Three-step economical and green alternative to Donepezil intermediate

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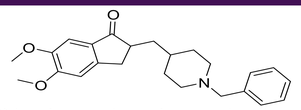
Abstract

A three step economical and green alternative has been developed for the synthesis of the Donepezil intermediate. Donepezil is an acetylcholinesterase inhibitor used to improve cognitive functions in Alzheimer's disease (AD) patients. AD is a progressive neurodegenerative disorder characterized by the loss of memory and dementia and has been shown to cause the death of cholinergic neurons and a decline in acetylcholine. Multiple studies showed that the use of anticholinergic agents cause amnesia and learning disabilities which confirm the importance of acetylcholine against dementia. The use of acetylcholinesterase inhibitor inhibits the enzyme acetylcholinesterase increasing, thus, the levels of acetylcholine. The three steps synthesis proposed involve the conversion of 3,4-dimethoxycinnamic acid to 3-phenylpropionic acid via Pd/C catalysis (1) followed by the conversion of 3-phenylpropionic acid to 5,6-dimethoxy-1-inandone via intramolecular Friedel-Craft acylation using ethyl acetate for extraction as a green alternative to dichloromethane (3). 5,6-dimethoxy-1-inandone and 4-Pyridinecarboxaldehyde were added together to form our Donepezil intermediate.

Background



Alzheimer's disease (AD) is a degenerative and progressive disease resulting in the loss of memory and decline in activities of daily living (ADLs). Because no cure for AD currently exists, the most effective treatment involves slowing down the functional and cognitive loss in patients. Donepezil is the most commonly used drug in the market to treat AD, and has been proven in several different studies to slow cognitive loss and decline in ADLs. Elati and coworkers were able to reduce the cost and waste of production of Donepezil by refluxing using p-toluene sulfonic acid in toluene as an alternative to sub-zero temperature conditions and the hazardous n-butyl lithium (2). Here, we report a three step synthesis of 5,6-dimethoxy-indan-1-one to both reduce/maintain the cost of Donepezil synthesis and eliminate the use of dichloromethane, a hazardous reagent.

The first step was the conversion of 3,4-dimethoxycinnamic acid to 3-phenylpropionic acid via Pd/C catalysis followed by the conversion of 3-phenylpropionic acid to 5,6-dimethoxy-1-inandone via intramolecular Friedel-Craft acylation using ethyl acetate for extraction as a green alternative to dichloromethane. The Donepezil intermediate was then made by refluxing 5,6-dimethoxy-1-inandone, p-toluene sulfonic acid and 4-Pyridinecarboxaldehyde in toluene.

The use of ethyl acetate for extraction was significant because it is less toxic to both humans and the environment as well as less expensive when compared to dichloromethane. In addition, extraction via dichloromethane unnecessarily produces carcinogenic chlorinated water waste which is eliminated with the use of ethyl acetate

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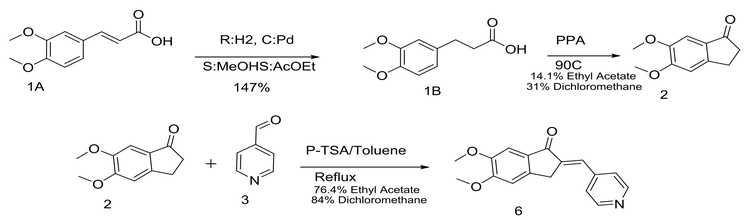
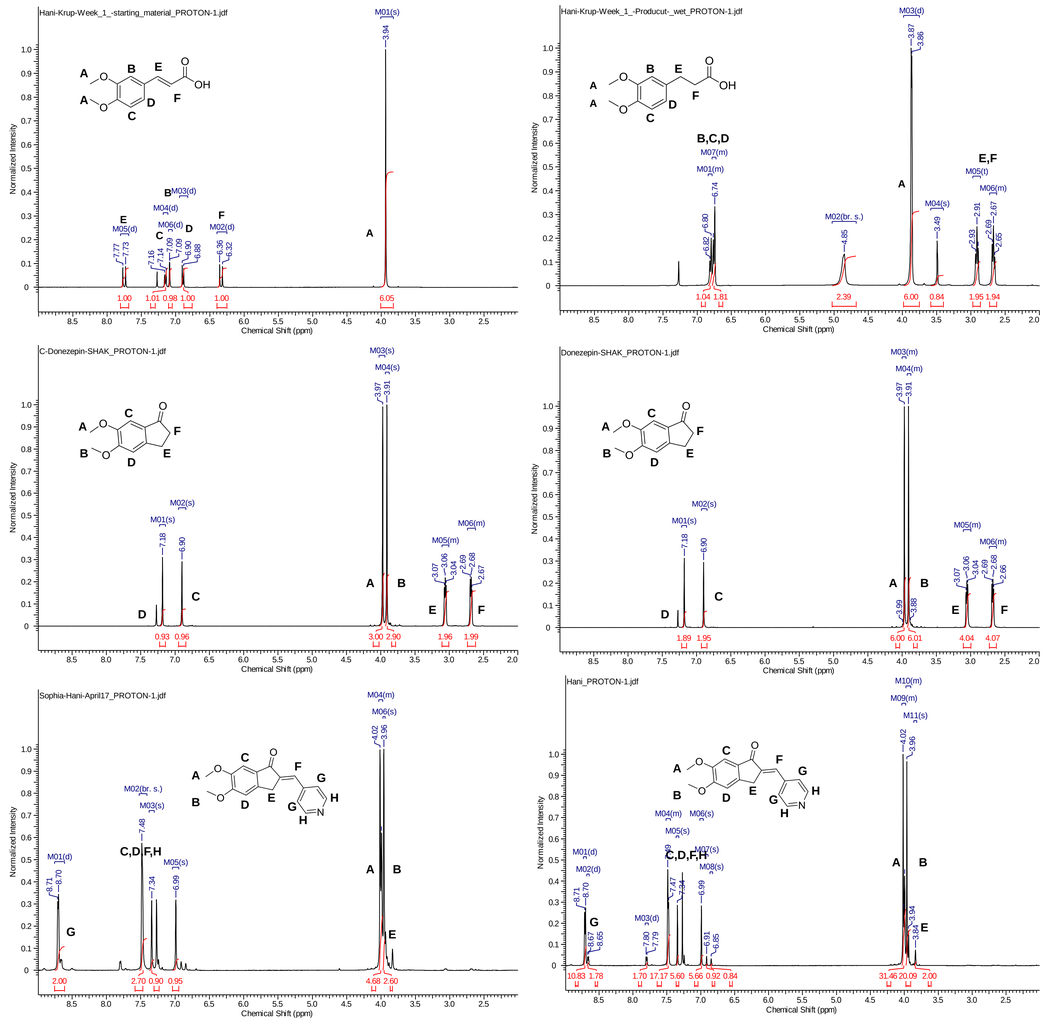
Background on Green Chemistry

