Green Synthesis of Privileged Benzimidazole Scaffolds using Active Deep Eutectic Solvent

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Electronic Supplementary Material

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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} precoated 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).

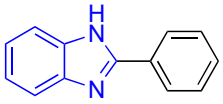
The appropriate aldehyde (1 mmol) was added to the ChCl:o-PDA (1:1) eutectic mixture (1 mL) under magnetic stirring. The resulting mixture was stirred at 80 °C for 8–10 min. The reaction was monitored by TLC and GC/MS analysis. After this time, 2 mL of H_2O were added. The resulting aqueous suspension 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.

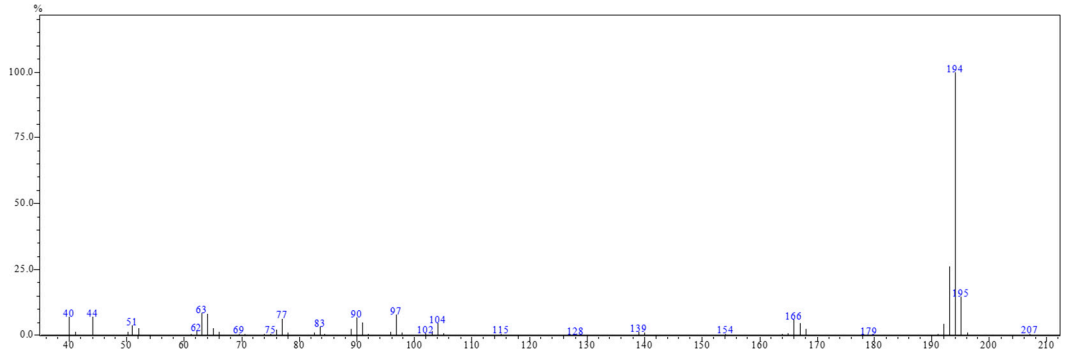
General Procedure for the Synthesis of 1,2-Substituted Benzimidazoles 1b–8b in the DES ChCl:o-PDA (1:1).

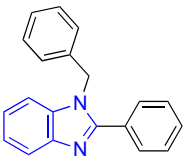
The appropriate aldehyde (2 mmol) was added to the ChCl: o-PDA (1:1) eutectic mixture (1 mL) under magnetic stirring. The resulting mixture was stirred at 80 °C for 8–10 min. The reaction was monitored by TLC and GC/MS analysis. After this time, 2 mL of H_2O were added. The resulting aqueous suspension 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



1a





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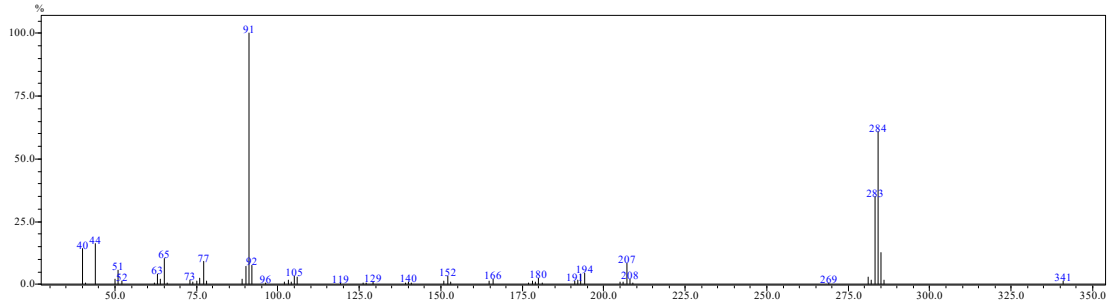

