Microwave-Assisted Synthesis of *N*-Heterocyclic Carbene Precursors

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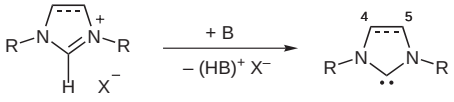
Abstract: A very simple and efficient procedure is reported for the synthesis of 1,3-diarylimidazolinium chlorides by cyclization of *N*,*N*′-diarylethylenediamines dihydrochlorides with triethyl orthoformate under microwave irradiation.

Key words: amines, cyclizations, heterocycles, imidazolinium salts, ligands

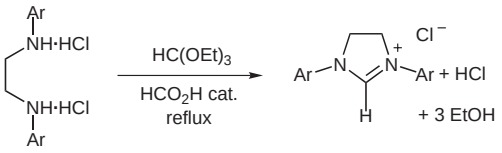
Stable *N*-heterocyclic carbenes (NHCs) are neutral, two-electron donor ligands with a negligible π-back-bonding tendency.[1] These divalent carbon species behave as phosphine mimics, yet they are better σ-donors and they form stronger bonds to metal centers than most phosphines.[2] Their electronic and steric properties can be fine-tuned simply by varying the substituents on the nitrogen atoms and they not only bind to any transition metal, whether in high or low oxidation state but also to main group elements such as lithium or beryllium.[3] During the last decade, they have already afforded a whole new generation of organometallic catalysts that are revolutionizing key areas of synthetic organic chemistry.[3,4] Stable carbenes have also a place on their own as reagents and catalysts since they behave as nucleophilic agents. Transesterification, cycloaddition, nucleophilic aromatic substitution, and acylation are classes of reactions that have recently benefited from the participation of NHCs in stoichiometric or catalytic amounts, sometimes in an asymmetric fashion.[5]

Currently, the NHCs most commonly encountered in organic synthesis are imidazol-2-ylidene and imidazolin-2-ylidene derivatives (with or without a formal double bond between C4 and C5, respectively). They are usually obtained by deprotonation of the corresponding imidazol(in)ium salts with a strong base (Equation 1).[6] Due to the high sensitivity of the free carbenes toward oxygen and moisture, this reaction is often carried out in situ. Therefore, imidazol(in)ium salts serve de facto as stable NHC ligand precursors in many catalytic applications.[7]

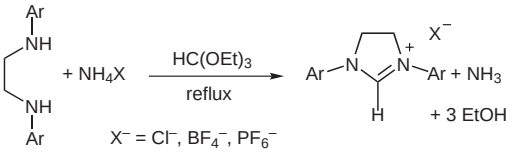


Equation 1

The preparation of imidazolinium salts bearing aryl substituents is usually achieved via condensation of a *N*,*N*′-diarylethylenediamine dihydrochloride with triethyl orthoformate in the presence of a catalytic amount of formic acid (Equation 2). The orthoester serves both as a solvent and a reagent. Several variations on this experimental procedure have been published in the literature.[7a,8] They all require prolonged heating under reflux conditions in order to reach satisfactory conversions. Thus, reaction times of 24–72 hours are standard, unless ethanol is distilled off the reaction mixture after a few hours in order to drive the cyclization more rapidly to completion. Alternatively, the diamine-free base can also be used as a starting material providing that a stoichiometric amount of an ammonium salt is added to the reaction mixture (Equation 3). In this case, reflux periods of 2–5 hours are usually sufficient to complete the transformation.[9]



Equation 2



Equation 3

Microwave-assisted organic synthesis (MAOS) has received increasing attention in recent years as a valuable technique for accelerating chemical reactions.[10] The development of safe and reliable mono- or multimodal microwave reactors specifically designed for chemical applications has significantly invigorated time-honored laboratory practices. Reductions in reaction time, increases in yield, and suppression of side-product formation are often claimed when switching from conductive to microwave heating.[11] Condensation reactions leading to heterocyclic products are particularly prone to microwave irradiation enhancements.[12] Dramatic accelerations have been reported for the synthesis of imidazoles from acyclic precursors under various experimental conditions.[13] Mono-N-alkylation of imidazole and benzimidazole in a

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microwave oven has also been described.[14] Yet, to the best of our knowledge, MAOS had never been extended to the preparation of imidazol(in)ium salts so far.

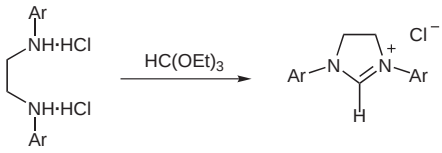
In this letter, we disclose a very simple and efficient procedure for the microwave-assisted synthesis of 1,3-diarylimidazolinium chlorides by cyclization of *N*,*N*′-diarylethylenediamines dihydrochlorides with triethyl orthoformate.

Our initial efforts focused on optimizing the experimental conditions for obtaining 1,3-dimesitylimidazolinium chloride from the corresponding diamine dihydrochloride in a single-mode microwave reactor. Preliminary experiments showed that neat triethyl orthoformate was a rather poor solvent in terms of microwave absorbance. However, the presence of ionic compounds and the release of ethanol (a strong microwave absorber[15]) in the reaction mixture proved sufficient to ensure efficient energy transfers. The influence of the reaction time, temperature, and microwave power on the product yield was thoroughly investigated. By analogy with the classical reflux conditions, a temperature of 145 °C was elected for most of the trials (bp of triethyl orthoformate: 146 °C). It turned out to be adequately suited. With 50-W microwave power, this temperature was reached within one minute in a mixture consisting of 1 mmol of substrate and 1 mL of orthoester. The whole reaction was complete in less than five minutes and led to high, reproducible yields of pure product (93–94%). Reagent grade triethyl orthoformate could be used without any further purification or drying. Adding a catalytic amount of formic acid did not seem to affect the course of the reaction, while increasing the temperature or applying a higher power level led to reduced yields and formation of unidentified colored by-products.

