Potential Celecoxib analogue precursors derived via Aldol condensation

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ABSTRACT

Various indanone compounds, 1-indanone specifically, have the potential to undergo Aldol condensations to form precursors to compounds structurally similar to the Non-Steroidal Anti-Inflammatory Drug (NSAID) CELEBREX (celecoxib). A series of potential analogous precursors in the form of alpha-beta unsaturated ketones have been developed. The conversion of these precursors into pyrazoline compounds was attempted. After oxidation of the pyrazoline compounds, they could potentially have biological activity by acting through CycloOxygense-2 (COX-2) in the same manner to CELEBREX.

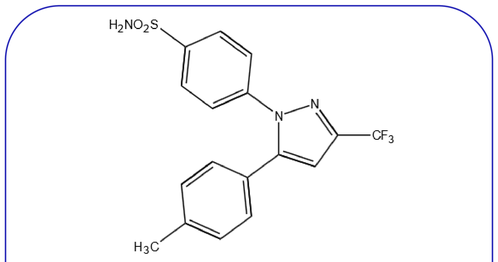
INTRODUCTION

The extensive objective of this research was to produce viable, or superior, analogs for the prescription drug CELEBREX. CELEBREX is in the NSAID class of medications. NSAIDs are used to inhibit COX-2 (CycloOXygenase-2), which is a promoter of inflammation. CELEBREX is a unique compound as it does not inhibit COX-1 as other NSAIDs do. Other NSAIDs inhibit the activity of COX-1, which ultimately thwarts the stomach from producing enough of a mucus coating to protect it from its digestive acids; this can lead to ulcers in long term use. Celecoxib is selective for COX-2 due to steric interactions. Celecoxib's relatively bulky structure fits into the pocket in the channel for COX-2. COX-1 does not have this channel making it not able to react with COX-1. This is due to the two enzymes being isoforms, which means that the channels share the same chemical structure, but differ in spatial orientation. Figures 1 and 2 below depict reaction schemes for generic Aldol Condensations and Imine formations used in the experiment.

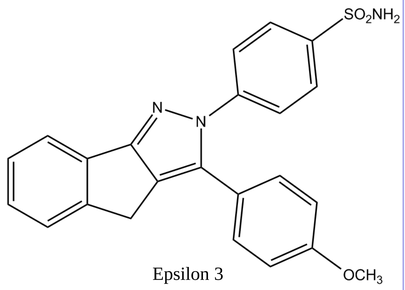
DISCUSSION

There has been success with these procedures in regard to percent yields, as they ranged between single digits to mid-eighties. Analysis of the Gamma, Delta, and Epsilon compounds was done by NMR (Nuclear Magnetic Resonance). Compounds were a success if an aromatic region was shown near 6-8 ppm (parts per million), and if the starting material functional groups disappeared from the spectra (aldehyde and starting reaction peaks at ~10 ppm and 3.5 ppm, respectively). IR (Infrared) analysis was also done to deem a successful compound. For them to be a success, increased conjugation of the product shows a right-ward shift around 1700 wavenumbers (Carbonyl region). Several compounds were deemed to have potential, but required further investigation. Increasing initial solvent (ethanol) volumes increased the yield of products. Also, increasing the reflux time of *Delta* compounds seemed to give better data analysis. Epsilon compound was deemed successful if a C=C region was seen when looking at the IR data.

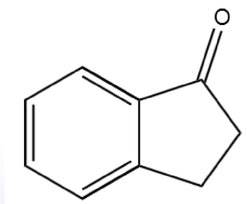
COMPOUNDS



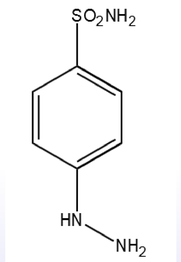
4-(5-(p-tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (CELEBREX)



