Chinese Chemical Letters 26 (2015) 85–88

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

An efficient synthesis of imidodicarbonic diamides from 1,3-thiazetidin-2-ones with $NH_2OH{\cdot}HCl$ *via* ring-opening reaction

Wen-Yuan Tang [a], Jing-Jing Guo [b], Xing-Xing Gui [b], De-Man Han [a], Jian-Jun Li [b,*]

[a] *College of Pharmaceutical and Chemical Engineering, Taizhou University, Zhejiang 317000, China*

[b] *Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, China*

ARTICLE INFO

Article history:
Received 8 July 2014
Received in revised form 9 September 2014
Accepted 9 October 2014
Available online 1 November 2014

Keywords:
Imidodicarbonic diamides
1,3-Thiazetidin-2-one
Hydroxylamine hydrochloride
Ring-opening

ABSTRACT

A ring-opening process of 4-imino-1,3-thiazetidin-2-ones with $NH_2OH{\cdot}HCl$ was described for the first time. Two different scaffolds of imidodicarbonic diamide were obtained selectively in good yields in the presence of organic base. The obtained imidodicarbonic diamides were demonstrated by X-ray diffraction analysis.

1. Introduction

Imidodicarbonic diamides (Fig. 1) exhibit a wide range of biological activities, such as anti-tumor and antioxidation [1–4]. Furthermore, they play a key role in the synthesis of macrocyclic nitrogen-containing compounds such as mononitrobiuret (MNB) and 1,5-dinitrobiuret (DNB) [5–8]. In general, they can be obtained from a certain purines by oxidation or decomposition [9,10]. However, the synthesis of these compounds has received very little attention.

It is well known that the four-membered heterocycle 4-imino-1,3-thiazetidin-2-ones **1** are useful organic intermediates in organic synthesis. Recently, our group [11] reported the ring-opening reaction of **1** with $N_2H_4{\cdot}H_2O$ (Scheme 1). As an extension, herein, we wish to study the ring-opening reaction in the presence of hydroxylamine. The experiment results showed the title products were imidodicarbonic diamides **2** rather than 1,2,4-oxadiazol-5-ones.

2. Experimental

Analytical grade solvents and commercially available reagents were used without further purification. The flash column chromatography was carried out over silica gel (200–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Melting points were determined on a Büchi B-540 capillary melting point apparatus and uncorrected. IR spectra was recorded on an AVATAR-370, samples were prepared as KBr plates. ^1H NMR and ^{13}C NMR spectra were recorded at VARAIN-400 using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS, the coupling constants J are given in Hz. Mass spectra were measured with Thermo Finnigan LCQ-Advantage. High resolution mass spectral (HRMS) analyze were measured on an Agilent 6210 TOF LC/MS using ESI or EI (electrospray ionization) techniques. The X-ray data was recorded on Gemini Ultra EXXH-236/09.

Syntheses of 4-(arylimino)-1,3-thiazetidin-2-ones **1a**–**1j**: To a mixture of ethyl acetate (25 mL), sodium bicarbonate (11.5 mmol, 0.97 g) and thioureas (5 mmol), BTC [bis(trichloromethyl)carbonate] (1.7 mmol, 0.5 g) was added carefully in portions. The reaction mixture was stirred at room temperature for 15 min. After completion (by TLC), the mixture was filtered, the organic solvent was condensed and the compounds **1** were obtained as crystal almost quantitative.

Syntheses of imidodicarbonic diamides **2a**–**2h** and **3f**–**3h**: 3-Aryl-4-(arylimino)-1,3-thiazetidin-2-ones **1** (1 mmol) were added into a mixture of hydroxylamine hydrochloride (1.2 mmol) and imidazole (1.2 mmol) in ethanol (15 mL). The reaction would last about 25 min at room temperature and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1/6) to provide the pure product.

