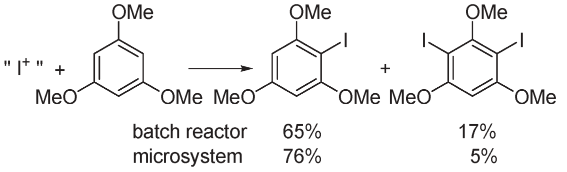

(6)

In summary, $(CH_3CN)_2I^+$ was found to be the major species generated by anodic oxidation of I_2 in CH_3CN by using CSI-MS. It was also revealed that the reaction with aromatic compounds using micromixing led to selective monoiodination. The effect is ascribed to extremely fast micromixing, which solves the problem of disguised chemical selectivity. The present results speak well for the potential of the combination of electrochemical generation of a highly reactive species and the use of microsystems for selective organic synthesis.[16–18] Further work aimed at revealing the precise mechanism and the synthesis of various aromatic iodides in larger scale[19] is now in progress.

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