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Intermolecular cyclocondensation reaction of 3,4-dihydropyrimidine-2-thione under the Mitsunobu reaction conditions

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Abstract

A self-intermolecular cyclocondensation reaction of 3,4-dihydropyrimidine-2-thione (DHPM) to give a novel tricyclic structure containing DHPM core in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) at room temperature is reported.

Keywords: Mitsunobu reaction; Cyclocondensation; 3,4-Dihydropyrimidine-2-thiones

In the past decades, 3,4-dihydropyrimidinones (Biginelli compounds or DHPMs) [1] and their derivatives have attracted considerable interest [2] due to their heterocyclic scaffold and interesting pharmacological properties, such as calcium channel modulation, anti-hypertension, α_{1a} adrenergic agonist and mitotic kinesin inhibition, and hepatitis B virus replication suppression. The *N*-substituted reaction of dihydropyrimidinones is one approach to functionalizing the dihydropyrimidinone ring in order to achieve important bioactive properties [3]. For instance, substitution at the third nitrogen is possible, and the products can be strongly rendering strong anti-inflammatory, antihypertensive, analgesic, and anticancer activities [4].

In recent publications, we have disclosed some methods for the scaffold decoration of DHPMs [5]. In continuation of our interest in the generation of diversely substituted and novel types of privileged scaffolds of the DHPM core, we herein report the self-intermolecular cyclocondensation reaction of 3,4-dihydropyrimidine-2-thione under the Mitsunobu reaction conditions.

During the course of our recent attempts to synthesize the N1-propargylic DHPMs, we used 3,4-dihydropyrimidine-2-thione (**1a**) and propargylic alcohol as starting material in tetrahydrofuran (THF) in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) at room temperature for 24 h (Scheme 1). Incidentally, we did not obtain the desired product N1- or N3-propargylic 3,4-dihydropyrimidine-2-thione. Instead, a new compound, as a

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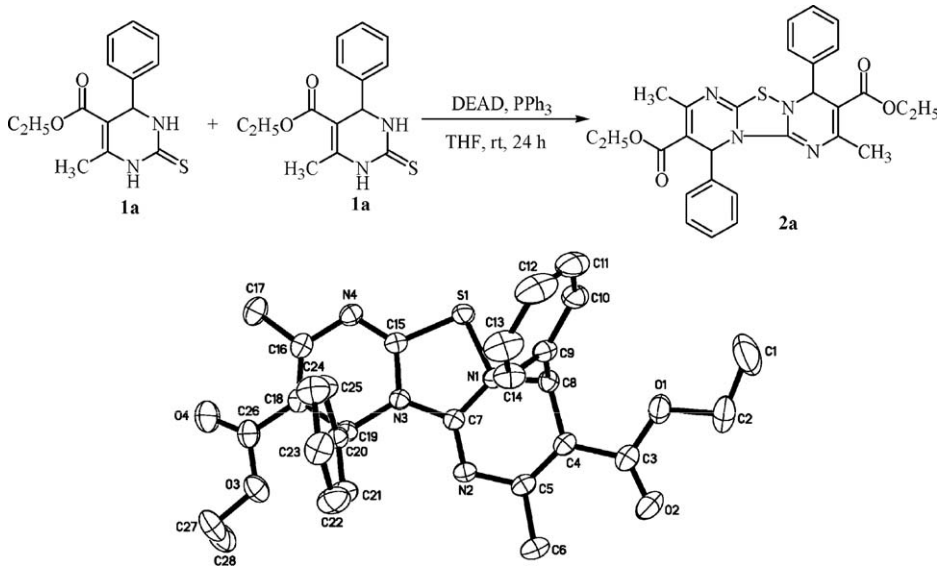
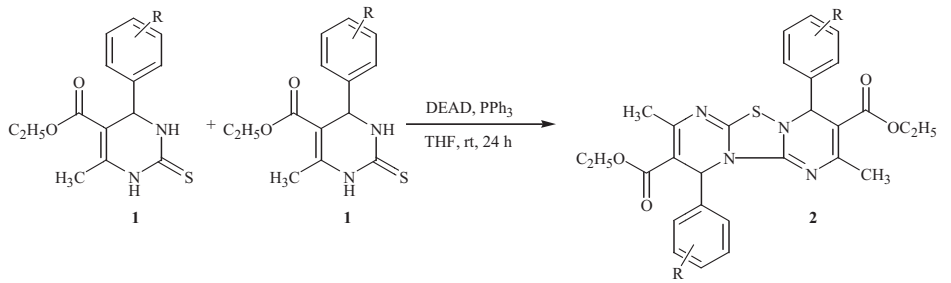


Scheme 1. The reaction of DHPM **1a** under Mitsunobu conditions.

single product, was isolated in 85% yield after 24 h. Extensive analysis of this compound was performed to elucidate the structure. To our surprise, mass spectrometry indicated that this product resulted from the elimination of one sulphur atom and four hydrogen atoms between two molecular of 3,4-dihydropyrimidine-2-thione. Elemental analysis confirmed this finding. The ^{1}H NMR was clean and exhibited five symmetrical signals, which devoted to CH_3, $\underline{CH_3}CH_2O$, $CH_3\underline{CH_2}O$, CH_2O, and CH groups, respectively. These facts along with the ^{13}C NMR spectrum led us to propose the tricyclic structure **2a**. This hypothesis was eventually confirmed by a single-crystal X-ray diffraction study (Scheme 1) which demonstrated the tricyclic structure of compound **2a** [6]. It should be emphasized that it is the first example of a self-intermolecular cyclocondensation reaction between two 3,4-dihydropyrimidine-2-thione molecular.

Next, isopropanol was used to replace propargylic alcohol and compound **2a** was also obtained in good yield. Interestingly, **2a** was also obtained in yield 84% in the absence of any alcohol under above described reaction conditions [7]. Optimization studies demonstrated that utilizing anhydrous THF as solvent showed excellently high performance than acetone, CH_2Cl_2, and MeCN. It is also demonstrated that clean completion of this reaction needed 24 h at r. t. in THF needing two equivalents of TPP and DEAD. We further carried out the self-intermolecular cyclocondensation reaction of other substituted 3,4-dihydropyrimidine-2-thiones. Treatment of dihydropyrimidine-thiones **1b–e** with 2 equiv. of DEAD and TPP in THF for 24 h gave the corresponding coupling products **2b–e** in good yields (Scheme 2). However, *o*-position at the phenyl ring has apparent affect on the yields of products. For instance, the chloro and methoxyl group at the *o*-position of phenyl ring could not be transformed into corresponding cyclocondensation products, but a coupling product similar as compound **7** in Scheme 3 was detected by LC-Mass experiments. Extension of this preliminary work is undergoing in our laboratory now.



2a: R = H, 84%: **2b**: R= 4-CH_3, 86%; **2c**: R = 4-CH_3O, 83%; **2d**: R = 4-Cl, 82%; **2e**: R = 4-NO_2, 78%.

Scheme 2. The reactions of DHPMs under Mitsunobu conditions.