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2-Acylimino-3-alkyl-3*H*-thiazoline derivatives: one-pot, three-component condensation synthesis of novel β-turn mimics

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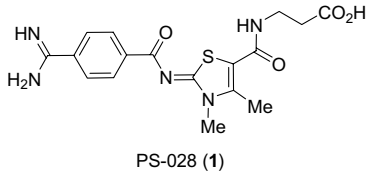
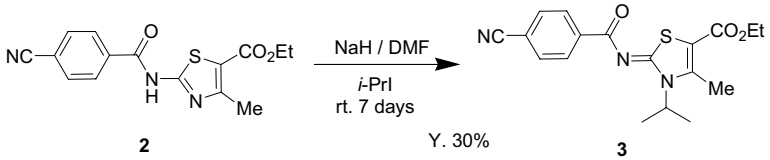
Abstract—One-pot, three-component condensation of aroylthiourea, primary amine and α-halocarbonyl derivatives for the synthesis of 2-acylimino-3-alkyl-3*H*-thiazoline derivatives is described. This method is useful for simultaneously incorporating diverse functional groups at four positions in the 3*H*-thiazoline skeleton to obtain β-turn tripeptide mimics.

The β-turn structure is formed by intramolecular hydrogen bonding in a tripeptide substructure at the protein surface, and is well known to be recognized as a ligand by various receptors.[1] Numerous studies have been conducted on low-molecular-weight compounds, which mimic the β-turn substructure of natural polypeptide ligands to overcome the pharmacokinetic disadvantages of peptide ligands. Several low-molecular-weight mimics of the RGD sequence on fibrinogen have been reported, and these exhibit strong inhibitory activities against the binding of fibrinogen to its receptor GPIIb/IIIa.[2] We have also reported a unique 3-alkyl-3*H*-thiazoline derivative PS-028 (**1**) as a potent and selective GPIIb/IIIa antagonist (Fig. 1, $K_i = 46.5 \pm 5.8$ pM).[3] The 3-alkyl-3*H*-thiazoline skeleton of PS-028 can be functionalized at four positions, and therefore has potential as a versatile template for other β-turn mimics. In course of an investigation of functionalization on 3-alkyl-3*H*-thiazoline skeleton, we have found that the introduction of a substituent other than a small alkyl group at the 3-position of the skeleton is limited by the low reactivity toward alkyl halides (Scheme 1). As an alternative method to prepare 3-alkyl-3*H*-thiazoline skeleton, condensation reaction of *N*-acyl-*N*′-alkylthiourea and α-halocarbonyl derivative is reported.[4] However, there are few examples to apply this method for functionalization on the 3*H*-thiazoline ring system (Scheme 2). Therefore, we explored a versatile method for the introduction of functional groups on the 3-alkyl-3*H*-thiazoline skeleton using various acyl thioureas and α-halocarbonyl reagents by a one-pot, three-component condensation.



PS-028 (**1**)

Figure 1.



2 **3**

Scheme 1.

Keywords: Thiazoline; One-pot procedure; β-Turn mimic.
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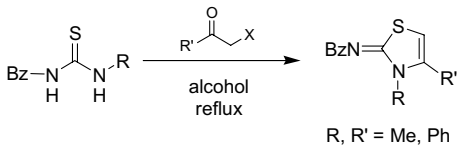