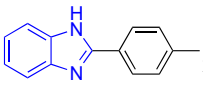

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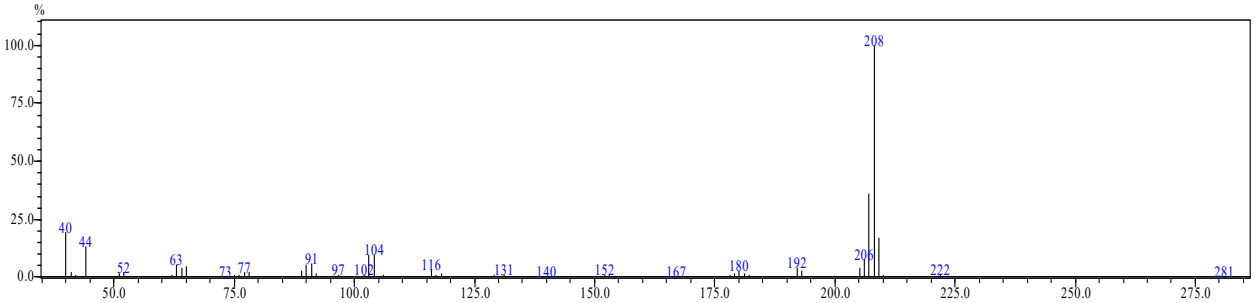
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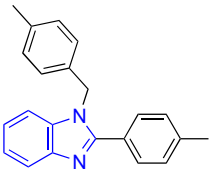

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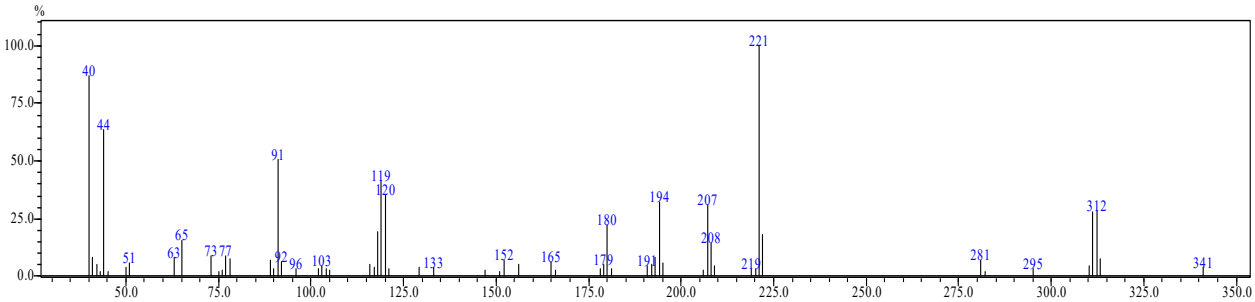
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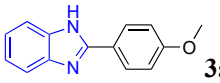

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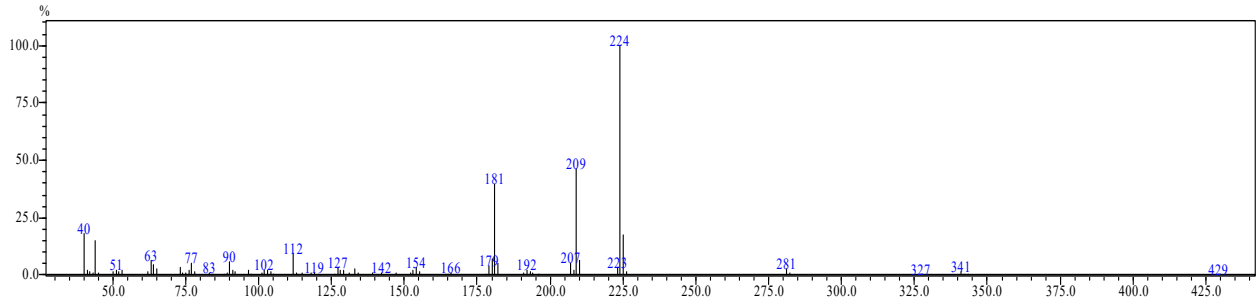
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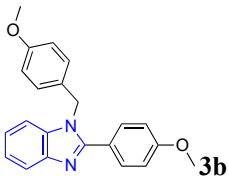

