Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 679–682
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

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

Yu Xia Da, Zhang Zhang, Zheng Jun Quan *

Key Laboratory of Eco-Environment-Related Polymer Materials, Ministry of Education, Gansu Key Laboratory of Polymer Materials, College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, China

Received 11 October 2010

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.

© 2010 Zheng Jun Quan. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.

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

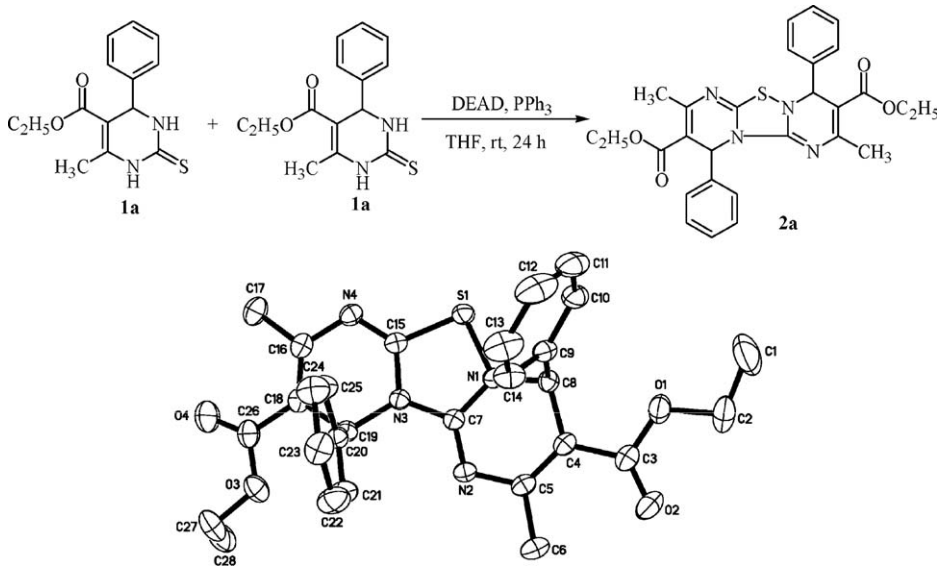
In the past decades, 3,4-dihydropyrimidinones (Biginelli compounds or DHPMs) [1] and their derivatives have attracted considerable interest [2] due to their heterocyclic scaffold and interesting pharmacological properties, such as calcium channel modulation, anti-hypertension, α_{1a} adrenergic agonist 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

* Corresponding author.
E-mail address: quanzhengjun@hotmail.com (Z.J. Quan).

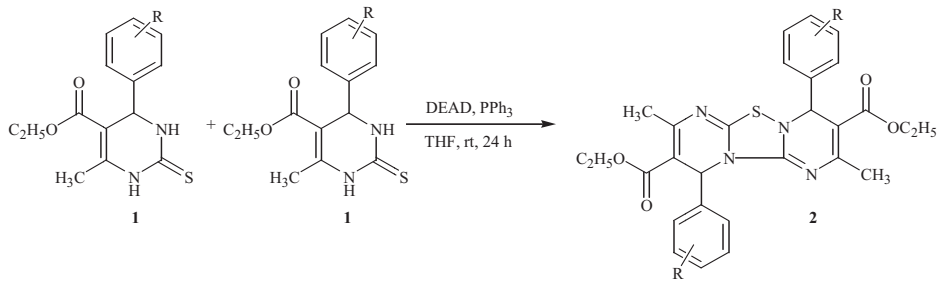
1001-8417/$ – see front matter © 2010 Zheng Jun Quan. Published by Elsevier B.V. on behalf of Chinese Chemical Society. All rights reserved.
doi:10.1016/j.cclet.2010.12.041



