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Thermolysis reactions of N-alkyl-N′-CBZ amino acid amides. A route to substituted imidazolidine-2,4-diones

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ABSTRACT

Reaction of N-alkyl-N′-CBZ amino acid amides under microwave conditions in water and in the presence of an acid catalyst results in the formation of N-substituted imidazolidine-2,4-diones in good yields.

Introduction and discussion

β-Phenylethylamino acid amides of the general structure **3** have been shown to be effective fungicidal agents against various species of phytopathogenic fungi, especially *Plasmopara viticola*.[1] During the course of investigation of these compounds, we found that such compounds can undergo tandem cyclization reactions when subjected to Bischler-Napieralski reaction conditions to afford dihydroimidazoisoquinolin-3(2H)-ones **4**.[2] This reaction was observed to be a one-pot, tandem cyclization affording dihydroimidazoisoquinolin-3(2H)-one products in low yields when the aromatic ring of **3** was appropriately electronically activated. When the aromatic ring was electron deficient or lacked appropriate activation, the cyclization was arrested at the imidazolidine-2,4-dione **5** (Scheme 1).

These results prompted us to further investigate the reaction in order to determine if the dihydroimidazoisoquinolin-3(2H)-ones **4** were formed through the intermediacy of the imidazolidine-2,4-dione derivatives **5**. To test the hypothesis, preparation of the arylethylamino imidazolidine-2,4-dione **5a** and **5b** were required and prepared in excellent yield from the condensation reaction of the requisite imidazolidine-2,4-dione **7** and β-arylethyl bromide **6**. However, neither **5a** nor **5b** afforded **4** in significant quantities upon reaction with $POCl_3$. Compound **4** was only observed *via* GC–MS in trace quantities when **5a** and a significant excess of $POCl_3$ was added. Treatment of **5a** and **5b** with acids such as *p*-toluene sulfonic acid and concentrated sulfuric acid likewise did not afford **4** (Scheme 2).

While attempting to characterize the amino acid amides of the type **3** by GC–MS, we observed a molecular ion corresponding to the imidazolidine-2,4-dione derivative **4;** indeed, the mass spectrum and GC retention time for **5b** was identical to that observed for **3b** thereby indicating that the imidazolidine-2,4-dione was formed *via* high temperature heating of the corresponding amino acid amide. To date, this type of thermal-mediated cyclization has not been reported in the literature and the quantitative conversion of **3**–**5** observed in the GC–MS at high temperatures represents a novel route toward imidazolidine-2,4-dione compounds with potential industrial and drug design applications. A somewhat similar reaction utilizing a Tf_2O-mediated cyclization of amino amides in dichloromethane has been reported.[3] Imidazolidine-2,4-dione (hydantoin) compounds have been widely employed as anticonvulsant medications rendering their synthesis an important area of research.[4] Armed with this information, we have focused on defining the scope and limitations of the conversion of **3**–**5** (Table 1).

Initial efforts to carry out the cyclization under purely thermal conditions were met with limited success. For example, simple, CBZ-protected phenylethylamino acid amides such as alanine and valine were shown to cyclize under different thermolysis conditions such as in DMSO and when no solvent was used. However, significant thermal degradation of both reactants and solvent in addition to low product yields were observed in these reactions, even when the reactions were carried out in a Biotage microwave synthesizer. Cyclization attempts utilizing

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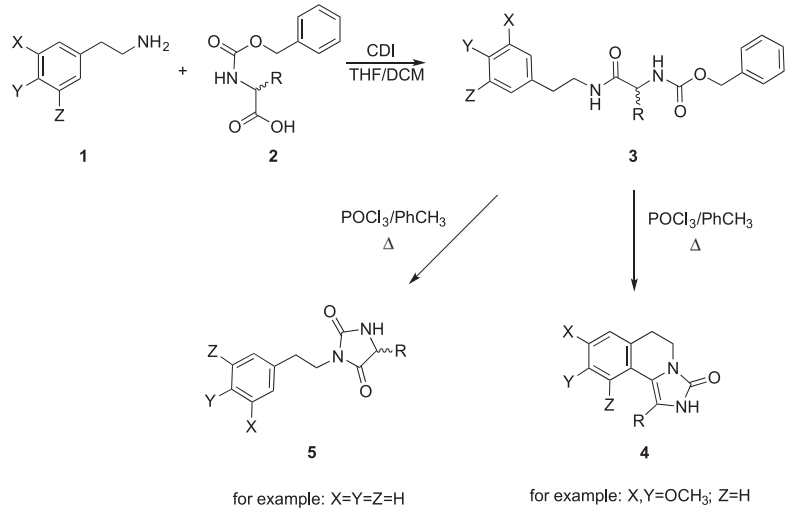
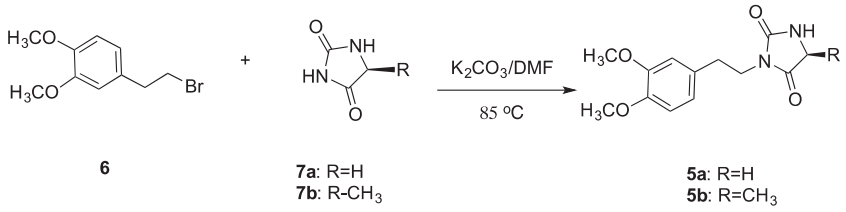
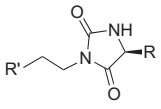


Scheme 1.



