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Expeditious synthesis of N′-substituted *N*-mesitylimidazolium salts as NHC precursors

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ABSTRACT

In contrast to time-consuming, conventional thermal approaches, microwave irradiation provides rapid and convenient access to unsymmetrical N′-substituted *N*-mesitylimidazolium salts, which are important precursors for NHC ligands used in the construction of metal–NHC complexes.

N-Heterocyclic carbenes (NHCs) have attracted considerable attention as electron-donating ligands for transition metals in various oxidation states.[1,2] The isolation of stable NHC–carbenes was first described by Arduengo et al.[3] in 1991, and reports of analogues containing simple alkyl, aryl or even highly functionalised substituents have followed.[4–6] NHCs are generally much stronger σ-donors and weaker π-acceptors than phosphine ligands. These properties permit the formation of strong metal–NHC bonds[4,5,7,8]—advantages exploited in the development of the widely used Grubbs II catalyst.[9] The catalytic activity and efficiency of NHC–metal complexes can be customized by changing the electronic, steric and even stereochemical features of the ring substituents.[9–12] N′-Substituted *N*-mesitylimidazolium salts provide stable precursors for NHC–metal complexes and are generally obtained via a two-step sequence, involving the preparation of *N*-mesitylimidazole[6] and subsequent alkylation at the second nitrogen.[6,13–25] Our interest in imidazolium salts arises from an ongoing programme directed at the development of novel metathesis catalysts.[26] The practical difficulties encountered in the preparation and isolation of the critical imidazolium salts as carbene precursors prompted us to explore a microwave-assisted approach. Applications of microwave-assisted organic synthesis (MAOS), first reported in the mid-eighties,[27,28] have advanced significantly, with sophisticated laboratory equipment replacing domestic microwave ovens.[29,30] While improvements in selectivity, reaction time and efficiency using conventional protocols[30] have been reported,[12,29,30] the dramatic advantages offered by a microwave-assisted approach in the rate of formation and ease of isolation of strategically important *N*-mesitylimidazolium salts may well facilitate research into the development of novel analogues of the Grubbs type II ruthenium-based metathesis catalysts.

The key precursor, *N*-mesitylimidazole (**4**) was prepared in excellent yield (98%) by reacting 2,4,6-trimethylanilinium chloride (**1**) with glyoxal (**2**) and formaldehyde (**3**) (Scheme 1).[6] The subsequent alkylation, first reported by Arduengo et al.[3] then typically leads to the corresponding N-substituted imidazolium salt—a well documented and versatile route to NHC proligands. However, the final alkylation step tends to be very slow using conventional methods, with the reaction mixtures requiring stirring at room temperature or under reflux for as long as seven days.[6,13–25] In the methodology reported herein, *N*-mesitylimidazole (**4**) was reacted in toluene, under microwave-assisted conditions, with a series of eight different alkyl halides to afford the corresponding N-substituted mesitylimidazolium salts **8**–**15** in 30–120 min (Table 1), with the desired salt typically precipitating out of the reaction mixture in high purity.

As is evident from the data in Table 1, the N′-substituted *N*-mesitylimidazolium salts **9**–**13** and **15** were isolated in moderate to good yields. Unfortunately, the malonate ester derivative **8**, required for our research on the development of novel tridentate ligands, was obtained in very low yield. *N*-Mesitylimidazole (**4**)[24] and diethyl (3-chloropropyl)malonate (**7**)[31,32] were prepared

Table 1
N′-Substituted *N*-mesitylimidazolium salts obtained under microwave-assisted conditions[a] via Scheme 1

Entry	Reactant	Product	Time (min)	Isolated yield (%)
1	Diethyl (3-chloropropyl)malonate (**7**)	**8**	120	7
2	3-Chloropropanol (**16**)	**9**	60	74[c]
3	Allyl iodide (**17**)	**10**	30	69[d]
4	Benzyl bromide (**18**)	**11**	30	80[e]
5	Ethyl 2-bromopropionate (**19**)	**12**	30	77
6	1-Bromodecane (**20**)	**13**	30	61
7	2-(Bromomethyl)-pyridine·HBr (**21**)	**14**[b]	30	39
8	1-Bromo-3-chloropropane (**6**)	**15**	30	70

[a] Reactions conducted in toluene at 150 W, 85 °C.
[b] Reaction conducted in EtOH at 150 W, 85 °C.
[c] Previously isolated in 69% yield after conventional heating for 15 h (see Ref. 14).
[d] Previously isolated in 70% yield after conventional heating overnight (see Ref. 15).
[e] Previously isolated in 100% yield after conventional heating for 16 h (see Ref. 13).

