Synthesis using a Mass Spectrometer

DOI: 10.1002/anie.201206632

Accelerated Carbon–Carbon Bond-Forming Reactions in Preparative Electrospray**

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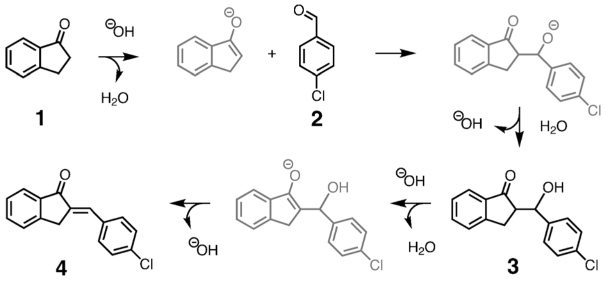
The chemistry of life occurs in spatially limited volumes—cells—the structural and functional units of living organisms. Biochemical reactions can also take place within the confines of interfaces, for example, those between air and water[1] in atmospheric aerosols. These unique chemical environments can be mimicked by performing reactions in enclosed volumes, for example, in micelles or microemulsions.[1f,2] Inside these compartmentalized liquids, limiting phase boundaries as well as significant changes in local concentrations can enhance reaction rates,[2a] induce regioselectivity,[3] and help to overcome reagent incompatibilities.[2b] Although electrospray has been used for the production of inorganic nanoparticles[4] and thin organic polymer films,[5] it is most widely associated with ionization in mass spectrometry (MS).[6] Recent MS experiments have revealed that charged microdroplets can serve as the locus for simple as well as complex and multistep reactions.[7]

Here we show that ordinary carbon–carbon bond reactions can be performed on a microscale by collecting the sprayed droplets. As a model system we investigated the base-catalyzed Claisen–Schmidt condensation of 1-indanone (**1**) and 4-chlorobenzaldehyde (**2**) (see Scheme 1). Absorption spectroscopy allows ready distinction of reagents **1** and **2** and quantification of the product 2-(4-chlorobenzylidene)indan-1-one (**4**). The freshly prepared methanolic reaction mixture was treated in two contrasting ways: 1) the solution was electrosprayed and the products were collected at a surface, and 2) the reaction mixture was simply allowed to stand at room temperature. In both the droplet and bulk experiments the rates of product formation were determined by UV/Vis spectroscopy and by using reversed-phase high-performance liquid chromatography mass spectrometry (RP-HPLC-MS). Note that the spray process (Figure 1) used the small droplet experiment known as electrosonic spray ionization (ESSI).[6c]



Scheme 1. Mechanism of the base-catalyzed Claisen–Schmidt condensation of 1-indanone (**1**) and 4-chlorobenzaldehyde (**2**) to 2-(4-chlorobenzylidene)indan-1-one (**4**). Negatively charged intermediates are drawn in grey.

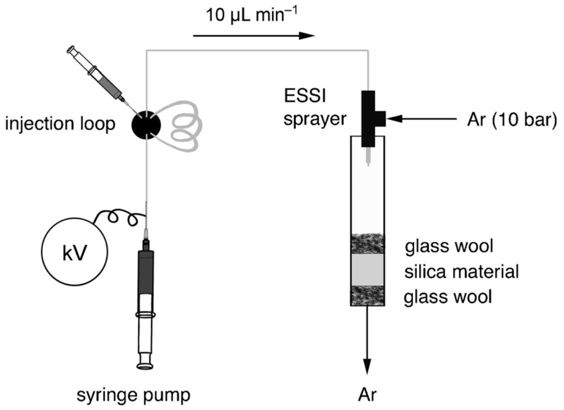


Figure 1. Synthesis using an electrosprayer enclosed in a polypropylene vessel bottom sealed with glass wool and silica. The high voltage was applied through the stainless steel needle of the syringe, while a grounded aluminum foil covered the vessel.

