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A diastereoselective synthesis of functionalized bis-spirorhodanine-linked cyclopentanes *via* C(sp^3)–H activation

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ABSTRACT

A diastereoselective synthesis of bis-spirorhodanine-linked cyclopentane derivatives *via* the [2 + 2+1] cycloaddition reaction between alkyl (*Z*)-2-(3-alkyl-4-oxo-2-thioxothiazolidin-5-ylidene)acetates (alkylidenerhodanines) and azomethine ylides, prepared *in situ* from iodine mediated reaction of 2-methylquinoline and pyridine in the presence of base, has been developed. The structure of a typical product was confirmed by X-ray crystallography.

1. Introduction

The five-membered carbocycle is a familiar and widespread structural motif in natural product architectures. As a result, the collection of chemical reactions that construct cyclopentanes represents an indispensable toolbox for synthetic chemists [1]. Moreover, methods that build cyclopentanes with control of sp^3-hybridized stereocenters are particularly valuable. The importance of creating substituted cyclopentanes with control of stereochemistry has been a driving force inspiring the creation of synthetic methods and strategies for building functionalized five-membered carbocycles.

2-Thioxo-4-thiazolidinone skeletons, commonly known as "rhodanine", are important structural units which have been proved to have anticancer [2a,b,3b], antidiabetic [2b,3a], anti-alzhemers [3c], antimalarial [3d], antioxidant [3e], antibacterial [2a,3f-i], anti-inflammatory [3j], and pesticidal properties. Moreover, rhodanine derivatives have been utilized as an efficient electron acceptor in a series of organic dye-sensitized solar cells [4].

The construction of spirocycles has been a challenge for many chemists since the beginning of 20th century [5]. General interest in spirocyclic structures comes not only from their structural properties but also from their biological activities and their occurrence in a wide range of natural products. For example, the spirorhodanines **A** and **B** exhibit antidiabetic and antiviral activities, respectively (Fig. 1) [3a,6a]. Pactamycin, a potent antitumor and antibiotic, possesses a densely functionalized cyclopentane core structure [6b]. Palau'amine is a bis-guanidine spirocyclopentane antibiotic obtained from the sponge *Stylotella agminata* that displays potent cytotoxic activities [6c]. Spirocyclopentaneoxindole moiety is found in alkaloids such as citrinadin A (Fig. 1) [6d].

Thus, the development of efficient strategies for the construction of spirorhodanine-cyclopentanes with several motifs integrated together is valuable for the structural diversity of spirorhodanines and spirocyclopentanes, as well as for the discovery of new drugs. In particular, some researchers have been attracted by the synthesis of spirorhodanines [7] or spirocyclopentanes [8] because of their potential pharmaceutical activities and the significance of synthetic methodology. In 2012, Ye and co-workers reported the synthesis of spirocyclohexane rhodanines through a diamine-catalyzed asymmetric tandem reaction between α,β-unsaturated ketones and rhodanine derivatives [7b]. Furthermore, a novel organocatalytic strategy for the synthesis of spirocyclopentaneoxindoles, employing simple nitrostyrenes and 3-substituted oxindoles as starting materials, has been reported [8d].

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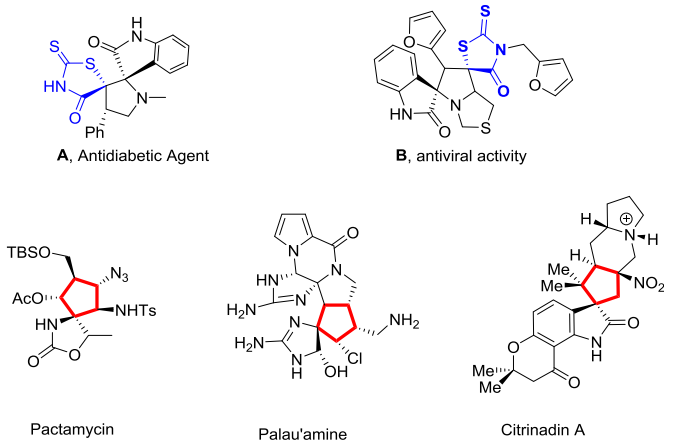


Fig. 1. Biologically active spirocycles containing the rhodanine and cyclopentane moieties.