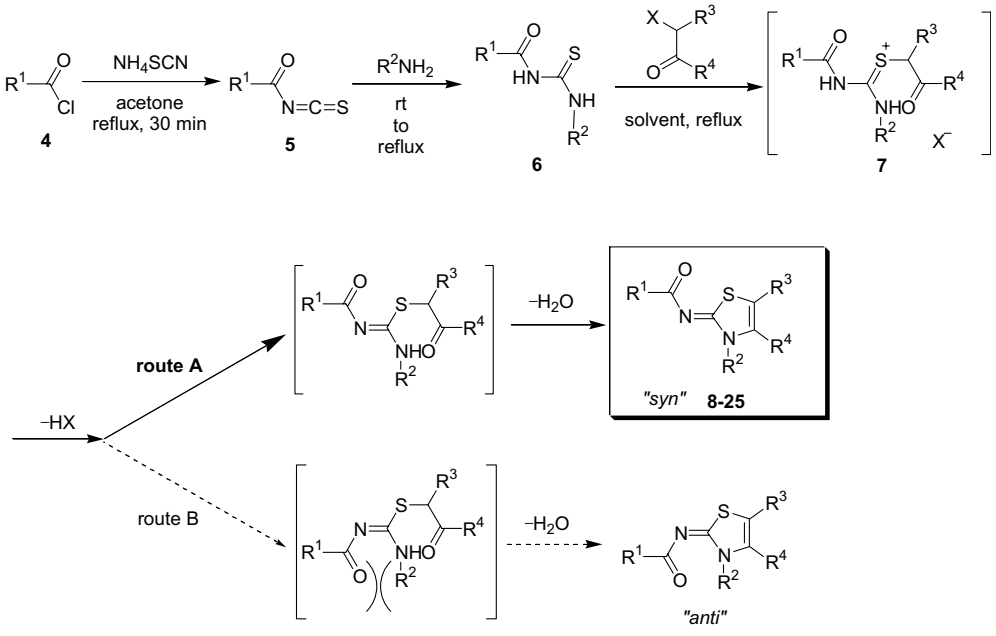
Scheme 2.

The efficient synthetic method for 3-alkyl-3*H*-thiazoline is shown in Scheme 3. Thus, aroylisothiocyanates **5** prepared from the corresponding acyl chlorides **4** and ammonium thiocyanate[5] reacted smoothly with various amines to afford acylthioureas **6**. Without isolation, these intermediates were condensed with α-halocarbonyl derivatives to construct a 3-alkyl-3*H*-thiazoline template. The configuration of the acylimino moiety was confirmed to be *syn* by direct comparison of its melting point and spectral data with those of the authentic 3-*n*-butyl derivative synthesized by the previous method.[3] The *syn* selectivity in this reaction is likely due to the steric hindrance of the acyl group and the R^2 group in the isothiourea intermediates. As shown in Scheme 3, elimination of hydrogen halide from sulfonium intermediates **7** proceed via route A so as to avoid intermolecular steric hindrance (route B).

The reaction was performed in a non-polar solvent such as benzene, toluene or xylene at reflux temperature with water separator for the efficient removal of water and hydrogen chloride generated by the reaction. For the less soluble acylthiourea derivatives (e.g., R = Ph), acetic acid was preferable for the solvent to accelerate the reaction. In that case, the yield and purity of the product were slightly decreased (entries 3 and 10). Contrary to the description in the previous paper,[4] reactions in ethanol or with a base such as potassium carbonate or triethylamine did not proceed and gave unidentified yellow precipitates. At least 2 equiv of α-halocarbonyl reagent were necessary for the reaction to proceed to completion. When the reaction was performed with 1 equiv of α-halocarbonyl reagent, the reaction stopped when about half of the acylthiourea was consumed.

The variety of the substituents R^1–R^4 are summarized in Table 1. With regard to R^1, while aromatic derivatives with both electron-withdrawing and -donating groups were suitable for this reaction, alkyl derivatives were not (entries 19 and 20). The reaction of acetyl isothiocyanate or phenylacetyl isothiocyanate with primary amines gave the corresponding amides instead of acylthiourea derivatives.

The introduction of an R^2 group with primary amines was widely tolerated. For example, 3-isopropyl-3*H*-thiazoline derivatives, which required several days at room temperature by alkylation of **2** (Scheme 1), were obtained in yields of 77–92% with only a few hours operation (entries 1, 12, 14). This procedure also made it possible to introduce a cycloalkyl group (entries 4–7), a phenyl group (entries 10 and 11) and a functionalized alkyl group (entries 7 and 8) as R^2. However, introduction of a methyl group failed due to the insolubility of the intermediate thiourea derivative. Condensation of the acylthiourea intermediate with 2-chloroacetylacetone, chloroacetone or diethyl 2-bromomalonate smoothly gave the corresponding products, which possessed an acetyl group, a hydrogen atom and an ethoxycarbonyl group as R^3, and methyl, and hydroxyl groups as R^4 (entries 16–18). In addition, the introduction of amino moieties to the R^4 methyl group was achieved by bromination with *N*-bromosuccinimide in the presence of *N*,*N*-azobis(isobutyronitrile), followed by treatment with amines.[3]



Scheme 3.