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Stereoisomerism of chalcogen isologues of a sterically hindered benzamide

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Conformation of organic molecule is a determinant for the function of molecule. In the field of medicinal chemistry, biological activities and drug-like properties of bioactive compounds could be altered by the change of three-dimensional architecture of the molecules. Therefore, manipulating the conformation of drug candidate compounds is an important issue in drug development.[1] Amide compound is one of the most abundant substances in drug molecules, natural products and biomolecules. Planarity of amide bond arising from its resonance structure has been widely recognized as a general property of amide compound, resulting transient *E*/*Z* stereoisomers. We thought that the well-known *E*/*Z* isomerism could be applicable for the modulation of biological activities by improvement of the kinetic stability of each isomer. We selected *othro*-di-dubstituted benzamide derivatives as model compounds in this study. This class of compounds has a rotationally restricted C-C bond in addition to the amide C-N bond, resulting in four stereoisomers (Fig. 1)[2]. To improve the kinetic stability, substitution of oxygen atom of amide compounds to other chalcogen atoms were investigated. The thioamides and selenoamides exhibited higher rotational barrier than the corresponding oxoamide, and the half-lives of the separated *E*/*Z* isomers were several days at ambient temperature. No racemization of the atropisomers of the thoamide and the selenoamide was observed. The four stereoisomers of thioamide **1** could be separated, indicating that our thioamide system can be used as an element to generate three-dimensional diversity (Fig 2). Furthermore, we found that the thioamide and the selenoamide undergo photo-induced isomerization, in which both C-C and C-N bond rotate simultaneously,[3] and experimentally and theoretically demonstrate the C-C/C-N dual bond rotation.[4] As a whole, the thioamide system exhibited different molecular movement depending on the heat or light. This unique property could be applicable for the modulating biological activity of small molecules.

Fig 1.

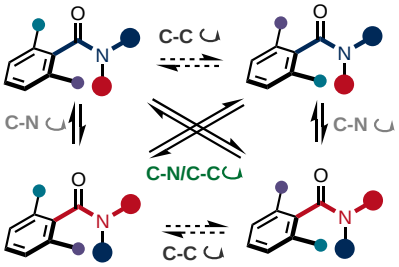
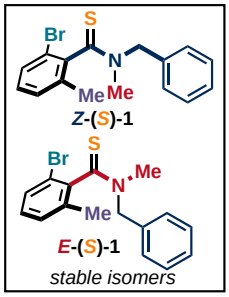
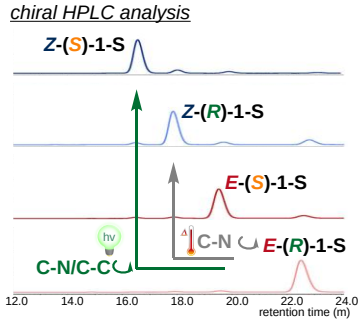


Fig 2.





Reference

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