Scheme 2.

Table 1
Preparation of imdiazolidine-2,5-diones.



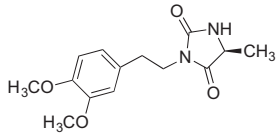
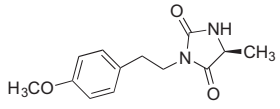
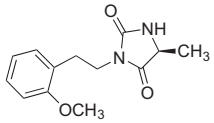
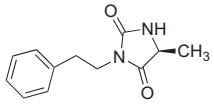
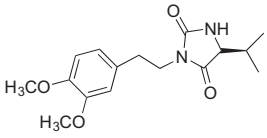
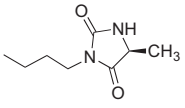
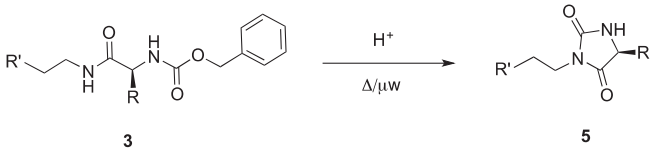
Imidazolidine-2,5-dione	Conditions	Yield
5a 	Microwave Synthesizer 6 h; 200 °C 17.4% PTSA by weight	73%
5b 	Microwave Synthesizer 6 h; 200 °C 35.7% PTSA by weight	68%
5c 	Microwave Synthesizer 12 h; 200 °C 21.2% PTSA by weight	71%
5d 	Microwave Synthesizer 10 h; 200 °C 19.5% PTSA by weight	73%

Table 1 (*continued*)

Imidazolidine-2,5-dione	Conditions	Yield
5e 	Microwave Synthesizer 6 h; 200 °C 21.0% PTSA by weight	89%
5f 	Microwave Synthesizer 10 h; 200 °C 20.7% PTSA by weight	79%

various other polar solvent systems such as water, 1,4-dioxane, and acetonitrile all failed to induce any product formation. Interestingly, efforts making use of an acid catalyst in deionized water have led to successful cyclization. *p*-Toluene sulfonic acid was used in ratios ranging between 17.4 and 37.8 wt% of the substrate. Additionally, all of the reactions studied were run at a temperature of 200 °C in the Biotage microwave synthesizer.



Scheme 3.

However, the reaction times required for significant cyclization to occur (as determined by ^{1}H NMR) varied and ranged between 6 and 12 h (Scheme 3).

Conclusion

In light of the ongoing interest in hydantoin derivatives as indicated by recent review articles,[5,6] this methodology[7] serves to complement currently existing methods for the preparation of these valuable derivatives. Six derivatives of **3** have successfully been observed to form **5** under microwave reaction conditions with isolated purified yields ranging from 68 to 89%. Future work will involve examining the results of cyclization experiments using other N-protecting groups on **3** such as BOC and FMOC groups. Other amino acid side chains will also be studied such as hydrophilic side chains and sterically unhindered glycine compounds. Finally, other solvent systems and catalysts will be examined under catalytic conditions in an effort to shorten reaction times.

Acknowledgements

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7. *General procedure for the preparation of Imidazolidine-2,4-diones **5** from amino acid amides **3**. Preparation of 3-(3,4-dimethoxyphenethyl)-5-methylimidazolidine-2,4-dione **5a***. Benzyl (S)-(1-((3,4-dimethoxyphenethyl)amino)-1-oxopropan-2-yl)carbamate (155 mg was charged to a 5 ml Biotage Microwave Synthesizer vial along with 27 mg PTSA, 3.0 ml DI water, and a magnetic stir bar. The vial was sealed and heated in the Biotage Microwave Synthesizer at 200 °C for 6 hours and an absorption level of setting of low. Dilution of the aqueous layer to 10 mL with water then washing with portions of DCM (2 × 20 mL). The combined organic layers were washed with 2 × 20 ml portions of $NaHCO_3$ (2 × 20 mL), dried over MgSO4, filtered, condensed, and characterized with proton NMR. Purification was accomplished via column chromatography on the Biotage Isolera using a gradient of 7:3 ethyl acetate:hexanes to 9:1 ethyl acetate hexanes. A 10 g silica gel column was used along with a 20 ml/min flow rate. Fractions containing purified hydantoin product were condensed and characterized via NMR and IR spectroscopy. The product was obtained as a light yellow solid (81 mg, 73%), mp 115 °C, IR (cm^{-1}): 3230.3, 1712.8; ^{1}H NMR (400 MHz; $CDCl_3$): δ 6.76–6.75 (m, 2H, J = 1.96 Hz), 6.73 (s, 1H), 5.31 (s, 1H), 4.02–3.96 (q of d, 1H, J = 7.05 Hz, J′ = 1.39 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.74–3.69 (sextet, 2H, J = 3.91 Hz), 2.90–2.86 (t, 2H, J = 7.49 Hz), 1.35–1.34 (d, 3H, J = 7.16 Hz); ^{13}C NMR (400 MHz; $CDCl_3$): δ 174.3, 156.9, 148.9, 147. 8, 130.2, 121.0, 112.1, 111.2, 55.9, 52.7, 39.7, 33.4, 17.7. Calc'd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C: 60.38; H, 6.84; N, 9.73.