Green Synthesis of Privileged Benzimidazole Scaffolds using Active Deep Eutectic Solvent

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Electronic Supplementary Material

Table of Contents

Experimental section

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by GC/MS analysis and TLC on silica Merck 60 F_{254} pre-coated aluminum plates. The GC-MS Shimadzu workstation was constituted by a GC 2010 (equipped with a 30 m-QUADREX 007-5MS capillary column, operating in "split" mode, 1 mL min-1 flow of He as carrier gas) and a 2010 quadrupole mass-detector. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Brüker spectrometer at 300 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (J) are reported in Hertz. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (^{13}C NMR) spectra

were recorded on a Brüker at 75 MHz. Chemical shifts are reported in δ units (ppm) relative to $CDCl_3$ (δ 77.0).

General Procedure for DESs Preparation.

The ChCl:urea (1:2) DES was prepared as follows: choline chloride (6.98 g, 50 mmol) and urea (6.00 g, 100 mmol) were added in a round-bottom flask under inert atmosphere. The mixture was magnetically stirred for 60 min at 80 °C until a clear colourless liquid was obtained. The obtained DES was used without need of purification.

For the preparation of ChCl:o-PDA (1:1) DES the following procedure was used: choline chloride (6.98 g, 50 mmol) and o-phenylendiamine (5.40 g, 50 mmol) were mixed in a round-bottom flask under inert atmosphere. The mixture was magnetically stirred for 2 h at 80 °C until a clear yellow liquid was obtained. The obtained DES was characterized by DSC analysis and used without further purification.

General Procedure for the Synthesis of 2-Substituted Benzimidazoles 1a-8a in the DES ChCl:o-PDA (1:1).

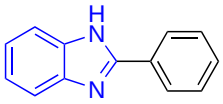
The appropriate aldehyde (1 mmol) was added to the ChCl:o-PDA (1:1) eutectic mixture (1 mL) under magnetic stirring. The resulting mixture was stirred at 80°C for 8-10 min. The reaction was monitored by TLC and GC/MS analysis. After this time, 2 mL of H_2O were added. The resulting aqueous suspension was then extracted with AcOEt (3 x 2 mL). The organic phases were dried over Na_2SO_4, followed by evaporation under reduced pressure to give the corresponding products **1a-8a**. Spectral data were in accordance with the literature [21].

The reaction of benzaldehyde in the ChCl:o-PDA DES to give 1a was scaled up using 20 mol (entry 1, Table 3, footnote c). The reaction was complete in 30 min with 93% isolated yield after simple water addition (10 mL) and extraction with 10 mL ethyl acetate.

General Procedure for the Synthesis of 1,2-Substituted Benzimidazoles 1b-8b in the DES ChCl:o-PDA (1:1).

The appropriate aldehyde (2 mmol) was added to the ChCl: o-PDA (1:1) eutectic mixture (1 mL) under magnetic stirring. The resulting mixture was stirred at 80°C for 8-10 min. The reaction was monitored by TLC and GC/MS analysis. After this time, 2 mL of H_2O were added. The resulting aqueous suspension was then extracted with AcOEt (3 x 2 mL). The organic phases were dried over Na_2SO_4, followed by evaporation under reduced pressure to give the corresponding products **1b-8b**. Spectral data were in accordance with the literature [21].

MS(EI) spectra of benzimidazole derivatives



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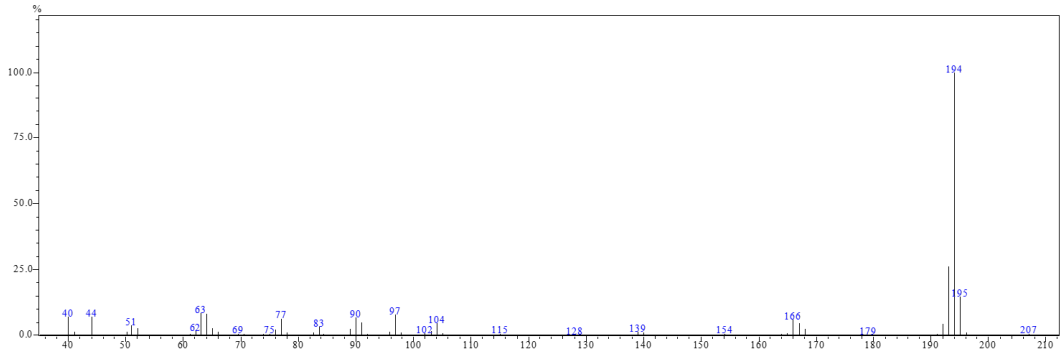

