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Aust. J. Chem. **2015**, *68*, 1657–1661
http://dx.doi.org/10.1071/CH15342

Communication

A Facile Preparation of α-Aryl Carboxylic Acid via One-Flow Arndt–Eistert Synthesis

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An efficient, one-flow Arndt–Eistert synthesis was demonstrated. A sequence of acid chloride formation–nucleophilic acyl substitution–Wolff rearrangement–nucleophilic addition was performed in a microflow system without isolating any intermediates, which included a potentially explosive compound. The microflow system was made from simple, inexpensive, and readily available instruments and tubes. α-Aryl esters **2a** and **2b** were prepared in yields of 33 and 23 % (three steps) respectively.

Manuscript received: 10 June 2015.
Manuscript accepted: 14 July 2015.
Published online: 11 August 2015.

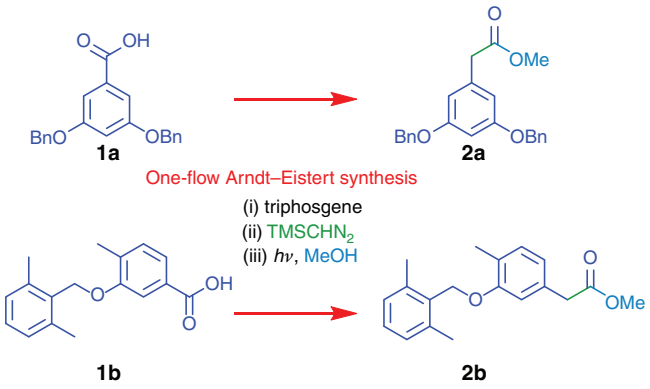
The Arndt–Eistert synthesis is a one-carbon homologation of carboxylic compounds via a sequence of acid chloride formation–nucleophilic acyl substitution–Wolff rearrangement–nucleophilic addition.[1] This sequence is one of the most widely used homologation methods in organic synthesis. However, the Arndt–Eistert synthesis has several drawbacks. The homologation requires the treatment of potentially hazardous reagents for the introduction of a diazo group, and the resultant α-diazo carbonyl compounds are also potentially hazardous.[2] In addition, the key step of the Arndt–Eistert synthesis, the Wolff rearrangement,[3] is usually carried out using a silver ion catalyst. However, this procedure usually requires freshly prepared catalyst, an extended period of reaction time, and high temperature in order to obtain the desired products in high yields.[3a,4] Further, another conventional procedure that includes a photochemical process is attractive, because no catalysts are required. However, photochemical reactors are usually expensive, and the scale-up of photoreactions is not simple because they usually require high-dilution conditions.

Microflow technology[5] offers solutions for these problems. Light-penetration efficiency can be improved in microflow photoreactions because the microflow photoreactor requires only a thin reaction space.[5h,6] In addition, the risks associated with the treatment of hazardous compounds are minimized owing to the very small internal volume of the microflow reactor. Moreover, one-flow, multistep syntheses enhance the synthetic efficiency, because they require no intermediate purification.[5g] Recently, Konopelski,[7] Danheiser,[8] Basso,[9] and their coworkers demonstrated a Wolff rearrangement in a microflow reactor for the synthesis of β-lactams,[7] aromatics,[8] and acyloxyacrylamides.[9] More recently, Kappe and coworkers reported microflow Arndt–Eistert homologation using a tube-in-tube reactor in order to safely treat hazardous diazomethane.[10] They also demonstrated an efficient one-flow synthesis of β-amino acids.[11]

We have reported microflow syntheses including photochemical reactions for the preparation of vitamin D_3 and its analogues.[12] Recently, we also reported the microflow synthesis of α-aryl carboxylic acid from α-diazo ketone **5** via photochemical Wolff rearrangement for the efficient preparation of *N*-allyloxycarbonyl-3,5-dihydroxyphenylglycine.[12f] Herein, we wish to report a more efficient, one-flow Arndt–Eistert homologation of substituted benzoic acid **1a** to α-aryl ester **2a** (Scheme 1). In addition, we also report a one-flow synthesis of α-aryl ester **2b**, which is the precursor of a biologically active compound.[13]

