ACS Combinatorial Science

RESEARCH ARTICLE

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Diversity-Oriented Synthesis of Spiro-Substituted 1,3-Thiazine Library via a One-Pot, Two-Step, Three-Component Reaction

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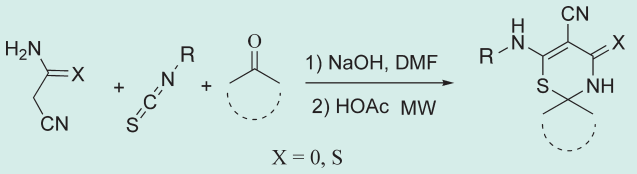
Supporting Information

ABSTRACT: A sequential one-pot, two-step, three-component reaction for efficient synthesis of spiro-substituted 1,3-thiazine library has been developed. The syntheses were achieved by reacting cyanoacetamide with isothiocyanate derivatives to give rise to 2-cyano-3-mercaptoacrylamides, which are trapped in situ by various cycloketones through cyclization, providing multifunctionalized spiro-substituted 1,3-thiazine analogues. This procedure features short reaction time, generally good to excellent yields, easily available starting materials, and operational simplicity. This chemistry provides an efficient and promising synthetic strategy to diversity-oriented construction of the 1,3-thiazine skeleton.



KEYWORDS: diversity-oriented synthesis, cyanoacetamide, spiro-substituted 1,3-thiazine

INTRODUCTION

Design and synthesis of biologically active molecules is one of the main challenges in medicinal chemistry.[1] Potential efforts have been focused on synthesizing libraries of small heterocyclic molecules because of their high degree of structural diversity and extensive utility as therapeutic agents.[2] Diversity-oriented synthesis (DOS) of small molecules is a new algorithm that enables efficient synthesis of complex molecules.[3] The accessible complexity of the molecules, consecutive reaction pattern, high reaction rate and efficiency, and minimal environmental impact are among the described advantages of DOS. Thus, the design and development of new DOS for the collections of small bioactive molecules has been receiving growing interest.

Thiazine and its derivatives are an important class of heterocyclic compounds possessing broad biological activities, such as COX-1 inhibition[4] and anti-inflammatory,[5] antiproliferative,[6] antihistaminic,[7] and anti-HIV activities.[8] For these reasons, much attention has been paid to the synthesis and biological evaluation of 1,3-thiazine derivatives.[9] Several methods have been reported for the synthesis of 1,3-thiazine derivatives through reaction between thioenols and ketones.[10] However, these reactions have suffered from long reaction times and a narrow scope of substrates, and only one spiro-substituted 1,3-thiazine derivative was obtained. Therefore, the development of an efficient, rapid, and clean synthetic route toward focused libraries of such compounds is of great importance to both medicinal and synthetic chemists.

Although the diverse synthetic routes to 1,3-thiazine derivatives have been developed, utilization of diversity-oriented strategy to build a 1,3-thiazine framework in a one-pot fashion has not stimulated much interest so far. As a continuation of our research devoted to the development of multicomponent reactions,[11−13] in this paper, we report a one-pot, two-step, three-component reaction for the diversity-oriented synthesis of a spiro-substituted 1,3-thiazine library from the readily available starting materials of cyanoacetamide (Figure 1), isothiocyanates (Figure 2), and cycloketones (Figure 3) (Scheme 1).

RESULTS AND DISCUSSION

Basheer et al. have reported a two-step reaction for the generation of several 1,3-thiazine derivatives by using cyanoacetamide, isothiocyanates, and cycloketones as starting materials.[10c] The procedure involved initial condensation of isothiocyanatobenzene with cyanoacetamide in the presence of sodium hydroxide to provide thioenols. Subsequently, the resulting thioenol was empolyed to react with ketones to give 1,3-thiazines. We envisioned this reaction can be realized in a one-pot, two-step manner due to the facts that first, isothiocyanates were converted to corresponding thioenol in quantitative chemical yields catalyzed by sodium hydroxide; second, sodium hydroxide was easily neutralized by protonic acids; and third, thioenol favors reaction with ketones in the presence of protonic acid. On the basis of these analyses, an attempted reaction of *p*-tolyl isothiocyanate (1.0 mmol) with cyanoacetamide (1.0 equiv) was performed in DMF-catalyzed sodium-hydroxide (0.2 equiv) for 30 min at room temperature, and then HOAc (1.0 mL) and cyclobutanone