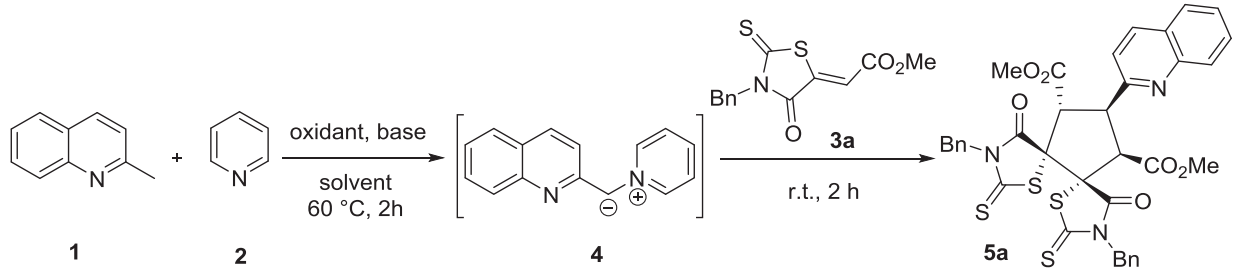
The cycloaddition reactions of azomethine ylides are generally stereospecific, with the stereochemistry of the dipole and dipolarophile retained in the cycloadduct. Cycloadditions with azomethine ylides have been extensively investigated in recent years and these have been applied in asymmetric and natural product synthesis, as well as the syntheses of biologically interesting compounds. In this work, a method has been developed for the generation of azomethine ylides *via* C–H activation of unreactive C(sp^3)–H bonds. Aromatic C–H bond activation is well-established [9], but the C–H bond activation of alkyl substituted azaarenes has become increasingly important for the formation of functionalized organic compounds [10]. In recent years, several research groups have investigated the C–H bond functionalization of azaarenes such as quinolines and pyridines, which potentially provides a new synthetic tool for the synthesis of bioactive compounds [11]. The C(sp^3)–H bond activation of 2-methylazaarenes by Lewis acidic activators [12] and by iodine has been reported [13].

Recently, we reported the synthesis of functionalized cyclopropanes and indolizines from azomethine ylides *via* iodine-mediated reaction of 2-methylquinoline (**1**) with pyridine [14]. In this paper, we report the cyclopentanation reaction of olefinic bond of alkyl (*Z*)-2-(3-alkyl-4-oxo-2-thioxothiazolidin-5-ylidene)acetates **3** with azomethine ylides **4**, prepared by iodine-mediated C(sp^3)–H bond activation of **1** for the synthesis of bis-spirorhodanine cyclopentane derivatives **5**.

2. Results and discussion

The alkylidenerhodanines **3** were synthesized from alkynes, carbon disulfide (CS_2), and amines, according to the literature [15]. In order to assess the feasibility of the proposed transformation shown in Table 1, we started our studies by testing the model reaction between **1**, **2**, and methyl (*Z*)-2-(3-alkyl-4-oxo-2-thioxothiazolidin-5-ylidene)acetate (**3a**). Thus, a mixture of **1**, **2**, and various Lewis acids was warmed to 60 °C for 2 h in different solvents. The reaction mixture was allowed to reach ambient temperature, then, **3a** and base were added. As shown in Table 1, copper salts such as CuBr, CuI and $Cu(OAc)_2$ were found to be less effective catalysts to catalyze the reaction (Entries 1–3). Lewis acids such as $AlCl_3$ and $BF_3{\cdot}Et_2O$ did not promote the desired reaction (Entries 4–5). The yield of isolated bis-spirorhodanine cyclopentane **5a** was further improved (67%) by using molecular iodine (100 mol%) as an oxidant (Table 1, entry 6). Next, we focused on the screening of bases, such as $NaHCO_3$, Na_2CO_3, K_2CO_3, Et_3N, DBU, and DIPEA (*N*,*N*-diisopropylethylamine); the presence of a base is crucial to remove proton and form azomethine ylide **4** (Table 1, entries 6–11). In the presence of a weak base, such as sodium bicarbonate, **5a** was obtained in 5% yield (Table 1, entry 8). Thus, DIPEA was found to be more effective than the other bases (Table 1,

Table 1
Optimization of condition for the iodine-mediated cyclopentanation reaction.[a]



Entry	Oxidant	Base	Solvent	Yield (%)[b]
1	CuBr	DIPEA	MeCN	No reaction
2	CuI	DIPEA	MeCN	No reaction
3	$Cu(OAc)_2$	DIPEA	MeCN	No reaction
4	$AlCl_3$	DIPEA	MeCN	No reaction
5	$BF_3{\cdot}Et_2O$	DIPEA	MeCN	No reaction
6	I_2	DIPEA	MeCN	67
7	I_2	Et_3N	MeCN	57
8	I_2	$NaHCO_3$	MeCN	trace
9	I_2	Na_2CO_3	MeCN	trace
10	I_2	K_2CO_3	MeCN	trace
11	I_2	DBU	MeCN	trace
12	I_2	DIPEA	CH_2Cl_2	45
13	I_2	DIPEA	DMF	60
14	I_2	DIPEA	toluene	No reaction

[a] Reaction conditions: (i) **1** (1.1 mmol), **2** (2.2 eq), oxidant (100 mol%), solvent (5 mL), 2 h, 60 °C; (ii) base (2 eq.), **3a** (2.0 mmol), r.t., 2 h.
[b] Isolated yield.