The conversion of 3,5-bis(benzyloxy)benzoic acid (**1a**) to the corresponding acid chloride in a microflow reactor was examined using a microflow system, as shown in Fig. 1. MeCN was used to dissolve the activator in accordance with our previous observations.[12e] We also attempted to use MeCN to dissolve the carboxylic acid **1a**, because MeCN was the best solvent for the later photochemical Wolff rearrangement in our previous examination.[12f] However, the carboxylic acid **1a** was not soluble in MeCN. Thus, we examined the use of 1,4-dioxane and cyclopentyl methyl ether, which would not inhibit a later photochemical Wolff rearrangement. The use of 1,4-dioxane for dissolving **1a** afforded the best result.

We connected a T-shape mixer with Teflon® tubing and immersed them in a water bath (80°C). A solution of carboxylic acid **1a** and DMF with or without *N*,*N*-diisopropylethylamine (DIEA) in 1,4-dioxane was introduced into the T-shape mixer with a syringe pump. A solution of triphosgene, thionyl chloride, or oxalyl chloride in MeCN was also introduced into the T-shape mixer with a syringe pump. We evaluated acid chloride formation by converting the generated acid chloride to the amide **3** in a



Scheme 1. One-flow Arndt–Eistert synthesis of α-aryl esters **2a** and **2b** from substituted benzoic acids **1a** and **1b**. Bn, benzyl; Me, methyl; TMS, trimethylsilyl.

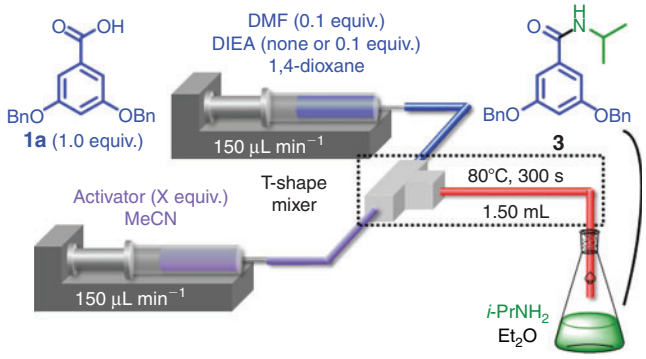


Fig. 1. Activation of 3,5-bis(benzyloxy)benzoic acid (**1a**) in a microflow reactor. DMF, *N*,*N*-dimethyl formamide; DIEA, *N*,*N*-diisopropylethylamine; Pr, propyl; Et, ethyl.

Table 1. Examination of the activation of 3,5-bis(benzyloxy)benzoic acid (1a) in a microflow reactor
'X' refers to the amount of activator

Entry	Activator	X equiv.	DIEA	Yield of **3**[A] [%]
1	Triphosgene	0.40	–	78
2	Triphosgene	0.50	–	84
3	Triphosgene	0.40	0.1 equiv.	58
4	Triphosgene	0.50	0.1 equiv.	88
5	Thionyl chloride	1.20	–	70
6	Thionyl chloride	1.50	–	85
7	Oxalyl chloride	1.50	–	–[B]

[A]Isolated yield based on **1a**.
[B]The desired amide **3** was obtained as an inseparable mixture with *N*,*N*,*N*,*N*-tetraisopropyl oxalamidine. The ratio of **3** to the oxalamidine was 2.7 : 1, as determined by ^{1}H NMR analysis.

flask that contained a solution of isopropylamine in Et_2O. The results obtained are shown in Table 1. The use of triphosgene (entries 1 and 2) and thionyl chloride (entries 5 and 6) afforded comparable results, whereas the use of oxalyl chloride afforded an inseparable mixture of the desired amide **3** and *N*,*N*,*N*,*N*-tetraisopropyl oxalamidine[14] (entry 7). The addition of DIEA did not have much influence on the yields (entries 3 and 4). The following examination was performed using 0.50 equiv. of triphosgene without adding DIEA (entry 2).