---

[*] Corresponding author.
E-mail address: lijianjun@zjut.edu.cn (J.-J. Li).

http://dx.doi.org/10.1016/j.cclet.2014.10.015
1001-8417/

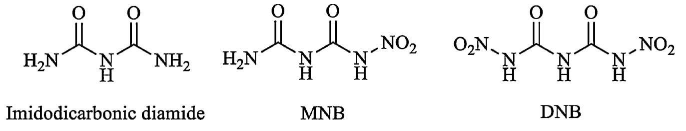
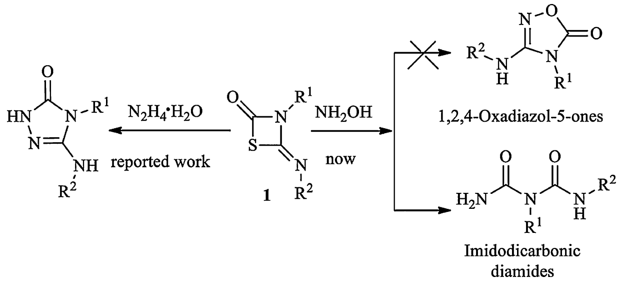


Fig. 1. Structures of imidodicarbonic diamide, MNB and DNB.



Scheme 1. Ring-opening reaction of **1** with $N_2H_4·H_2O$ or $NH_2OH·HCl$.

Syntheses of 1-alkyl-1-arylureas **4i** and **4j**: **1** (1.0 mmol) were added into a mixture of hydroxylamine hydrochloride (1.2 mmol) and imidazole (1.2 mmol) in ethanol (15 mL). The reaction would last about 3 h at room temperature and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1/8) to provide the pure product.

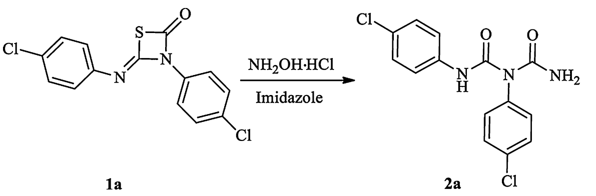
Syntheses of 1-carbamothioyl-1-phenylureas **5f** and **5j**: **1** (1.0 mmol) were added into a mixture of hydroxylamine hydrochloride (1.2 mmol) and pyridine (1.2 mmol) in methanol (15 mL). The reaction would last about 2 h at room temperature and the crude product was purified by flash chromatography (ethyl acetate/petroleum ether, 1/6) to provide the pure product.

Physical and chemical data of the chosen product is demonstrated below.

1-Carbamoyl-1,3-bis(4-chlorophenyl)urea (**2a**): White solid; mp: 177.6–179.8 °C. IR (KBr, cm^{-1}): υ_{max} 3489, 3172, 1681, 1596, 1404. ^1H NMR (400 MHz, $CDCl_3$): δ 10.73 (s, 1H), 7.49 (d, 2H, J = 8.8 Hz), 7.40 (d, 2H, J = 8.8 Hz), 7.28 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 5.18 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.7, 151.8, 136.0, 135.6, 135.2, 130.6 (CH × 2), 130.4 (CH × 2), 128.9, 128.8 (CH × 2), 121.2 (CH × 2). MS (ESI): m/z 346 $[M+Na]^+$. HRMS-ESI: calcd. for $C_{14}H_{11}Cl_2N_3NaO_2$: 346.0126; found: 346.0130.

1-Carbamoyl-1-(4-chlorophenyl)-3-phenylurea (**3f**): White solid; mp: 144.7–147.5 °C. IR (KBr, cm^{-1}): υ_{max} 3482, 3221, 1677, 1602, 1446. ^1H NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.48 (d, 2H, J = 8.4 Hz), 7.43 (d, 2H, J = 8.4 Hz), 7.31–7.26 (m, 4H), 7.07 (t, 1H, J = 7.6 Hz), 5.31 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 152.3, 137.1, 136.5, 130.4 (CH × 2), 129.7, 129.4 (CH × 2), 129.0 (CH × 2), 128.9, 121.4 (CH × 2). MS (ESI): m/z 312 $[M+Na]^+$. HRMS-ESI: calcd. for $C_{14}H_{12}ClN_3NaO_2$: 312.0516; found: 312.0527.

