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Dissertation abstract

Reductive amination of 2-(2-formylphenoxy)alkanoic acids and their derivatives. Application of the process to the synthesis of heterocyclic compounds.

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The dissertation was aimed at the development of a practical method for the synthesis of alkyl 2-{2-[(phenylamino)metyl]phenoxy}alkanoates as compounds that can be both potential biologically active and precursors of the heterocyclic 4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one system. The reductive amination processes of alkyl 2-(2-formylphenoxy)alkanoates with aniline and 4-methoxyaniline *via* the corresponding Schiff bases, as well as attempts to apply the obtained amino esters in the synthesis of *N*-substituted 4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-ones were carried out. The study of the synthesis of 2-alkyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-ones involving the reaction of alkyl 2-(2-formylphenoxy)alkanoates with hydrazine *via* azines was performed.

The alkyl 2-(2-formylphenoxy)alkanoates required were synthesized by *O*-alkylation reaction of 2-hydroxyl-5-nitro- and 2-hydroxyl-3-methoxy-5-nitrobenzaldehyde with methyl 2-bromobutanoate, -pentanoate, -hexanoate, and ethyl chloroacetate. The syntheses were conducted in *N*,*N*-dimethylformamide in the presence of anhydrous potassium carbonate as a base. In that way, eleven formyl esters were obtained in 66–98% yield. Additionally, methyl 2-(2-formylphenoxy)butanoate and methyl 2-(2-formyl-4-nitrophenoxy)pentanoate were hydrolyzed to the corresponding acids in 85 and 80% yields.

A direct and indirect reductive amination of the formyl esters using sodium triacetoxyborohydride, hydrogen, and zinc dust as reducing agents were investigated. The optimization of direct reductive amination involving the model reaction of methyl 2-(2-formyl-4-nitrophenoxy)butanoate with aniline and sodium triacetoxyborohydride was performed. It was found that the highest product yield can be achieved when the process is carried out at room temperature for four hours in 1,2-dichloroethane with the addition of acetic acid. Under these conditions, methyl 2-{2-[(phenylamino)methyl)]phenoxy}butanoate,

-pentanoate, and -hexanoate as well as their nitro and methoxy analogs (a total of seven amino esters) were obtained in 71–86% yield. Mild reaction conditions for the direct reductive amination of methyl 2-(2-formylphenoxy)butanoate and its methoxy analog with aniline using both, hydrogen and zinc dust as reducing agents, were also developed. The hydrogen reduction led to the corresponding amino esters in 92–96% yield, while the use of zinc resulted in the synthesis of amino esters in 70–73% yield.

Comparative attempts of direct reductive amination of 2-(2-formylphenoxy)butanoic acid using sodium triacetoxyborohydride and hydrogen as reducing agents were carried out. The reactions were conducted at room temperature and 2-{2-[(phenylamino)methyl]-phenoxy}butanoic acid was obtained in 80% yield, after 24 hours using sodium triacetoxyborohydride, and in 92% yield, after 6 hours using hydrogen.

The indirect (two-step) process of amino esters synthesis *via* Schiff bases was studied. The Schiff bases were synthesized by the reaction of methyl 2-(2-formyl-4-nitrophenoxy)butanoate, -pentanoate, -hexanoate and their methoxy analogs, methyl 2-(2-formylphenoxy)butanoate and its methoxy analog and ethyl 2-(2-formyl-6-methoxy-4-nitrophenoxy)acetate, with aniline and 4-methoxyaniline. Syntheses were carried out in methanol with the addition of acetic acid using an equimolar amount of reactants at room temperature. Fifteen new Schiff bases were obtained in 71–95% yield.

