Organic LETTERS

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Ring-Opening Cyclization of Cyclohexane-1,3-dione-2-spirocyclopropanes with Amines: Rapid Access to 2-Substituted 4-Hydroxyindole

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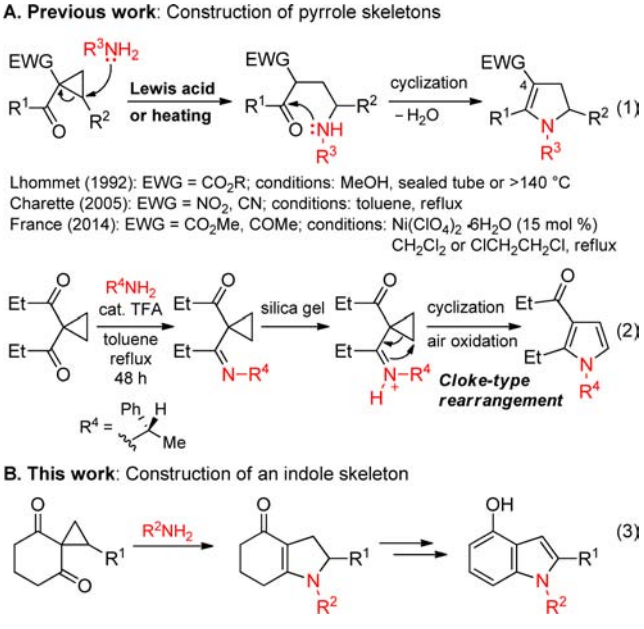
Supporting Information

ABSTRACT: An efficient ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes with primary amines has been developed. The reaction proceeded at room temperature without any additives to provide 2-substituted tetrahydroindol-4-ones in good to excellent yields without the formation of the 3-substituted isomers. The obtained product was readily converted into a 2-substituted 4-hydroxyindole derivative via a synthetically useful indoline intermediate.

Cyclopropanes serve as valuable building blocks in organic synthesis.[1] They have strong ring strain, and the relief of the strain provides a high chemical reactivity. Among the large variety of interesting and efficient reactions of cyclopropanes,[1] one of the most extensively investigated reactions is the formal cycloaddition of doubly activated cyclopropanes for the construction of highly functionalized carbo- and heterocyclic compounds,[2,3] in which ring opening of their cyclopropanes results in the formation of a 1,3-dipole equivalent as a C_3 unit. Another unique application of activated 1-acylcyclopropanes is as C_4 units (from three cyclopropane carbons and one carbonyl carbon); this has been used for the synthesis of heterocycles.[4−7] Thus, 1-acyl-1-(alkoxycarbonyl)cyclopropanes have been reacted with primary amines at >140 °C to produce 4-alkoxycarbonyl-2,3-dihydropyrroles (Scheme 1, eq 1).[4] Similar reactions using various activating groups such as nitro and cyano groups[5] and Lewis acid activation[6] have also been reported. In these reactions, a nucleophilic attack of amine at the doubly activated β-carbon of the acyl group results in formation of a γ-amino ketone, which easily undergoes cyclization to construct the pyrrolidine ring. As an alternative approach, Jabin and co-workers have reported a pyrrole synthesis involving a ring-opening cyclization of a 1,1-diacylcyclopropane.[7] The reaction of a 1,1-diacylcyclopropane with amine in the presence of a catalytic amount of trifluoroacetic acid (TFA) in toluene at reflux provides an α-cyclopropyl imine, which when treated with silica gel, followed by air oxidation, gives the corresponding pyrrole through a Cloke-type rearrangement[8] (Scheme 1, eq 2). These examples offer useful synthetic tools for obtaining nitrogen-containing 5-membered rings.

Indoles that possess a cyclohexane-fused pyrrolidine framework are important structural components of a wide range of biologically active alkaloids and pharmaceutical agents.[9] Although many synthetic methodologies for indoles have been investigated,[10] much effort continues to be devoted to developing efficient synthetic routes, especially to highly substituted indoles.[11] As a part of our efforts on the synthesis of functionalized indoles,[12] we investigated the ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropane with primary amines as a new potential route to indole frameworks (Scheme 1, eq 3). Herein, we report that ring-opening cyclizations of cyclohexane-1,3-dione-2-spirocyclopropane with amines proceed smoothly at room temperature without any additives to give 2,3,6,7-tetrahydro-1*H*-indol-4(5*H*)-ones, which are readily converted to highly substituted indoles through the indoline intermediate.