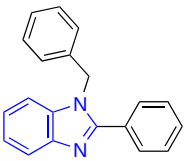

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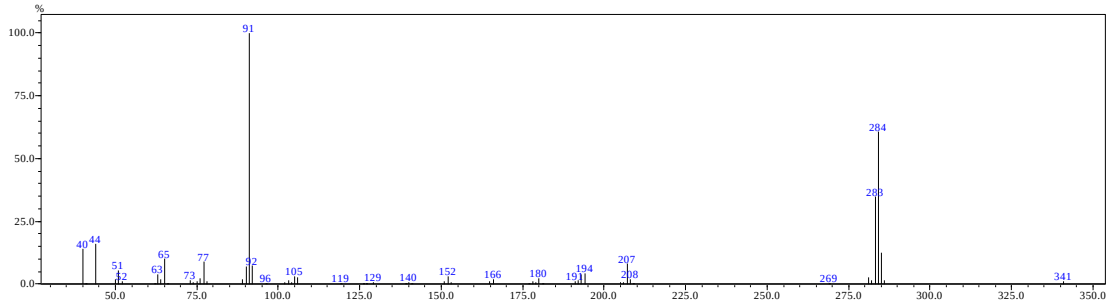

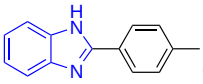

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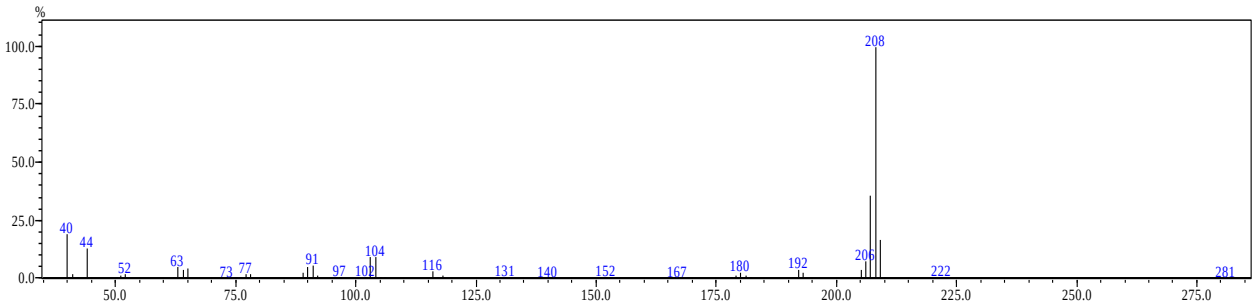
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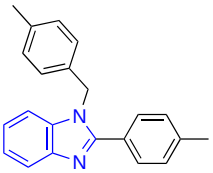

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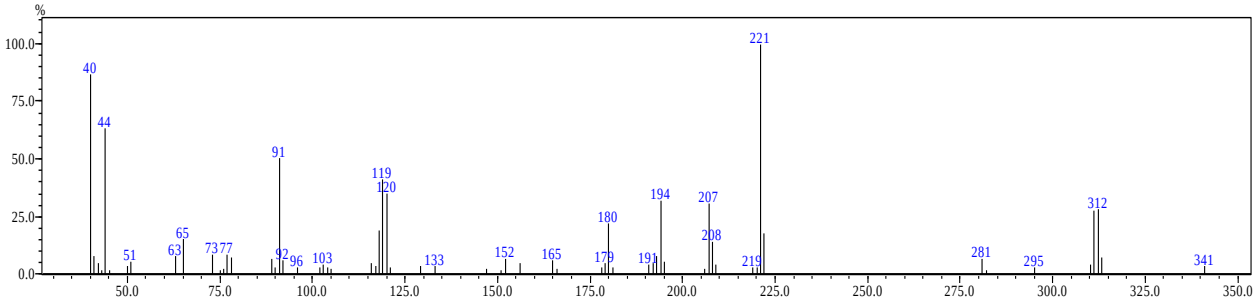
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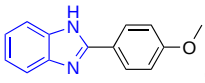