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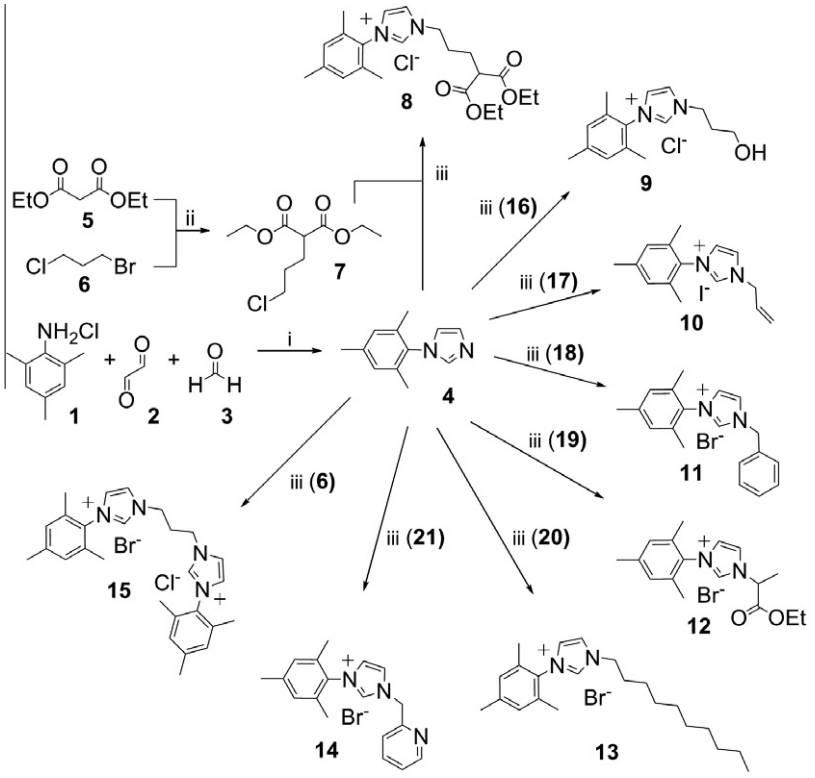

Scheme 1. Preparation of N′-substituted *N*-mesitylimidazolium salts under microwave-assisted conditions. Reagents and reaction conditions: (i) NH_4Cl, H_2O, 1,4-dioxane, 100 °C, then NaOH, 0 °C; (ii) NaH, THF, reflux; (iii) MW, 150 W, 85 °C, alkyl halide (**6**,**7**, **16**–**21**, Table 1), toluene or EtOH.

following the literature methods, the N′-substituted *N*-mesitylimidazolium salts **8**–**15** using a general procedure, and all new compounds were fully characterized.[34]

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34. *General procedure for the alkylation of N*-mesitylimidazole (**4**). A solution of *N*-mesitylimidazole (**4**) and an equimolar equivalent of the alkyl halide in toluene or EtOH (1 mL) was heated at 85 °C, 150 W with stirring in a CEM Discover single-mode microwave apparatus, producing controlled irradiation at 2450 MHz, using a standard 10 mL silicon–septum sealed glass pressure vial. The reactions were optimized using the temperature–time mode of operation and the temperature was monitored by means of an IR sensor directed at the outside wall of the reaction vial. The reaction times (Table 1) refer to hold times at the indicated temperature and not total irradiation times. Upon completion, the reaction mixture was cooled to below 50 °C via propelled air flow, and the precipitate was washed with toluene and, in some cases, with acetone or Et_2O to give the desired N′-substituted *N*-mesitylimidazolium salts **8**–**15**. Alkylations were typically repeated using 100–250 mg of the starting material. The largest quantity of starting material used in a reaction was 500 mg and the reaction proceeded as normal.
1-[4,4-Bis(ethoxycarbonyl)butyl]-3-mesitylimidazol-2-ium chloride **8** (15 mg, 7%) as a brown oil (found: M^+ 387.2273. $C_{22}H_{31}N_2O_4$ requires *M*, 387.2284); ν_{max}/cm^{-1} 1722 (C=O), and 1546 (C=N); δ_H (400 MHz; $CDCl_3$) 1.25 (6H, t, *J* 7.1, 2 × CH_2CH_3), 1.94 (2H, m, CH_2CH), 2.07 (6H, s, 2 × *o*-CH_3), 2.08 (2H, m, $CH_2CH_2CH_2$), 2.33 (3H, s, *p*-CH_3), 3.42 (1H, t, *J* 7.0, CH), 4.17 (4H, m, 2 × OCH_2), 4.80 (2H, t, *J* 6.9, NCH_2), 6.98 (2H, s, 2 × ArH), 7.14 and 7.71 (2H, 2 × s, 4- and 5-H) and 10.64 (1H, s, NCHN); δ_C (100 MHz; $CDCl_3$) 14.0 (q, 2 × CH_2CH_3), 17.5 (q,

