

A green synthesis of tetrahydrobenzo[b]pyran derivatives through three-component condensation using fumaric acid

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Background and Aims: In recent years, 4H-benzo[b]pyrans and their derivative become of considerable interest due to their wide range of biological properties such as spasmolytic, diuretic, anti-coagulant, anti-cancer, anti-anaphylactic activity. Also they can be used as cognitive enhancers for the treatment of neurodegenerative disease including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, AIDS associated dementia and Down's syndrome as well as for the treatment of schizophrenia and myoclonus.

Methods: A mixture of aromatic aldehyde (1 mmol), alkyl malononitril (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (1 mmol), and fumaric acid (20 mol%) in a mixture of H₂O (2.5 mL) and EtOH (2.5 mL) was stirred at 50 °C for appropriate time. After completion of the reaction which was monitored by TLC, the mixture was cooled to room temperature. The solid product was collected by filtration, washed with water and aqueous ethanol and purified by recrystallization from ethanol (96%).

Results: Initially, the synthesis of compound 2-Amino-3-cyano-4-(4-chloro-phenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran was selected as a model reaction to optimize the reaction conditions. The reaction was carried out by heating a mixture of dimedone, 4-chlorobenzaldehyde and malononitrile in the presence of fumaric acid as the catalyst in different solvents. All the aforementioned reactions delivered excellent product yields and accommodated a wide range of aromatic aldehydes bearing both, electron-donating and electron-withdrawing substituents.

Conclusions: We have developed an efficient and ecologically safe method for the synthesis of 4H-benzo[b]pyrans and derivatives using a green procedure. This methodology has some advantages such as operational simplicity, neutral conditions, high yields, use of fumaric acid as a green, expensiveness, nontoxic and efficient catalyst, and easy work-up.

Keywords: Fumaric acid; Tetrahydrobenzo[b]pyran; Spasmolytic; Down's syndrome; Anti-coagulant