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The regioselective preparation of 1,3-diketones within a micro reactor

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We demonstrate a simple method for the regioselective preparation of 1,3-diketones within a micro reactor from silyl enol ethers where the products are free from both competing *O*-acylation and diacylation products.

Over the past three years, there has been a rapid growth in the development of micro reaction technology exploiting the technique of electroosmotic flow (EOF).[1] Recent research has demonstrated that along with multi-component reactions such as the Suzuki coupling[2] and the Wittig reaction,[3] multi-step peptide synthesis can also be performed within a micro reactor.[4]

The enolate has been described as the most important intermediate in C–C bond formation. Its ambident nature however, allows the formation of bonds at either the carbon or the oxygen. In the case of acylation, this can result in the formation of a mixture of *O*- and *C*-acylated products which are difficult to separate, often resulting in low yields.[5] A large amount of work has been undertaken in order to explore and understand the reaction conditions that promote the regioselective acylation of enolates, these include; the nature of the counter ion, reaction temperature, solvent, stoichiometry of reagents, order of reagent addition and type of acylating reagent.[6,7] Although careful selection of the aforementioned conditions has been shown to influence the regioselectivity of the acylation, the 1,3-diketones produced remain contaminated with small amounts of *O*-acylated products.[8,9,10] The procedure is however, still regarded as being heavily substrate dependent.[11]

We recently demonstrated a simple technique for the regioselective preparation of uncontaminated 1,3-diketones in high to excellent conversions (> 95%) *via* the reaction of silyl enol ethers with acyl fluorides (1 h) and cyanides (24 h) in the presence of a catalytic amount of *anhydrous* TBAF (tetrabutylammonium fluoride).[12] We found that α-substituted ketones react with both acyl fluorides and cyanides to give 100% *C*-acylated products compared with non α-substituted ketones which gave 100% *O*-acylated products when reacted with acyl fluorides and *C*-acylated products when reacted with acyl cyanides. In this paper we wish to demonstrate the regioselective acylation of silyl enol ethers within a micro reactor using catalytic amounts of *anhydrous* TBAF. We also report reduced reaction times within a micro reactor in comparison to traditional batch reactions.

The borosilicate micro reactor used in this work was prepared using a standard fabrication procedure developed at Hull.[13] The reactions were carried out using a 4 channel micro reactor, as illustrated in Fig. 1, with approximate channel dimensions of 100 × 50 μm and outer dimensions of 20 × 20 × 25 mm. Micro porous silica frits were placed within the channels in order to minimise hydrodynamic effects.[14] An in-house LabVIEW™ program was used to set and monitor the voltages applied to platinum electrodes placed in the reservoirs (power supply was built by Kingfield electronics).

All micro reactions were carried out under fume extraction in order to minimise exposure to the reagents used. The micro reactions were performed over a period of 20 min in order to ensure a sufficient volume of product was generated for analysis

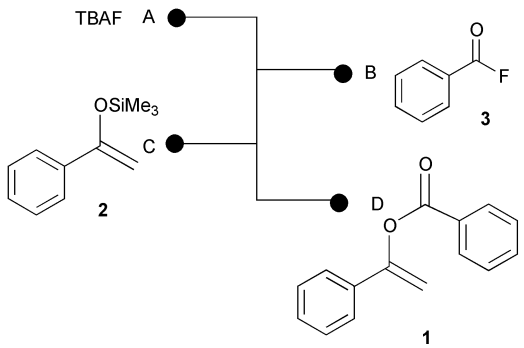


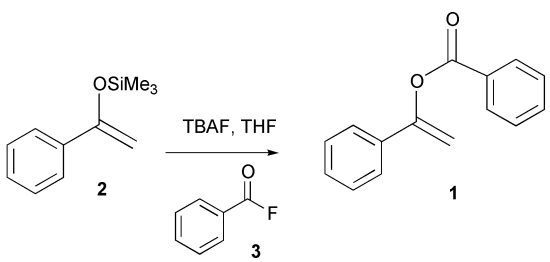
Fig. 1 Schematic of the micro reactor used in the synthesis of **1**.

(Typical flow rates of 0.3–0.4 μl min^{-1} were observed from each reservoir). Reaction products were determined by GC-MS *via* the comparison of retention times and spectra with those obtained from synthetically prepared standards.[12]

A synthetic standard of product **1** was prepared *via* the dropwise addition of the enol ether of acetophenone **2** (0.1 g, 0.52 mmol) to a stirred solution of *anhydrous* TBAF (0.014 g, 0.05 mmol) and benzoyl fluoride **3** (0.06 g, 0.52 mmol) in anhydrous THF (10 ml)(Scheme 1). The reaction mixture was stirred for 1 h, subsequent analysis by GC-MS showed that 100% conversion of the silyl enol ether of acetophenone **2** to the product **1** had been achieved.

Having demonstrated that **1** could be prepared from the silyl enol ether **2**, this represented a synthetic target for preparation within a micro reactor (Fig. 1). Prior to the synthesis, the micro reactor was primed with anhydrous THF in order to remove any air or moisture from the channels and micro porous silica frits. A standard solution of TBAF (40 μl, 0.1 M) in anhydrous THF was placed in reservoir A, a solution of benzoyl fluoride **3** (40 μl, 1.0 M) in anhydrous THF in reservoir B and the silyl enol ether of acetophenone **2** (40 μl, 1.0 M) in anhydrous THF was placed in reservoir C. The reaction products were collected in anhydrous THF in reservoir D over a period of 20 min. The reagents were manipulated within the device by the application of the following applied fields; 333, 455, 333 and 0 V cm^{-1}, resulting in 100% conversion to **1** (no products of *C*-acylation **4** or diacylation were observed).