2 × *o*-CH_3), 21.0 (q, *p*-CH_3), 25.0 (t, *C*H_2CH), 27.9 (t, $CH_2CH_2CH_2$), 49.8 (t, NCH_2), 50.9 (d, CH), 61.6 (t, 2 × OCH_2), 122.4 and 123.0 (2 × d, C-4 and C-5), 129.8 (d, 2 × ArCH), 130.8 (s, ArC), 134.2 (s, 2 × ArC), 139.2 (d, NCHN), 141.3 (s, ArC) and 168.9 (s, 2 × C=O).

1-(3-Hydroxypropyl)-3-mesitylimidazol-2-ium chloride **9** (560 mg, 74%), white solid, mp 180–182 °C (from MeOH) (lit.,[14,20] no mp reported).

1-(Prop-2-enyl)-3-mesitylimidazol-2-ium iodide **10**[15,35] (68.4 mg, 69%) brown solid, mp 166–167 °C (from CH_2Cl_2–Et_2O).

1-Benzyl-3-mesitylimidazol-2-ium bromide **11** (78 mg, 80%), white solid; mp 249–251 °C (from CH_2Cl_2–Et_2O) (lit.,[15] 237–238 °C).

1-[(1-Ethoxycarbonyl)ethyl]-3-mesitylimidazol-2-ium bromide **12**[18] (69 mg, 77%), yellow oil.

1-Decyl-3-mesitylimidazol-2-ium bromide **13** (67 mg, 61%), grey solid; mp 105–106 °C (found: M^+ 327.2788. $C_{22}H_{35}N_2$ requires *M*, 327.2800); ν_{max}/cm^{-1} 1541 (C=N); δ_H (400 MHz; $CDCl_3$) 0.87 (3H, t, *J* 6.8, CH_2CH_3), 1.24 (10H, br s, 5 × CH_2), 1.35 (4H, m, 2 × CH_2), 1.98 (2H, m, CH_2), 2.08 (6H, s, 2 × *o*-CH_3), 2.33 (3H, s, *p*-CH_3), 4.74 (2H, t, *J* 7.2, NCH_2), 6.99 (2H, s, 2 × ArH), 7.15 (1H, s, NCH), 7.63 (1H, s, NCH) and 10.50 (1H, s, NCHN); δ_C (100 MHz; $CDCl_3$) 14.0 (q, CH_2CH_3), 17.7 (q, 2 × *o*-CH_3), 21.1 (q, *p*-CH_3), 22.6, 26.1, 29.0, 29.2, 29.3, 29.4, 30.6 and 31.8 (8 × t, 8 × CH_2), 50.6 (t, NCH_2), 122.4 (d, NCH), 123.0 (d, NCH), 129.9 (d, 2 × ArCH), 130.7 (s, ArC), 134.2 (s, 2 × ArC), 138.6 (d, NCHN) and 141.4 (s, ArC).

1-[(Pyridin-2-yl)methyl]-3-mesitylimidazol-2-ium bromide **14** (120 mg, 39%) as a light brown solid, mp 128–130 °C (from MeOH) [lit.,[33] 210 °C (decomp.)].

1,3-Bis-(3-mesitylimidazolium-2-yl)propane dihydrogen halide salt **15**[35] (52 mg, 70%), white solid; mp 148–149 °C; ν/cm^{-1} 1549 (C=N); (found: M-1 413.2706. $C_{27}H_{33}N_4$ requires, *M*-1 413.2705); δ_H (400 MHz; $CDCl_3$) 2.07 (12H, s, 4 × *o*-CH_3), 2.35 (6H, s, 2 × *p*-CH_3), 3.22 (2H, m, 2-H_2), 4.99 (4H, t, *J* 7.7, 2 × NCH_2), 7.01 (4H, s, 4 × ArH), 7.09 (2H, s, 2 × 4′-H), 8.51 (2H, s, 2 × 5′-H) and 9.98 (2H, s, 2 × 2′-H); δ_C (100 MHz; $CDCl_3$) 17.5 (q, 4 × *o*-CH_3), 20.9 (q, 2 × *p*-CH_3), 32.0 (t, C-2), 47.0 (t, 2 × NCH_2), 122.9 (d, 2 × C-4′), 124.8 (d, 2 × C-5′), 129.7 (d, 4 × ArCH), 130.6 (s, 2 × ArC), 134.1 (s, 4 × ArC), 137.1 (d, 2 × C-2′) and 141.2 (s, 2 × ArC).

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