Received: October 13, 2010
Revised: October 26, 2010
Published: November 17, 2010

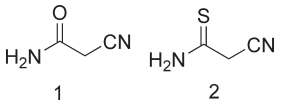


Figure 1. Diversity reagents **1**{*1,2*}.

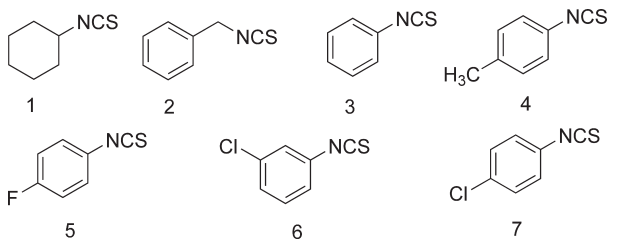


Figure 2. Diversity reagents **2**{*1*−*7*}.

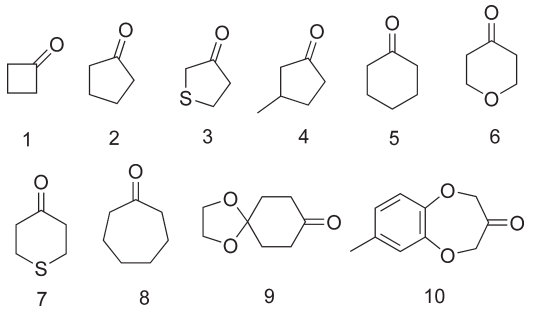
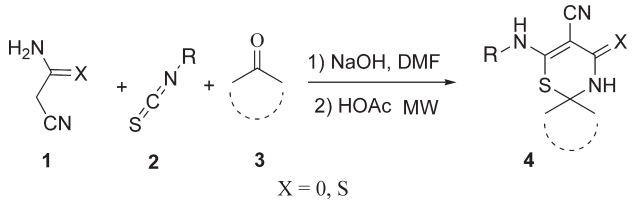


Figure 3. Diversity reagents **3**{*1*−*10*}.

Scheme 1. One-Pot, Two-Step, Tandem Synthesis of 1,3-Thiazine Derivatives



3{*1*}, respectively, were added into the reaction system. Subsequently, the mixture was heated under microwave irradiation at 60 °C. The pale yellow solid was obtained in 78% chemical yield. The polysubstituted, spiro-substituted 1,3-thiazine **4**{*1,4,1*} was fully characterized by ^{1}H and ^{13}C NMR and IR spectra, and its structure was also confirmed by single-crystal X-ray diffraction determination of **4**{*1,4,1*} (Figure 4). During this reaction process, a tedious workup procedure can be avoided, since the products directly precipitate out after the reaction is finished and when its mixtures are diluted with cold water.

Encouraged by the above interesting result, we next screened for the practical temperature for the synthesis. Similar reactions were conducted at 80 and 100 °C. The cycloketone was converted to product **4**{*1,4,1*} in 86% yield when the reaction temperature was increased from 60 to 80 °C. Increasing reaction temperature to 100 °C did not improve chemical yields.