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

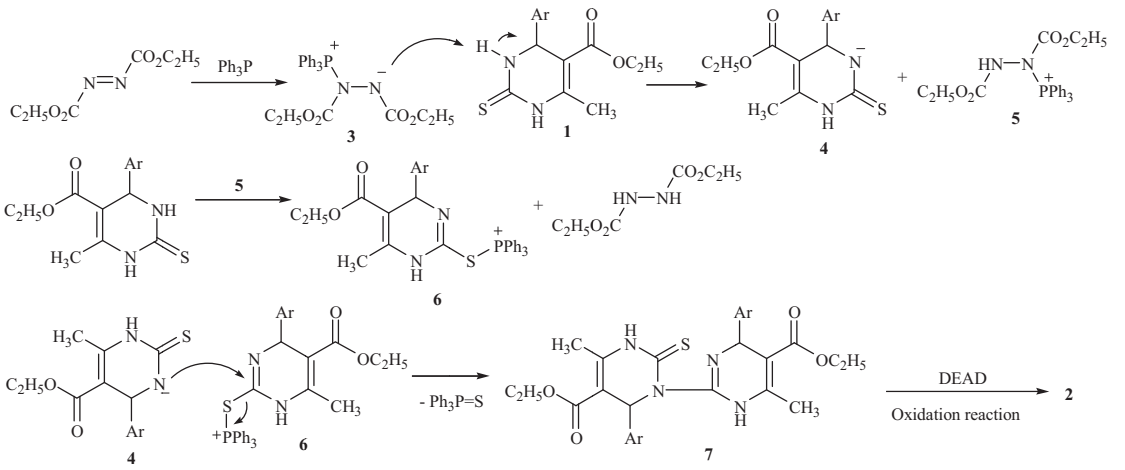
single product, was isolated in 85% yield after 24 h. Extensive analysis of this compound was performed to elucidate the structure. To our surprise, mass spectrometry indicated that this product resulted from the elimination of one sulphur atom and four hydrogen atoms between two molecular of 3,4-dihydropyrimidine-2-thione. 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.



Scheme 3. The plausible mechanism.

It has been reported that treatment of 2-thioxo-4-quinalinone with DEAD afforded [1,3,4]thiadiazolo[2,3- b:5,4-b']diquinazoline-12,15-dione as the main product [8]. However, the same material 2-thioxo-4-quinalinone was transformed to [1,2,4]thiadiazolo[3,2-b:5,4-b′]diquinazoline-8,15-dione by an oxidative cyclocondensation in the presence of P_2O_5, sulfuric acid or iodine [9]. Thus a possible pathway in the cyclocondensation process of 3,4-dihydropyrimidin-thione is shown in Scheme 3. The first step is the irreversible formation of the Morrison–Brunn–Huisgen (MBH) betaine **3** [10]. In step 2, this betaine **3** deprotonates the 3,4-dihydropyrimidin-thione **1** to form the ionic species **4** and **5**. **5** upon reacting with another 3,4-dihydropyrimidin-thione **1** forms the key phosphonium salt **6** and the hydrazine $EtO_2CNH\text{-}NHCO_2Et$. At this stage, **4** attacks **6** to lead to **7** as well as the triphenylphosphine sulfide $Ph_3P(S)$. Formation of the product **2** is a completed by the oxidative cyclocondensation of **7** in the presence of DEAD as an oxidizing agent.

In conclusion, we reported here an efficient cyclocondensation reaction between two 3,4-dihydropyrimidine-2-thiones under the Mitsunobu reaction conditions. Yields are generally high, and the reaction occurs readily under very mild conditions with excellent chemoselectivity. We think this reaction affording a novel tricyclic structure containing DHPM core could be of great interest since to our knowledge there has no example of direct cyclocondensation reaction between 3,4-dihydropyrimidine-2-thiones.

Acknowledgments

We are thankful for the financial support from the National Nature Science Foundation of China (No. 20902073), the Natural Science Foundation of Gansu Province (No. 096RJZA116), and Scientific and Technological Innovation Engineering program of Northwest Normal University (nwnu-kjcxgc-03-64).

References

[1] P. Biginelli, Gazz. Chim. Ital. 23 (1893) 360.
[2] For reviews on the Biginelli reaction, see:
(a) C.O. Kappe, Tetrahedron 49 (1993) 6937;
(b) C.O. Kappe, Acc. Chem. Res. 33 (2000) 879;
(c) C.O. Kappe, A. Stadler. Org. React. 63 (2004) 1;
(d) D. Dallinger, A. Stadler, C.O. Kappe, Pure Appl. Chem. 76 (2004) 1017;
(e) L.Z. Gong, X.H. Chen, X.Y. Xu, Chem. Eur. J. 13 (2007) 8920;
(f) M.A. Kolosov, V.D. Orlov, Mol. Diversity 13 (2009) 5;
(g) Z.J. Quan, Z. Zhang, Y.X. Da, et al. Chin. J. Org. Chem. 29 (2009) 876 (in Chinese).
[3] (a) C.O. Kappe, Eur. J. Med. Chem. 35 (2000) 1043;
(b) K. Singh, D. Arora, K. Singh, et al. Mini Rev. Med. Chem. 9 (2009) 95, references cited therein.

