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Highly selective Friedel–Crafts monoalkylation using micromixing†

Seiji Suga, Aiichiro Nagaki and Jun-icih Yoshida*
Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan. E-mail: yoshida@sbchem.kyoto-u.ac.jp;
Fax: +81-75-753-5911; Tel: +81-75-753-5651

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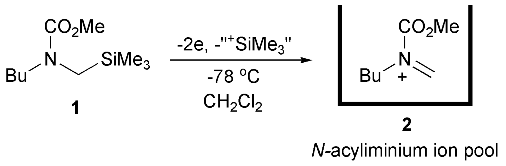
Highly selective Friedel–Crafts monoalkylation of aromatic compounds with *N*-acyliminium ions has been achieved by efficient 1 : 1 mixing using a multilamination-type micromixer.

Microreactors (miniaturized chemical reactors)[1]are expected to make a revolutionary change in chemical synthesis[2] from both academic and industrial viewpoints.[3] With the advancement of microfabrication technology, development of new synthetic methodologies based upon the inherent features that exist at the micrometer scale is strongly needed. It is generally expected that extremely fast and exothermic reactions can be conducted in a highly controlled manner in micro-structured reactors by virtue of the advantages of efficient mixing and heat transfer. Thus, we have examined the reaction of *N*-acyliminium ion pools,[4] which has been developed by our group as a highly reactive species toward various nucleophiles, using a micro-structured device. We chose Friedel–Crafts type alkylation reactions of aromatic compounds[5] because the use of a conventional macro-scale batch reactor usually leads to the formation of significant amounts of polyalkylation products together with a desired monoalkylation product.[6] We envisioned that efficient 1 : 1 mixing using a micro-scale mixer[7] would facilitate the selective formation of a monoalylation product.[8]

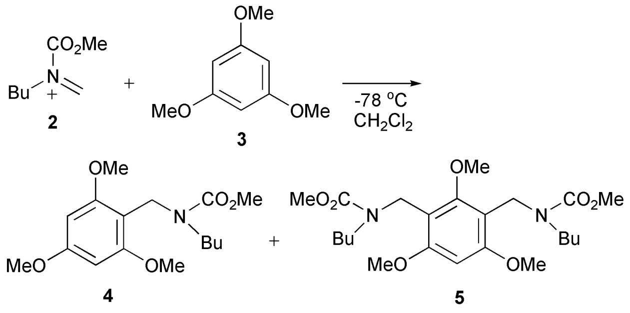
N-Acyliminium ion **2** is generated by the anodic oxidation[9] of carbamate **1** having a silyl group as an electroauxiliary[10] in CH_2Cl_2 and is stable in the absence of a nucleophile as shown in Scheme 1.

Prior to using a micromixer, the reaction using a conventional batch reactor was examined. The addition of **2** (produced from 1.2 equiv. of **1**)[11] to aromatic compound **3** resulted in the formation of an essentially 1 : 1 mixture of monoalkylation product **4** and dialkylation product **5** (Scheme 2). The reverse addition and the simultaneous addition of the solution of **2** and that of **3** to a batch reactor also gave essentially the same results. These observations indicated that it is quite difficult to avoid dialkylation using a conventional batch reactor presumably because of inefficient mixing.

To effect the desired efficient 1 : 1 mixing for monoalkylation, we used a multilamination-type micromixer produced by IMM (Institut für Mikrotechnik Mainz GmbH) as shown in Fig. 1. In this micromixer the fluids to be mixed are introduced into the mixing element as two counter-flows and the fluids stream into an interdigital channel (channel width = 25 μm) configuration. In the next stage, a periodical flow configuration consisting of the lamellae of the two fluids is generated by means of the slit-shaped interdigital channel. Then, the lamellated flow leaves the device perpendicular to the direction of the feed flows. The reaction of the *N*-acyliminium ion **2** with aromatic compound **3** using the micromixer was carried out as follows. The solutions of **2** (produced from 1.2 equiv. of **1**)[11] and **3** were introduced to the mixer by syringe pumping technique (flow rate: 5.0 mL min^{-1}) at −78 °C and the product solution that left from the device was immediately quenched with triethylamine in order to avoid further reactions.[12] To our surprise, the monoalkylation product **4** was obtained in excellent selectivity, and the amount of dialkylation product **5** was extremely small (**4** : **5** = 96 : 4, total yield 96%). A T-shaped tube mixer (ϕ = 500 μm) was also examined, but the selectivity was essentially the same as the batch reactor.



Scheme 1



reactor	**4** (%)	**5** (%)	**4** : **5**
batch	37	32	54 : 46
T-shaped tube (ϕ = 500 μm)	36	31	54 : 46
micromixer (channel width = 25 μm)	92	4	96 : 4

Scheme 2

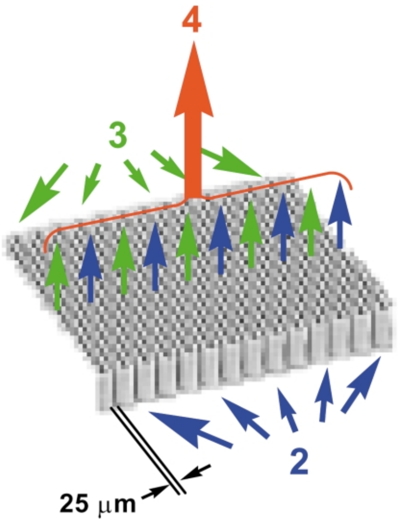


Fig. 1 Schematic diagram of mixing using an IMM micromixer (channel width = 25 μm).

