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New applications of L-proline derivatives for the synthesis of optically active polyheterocyclic compounds

The enantiomerically pure, commercially available L-proline was used as a key substrate for the synthesis of (*S*)-2-aminomethylpyrrolidine (L-prolinamine), (*S*)-2-azidomethyl-*N*-Boc-pyrrolidine (L-proline azide) and (*S*)-2-hydroxymethylpyrrolidine (L-prolinol) based on the known literature protocols.

Reactions of L-prolinamine with arylisothiocyanates were carried out to give a series of *N*,*N*'-diaryl-substituted thiourea derivatives, which after deprotection meet the objectives of bifunctional organocatalysts.

In the following study reactions between L-prolinamine and its *N*-protected benzyl derivative with dialkyl dicyanofumarates used as reactive Michael acceptors, were performed. In the first case, as products of a multi-stage reaction a series of enantiomerically pure bicyclic 2-oxopiperazines was obtained. In the second series, after the sequence of the addition/elimination reaction, new enamines were isolated in high yields. For the later compounds, configuration *Z*- was attributed based on the spectroscopic analysis supported by the results of an earlier X-ray diffraction study.

As a result of condensation of Boc-protected L-prolinamine with paraformaldehyde the corresponding formaldimine was obtained. It underwent a rapid trimerization in the $CDCl_3$ solution to give the corresponding 1,3,5-hexatriazine derivative. This heterocycle, existing in solution, in an equilibrium with the monomeric form, was used for the reaction with selected α-(hydroxyimino)ketones to give a series of enantiomerically pure bicyclic, 2-unsubstituted imidazole *N*-oxides bearing the pyrrolidine ring at *N*(1), in good yields.

After the deprotection of the pyrrolidine ring, the obtained imidazole *N*-oxides were treated with excess acetic anhydride at room temperature. Surprisingly, the formation of new fused heterocycles, instead of the expected imidazol-2-ones or their *N*-acetylated derivatives, was observed. A mechanism of the heterocyclization reaction, in which the key step is the initial formation of a highly reactive imidazolium cation, was formulated.

Some of the obtained imidazole *N*-oxides bearing pyrrolidine ring as a substituent at *N*(1), were used for the deoxygenation reaction leading to a series of the corresponding 2-unsubstituted imidazoles. The latter compounds were subsequently used as starting materials for the preparation of 2-iodoimidazole derivatives. These compounds were used for the Sonogashira coupling with (ethynyl)trimethylsilane to give a series of 2-ethynylimidazoles, which were explored as reactive dipolarophiles for the [3+2]-cycloaddition reaction (Huisgen reaction) with L-proline azide in the presence of CuI. These reactions allowed the preparation of a series of optically active, new tricyclic products containing pyrrolidine, imidazole and 1,2,3-triazole rings.

In the last part of the study, reactions of L-prolinol with selected aryl glyoxals, leading to a series of labile, bicyclic 1,3-oxazolidine derivatives were performed. Unexpectedly, in the presence of trace amounts of an acidic catalyst (TFA or silica gel) the later compounds isomerized spontaneously to the thermodynamically stable, bicyclic α-morpholinones, which were isolated and identified by means of

spectroscopic methods. In addition, in one case the structure of the product was confirmed by X-ray diffraction analysis.

Both, bicyclic aryloyl 1,3-oxazolidines and bicyclic α-morpholinones were used for nucleophilic trifluoromethylation reaction using the Ruppert-Prakash reagent in the presence of CsF as a catalyst. It was found that trifluoromethylation of aryloyl 1,3-oxazolidine derivatives occurred with low diastereoselectivity. On the other hand, diastereoselectivity of the nucleophilic trifluoromethylation of bicyclic α-morpholinones was complete in all cases studied.

The obtained thioureas and polycyclic nitrogen heterocycles are enantiomerically pure organic compounds, which can be considered as potentially useful substances for new applications in diverse fields of organic synthesis, including asymmetric synthesis and organocatalysis.