1-Isopropyl-1-phenylurea (**4i**): White solid; mp: 154.9–159.5 °C. IR (KBr, cm^{-1}): υ_{max} 3347, 3187, 1693, 1555, 1442. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, 4H, J = 7.2 Hz), 7.02–7.05 (m, 1H), 6.70 (s, 1H), 3.97 (m, 1H), 1.15 (dd, 6H, J_1 = 2.0 Hz, J_2 = 6.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 129.3 (CH × 2), 123.6, 120.9 (CH × 2), 42.4, 23.6 (CH × 2). MS (ESI): m/z 179 $[M+1]^+$. HRMS-ESI: calcd. for $C_{10}H_{15}N_2O$: 179.1184; found: 179.1186.



Scheme 2. Unexpected **2a** was synthesized by **1a**.

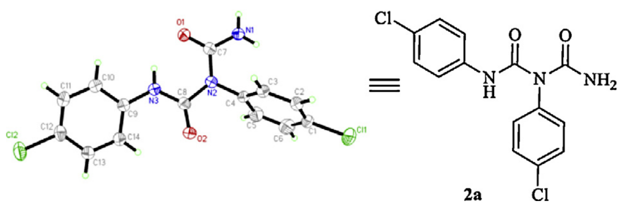


Fig. 2. The X-ray structure of **2a**.

1-(4-Chlorophenyl)-1-(phenylcarbamothioyl)urea (**5f**): White solid; mp: 117.6–120.1 °C. IR (KBr, cm^{-1}): υ_{max} 3435, 3265, 1702, 1534, 1033. ^1H NMR (400 MHz, $CDCl_3$): δ 12.46 (s, 1H), 7.56 (d, 2H, J = 7.6 Hz), 7.41–7.36 (m, 4H), 7.26 (d, 1H, J = 7.2 Hz), 7.14 (dd, 2H, J_1 = 2.0 Hz, J_2 = 7.6 Hz), 3.75 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.0, 156.2, 140.0, 136.9, 131.8, 130.5, 129.1 (CH × 2), 128.8, 128.7, 128.2, 126.2 (CH × 2), 125.0, 54.6. MS (ESI): m/z 321 $[M+1]^+$. HRMS-ESI: calcd. for $C_{15}H_{14}ClN_2O_2S$: 321.0465; found: 321.0465.

3. Results and discussion

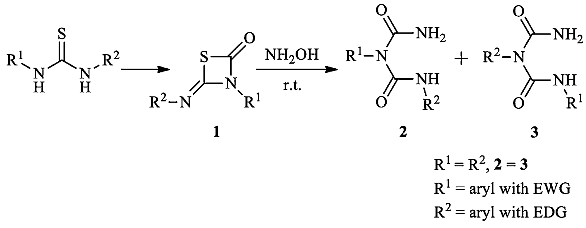
3-(4-Chlorophenyl)-4-((4-chlorophenyl)imino)-1,3-thiazetidin-2-one **1a** was selected as the starting material for the ring-opening reaction in our initial studies, which was synthesized from thiourea with triphosgene in excellent yield (up to 95%) [12]. Then **1a** was treated with hydroxylamine hydrochloride in the presence of imidazole under reflux conditions for 35 min. It was found that **1a** reacted with hydroxylamine quickly with the release of H_2S (Scheme 2). A novel compound **2a** was gotten in 88% yield. The structure **2a** was confirmed *via* single crystal X-ray diffraction analysis (Fig. 2, details see Supporting information).

Then, we focused on screening for the reaction conditions promoted by these results in mild conditions. In order to minimize the generation of side products that could arise from the reaction between substrate **1a** and organic base imidazole, the procedure

Table 1
Preparation of **2a** from **1a** in different solvents[a].

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)[b]
1	H_2O	Reflux	30	ND[c]
2	EtOH	Reflux	35	88
3	CH_2Cl_2	Reflux	20	80
4	Toluene	Reflux	30	73
5	EtOH	r.t.	25	87
6	CH_2Cl_2	r.t.	30	75
7	Toluene	r.t.	20	70
8	EtOH	0	50	82

[a] All reactions were run with the molar ratio of **1a**:$NH_2OH·HCl$:imidazole = 1:1.2:1.2.
[b] Isolated yield based on **1a**.
[c] No desired product was detected.



Scheme 3. Regioselective synthesis of **3** from **1**.