Under the above optimized conditions, the substrate scope of this reaction was examined by using readily available starting materials. As revealed in Table 1, a range of isothiocyanates are

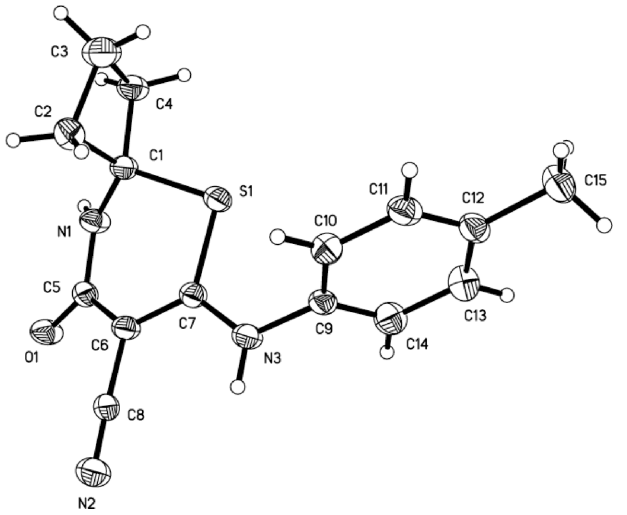


Figure 4. X-ray crystallopraphy structure of compound **4**{*1,4,1*}.

suitable for reacting with various cycloketones **3** and cyanoacetamide **1**{*1*} under microwave heating. In addition, the scope of cycloketones **3**, which include normal cycloketones (cyclobutanone **3**{*1*}, cyclopentanone **3**{*2*}, and cycloheptanone **3**{*8*}) and heteroatom (O and S)-attached cycloketones, such as tetrahydropyran-4-one **3**{*6*} and tetrahydrothiopyran-4-one **3**{*7*}, was also proven to be remarkable. Particularly, the 1,4-dioxaspiro-[4.5]decan-8-one **3**{*9*} allowed a one-pot access to polycyclic dispiro products **4**{*1,1,9*}−**4**{*1,7,9*} in good yields, whereas the use of 7-methyl-2*H*-benzo[*b*][1,4]dioxepin-3(4*H*)-one (Watermelon ketone) **3**{*10*} yielded polycyclic chemset **4** from different isothiocyanates. It should be mentioned that the resulting benzo-[*b*][1,4]dioxepine-containing multiheterocycles would be endowed with many significant pharmacological properties, such as selective serotonin reuptake inhibitors (SSRIs)[14] and the receptor binding affinities.[15]

In addition to cyanoacetamide (**1**{*1*}) substrate, thiocyanoacetamide (**1**{*2*}) was also proven to be suitable for the reaction with isothiocyanates (**2**) and nine cycloketones, including normal cycloketones (**3**{*1*}, **3**{*8*}, **3**{*9*}, 3-methylcyclopentanone **3**{*4*}, and cyclohexanone **3**{*5*}) and heteroatom (O and S)-attached cycloketones, such as **3**{*7*}, **3**{*10*}, and dihydrothiophen-3(2*H*)-one **3**{*3*} to give the corresponding spiro-substituted 1,3-thiazine **4**{*2,3,1*}−**4**{*2,3,10*}) in good yields (81−85%) (Table 1). The structures of all the synthesized compounds were established on the basis of their spectroscopic data. Moreover, the structures of **4**{*1,4,1*} and **4**{*1,3,2*}were established by X-ray crystallography (see the Supporting Information).