The optimal reaction conditions for the selective reduction of the nitro group containing Schiff bases using sodium triacetoxyborohydride as a reducing agent were developed. The products in which only the azomethine group was reduced, were obtained by conducting reactions at room temperature for four hours in 1,2-dichloroethane with the addition of acetic acid and sesquiamol excess of the reducing agent. In this way, methyl 2-{4-nitro-2-[(phenylamino)methyl]phenoxy}butanoate, -pentanoate and -hexanoate, methyl 2-{2-methoxy-4-nitro-6-[(phenylamino)methyl]phenoxy}butanoate, -pentanoate, -hexanoate and ethyl -acetate as well as methyl 2-{2-[(4-methoxyphenylamino)methyl]-4-nitrophenoxy]butanoate and -pentanoate together with their 6-methoxy analogues were obtained in 55–99% yield. The hydrogenation of Schiff bases in the presence of the palladium catalyst yielded the following five diamines and two amines: methyl 2-{4-amino-2-[(phenylamino)methyl]phenoxy}-butanoate, -hexanoate, methyl 2-{4-amino-2-methoxy-6-[(phenylamino)methyl]phenoxy}-butanoate, -pentanoate, -hexanoate, and methyl 2-{2-[(phenylamino)methyl]phenoxy}-butanoate and its methoxy analog in 71–87% yield. The reduction of Schiff bases of formyl esters without nitro groups with zinc dust in acetic acid

led to methyl 2-{2-[(phenylamino)methyl]phenoxy}butanoate and its methoxy analog in 63% and 68% yields, respectively.

The stepwise procedure for the preparation of primary amino esters *via* azines was investigated. The reaction of methyl 2-(2-formylphenoxy)butanoate, -pentanoate, -hexanoate, and methyl 2-(2-formyl-6-methoxyphenoxy)butanoate with hydrazine resulted in four azines in 83–90% yield. The reduction of azines of methyl 2-(2-formylphenoxy)alkanoates was carried out in ethanol in the presence of ammonia-water mixture using aluminum amalgam as a reducing agent. The primary amino esters, generating as intermediates in the reaction, spontaneously underwent cyclization reaction to form the 2-alkyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-ones in 40–47% yield.

The next step of the research was the synthesis of 4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-one using the amino esters as precursors. It was found that methyl 2-[2-(aminomethyl)phenoxy]butanoate, -pentanoate, and -hexanoate, having a primary amino group, easily underwent intramolecular ester aminolysis leading to the corresponding 2-alkyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(2*H*)-ones. The cyclisation of the secondary amino ester, methyl 2-{4-nitro-2-[(phenylamino)methyl]phenoxy}butanoate, can be achieved by conducting the reaction at 200°C. Whereas, 4,5-dihydro-7-nitro-4-phenyl-2-propylbenzo[*f*][1,4]oxazepin-3(2*H*)-one, its 2-butyl homologue and 4,5-dihydro-9-methoxy-7-nitro-4-phenyl-2-propylbenzo[*f*][1,4]oxazepin-3(2*H*)-one were synthesized by the cyclization process under microwaves irradiation. Furthermore, the following 2-ethyl-4,5-dihydro-7-nitro-4-phenyl-benzo[*f*][1,4]oxazepin-3(2*H*)-one and its 2-butyl and 2-propyl homologues were obtained in 58-66% yield from the corresponding amino esters as a results of the hydrolysis and next cyclisation of the intermediately formed amino acids.

Several new compounds were synthesized within the research carried out in the framework of the present dissertation. Their structures were determined using spectroscopic methods such as ^{1}H and ^{13}C NMR, IR and MS.

The eleven Schiff bases, the six amino esters and their hydrochloric salts were evaluated against selected four Gram-positive and three Gram-negative bacteria strains. It was found that Schiff bases such as: methyl 2-{4-nitro-2-[(*E*/*Z*)-(phenylimino)methyl]phenoxy}butanoate, -hexanoate, methyl 2-{2-methoxy-4-nitro-6-[(*E*/*Z*)-(phenylimino)methyl]phenoxy}butanoate, -pentanoate, -hexanoate, as well as hydrochloride salts of methyl 2-(4-nitro-2-[(phenylamino)methyl]phenoxy}butanoate, -pentanoate, -hexanoate, methyl 2-{2-methoxy-4-nitro-6-[(phenylamino)methyl]phenoxy}pentanoate and

-hexanoate were active against Gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus mutans*).

The tested compounds showed weak and medium fungicidal activity against seven common plant pathogens: *Alternaria alternata*, *Botrytis cinerea*, *Fusarium culmorum*, *Phytophthora cactorum*, *Rhizoctonia solani*, *Phoma betae* and *Blumeria graminis*. Methyl 2-{2-methoxy-4-nitro-6-[(phenylamino)methyl]phenoxy}butanoate was the one from the tested compounds showing insecticidal activity against housefly (*Musca domestica L.*), eastern cockroach (*Blatta orientalis L.*) and hop-spider mite (*Tetranychus urticae*).

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