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Novel Lewis Acid Catalyzed (E)/(Z)-Arylidene Thiohydantoin Formation

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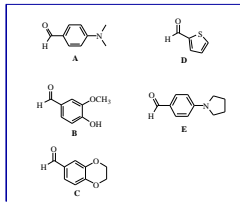
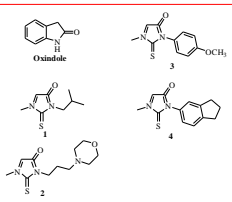
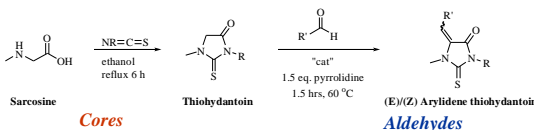
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Abstract

The novel Lewis acid catalyzed condensation of aldehydes with 3-alkyl-1-methyl-thioxo-imidazolidin-4-ones (thiohydantoin) to generate the corresponding (E)/(Z) 5-arylidene-3-alkyl-1-methyl-2-thioxo-imidazolidin-4-ones (arylidene thiohydantoin) is presented. A survey of various catalysts was conducted (either indium(III) triflate, aluminum trichloride, or boron trifluoride diethyl etherate) and compared with the uncatalyzed reactions. In most examples, the Lewis acid promoted catalysis yielded reactions exhibiting increased reactivity, conversion and purity profiles as compared to the uncatalyzed reactions. Since arylidene thiohydantoin are reported in the literature as being biologically relevant moieties for antimicrobial, antiviral, immunosuppressive and potentially anticonvulsant indications, this validated protocol was then used as part of our parallel synthesis efforts to generate a library of approximately 400 target compounds.

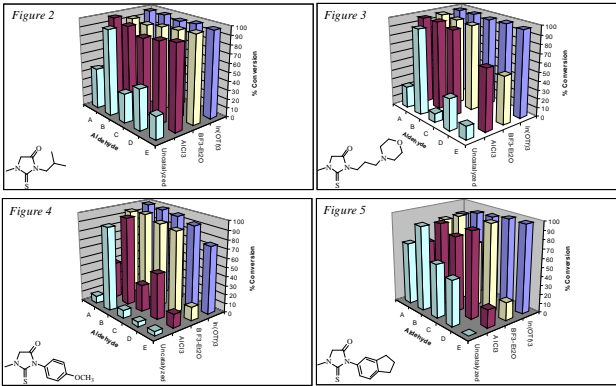
Introduction

The arylidene thiohydantoin moiety is known to be a biologically active heterocycle in areas of antimicrobial, antiviral, immunosuppressive and potentially anticonvulsant indications.¹⁻³ As part of Albany Molecular Research's library compound collection formation, we set out to prepare a library of such compounds. Reports in the literature for the preparation of (E)/(Z)-arylidene thiohydantoin typically involves the direct condensation of aldehydes with thiohydantoin in the presence of pyrrolidine and a solvent such as toluene or 1,4-dioxane. Similar results are found in the literature for the oxindole moiety as well.⁵⁻⁷ In general, reactions give modest yields of 65 to 80% and examples of sterically hindered aldehydes and/or thiohydantoin typically give poor results. The use of Indium(III) TSOH and KF/alumina have been reported for other similar substrates with good results for a limited number of examples. Most recently Nielsen *et al.*⁴ have reported the preparation of a small 28 member library of arylidene thiohydantoin via microwave mediated conditions with good results. Since our goal was the generation of a library of approximately 400 compounds, microwave irradiation did not seem to be a viable method of use. It was apparent that due to the diversity of the library ligand sets that we envisaged using, a reaction protocol which generated (E)/(Z)-arylidene thiohydantoin in good yield for a large diversity of R groups needed to be developed. As part of our library protocol validation we chose to investigate four thiohydantoin (**1-4**) (oxindole was also included as an extension of this study) and five aldehydes (**A-E**) that represented the wide range of steric and electronic properties that would later be found in the full library diversity set. Indium(III) triflate, aluminum chloride and boron trifluoride diethyl etherate were chosen as the catalyst to be studied for this set of reactions.