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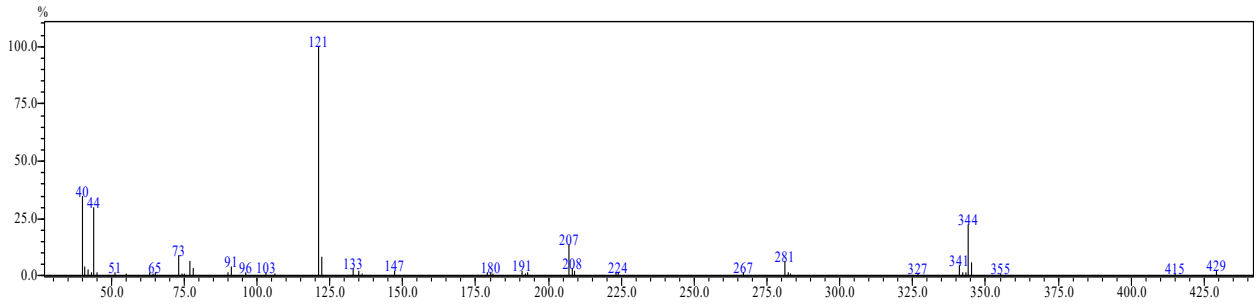
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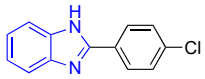
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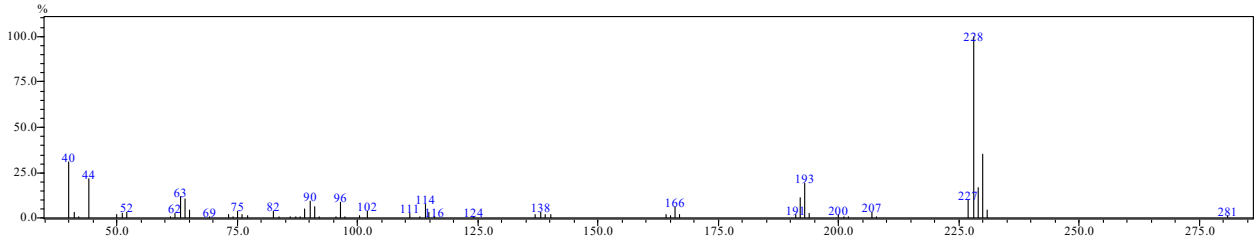
7a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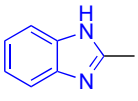

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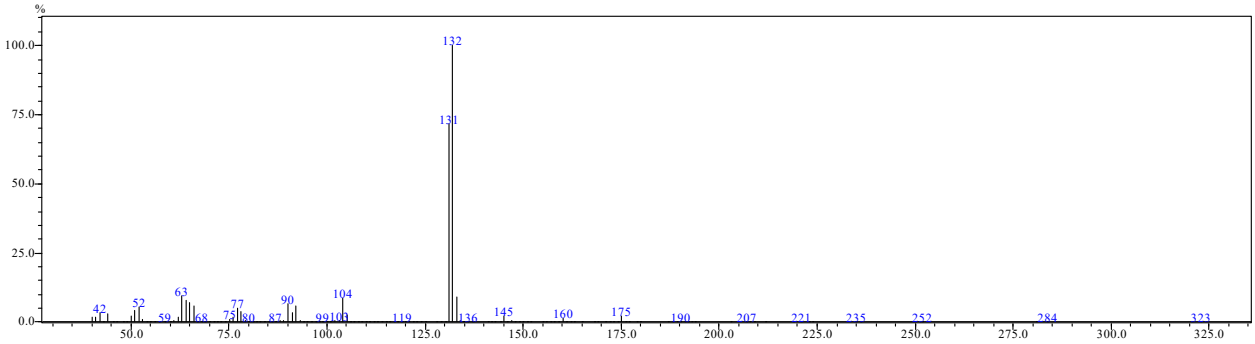
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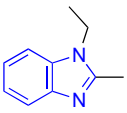