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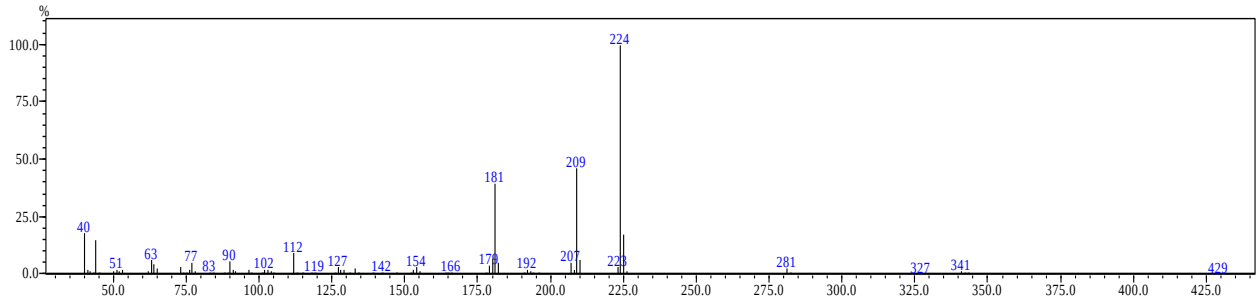
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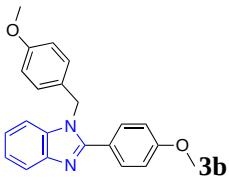

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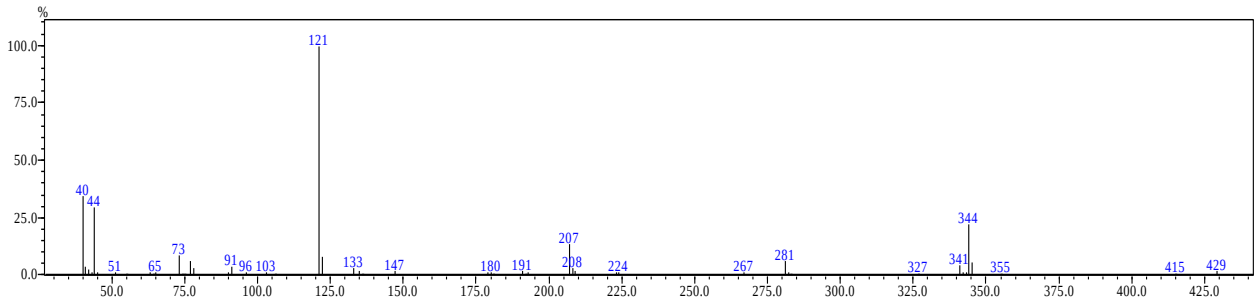
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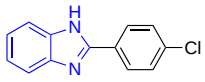
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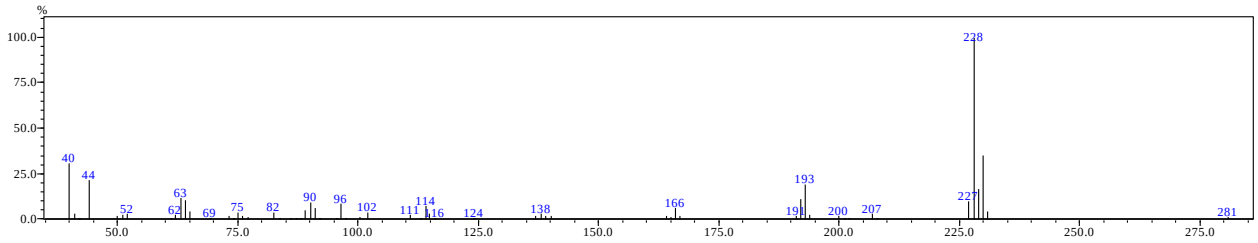
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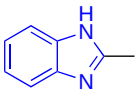

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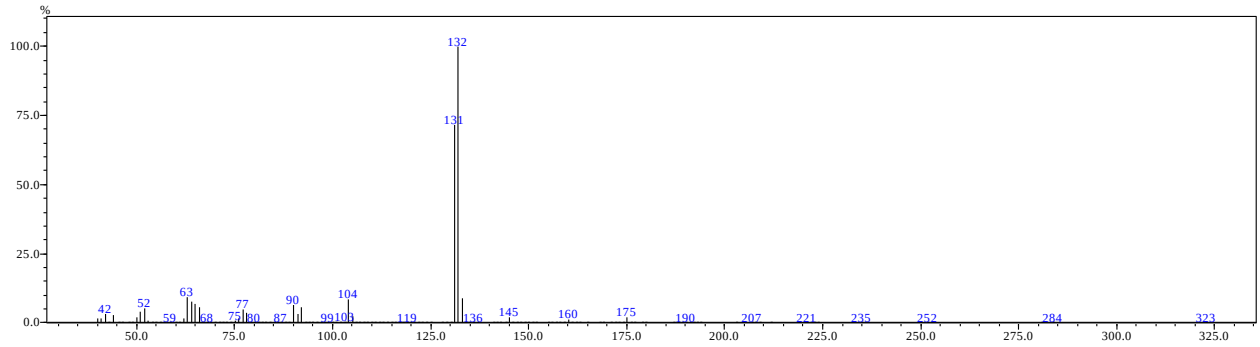
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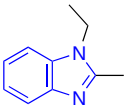