Scheme 1. Ring-Opening Cyclization of Cyclopropanes



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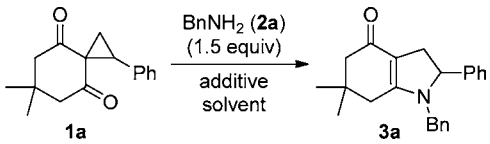
At the outset of this work, the ring-opening cyclization of spirocyclopropane was explored using the known 6,6-dimethyl-1-phenylspiro[2.5]octane-4,8-dione (**1a**), readily prepared by Müller's method,[13] and 1.5 equiv of benzylamine (**2a**). Among the reported conditions,[4−7] we first chose the use of $Ni(ClO_4)_2 \cdot 6H_2O$[14] as a catalyst in CH_2Cl_2 at reflux according to France's procedure,[6] due to the mild conditions at relatively low reaction temperature (Table 1, entry 1). The reaction proceeded with

Table 1. Ring-Opening Cyclization of Spirocyclopropane 1a with Benzylamine (2a)[a]



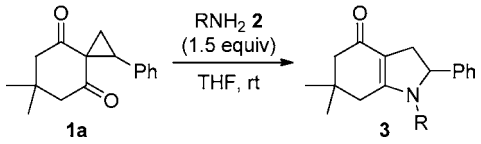
entry	additive	solvent[b] (M)	temp (°C)	time (h)	yield[c] (%)
1	$Ni(ClO_4)_2$[d]	CH_2Cl_2 (0.1)	reflux	9	97
2	TFA[e]	toluene (0.1)	reflux	0.5	83
3	$MgSO_4$[f]	CH_3CN (0.1)	80	1	95
4		toluene (0.1)	reflux	1	97
5		toluene (0.1)	rt	48	93
6		toluene (0.5)	rt	3	97
7		CH_2Cl_2 (0.5)	rt	3.5	93
8		CH_3CN (0.5)	rt	5	97
9		THF (0.5)	rt	3	97
10		THF (0.5)	reflux	0.5	97

[a]All reactions were performed on a 0.2 mmol scale. [b]Concentration of starting material **1a**. [c]Isolated yield. [d]A catalytic amount of $Ni(ClO_4)_2 \cdot 6H_2O$ (15 mol %) was used. [e]A catalytic amount of TFA (0.2 equiv) was used. [f]0.5 equiv of $MgSO_4$ was used.

ring-opening and cyclization, and 2-phenyl-substituted tetrahydroindol-4-one **3a** was obtained after 9 h in 97% yield with no evidence of the formation of the 3-phenyl-substituted product. Next, we tested the formation of the imine according to Jabin's method (entry 2).[7] Unexpectedly, the reaction of **1a** in the presence of a catalytic amount of TFA in toluene at reflux afforded, in 83% yield, the cyclization product **3a**, not the corresponding imine product. The use of $MgSO_4$ as a desiccant in CH_3CN at 80 °C[15] resulted in a high yield of **3a** (95% yield, entry 3). Since ring-opening reactions of doubly activated cyclopropane under heating conditions were reported by Lhommet[4] and Charette[5] (Scheme 1, eq 1), the reaction in toluene at reflux was examined (entry 4). As a result, a high product yield of **3a** was obtained without any additives (97% yield). To our surprise, the reaction proceeded at room temperature to afford **3a** in 93% yield, although a much longer reaction time (48 h) was needed to reach completion (entry 5). Remarkably, the reaction at a higher molar concentration of **1a** (0.5 M) shortened the reaction time to 3 h and led to high yield of **3a** (97% yield, entry 6). In contrast to the ring-opening of nonspirocyclopropanes which required further activation or heating conditions,[4−7] **1a** does not need any activation due to the spiro activation.[1b] A survey of solvents revealed that toluene and THF were suitable for this reaction in terms of product yield and reaction rate (entries 6−10).

Having optimized the reaction conditions, we investigated the reaction of **1a** with a range of amines **2** in THF (Table 2). The use of *p*-methoxybenzylamine ($PMBNH_2$, **2b**), allylamine (**2c**) and *n*-butylamine (**2d**) regioselectively afforded the corresponding 2-phenyl-substituted products **3b**, **3c**, and **3d**