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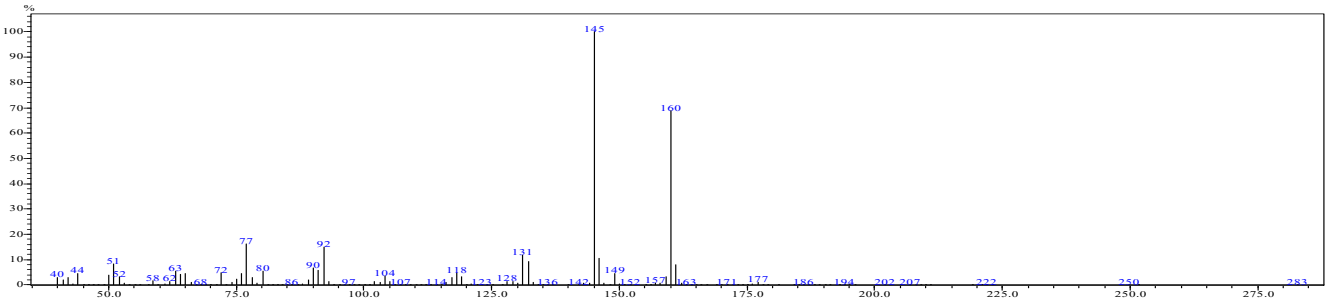
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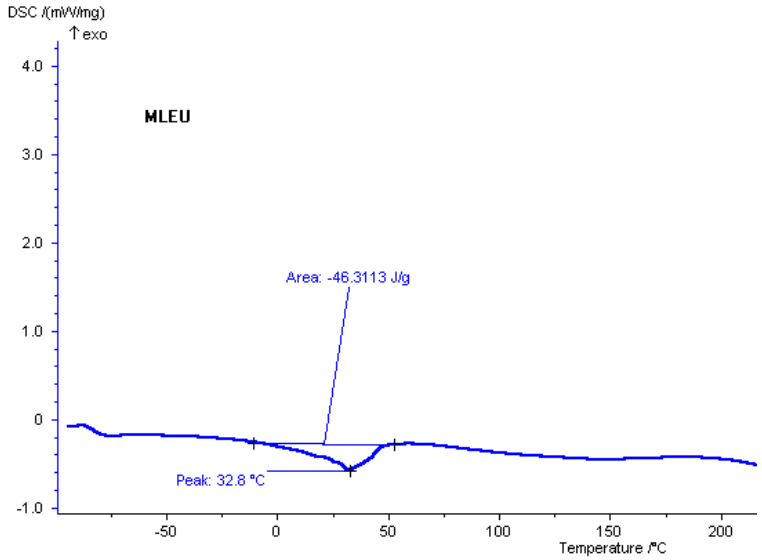
Differential Scanning Analysis (DSC) of ChCl:o-PDA (1:1)



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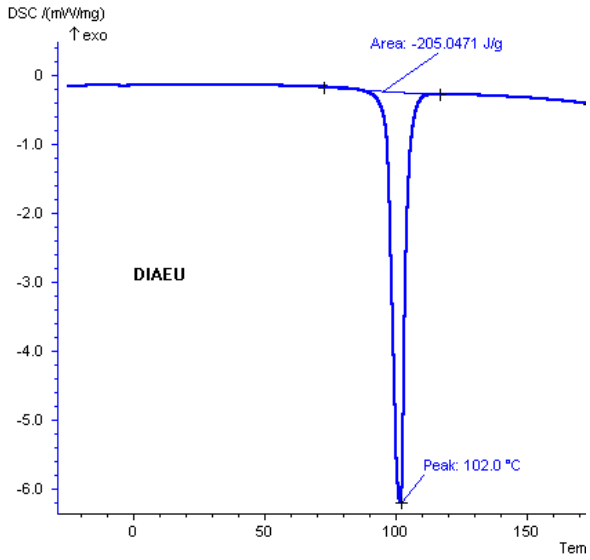
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DIAEU
Peak: 102.0 °C
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