The procedure was successfully extended to a range of other 1,3-diarylimidazolinium chlorides (Table 1).[16] In all but two cases, isolated yields obtained after five minutes of microwave irradiation outperformed those reached under reflux conditions during much longer periods of time. The most spectacular enhancement was recorded for the polar, deactivated 4-bromo-2,6-dimethylphenyl derivative (entry 10). In some instances, the ionic products remained soluble in the warm reaction mixtures. They eventually precipitated during cooling or upon addition of diethyl ether. Thus, isolation was always easily carried out by simple filtration and drying. No further purification of the imidazolinium salts was required, since comparison of their ^{1}H NMR and ^{13}C NMR spectra with those of authentic samples[7a,8a,17,18] confirmed their identity and purity. The most valuable spectroscopic feature for assessing the success of the cyclization was the appearance of a strongly deshielded imidazolinium H2 signal at ca. 9–10 ppm in the proton spectra.

We have also examined the possibility of scaling up the microwave-assisted synthesis of 1,3-dimesitylimidazolinium chloride. This salt is an immediate precursor of the important NHC nicknamed SIMes or H_2IMes that serves as an ancillary ligand in the second generation Grubbs[19] and Hoveyda–Grubbs[9b] metathesis catalysts, among other uses. A first experiment carried out on a 10 mmol scale in 10 mL of triethyl orthoformate using the same experimental protocol that was defined previously led to a 93% isolated yield. This result, almost identical to the one obtained on a 1 mmol scale (cf. entry 7 of Table 1), was deemed very gratifying, considering that a different type of single-mode microwave instrument was employed to accommodate larger reaction vessels. When the cyclization was performed with 20 mmol of starting material in 15 mL of orthoester, the microwave power had to be slightly increased (from 50 W to 75 W) to maintain a fast heating rate. This was the sole adjustment needed to scale up the reaction by factor 20. Under these conditions, the isolated yield peaked at 97% after five minutes at 145 °C.[20]

Table 1 Synthesis of 1,3-Diarylimidazolinium Chlorides Using Conductive or Microwave Heating



Entry	Aryl substituent	Thermal yield (%)[a]	Microwave yield (%)[b]
1	Phenyl	84[7a]	62
2	4-Biphenyl	80[7a]	82
3	1-Naphthyl	81[7a]	91
4	2-Methylphenyl (2-tolyl)	55[7a]	49
5	4-Methylphenyl (4-tolyl)	79[17]	96
6	2,6-Dimethylphenyl (2,6-xylyl)	79[7a]	90
7	2,4,6-Trimethylphenyl (mesityl)	80[8a]	94
8	2,6-Diisopropylphenyl (diip)	59[8a]	72
9	3,5-Dimethylphenyl (3,5-xylyl)	80[7a]	93
10	4-Bromo-2,6-dimethylphenyl	50[18]	98

[a] Isolated yields using conductive heating, up to 72 h reaction time.
[b] Isolated yields using microwave irradiation, 5 min reaction time.

In conclusion, we have devised a new efficient method for the preparation of 1,3-diarylimidazolinium salts from *N*,*N*′-diarylethylenes diamines. The reaction proceeds briskly under microwave irradiation and the work-up is equally rapid and straightforward. This easy access to NHC precursors opens the door to automated syntheses with potential applications for the generation of ligand libraries and fast screening of catalytic species.

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(16) **General Procedure for the Microwave-Assisted Synthesis of 1,3-Diarylimidazolinium Chlorides.**
A 10-mL glass vial equipped with a stirring bar was charged with a *N*,*N*′-diarylethylenediamine dihydrochloride (1 mmol) and triethyl orthoformate (1–2 mL). The vial was capped and irradiated 5 min at 145 °C (monitored by IR sensor) in a CEM Discover instrument with a 50-W microwave power. No ramp and no simultaneous cooling were applied. After rapid air cooling by the unit, the reaction mixture was diluted with Et_2O (3 mL) and filtered under vacuum. The precipitate was rinsed with a few milliliters of Et_2O and dried under vacuum to afford pure 1,3-diarylimidazolinium chloride.

(17) ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.35 (s, 6 H, *para*-CH_3), 4.55 ppm (s, 4 H, CH_2), 7.35 (d, *J* = 4.0 Hz, 2 H, CH_{ortho}), 7.60 (d, *J* = 4.0 Hz, 2 H, CH_{meta}), 10.13 (s, 1 H, im-CH^2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.5 (*para*-CH_3), 48.3 (CH_2), 118.4 (CH_{ortho}), 130.0 (CH_{meta}), 133.8 (C_{para}), 136.4 (C_{ipso}), 151.1 (im-CH_2).

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(20) **Scaled-up Preparation of 1,3-Dimesitylimidazolinium Chloride.**
A 20-mL glass vial equipped with a stirring bar was charged with *N*,*N*′-dimesitylethylenediamine dihydrochloride (7.39 g, 20 mmol) and triethyl orthoformate (15 mL). The vial was capped and irradiated 5 min at 145 °C (monitored by IR sensor) in a Biotage Emrys Optimizer instrument with a 75-W microwave power. No ramp was applied. After rapid cooling in an ice bath, the reaction mixture was diluted with Et_2O (20 mL) and filtered under vacuum. The precipitate was rinsed with Et_2O (2 × 10 mL) and dried under vacuum to afford pure 1,3-dimesitylimidazolinium chloride (6.57 g, 97% yield).