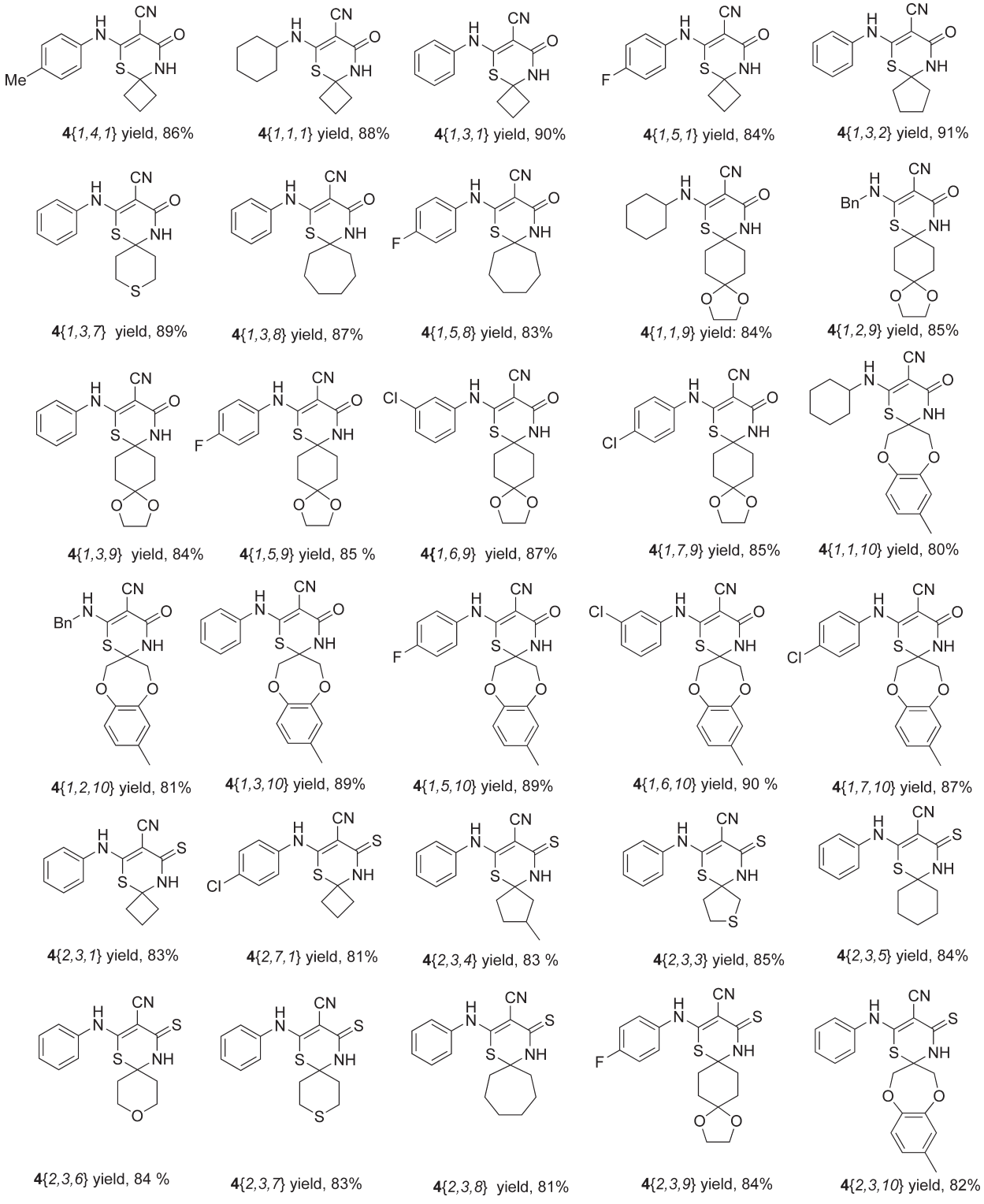
On the basis of all the above results, a possible mechanism has been proposed for the formation of spiro-substituted 1,3-thiazine derivatives, as shown in Scheme 2. The formation of chemset **4** involves a ring closure cascade process that consists of initial condensation, intermolecular nucleophilic addition (**5** to **6** or **5** to **6′**), intramolecular nucleophilic substitution (**6** to **4** or **6′** to **4**). A similar mechanism for synthesis of 1,3-thiazine derivatives has been reported by Basheer and Rappoport.[10c]

CONCLUSION

In conclusion, we have developed a one-pot, two-step, tandem reaction for the efficient synthesis of 1,3-thiazine derivatives. By using different types of cyclic ketones with cyanoacetamide and

dx.doi.org/10.1021/co100034v |*ACS Comb. Sci.* 2011, 13, 84–88

Table 1. One-Pot Two-Step Synthesis of Chemset 4



isothiocyanates, we could obtain novel libraries of 1,3-thiazine derivatives, which makes this methodology suitable for combinatorial and parallel synthesis. The proposed reactions proceed under mild conditions and give the products in good yields. The separation and purification processes are very simple and convenient, needing only recrystallization. Starting materials are inexpensive and commercially available.

