

Transformations of thioiminium salts derived α -bromoamides

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Our research group is constantly involved in the exploration of substitution and condition-dependent transformations of thioiminium salts derived from α -bromoamides to heterocycles containing nitrogen and sulfur. Originally, we intended to use abovementioned building blocks for synthesis of highly fluorescent 4-hydroxythiazoles. However, recently, we have found that the salts formed by reaction of 3-bromoindol-2-one with thioamides can also undergo thiophile-free *Eschenmoser* reaction under specific conditions, to give pharmaceutically valuable vinylogous amides [1]. Essentially, these two chemical transformations are competing each other and final reaction course depends both on reaction conditions (polarity of the solvent, temperature, base addition) and electronic effects.

In order to better understand to the reactivity, we further investigated possible transformation pathways of structurally related thioiminium salts derived from acyclic subst. 2-bromophenylacetamides (**1**) and their cyclic counterparts, i.e. 4-bromo-1,1-dimethyl-1,2-dihydroisoquinolin-3(4*H*)-ones (**2**) (Figure 1). Reaction of α -thioiminium salts derived from 2-bromophenylacetamide and prim./sec. thiobenzamides afforded 2,5-diaryl-4-hydroxythiazoles (**3**) or zwitterionic 3-methyl-2,5-diphenylthiazol-3-ium-4-olates (**4**) in moderate yields. When cyclic α -bromolactam **2** was reacted with prim. thioamides, 5,5-dimethyl-2-phenyl-4,5-dihydrothiazolo[4,5-*c*]isoquinoline (**5**) was isolated. Heating the same salts in the excess of thiophile (trimethyl phosphite) did not result in formation of conjugated vinylamines, but only *N*-methylation leading to thiazole **6** has occurred. On the other hand, reaction of cyclic bromoamide **2** with sec. thioamides led to an *Eschenmoser* reaction products **7** in moderate to good yields even without thiophile.

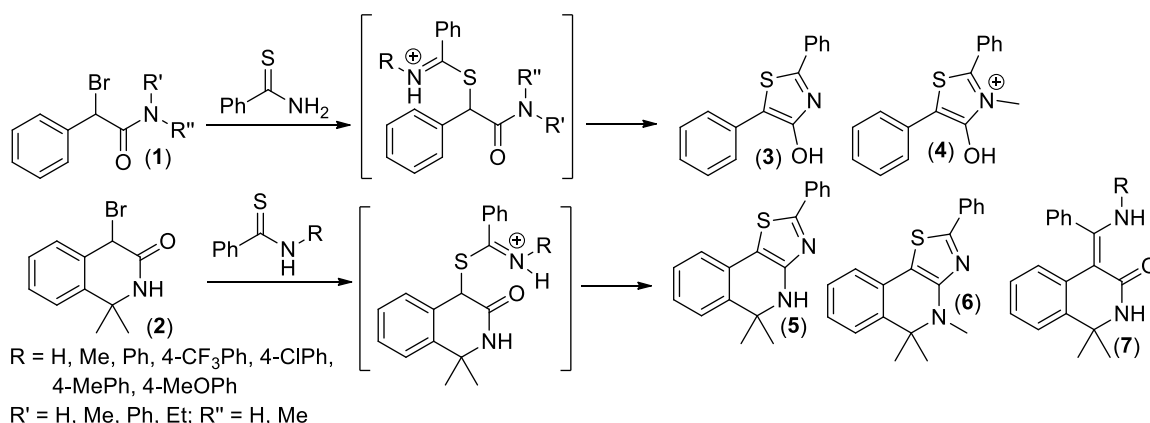


Figure 1. Structure scaffolds formed by reaction of (a)cyclic α -bromoamides and prim./sec. thioamides.

References:

[1] Marek, L.; Váňa, J.; Svoboda, J.; Hanusek, J. Synthesis of the Kinase Inhibitors Nintedanib, Hesperadin, and Their Analogues Using the *Eschenmoser* Coupling Reaction. *J. Org. Chem.* **2021**, 86(15), 10621-10629.