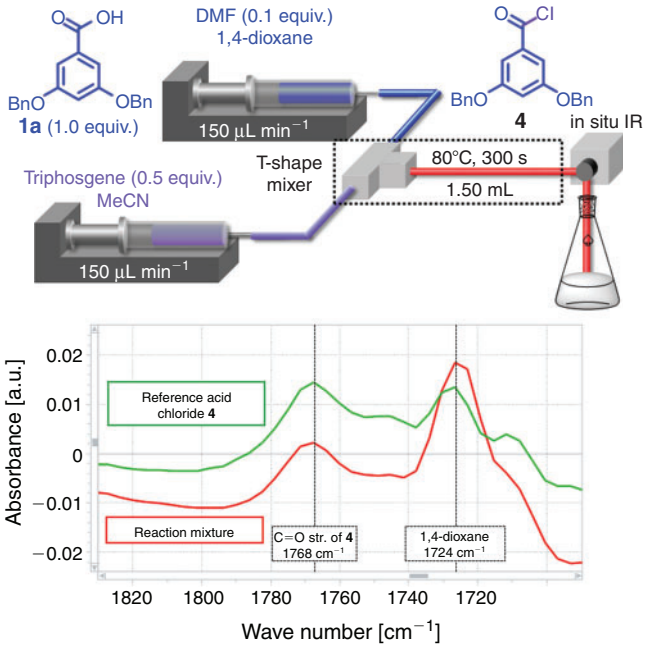


Fig. 2. Confirmation of the formation of acid chloride **4** by in situ IR measurement.

In order to confirm the desired acid chloride formation, in situ IR measurement was carried out using the optimal conditions (Table 1, entry 2) shown in Fig. 2. We separately prepared the reference acid chloride **4** (see Supplementary Material for synthetic details for **4**) and measured its IR spectrum. The comparison between the observed in situ IR spectrum of the obtained solution from the microflow system and the IR spectrum of the reference acid chloride **4** indicated that the desired acid chloride was generated in the microflow system. It should be noted that the desired acid chloride **4** was formed in only 5 min from unreactive, electron-rich carboxylic acid **1a** using the procedure we developed.[15]

Subsequent nucleophilic acyl substitution of the acid chloride **4** with trimethylsilyldiazomethane ($TMSCHN_2$)[16] was examined using the microflow system shown in Fig. 3. We connected two T-shape mixers with Teflon tubing. The temperature was controlled by immersing the T-shape mixers and the Teflon tubing in water baths. A solution of the acid chloride **4** that was obtained from the first reaction was introduced to the second T-shape mixer. A solution of $TMSCHN_2$ and DIEA in MeCN was also introduced into the second T-shape mixer with a syringe pump. The resultant solution was poured into a solution of acetic acid (AcOH) in MeOH and H_2O in a flask. The amount of $TMSCHN_2$ (3–5 equiv.) was examined (Table 2, entries 1–3). Increases in the amount of $TMSCHN_2$ employed did not have much influence on the yields, and neither did increases in the amount of DIEA employed (entry 4). We used 3 equiv. of $TMSCHN_2$ and 4 equiv. of DIEA for the following examinations.

In accordance with our previous observation,[12f] photochemical Wolff rearrangement and a subsequent nucleophilic addition were examined, as shown in Fig. 4. We connected three T-shape mixers using Teflon and fluorinated ethylene propylene copolymer (FEP) tubing. The temperature was controlled by immersing the T-shape mixers and the Teflon tubing into water baths. A solution of the α-diazo ketone **5** that was obtained from the second reaction was introduced into the third T-shape mixer. A solution of AcOH in MeOH was also introduced into the third