UV/Vis spectroscopy revealed (Figure 2A) remarkably different extents of product formation in bulk solution versus that in electrosonically generated droplets. The intensity of the absorption band at 323 nm indicated a comparably slow product formation in bulk solution, with complete reaction occurring after several hours. On the other hand, the UV/Vis spectrum of the electrosprayed and re-dissolved material (Figure 2A) almost matched the spectrum of product **4** (Figure 2B), that is, the conversion appeared to be essentially quantitative. In fact, when a solution of 0.83 mg of **1**, 0.88 mg of **2**, and catalytic amounts of KOH was electrosprayed using an array of four multiplexed ESSI sprayer tips (see Figure S1 in the Supporting Information), (1.47 ± 0.09) mg or 92.2 % of the main product **4** was produced within 2.5 min. Even this injection time (i.e. 2.5 min) was only required to spray this amount of reaction mixture. Reaction is complete on a time scale of less than 1 min.

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[**] This research is supported by the National Science Foundation under grant number CHE 0848650 (to R.G.C.)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201206632.

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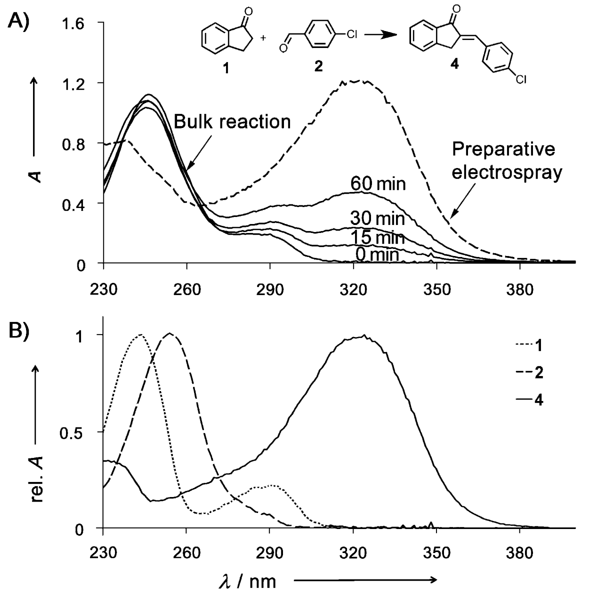

Figure 2. A) Time course of reactions in bulk solution (solid lines analyzed after 0, 15, 30, and 60 min) and in preparative electrospray after 10 min of spraying. Analysis is done by UV/Vis spectroscopy and the spectra are normalized to equal amounts of reagents **1** and **2** (A = absorbance). B) UV/Vis spectra (A at $\lambda_{max} = 1$) of **1** (dotted line), **2** (dashed line), and product **4** (solid line).

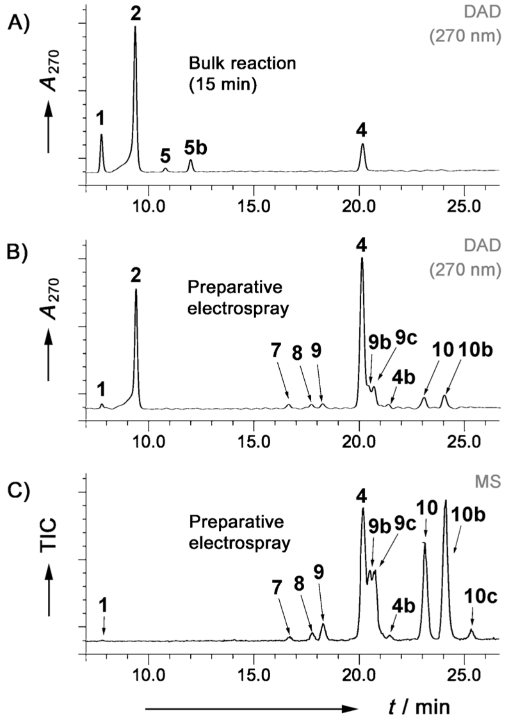

Figure 3. HPLC-APCI-MS product analysis with UV detection (DAD) at 270 nm: A) reaction mixture and B) product of the preparative electrospray. C) Total ion current (TIC) chromatogram for the HPLC analysis depicted in (B). For more details see Figure S2 and Tables S2 to S5 in the Supporting Information.