[4] For selected examples, see:
(a) C.O. Kappe, B. Jauk, T. Pernat, Molecules 5 (2000) 227;
(b) R.V. Chikhale, R.P. Bhole, P.B. Khedekar, et al. Eur. J. Med. Chem. 44 (2009) 3645;
(c) K. Deres, C.H. Schroeder, A. Paessens, et al. Science 299 (2003) 893;
(d) A.G. Gross, H. Wurziger, A. Schober, J. Comb. Chem. 8 (2006) 153;
(e) A.N. Chiang, J.C. Valderramos, R. Balachandran, et al. Bioorg. Med. Chem. 17 (2009) 1527;
(f) G.J. Grover, S. Dzwonczyk, D.M. McMullen, et al. Pharmacol. 26 (1995) 289;
(g) S.W. Fewell, C.M. Smith, M.A. Lyon, et al. J. Biol. Chem. 279 (2004) 51131.
[5] (a) X.C. Wang, Z.J. Quan, Z. Zhang, Tetrahedron 63 (2007) 8227;
(b) X.C. Wang, Z.J. Quan, Z. Zhang, et al. Lett. Org. Chem. 4 (2007) 370;
(c) X.C. Wang, Z.J. Quan, J.K. Wang, et al. Bioorg. Med. Chem. Lett. 16 (2006) 4592;
(d) Z.J. Quan, R.G. Ren, Y.X. Da, et al. Heterocycles 81 (2010) 1827.
[6] Crystallographic data for the structure analysis have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. CCDC 630760 for **2a**.
[7] Typical Experimental Procedure: To a solution of TPP (0.534 g, 2 mmol) in THF (5 mL) was added 3,4-dihydropyrimidine-2-thione **1** (1 mmol). To this clear solution was added DEAD (0.348 g, 2 mmol) over 5 min. The reaction was then stirred at room temperature for 24 h. Volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (10% EtOAc/hexane) to afford the pure products. Selected data for **2a**: colorless crystal; mp 177–178 °C. IR (KBr) (ν = 3033, 2981, 1703, 0676, 1608, 1514, 1369, 1315, 1237, 1148, 1078, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (*t*, 3H, J = 6.8 Hz), 1.19 (*t*, 3H, J = 6.8 Hz), 2.38 (s, 3H), 2.44 (s, 3H), 4.03 (q, 3H, J = 7.2 Hz), 4.11 (q, 3H, J = 7.2 Hz), 5.36 (s, 1H), 6.23 (s, 1H), 6.76–6.99 (m, 2H), 7.01–7.15 (m, 2H), 7.16–7.18 (m, 2H), 7.25–7.33 (m, 2H), 7.39–7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.8, 23.1, 55.8, 59.9, 60.1, 60.4, 104.1, 106.4, 127.1, 128.1, 128.3, 128.6, 128.7, 128.8, 139.1, 140.5, 150.8, 153.9, 155.7, 158.3, 165.6, 165.9. MS (ZAB): m/z (%) = 516 (46) [M^+], 439 (100) [M-77]. Anal. calcd. for $C_{28}H_{28}N_4O_4S$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.34; H, 5.57; N, 10.74.
[8] L.I. Giannola, G.B. Giannola, Carlisi, et al. J. Heterocycl. Chem. 18 (1981) 1557.
[9] (a) N.I. Mukarramov, B.A. Urakov, K.M. Shakhidoyatov, Chem. Heterocycl. Comp. 42 (2006) 540;
(b) N.I. Mukarramov, B.A. Urakov, K.M. Shakhidoyatov, Chem. Heterocycl. Comp. 43 (2007) 1210.
[10] K.C.K. Swamy, N.N.B. Kumar, E. Balaraman, et al. Chem. Rev. 109 (2009) 2551.