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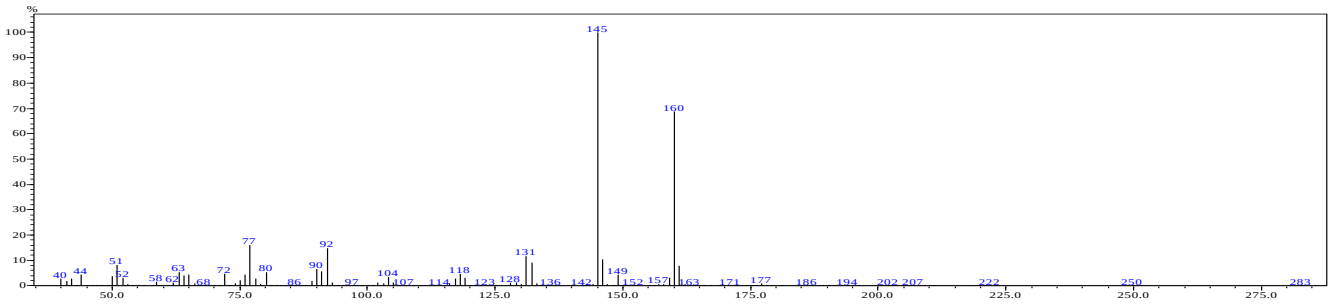
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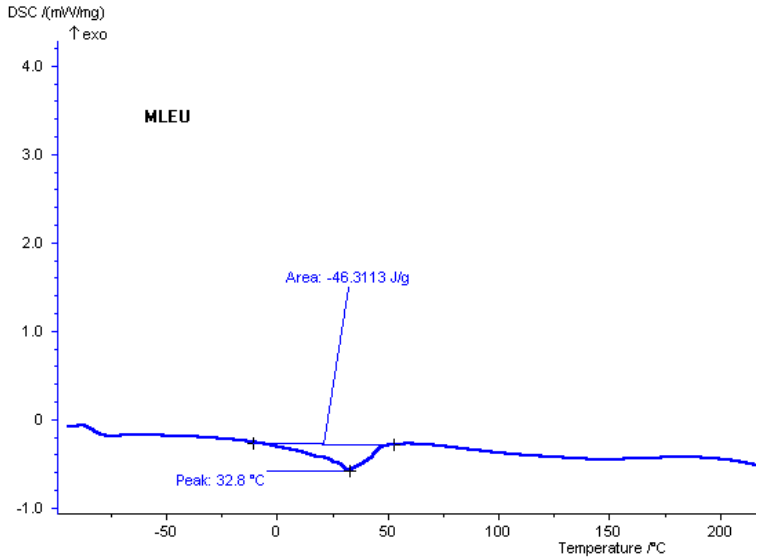
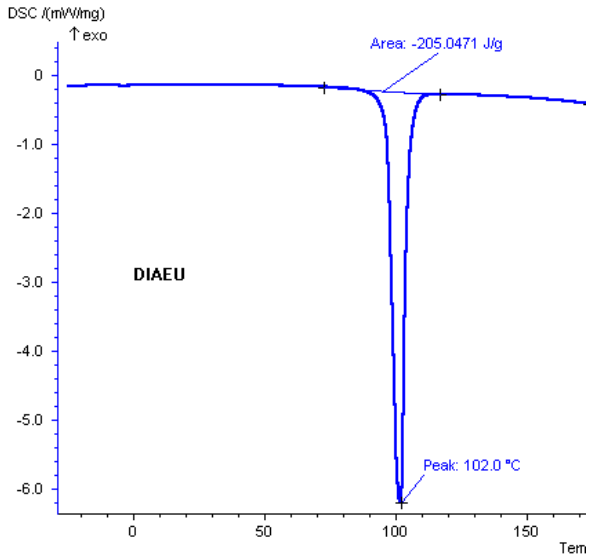
Differential scanning analysis (DSC) of ChCl:o-PDA (1:1)



Differential scanning analysis (DSC) of pure o-PDA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DIAEU
Peak: 102.0 °C
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