Dichloromethane is commonly used as an extraction solvent with an LD 50 of 1600 mg/kg and has been classified as carcinogenic and toxic to both humans and the environment. Ethyl acetate was chosen as a green alternative which is similar in price to dichloromethane. Ethyl acetate is less toxic than dichloromethane with an LD 50 of 5620mg/kg and has not been classified as carcinogenic. The use of dichloromethane produces carcinogenic chlorinated water therefore by extracting with ethyl acetate the production of unnecessary hazardous waste can be prevented.

Synthetic Scheme



NMR Data



Green Chemistry

Comparison Parameters	Ethyl Acetate	Dichloromethane
Hazards	Hazardous when ingested and inhaled. Slightly hazardous for eyes and skin	Very hazardous for eyes and in case of ingestion and inhalation. Hazardous for skin. Carcinogenic.
Cost	$34.45/L	$26.9/L
Percent Yield	14.1%	31%
E Factor	21.5%	88.6%
Reaction Time, Temp	90° C	90°C
Product Purity, byproducts	byproduct	Minimal Impurities
Waste produced	150mL ethyl acetate, 100 ml Sat. NaCl, traces of anhydrous sodium sulfate	150mL dichloromethane, 100 ml Sat. NaCl, traces of anhydrous sodium sulfate

Discussion

The starting material 3,4-dimethoxycinnamic acid was first converted to 3-phenylpropionic acid via Pd/C catalysis yielding a white solid (5.3 g, 147% yield). The product of step one was confirmed to be 3-phenylpropionic acid by proton NMR (see NMR results). NMR also confirmed that excess yield was due to the presence of residual methanol. The 3-phenylpropionic acid was then converted to 5,6-dimethoxy-1-inandone via intramolecular Friedel-Craft acylation using either ethyl acetate or dichloromethane for extraction. The ethyl acetate extraction yielded a yellow solid (1.132 g, 29% yield) with a byproduct that was purified via crystallization (14.1% yield) while the dichloromethane extraction yielded a yellow solid (0.918 g, 31% yield). The conversion to dimethoxy-1-inandone was confirmed for both the ethyl acetate extraction and the dichloromethane extraction by proton NMR (see NMR results). Because the two extractions gave such similar yields, it was reasonably concluded that ethyl acetate is a viable alternative to dichloromethane for the purpose of this synthesis. The dimethoxy-1-inandone was refluxed with 4-pyridinecarboxaldehyde and p-toluene sulfuric acid in toluene to give the Donepezil intermediate. The dimethoxy-1-inandone product resulting from the ethyl acetate extraction yielded a pale yellow solid (0.551 g, 102% yield) with impurities that that were purified via crystallization (76.4% yield) while the product resulting from the dichloromethane extraction yielded a pale yellow solid (0.501 g, 84% yield) both of which were confirmed to be the Donepezil intermediate via proton NMR (see NMR results).

Conclusion

The proposed green and economical three step process was successful in synthesizing the Donepezil intermediate using ethyl acetate as an alternative to dichloromethane for extraction in the second step.

Future Directions

The Donepezil intermediate synthesis shown can be used to proceed with the full synthesis of Donepezil. In addition, the substitution of ethyl acetate for dichloromethane for the purpose of extraction holds promise for reducing the environmental and health impact of other processes.

References

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