Having successfully demonstrated the *O*-acylation of acetophenone within a micro reactor, we wished to also demonstrate that *C*-acylation was possible.



Scheme 1 Formation of **1** *via* the silyl enol ether of acetophenone **2**.

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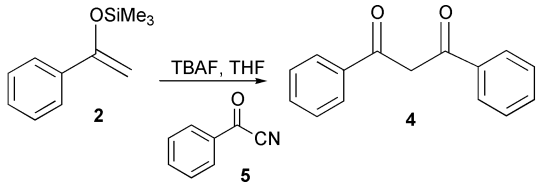
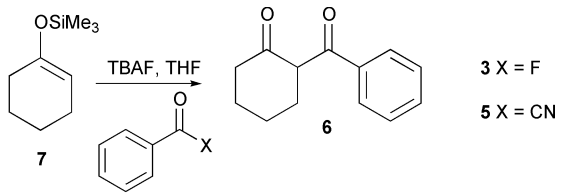
A synthetic standard of dibenzoylmethane **4** was prepared *via* the reaction of the silyl enol ether of acetophenone **2** and benzoyl cyanide **5** (Scheme 2). In order to obtain high conversion of the enol ether **2** to the product **4**, extended reaction times of 24 h were necessary. This is due to the reduced reactivity of benzoyl cyanide **5** compared with benzoyl fluoride **3**. Under the conditions stated above, 98% conversion with respect to the enol ether **2** was observed in bulk. Using a micro reactor, a standard solution of TBAF (40 μl, 0.1 M) in anhydrous THF was placed in reservoir A, a solution of benzoyl cyanide **5** (40 μl, 1.0 M) in anhydrous THF in reservoir B and the silyl enol ether of acetophenone **2** (40 μl, 1.0 M) was placed in reservoir C. The reaction products were collected in anhydrous THF in reservoir D over a period of 20 min. The reagents were manipulated within the device using the following applied fields; 416, 318, 476 and 0 V cm^{-1}, this resulted in 100% conversion of the enol ether **2** to product **4**. In order to demonstrate the generality of the technique, the silyl enol ethers of propiophenone and cyclohexanone were also investigated.



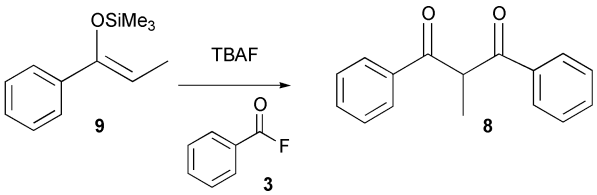
Scheme 2 Formation of **4** *via* the silyl enol ether of acetophenone **2**.

A synthetic standard of 2-benzoylcyclohexanone **6** was prepared *via* the reaction of the silyl enol ether of cyclohexanone **7** and benzoyl fluoride **3** (Scheme 3). Within 1 h, 100% conversion with respect to the silyl enol ether **7** was obtained in bulk. A standard solution of TBAF (40 μl, 0.1 M) in anhydrous THF was placed in reservoir A, a solution of benzoyl fluoride **3** (40 μl, 1.0 M) in anhydrous THF in reservoir B and the silyl enol ether of cyclohexanone **7** (40 μl, 1.0 M) was placed in reservoir C. The reaction products were collected in anhydrous THF in reservoir D over a period of 20 min. The reagents were manipulated within the device using the following applied fields; 208, 409, 357 and 0 V cm^{-1}. This resulted in 100% conversion of the silyl enol ether of cyclohexanone **7** to product **6**. The reaction was repeated using benzoyl cyanide (40 μl, 1.0 M) and the following applied fields; 208, 409, 381 and 0 V cm^{-1}, this resulted in 100% conversion of the enol ether of cyclohexanone **7** to 2-benzoylcyclohexanone **6**.



Scheme 3 Preparation of 2-benzoylcyclohexanone **6** *via* the silyl enol ether of cyclohexanone **7**.

We subsequently extended the technique to the preparation of product **8** within a micro reactor. A synthetic standard of **8** was prepared *via* the reaction of the silyl enol ether of propiophenone **9** with benzoyl fluoride **3** (Scheme 4). After stirring for 1 h, the reaction mixture was analysed by GC-MS and 99% of the



Scheme 4 Preparation of **8** *via* the silyl enol ether of propiophenone **9**.

silyl enol ether **9** was converted to product **8**. Using a micro reactor, a standard solution of TBAF (40 μl, 0.1 M) in anhydrous THF was placed in reservoir A, a solution of benzoyl fluoride **3** (40 μl, 1.0 M) in anhydrous THF in reservoir B and the silyl enol ether of propiophenone **9** (40 μl, 1.0 M) was placed in reservoir C. The reaction products were collected in anhydrous THF in reservoir D over a period of 20 min. The reagents were manipulated within the device using the following applied fields; 375, 455, 405 and 0 V cm^{-1}. This resulted in 100% conversion of the silyl enol ether of propiophenone **9** to product **8**.

In conclusion, we have developed a simple, room temperature route to the regioselective formation of uncontaminated 1,3-diketones or *O*-acylated products depending upon the acylating reagents used. In all instances, no competing diacylation products were observed. The use of ammonium enolates is also advantageous as it removes the effect of a metal counter ion along with the observed reactions between aminated bases and acylating reagents.

In the preparation of β-hydroxyketones from silyl enol ethers we previously demonstrated that enhancements in both reaction rates and conversion are observed when using micro reactors.[15] This work therefore re-emphasises the increase in reaction rates. Typically, the formation of **4** in batch required extended reaction times of 24 h due to reduced reagent reactivity however, when transferred to a micro reactor, quantitative conversions were observed in minutes.

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