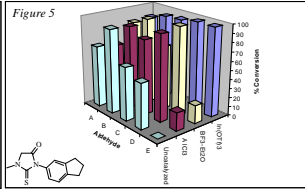
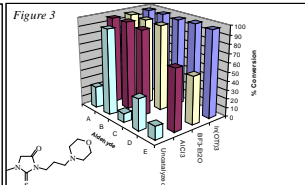
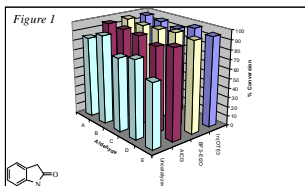


Results

The 3D charts shown here depict the results of the surveyed Lewis acid catalysts on the condensation reaction of aldehydes with the cores as compared to the uncatalyzed reaction after 30 minutes at 60 °C. As can be seen, in most all of the examples below, the catalyzed reactions show a substantial increase in % conversion as determined by HPLC (AUC analysis). Our results show that while all the catalysts surveyed showed increased % conversion as compared to the uncatalyzed reactions, the use of indium(III) triflate has a wider application of utility. Figures 3, 4 and 5 clearly show that the with aldehydes **D** and **E**, indium(III) triflate is the catalyst of choice



for these reactions. The use of the appropriate catalyst, in these examples indium(III) triflate, offers a convenient route to access a wide range of diversity that is associated with library production



Experimental Details

Thiohydantoin:

To a 200 mL single-neck round-bottomed flask fitted with a magnetic stir bar was charged sarcosine (1.5 g, 16.8 mmol) and anhydrous ethanol (100 mL). To the resulting solution was added the appropriate isothiocyanate (1.0 eq., 16.8 mmol) and the reaction was heated to reflux for 6 h after which time the reaction was allowed to cool to room temperature. The ethanol was removed under reduced pressure and the resulting crude material was taken up into a minimum of dichloromethane and purified by silica gel chromatography with ethyl acetate/hexanes to give the title compound.

Arylidene thiohydantoin catalyst survey:

To a 2 dram vial fitted with a magnetic stir bar was added the appropriate thiohydantoin (0.75 mmol), aldehyde (1.2 eq., 0.90 mmol), pyrrolidine (1.5 eq., 1.13 mmol) and 1,4-dioxane (1.5 mL). To the reactions was then added the desired catalyst (0.1 eq., 0.075 mmol) and the reaction was heated to 60 °C using a J-Chem heater block. Aliquots were removed and the samples analyzed after 30 minutes, 90 minutes, 5 hrs and 24 hrs by HPLC at 210 and 254 nm. For all reactions with indium(III) triflate as the catalysts, the reactions were concentrate to dryness under reduced pressure and the crude residue was chromatographed on silica gel with dichloromethane/methanol to give the title compound.

Conclusion

Indium(III) triflate, aluminum chloride and boron trifluoride diethyl etherate were all found to be efficient catalysts for the formation of (E)/(Z) arylidene thiohydantoin. Indium(III) triflate was chosen as the catalyst of choice for the subsequent library synthesis due to its easy of handling, air stability, reproducible results and cost. A library of 408 compounds was prepared with greater than 80% of the compounds being 85%+ purity, with and average purity of 92% and isolated yields of 45 mg.

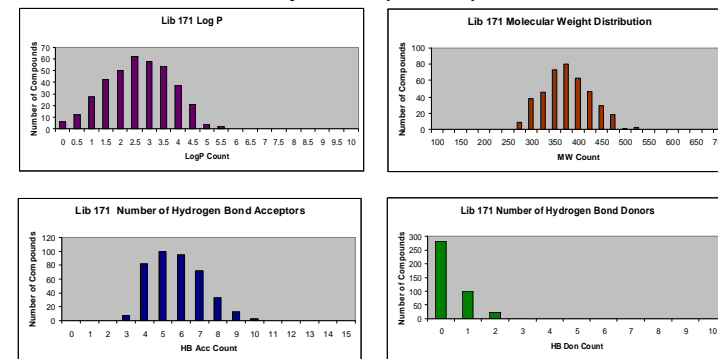
Acknowledgment

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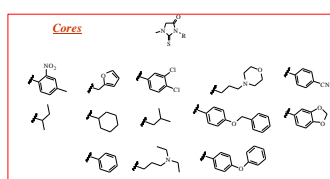
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Computational Analysis of Library



Library Protocol and Diversity



Arylidene thiohydantoin library protocol:

A solution of thiohydantoin (400 µL; 1M solution in 1,4-dioxane) was added to across the row of a 6 x 4 matrix of 2 dram vials. A solution of aldehyde (500 µL, 1M solution in 1,4-dioxane) was then added down the columns. Pyrrolidine (60 µL, 1.5 eq) was then added to each vial followed by indium(III) triflate (15 mg, 0.026 mmol, 0.06 eq). The reactions were sealed with a Teflon lined cap and heated to 60 °C for 1.5h. Saturated sodium bicarbonate (2 mL) and ethyl acetate (1.5 mL) were then added and the organic phase was removed and concentrated to dryness. The resulting crude products were then purified by reverse phase HPLC.



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