Table 2. Ring-Opening Cyclization of Spirocyclopropane 1a with a Variety of Amines 2[a]



	amine				
entry		R	time (h)	yield[b] (%)	
1	**2b**	PMB	3	**3b**	92
2	**2c**	allyl	5	**3c**	98
3	**2d**	^{n}Bu	2.5	**3d**	95
4	**2e**	^{t}Bu	60	**3e**	85
5	**2f**	Ph	4	**3f**	64
6[c]	**2f**	Ph	2	**3f**	76
7	**2g**	4-$MeOC_6H_4$	4	**3g**	39
8[c]	**2g**	4-$MeOC_6H_4$	1	**3g**	86
9	**2h**	H[d]	2	**3h**	31
10	**2i**	Cbz	24		

[a]All reactions were performed on a 0.2 mmol scale. [b]Isolated yield. [c]These reactions were conducted in toluene at 70 °C. [d]10 equiv of ammonia solution (25% in water) was used. PMB: *p*-methoxybenzyl.

in 92%, 98%, and 95% yields, respectively (entries 1−3). The reaction with *tert*-butylamine (**2e**) as a sterically hindered amine resulted in good yield of **3e**, but a significantly longer time was required to reach completion (60 h, 85% yield, entry 4). In the case of aromatic amines such as aniline (**2f**) and *p*-anisidine (**2g**), moderate product yields (39−64% yields) were obtained owing to the formation of several side products (entries 5 and 7). Gratifyingly, switching the solvent to toluene and heating at 70 °C greatly improved the product yields, providing the dihydropyrroles **3f** and **3g** in 76% and 86% yields, respectively (entries 6 and 8). The use of ammonia solution (25% in water) afforded the *N*-unprotected product **3h** in moderate yield (31% yield, entry 9). The reaction with $CbzNH_2$ and the corresponding amide prepared with NaH did not give the desired product (entry 10).

Using benzylamine (**2a**) as an amine nucleophile, we explored the scope of the reaction with respect to the substituents on the cyclopropane (Table 3). The reaction of *p*-tolyl-substituted cyclopropane **1b** proceeded smoothly to completion within 2.5 h, giving the 2-substituted tetrahydroindol-4-one **3i** as the sole product in 86% yield (entry 1). The use of 1-aryl-substituted spirocyclopropanes **1c** and **1d** with a chlorine atom present at the *para*- and *ortho*-positions on the benzene ring provided the corresponding products **3j** and **3k** in 97% yield (entries 2 and 3). The reaction of cyclopropane **1e**, bearing a 2,3,4,5,6-pentafluorophenyl group, resulted in a good yield of **3l**, although the reaction time was prolonged (48 h, 90% yield, entry 4). The use of cyclopropane **1f**, possessing an alkyl substituent on the cyclopropane ring, led to a high yield of **3m** (97% yield), but the reaction time was much longer (168 h) than those with aromatic substituents (entry 5). As might be expected, the reaction of **1f** in THF at reflux reduced the reaction time (8 h) and provided **3m** in 96% yield.[16] The ring-opening cyclization of simple cyclopropane substrate **1g**[17] proceeded uneventfully and afforded the desired product **3n** in 92% yield (entry 7).

A plausible mechanism for the ring-opening cyclization of spirocyclopropane **1** with amine **2** is shown in Scheme 2. On the basis of previous reports,[4−7] two routes to the 2-substituted

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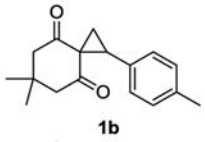
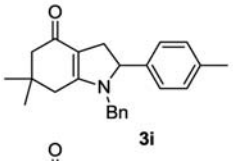
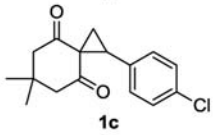
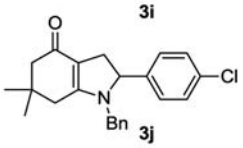
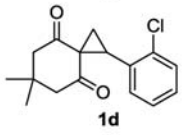
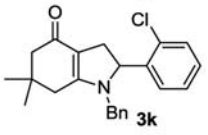
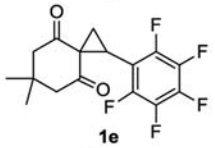
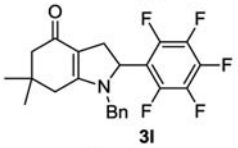
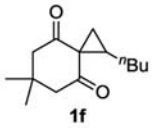
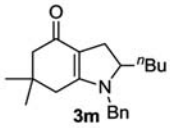
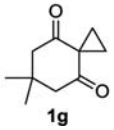
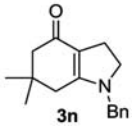
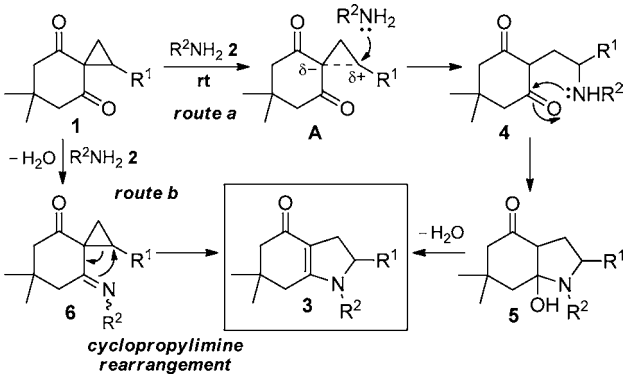
Table 3. Ring-Opening Cyclization of a Variety of Spirocyclopropanes 1b–g with Benzylamine (2a)[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **1b**	2.5	 **3i**	86
2	 **1c**	4.5	 **3j**	97
3	 **1d**	20	 **3k**	97
4	 **1e**	48	 **3l**	90
5	 **1f**	168	 **3m**	97
6[c]		8		96
7	 **1g**	36	 **3n**	92