LC-MS analyses using atmospheric pressure chemical ionization (APCI) were performed to obtain more information about the composition and purity of the bulk and sprayed reaction product mixtures (Figure 3). In the case of reaction in bulk solution, the minor side products **5** and **5b** were identified as methanol adducts of compound **4**. The m/z values of the protonated molecules ($[M+H]^+$) increased by 32 Da compared to their precursors (see Tables S2 and S3 in the Supporting Information).

In contrast, the analysis of the electrosprayed material (after washing from the collection surface) revealed a completely different pattern of minor products (Figure 3B and C). Besides the main product **4** (m/z 255) and residual reagents **1** and **2**, nine different compounds were observed in the product mixture (for a comprehensive summary of UV/Vis and APCI-MS data see Tables S2 to S5 in the Supporting Information). The formation of the side products **4b**, **7**, **8**, **9**, **9b**, **9c**, **10**, **10b**, and **10c** could readily be rationalized after their identification with the help of MS. Only **4b** (m/z 255), detected in traces, was found to be an isomer of **4** (most likely the Z-isomer of **4**) because of its similar m/z value and UV absorption properties. All eight other compounds had three features in common: 1) an UV spectrum similar to that of the reagent **1**, but 2) m/z values higher than that of **4** and 3) $[\mathbf{4}+H]^+$ as a fragment ion. These eight minor compounds are clearly products of secondary reactions, which exclusively can be observed in the charged microdroplet experiment. In the progression of the reaction and with decreasing concentrations of reagent **2**, negatively charged enolates of **1** also react with **4** to give **7** (m/z 401), **9**, **9b**, or **9c** (m/z 387). Moreover, the deprotonated **4** reacts further with **2** to form **8** (m/z 395) or with another molecule of **4** to give **10**, **10b** and **10c** (m/z 509). The extended π conjugation of **4**, which is responsible for the absorption maximum at 323 nm, is no longer present. Exemplary mass spectra and proposed constitutional formulae of **9** and **10** are depicted in Figure 4 (see Tables S2 to S5 in the Supporting Information).

Continuous and rapid solvent evaporation gives rise to increasing reagent concentrations which increase the rate of reaction—perhaps entirely through a concentration effect. The side products observed during preparative electrospray (even though in low yield) were not observed in solution experiments although their occurrence in the late stages of the reaction and at high concentrations is not precluded.

Optimization of the conditions to avoid side products and increase specificity and the overall yield of product **4** above the current 92.2% level should be straightforward. Since velocities between 100–200 m s^{-1} are reported for charged droplets 2 mm from the spray source[8] and the distance from the sprayer to the collection surface was in the range of 3 to 5 cm, the effective lifetime of a droplet is in the millisecond range. This is orders of magnitude less than a time scale of many minutes for the corresponding bulk solution experiment. The reaction rate (not rate constant) therefore must be dramatically enhanced up to several orders of magnitude, in agreement with recently published data[7a] and this rationalizes the observation that the spray time in the electrospray experiment (minutes) did not influence the composition of the product mixture (see Figure S4 in the Supporting Information). Several other experimental variables were

