Improved microwave oven synthesis of amides and imides promoted by imidazole; convenient transport agent preparation

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Microwave dielectric loss heating without solvent or support yields amides and imides from aromatic and sterically hindered acids in the presence of imidazole in good to excellent yields under mild irradiation conditions.

Our recent work has concentrated on the synthesis and evaluation of chelating agents for divalent metal cation transport. A series of Kemp's triacid derivatives has proven useful for transport of alkaline earth[1,2] and transition metal cations.[3] The recent increase in microwave oven use for organic synthetic preparations, as reviewed by Caddick,[4] suggested the possible use of the microwave oven to synthesize some of our Kemp's acid imide functional molecules. Previous syntheses of condensation products between carboxylic acids and nucleophiles involved the use of activated acids, or polar solvents or supports to absorb microwave energy,[5] requiring pre-treatment or removal of ancillary materials. Reactions related to our transport agents included simple imide synthesis from glycine and phthalic anhydride using high boiling polar solvents reported by Bose.[6] Imai reported the synthesis of nylon 6-6 in *meta*-cresol by pre-forming the acid salt of the monomers before irradiating.[7] Vázquez-Tato further reported amide synthesis without solvent from acids and amines, but these conditions yielded conjugated and sterically hindered amides in low yield.[8] We wished to find simple reaction conditions using unactivated acids without solvent or support to accomplish the synthesis of amides and imides. The conditions reported in this paper allowed the first solventless preparation of imides from sterically hindered acids in unsealed reaction vessels.

Our reaction modification involved the use of imidazole for amidation and imidation in a microwave oven under mild conditions. The reactions of veratric or benzoic acid with benzylamine under low power (500 W) conditions were not very successful (Table 1) as expected from the 52% yield from microwave irradiation (650 W) of veratric acid reported by Vázquez-Tato.† We decided to explore the advantages of imidazole to promote reaction of amines with a range of aromatic and sterically hindered carboxylic acids under mild irradiation conditions.

Imidazole exhibits useful promotion ability[9] and forms polar carboxylic acid salts for efficient microwave energy absorption.[10] Similar reactions conducted with triethylamine or 4-dimethylaminopyridine were unsuccessful or produced a complex reaction mixture, respectively. The reaction promoting ability in our experiments on di- and tri-carboxylic acids with imidazole results from the formation of anhydride species, generally considered to be fast reacting intermediates in condensation reactions. These experiments fit nicely with microwave formation of anhydrides by Villemin.[11] We also demonstrated the microwave absorbing ability of the system by irradiation of imidazole and benzoic acid alone, both absorbed very little heat. However, a mixture of imidazole and benzoic acid reached a temperature of 150 °C in 30 s of 500 W irradiation. The melting point of independently synthesized imidazolium benzoate was 98 °C, such that the reaction easily homogenized after heating. Thus imidazole homogenized the reactions at low microwave power and short irradiation time without the use of solvents or supports.[12]

Irradiation in the microwave oven (Mitsubishi RO-LT11) resulted in condensation reactions producing selected amides from monoacids and imides from polyacids (Table 1). Benzylamine reacted with a range of carboxylic acids; veratric acid (VA), benzoic acid (BA), cyclohexane carboxylic acid (CHA), phthalic acid (PA), *cis*-hexahydrophthalic acid (HHPA), Kemp's triacid (KA) and Kemp's geometric isomer triacid (KGIA). The conditions were simple: irradiation of a mixture of acid, amine and imidazole in a NMR tube, in the centre of the microwave turn-table for the specified times and power levels. Yields improved in the presence of imidazole for the mono- and di-acid cases, demonstrating the value of imidazole for promoting reactions difficult to perform on the acid–amine combinations alone. Of special note was the affect of imidazole on imidation of phthalic acid. Without imidazole, a small, but detectable, amount of amide–acid product remained after reaction, whereas addition of imidazole increased the yield and eliminated this undesirable side product. Kemp's triacid and its geometric isomer successfully reacted under the same conditions, and in the case of Kemp's triacid showed remarkable yield increase in the presence of imidazole. These acid imides were similar to previously synthesized transport agents shown to have high transport ability for calcium cation among other alkaline earth metal cations.[1] Furthermore, **1** (Scheme 1) gave effective and selective transport of transition and heavy metal cations.[3]