Epsilon 3



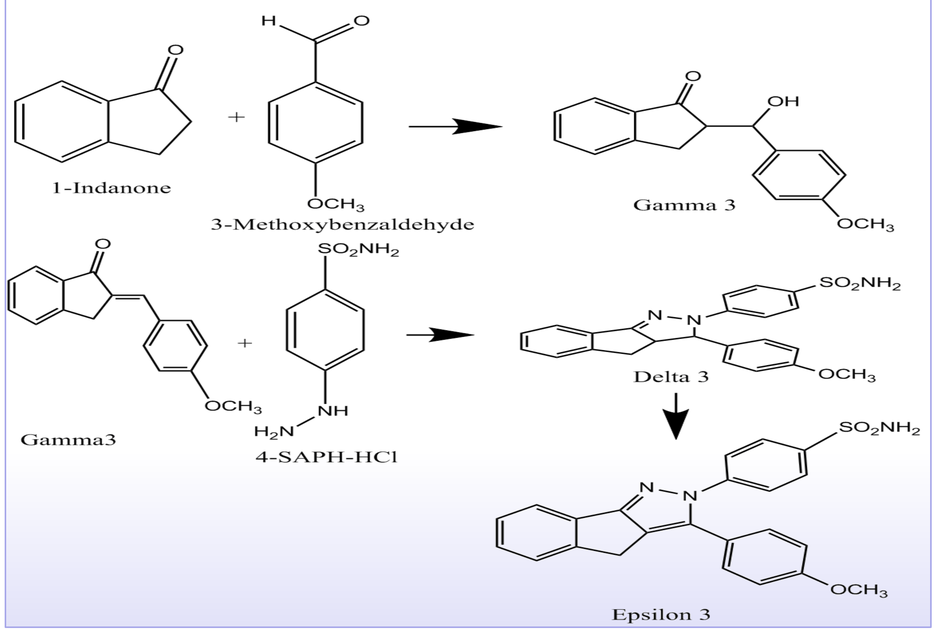
1-indanone



4-SAPH.HCl

Reaction Scheme

Reactions mechanism for base catalyzed Aldol condensation
for the complete scheme of producing Epsilon 3. Starting material is 1-indanone and 3-methoxybenzaldehyde to produce Gamma 3. Gamma 3 + 4-SAPH HCl produced Delta 3. Delta 3 + Bromine water produced Epsilon 3 (*Gamma 1*)



MATERIALS & METHODS

Generation of *Gamma* Compounds

Base Catalyzed Aldol Condensations

Combined 2.6062 g 1-indanone, ~2.3 mL 2-methoxybenzaldehyde, and ~20 mL ethanol into 50 mL round bottom flask while stirring. ~7 mL 1M NaOH was added drop wise until a cream colored precipitate formed. The mixture was placed into an ice bath for 30 minute intervals to allow the sample to cool. The resulting mixture was vacuum filtered and washed with methanol.

Generation of *Delta* Compounds

Forming an Imine to Produce a Ring Closure

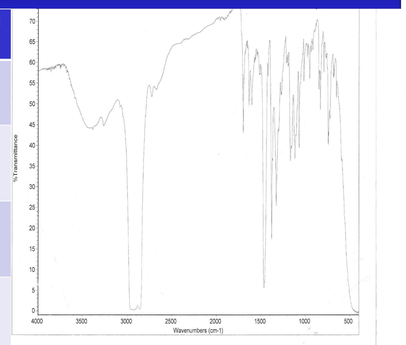
Added .4516 g *Gamma 3* compound, .1003 g 4-SAPH.HCl, and ~8.5 mL ethanol to 25 mL round bottom flask. The mixture was refluxed for 4 hours while stirring. Constant heat was also added. After cooling to room temperature, the mixture was vacuum filtered and washed with ethanol.

Generation of *Epsilon* Compounds

Added 1.75 mmol Delta 3, 1.75 mL of water to a 10 mL round bottom flask. A 2.625 mL .05 M Bromine water was produced (using concentrations) and then added to the sample for ~30 minutes. Stirring was done while adding the mixture. Product was then vacuum filtered and washed with ethanol.

RESULTS

Starting Material	Average Yield Normal Solvent v. Increased
3-methoxybenzaldehyde	65% v 78.19%
4-(trifluromethyl)-banzaldehyde	46% v 62.9%
4-fluorobenzaldehyde	54.37%v71.9%
2-methoxybenzaldehyde	76% v 85.6 %



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