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† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b2/b211433j/

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The amount of **2** is crucial for the selectivity. The use of 1.2 equiv. of precursor **1** gave the best results.[11] The use of 2.0 and 2.5 equiv. of **1** resulted in the formation of significant amount of **5** (**4**:**5** = 79:21 and 67:33, respectively). Probably surplus **2** further reacted with **4** to give **5**. The reaction temperature was also found to be an important factor governing the selectivity. With the increase of the temperature, the yield of **4** decreased dramatically, whereas the yield of **5** increased as depicted in Fig. 2. It is reasonable to consider that the present Friedel–Crafts type alkylation using the extremely reactive *N*-acyliminium ion seems to be very exothermic and that it is difficult to control the reaction temperature by using a conventional macro-scale reactor. In the case of a micromixer, however, precise control of the temperature could be achieved by virtue of high surface to volume ratio of micro-scale reactors.

The dramatic effect of the micromixing is generally observed for the alkylation of other aromatic compounds with *N*-acyliminium ion **2**. The reaction of **2** with thiophene in the micromixer took place smoothly to give the monoalkylation product **6** exclusively, while the reaction in the batch reactor gave significant amount of dialkylation product **7** as shown in Scheme 3. A similar tendency was also observed for the reaction of furan and *N*-methylpyrrole.[13]

The sequential alkylation reactions with two different alkylating agents were also achieved. The first alkylation was carried out with *N*-acyliminium ion **2** using the micromixer to obtain the monoalkylation product **6** (X = S), which was directly subjected to the second alkylation with a different *N*-acyliminium ion **8** in a batch reactor to obtain dialkylation product **9** (Scheme 4).

Therefore, the present method provides a simple and straightforward method for the selective introduction of two different alkyl groups on an aromatic ring.

In summary, micromixing provides a solution to Friedel–Crafts polyalkylation problem that complicates the conventional reactions. The present observations nicely illustrate the potential for using micromixing to effect chemical transformations that are difficult using more conventional chemical methods. It is hoped that numerous reactions of this type can be exploited in order to open new opportunities of chemical synthesis in ‘micro-world’.

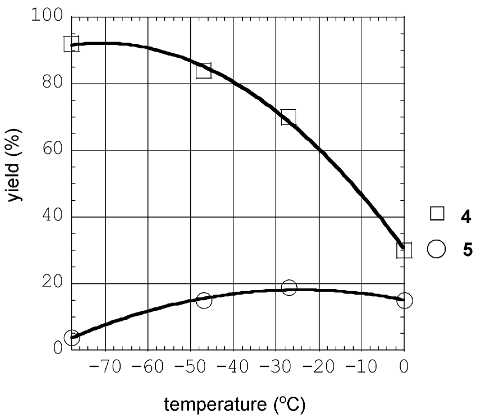
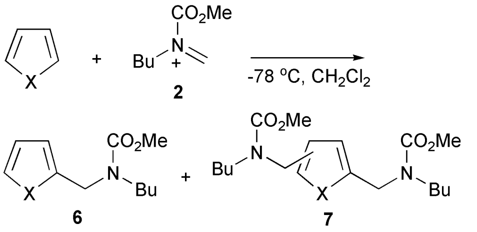
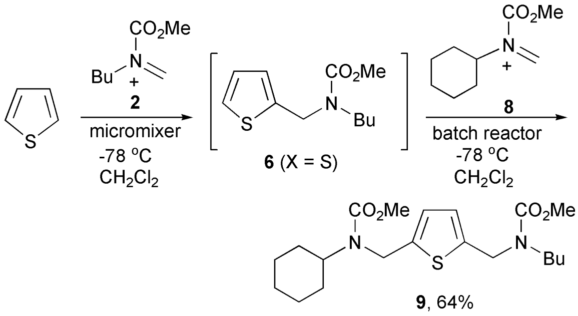


Fig. 2 Temperature effect of the reaction of **2** with **3**.



	reactor	**6** (%)	**7** (%)
X = S	batch	14	27
	micromixer	84	0
X = O	batch	11	5
	micromixer	39	trace
X = N-Me	batch	33	28
	micromixer	60	6

Scheme 3



Scheme 4

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11 The yield of **2** based on **1** is estimated as *ca.* 80% as judged by the yield of the reaction of **2** with excess allyltrimethylsilane, which is a highly reactive carbon nucleophile. Therefore, 1.2 equiv. of **1** was used. In these mixing experiments a 0.05 M solution of **2** (based on **1**) in CH_2Cl_2 and a 0.042 M solution of **3** in CH_2Cl_2 at −78 °C were quickly transferred to syringes which were kept cool with dry ice and immediately introduced to a micromixer cooled at −78 °C. Decomposition of **2** was thus avoided.

12 The separate reaction of **2** with triethylamine gave rather inactive species that did not give the allylated product upon treatment with allyltrimethylsilane, although the details are not clear at present. Triethylamine might also suppress the acid-promoted decomposition of the product.

13 A mixture of 2- and 3-substituted product (*ca.* 2:1) was obtained in the reaction of *N*-methylpyrrole. In cases of thiophene and furan 2-substituted products were obtained selectively.