[a]All reactions were performed on a 0.2 mmol scale with 1.5 equiv of benzylamine (**2a**) in THF at room temperature. [b]Isolated yield. [c]The reaction was conducted in THF at reflux.

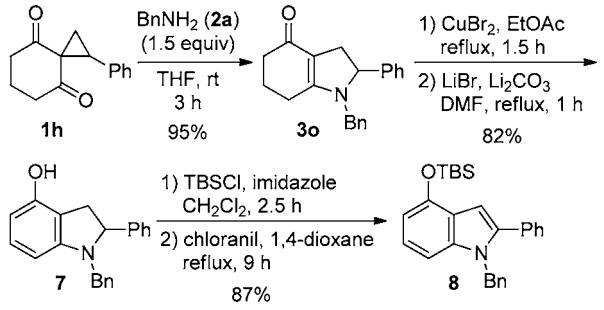
Scheme 2. Plausible Mechanism



tetrahydroindol-4-one **3** are proposed. In one route (route a), ring-opening of the spirocyclopropane **1** proceeds through an S_N2-like displacement by the nucleophilic amine **2** at the more electrophilic substituted carbon on the cyclopropane **A**,[5] leading to γ-amino ketone **4** regioselectively. Nucleophilic attack of amine to the carbonyl carbon **4** followed by dehydration of hemiaminal **5** provides tetrahydroindol-4-one **3**. An alternative route employing imine rearrangement[8,18] is also proposed (route b). However, the present reaction would proceed through γ-amino ketone **4** (route a) because the corresponding imine product **6** could not be detected even with a catalytic amount of TFA (Table 1, entry 2).[7]

Using the present protocol, we prepared the 4-hydroxyindole **8** (Scheme 3). Ring-opening cyclization of spirocyclopropane **1h**, prepared from 2-diazocyclohexane-1,3-dione and styrene according to the procedure of Müller,[13] with **2a** proceeded smoothly at room temperature to give tetrahydroindol-4-one **3o** in 95% yield. According to the literature procedure,[19] bromination of **3o** with $CuBr_2$ in EtOAc at reflux was followed by aromatization using a combination of LiBr and Li_2CO_3 to afford 4-hydroxyindoline **7** in 82% yield. Since indoline is a ubiquitous scaffold found in a large range of biologically active alkaloids and pharmaceutically active compounds,[20] this synthetic route to indoles via indoline intermediates offers a distinctive advantage. While dehydrogenation of indoline **7** possessing a free phenolic hydroxyl group gave a complex mixture of products, oxidation of *tert*-butyldimethylsilyl (TBS)-protected 4-hydroxyindoline with chloranil furnished 4-hydroxyindole derivative **8** in 87% yield from **7**.

Scheme 3. Synthesis of 4-[(*tert*-Butyldimethylsilyl)oxy]indole 8 from Spirocyclopropane 1h



In conclusion, we have developed a regioselective ring-opening cyclization of cyclohexane-1,3-dione-2-spirocyclopropanes with primary amines. The reaction proceeds at room temperature without any additives to provide tetrahydroindol-4-ones in good-to-excellent yields. To the best of our knowledge, this is the first example of the synthesis of indole frameworks using the ring-opening reaction of cyclopropanes. The present protocol is applicable to the synthesis of 2-substituted 4-hydroxyindoles via a synthetically useful indoline intermediate. Further application of this method to the synthesis of biologically active indole alkaloids as well as mechanistic studies are currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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