This unique heating method using an NMR tube as reaction vessel allowed convenient yield quantification using ^{1}H NMR spectroscopy by integration and comparison of the benzyl proton resonances of the starting amine and the product amide or imide in the crude reaction mixture after irradiation and dissolution in $CDCl_3$. Precise ^{1}H and ^{13}C NMR spectroscopic analysis came from the same sample by washing with aqueous acid and base to remove imidazole, unreacted amine and carboxylic acid, and then drying with $MgSO_4$.‡ Thus a tremendous amount of information can be obtained from

Table 1 Microwave synthesis of benzyl amides and imides[a]

Acid	Yield (%)[b] no imidazole	Yield (%)[b] with imidazole (equiv.)
VA	0	30 (1.0)
BA	13	61 (1.0)
CHA	44	63 (1.0)
PA[c]	91[d]	94 (1.0)
HHPA[c]	0	96 (1.0)
KA	0	98 (3.0)
KGIA	62	95 (3.0)

[a] The reactions were irradiated at 'half-power' (30 s, 500 W; 30 s, 0 W) for 4 min followed by 1 min at 500 W using an acid : amine molar ratio of 1 : 1 in the presence or absence of imidazole. [b] Yield calculated by ^{1}H NMR = (product benzylic CH_2 peak integral)/(total benzylic CH_2 peak integrals). [c] Identical reaction conditions as for monocarboxylic acids, however the heating was milder, only 3 min at the 'half-power' setting. [d] This reaction showed the additional presence of 2% amide in the product mixture.

reactions performed on a 0.1 mmol scale. This powerful combination of the microwave for fast reaction (*ca.* 5 min) and NMR spectroscopy for analysis allowed convenient optimization of reactions.

A ten-fold increase in reaction scale produced **1** (76%) and previously unknown **2** (52%) from reaction of Kemp's triacid or Kemp's geometric isomer triacid with *para*-butyl aniline,§ compared to the procedure requiring two steps for **1** which yielded 70% of Kemp's acid imide.¶ Thus aromatic amines also react well in the microwave with Kemp's triacid derivatives.

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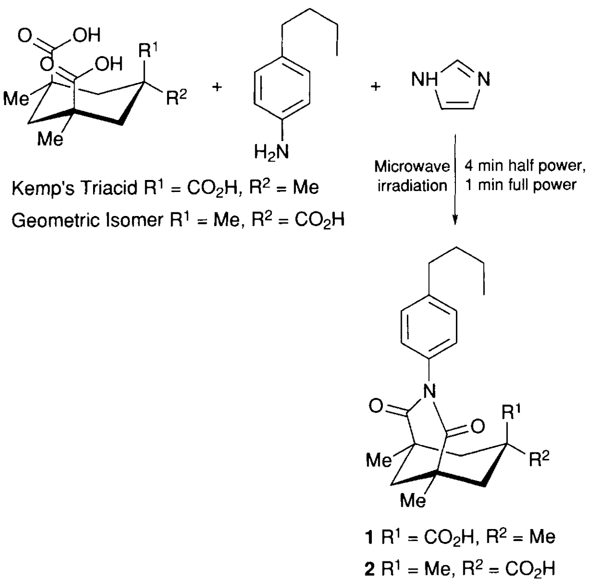

Scheme 1

Footnotes

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† The reaction of veratric acid and benzylamine on 10 mmol scale only occurred after 10 min of full power irradiation (500 W) in 44% recrystallized yield.

‡ The drying agent settles down in the bottom of the tube, below the level of the NMR probe coil.

§ The products were fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

¶ Unpublished data.

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