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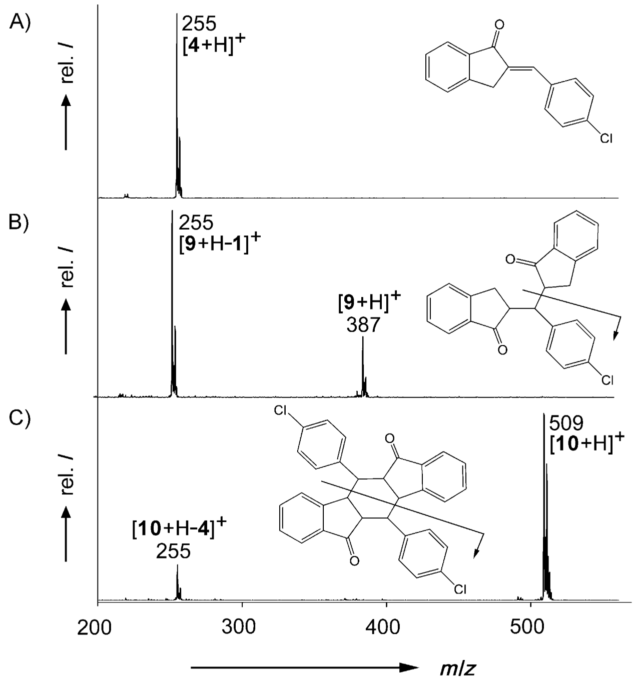

Figure 4. APCI-MS spectra of A) the main product **4** and B) the side product **9** as well as C) the side product **10** obtained from a preparative electrospray. The insets show the corresponding structural formulae and key fragments; rel. *I* = relative intensity.

altered but showed minor effects on the product formation (see Figures S4 to S7 in the Supporting Information).

Remarkably, normal analytical information on the composition of the reaction expected from electrospray ionization is not obtained under the small droplet size (ESSI) spray conditions used here. Instead the reaction is complete whether one sprays directly into the instrument or onto a surface for collection and subsequent analysis.

A second type of C–C bond formation reaction was also investigated. The so-called thiamine-catalyzed benzoin condensation[9] is a biomimetic C–C bond-forming reaction, in which a deprotonated thiazolium salt is used for the condensation of two benzaldehyde molecules (see Scheme S1 in the Supporting Information).

The relative signal intensities of catalyst, intermediates, and product obtained from a nano-ESI-MS analysis of the electrosprayed, collected, and re-dissolved material again differed dramatically from signal intensities obtained from the analysis of the bulk solution (Figure S9 in the Supporting Information).

Using ESSI it was furthermore possible to directly electrospray the freshly prepared reaction mixture into the mass spectrometer.[10] The mass spectrum (Figure S11 in the Supporting Information) matched that obtained from the electrosprayed, collected, and re-dissolved solid, that is, the collection process on a surface has no influence on the composition of the product mixture. It can therefore be concluded that the reaction must take place during the limited (millisecond) lifetime of the evolving charged microdroplets.

In summary we were able to successfully prepare milligram quantities of C–C synthetic products, in short periods of time. The scale-up was realized by use of an array of four multiplexed sprayer tips and could easily be further expanded. The use of an enclosed spray head together with an inert sheath gas enables oxygen- or moisture-sensitive compounds to be injected as reagents. If necessary, the silica adsorbent should allow an in situ purification or separation of the product. Due to the extraordinary chemical environment of evaporating charged microdroplets accelerated product formation was observed.

Experimental Section

Claisen–Schmidt condensation: A 1.8 M methanolic KOH solution (5 μL) was added to 25 mM methanolic solutions of **1** and **2** (500 μL). Aliquots of the freshly prepared solution were simultaneously used for reaction in bulk solution at room temperature as well as for preparative electrospray.

Preparative electrospray: An ESSI sprayer tip setup was used as previously reported.[6c] The argon or nitrogen pressures were at 120 to 145 psi. A high voltage potential of −2 to −5 kV was applied through the metal tip of the 500 μL Hamilton syringe. The flow rate of the syringe pump was 5 to 10 $\mu L\,min^{-1}$. After 10 min of reaction mixture injection, the dry product was collected by carefully rinsing the polypropylene vessel, glass wool, and silica material with methanol. For further details see the Supporting Information.

Received: August 16, 2012
Revised: September 17, 2012
Published online: October 9, 2012

Keywords: analytical methods · C–C coupling · electrospray · mass spectrometry · microscale synthesis

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