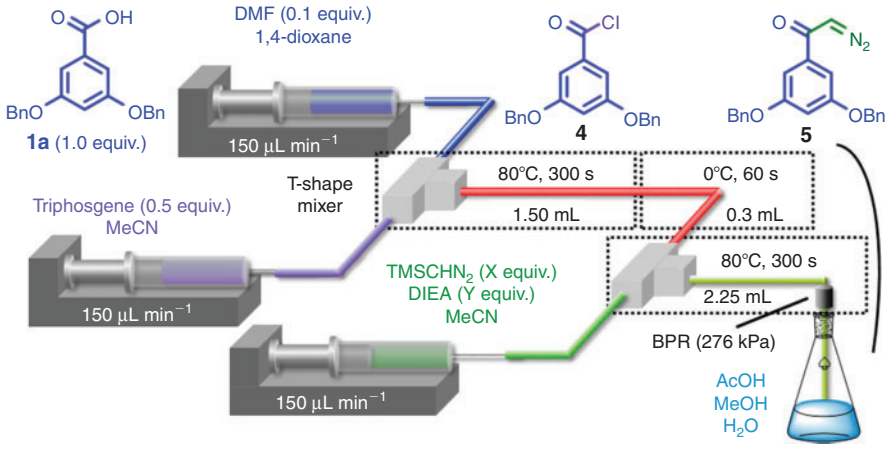


Fig. 3. Microflow synthesis of α-diazoketone **5**. BPR, back-pressure regulator.

Table 2. Examination of the amount of $TMSCHN_2$ and DIEA in the microflow nucleophilic acyl substitution reaction
X and Y refer to amounts of $TMSCHN_2$ and DIEA, respectively.

Entry	X equiv.	Y equiv.	Yield of **5**[A] [%]
1	3	4	63
2	4	4	59
3	5	4	67
4	3	6	58

[A]Isolated yield based on **1a** (two steps).

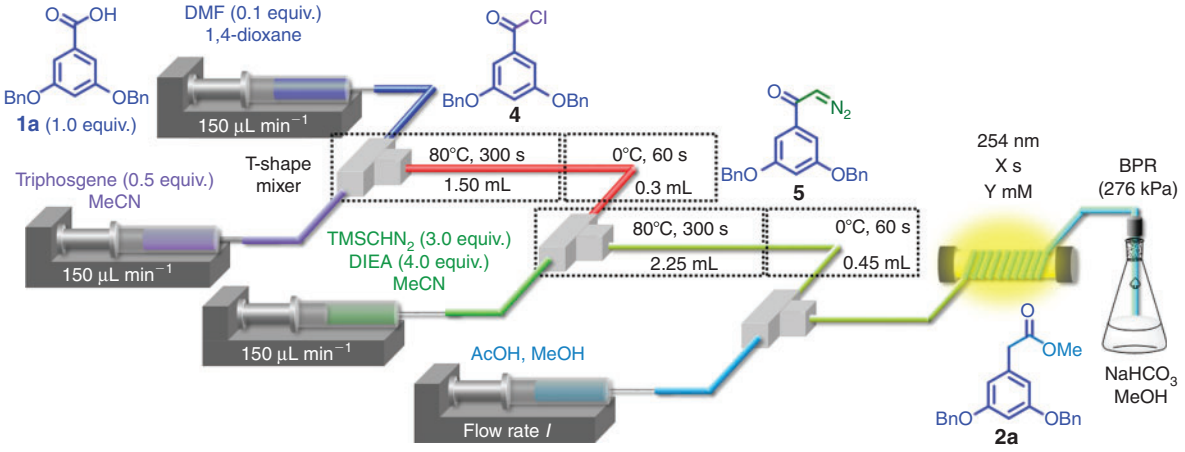


Fig. 4. Microflow synthesis of α-aryl ester **2a**.

T-shape mixer with a syringe pump. AcOH was used to decompose unreacted $TMSCHN_2$. The resultant solution flowed through the FEP tube and was irradiated by a 6-W portable UV lamp. The solution of the α-aryl ester **2a** was poured into a suspension of $NaHCO_3$ in MeOH. To the reaction mixture obtained, an excess amount of $NaBH_4$ was added in order to reduce the undesired substituted acetophenone that was probably generated from the triplet keto carbene species.[17] This treatment facilitated the removal of the undesired acetophenone derivative. The concentration and reaction time were examined by changing the flow rate *I* and the volume of the FEP tube, as shown in Table 3. The combination of 80 s and 14 mM afforded the best results (entry 2).