EXPERIMENTAL PROCEDURES

General. Microwave irradiation was carried out with microwave oven Emrys Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and were uncorrected. IR spectra were taken on a FT-IR-Tensor 27 spectrometer in KBr pellets and reported in cm^{-1}. ^1H NMR

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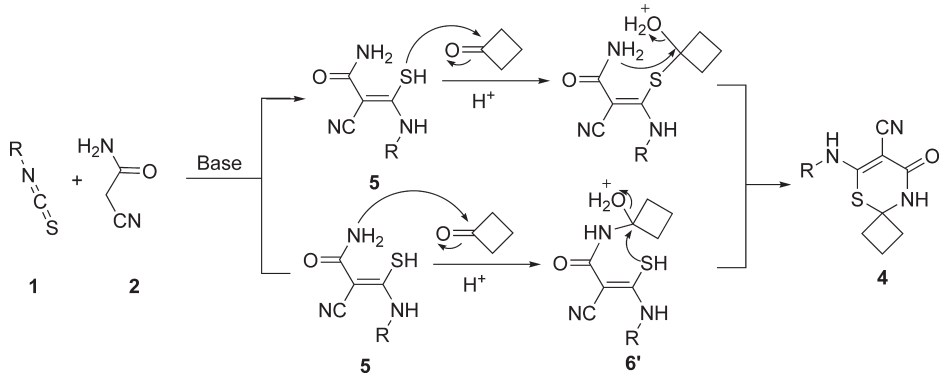
Scheme 2



spectra were measured on a Bruker DPX, 400 MHz spectrometer in DMSO-d_6 (100 MHz, ^{13}C NMR) with chemical shift (δ) given in parts per million relative to TMS as internal standard. ESI-MS was determined by using a LCQ Advantage HPLC/MS instrument (Thermo Finnigan). HRMS (ESI) was determined by using a microTOF-QII HRMS/MS instrument (BRUKER). X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer.

General Procedure for the Synthesis of 8-Oxo-6-*p*-tolylamino-5-thia-9-aza-spiro[3.5]non-6-ene-7-carbonitrile (4{*1,4,1*}) with Microwave Irradiation. Typically, in a 10 mL Emrys reaction vial, *p*-tolyl isothiocyanate (1.0 mmol) with cyanoacetamide (1.0 equiv) was performed in DMF-catalyzed sodium hydroxide (0.2 equiv) for 30 min at room temperature, and then HOAc (1.0 mL, excess) and cycloketones (1.1 equiv) were added into the reaction system. Subsequently, the mixture was irradiated by microwave at 80 °C for 8 min. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and filtered to give the crude products, which were further purified by recrystallization from 95% EtOH as a pale yellow solid. mp: 244−245 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.11(s, 1H, NH), 8.55 (s, 1H, NH), 7.21(d, J = 8.4 Hz, 2H, Ar−H), 7.13(d, J = 8.0 Hz, 2H, Ar−H), 2.47−2.34(m, 6H, CH_2), 1.91−1.78 (m, 2H, CH_2), 2.32 (s, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C) (δ, ppm): 166.0, 164.2, 136.6, 135.3, 129.5, 125.9, 116.4, 76.4, 62.4, 36.7, 20.6, 14.0. IR (KBr, ν, cm^{-1}): 3469, 3355, 3319, 3248, 3168, 2210, 1731, 1699, 1667, 1591, 1536, 1493, 1446, 1373, 1326, 1245, 1202, 1014, 869, 695. HRMS (ESI): m/z calcd for $C_{15}H_{16}N_3OS$, 286.1014; found, 286.1014.

■ ASSOCIATED CONTENT

Supporting Information. Representative experimental procedures, spectral data of chemset **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

We are grateful for financial support from the National Science Foundation of China (Nos. 21072163 and 21002083), Science Foundation in Interdisciplinary Major Research Project of XZNU (No. 09XKXK01), and the Qing Lan Project of Jiangsu Education Committee (No. 08QLT001).

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