We synthesized an α-aryl carboxylic acid **6**, which retained strong activity for the reduction of uric acid, as shown in Fig. 5.[13] The desired α-aryl ester **2b** was obtained using the one-flow Arndt–Eistert synthesis we developed in a 23 % yield (three steps). The obtained ester was converted to the desired carboxylic acid **6** in a high yield using batch conditions.

In summary, we demonstrated a one-flow, Arndt–Eistert synthesis. A sequence of acid chloride formation–nucleophilic acyl substitution–Wolff rearrangement–nucleophilic addition was performed to obtain α-aryl esters **2a** and **2b** in a microflow system without isolating any intermediates, which included a potentially explosive compound. The microflow system was made from simple, inexpensive, and readily available

Table 3. Examination of the effect of times and concentrations in the photochemical Wolff rearrangement and subsequent nucleophilic addition of methanol
X and Y refer to reaction times and concentrations of **5**, respectively.

Entry	X [s]	Y [mM]	Yield of **2a**[A] [%]
1[B]	53	22	27
2[C]	80	14	33
3[D]	80	22	28
4[E]	80	33	15
5[F]	128	22	26

[A]Isolated yield based on **1a** (three steps).
[B]Flow rate: 450 µL min^{-1}, volume of FEP (fluorinated ethylene propylene) tube: 800 µL.
[C]Flow rate: 1000 µL min^{-1}, volume of FEP tube: 1930 µL.
[D]Flow rate: 450 µL min^{-1}, volume of FEP tube: 1200 µL.
[E]Flow rate: 150 µL min^{-1}, volume of FEP tube: 800 µL.
[F]Flow rate: 450 µL min^{-1}, volume of FEP tube: 1930 µL.

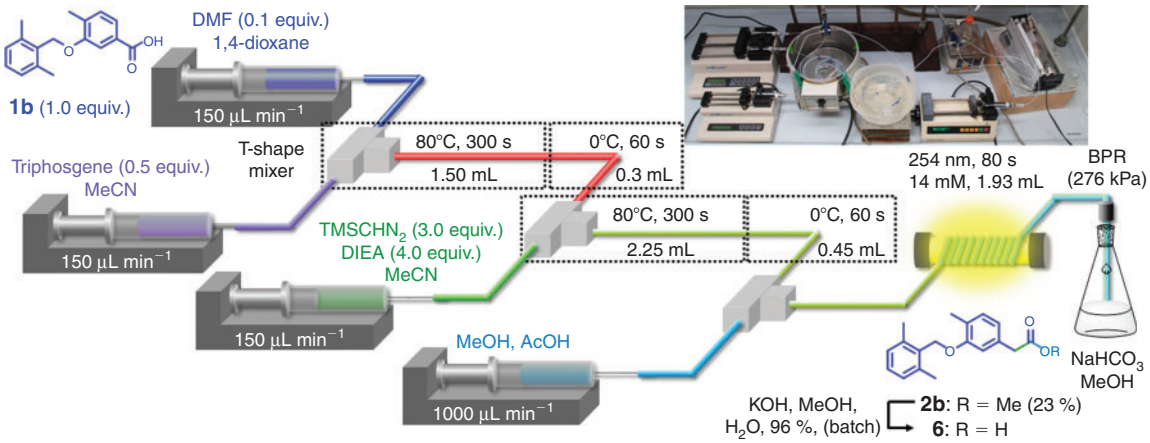


Fig. 5. Microflow synthesis of α-aryl carboxylic acid **6**.

instruments and tubes. It should be possible to scale up the developed process by either continuous running using high-pressure pumps such as plunger pumps or by increasing the number of microreactors. The developed procedure would be a valuable aid for the efficient preparation of α-aryl carbonyl compounds.

Supplementary Material

Full experimental details and NMR spectra of the products are available on the Journal's website.

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