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AQUEOUS SYNTHESIS OF (*R**,*R**)-BIS(SPIROPYRAZOLONE)CYCLOPROPANES THROUGH IODINE-PROMOTED CYCLIZATION OF ALDEHYDES AND PYRAZOLIN-5-ONES

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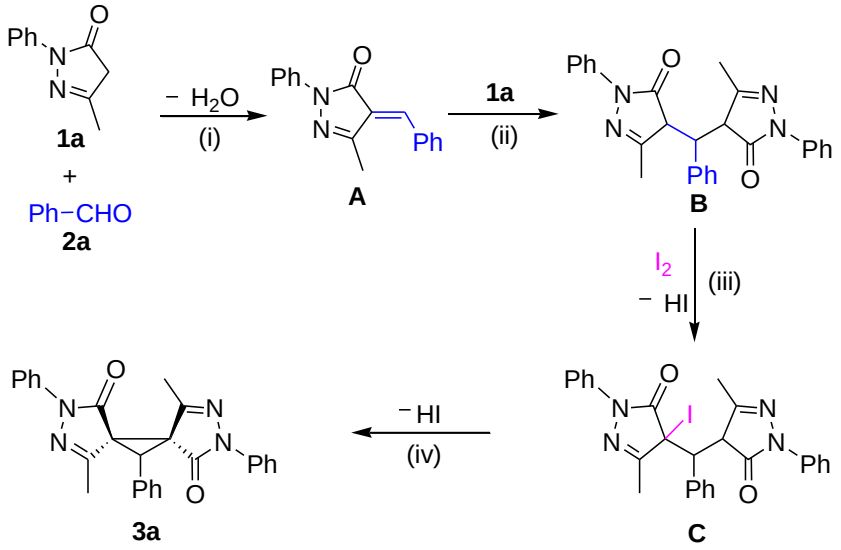
Abstract – The molecular iodine promoted cyclization of aldehydes and pyrazolin-5-ones was accomplished in water using tetrabutylammonium iodide as a phase transfer catalyst, affording a variety of substituted (*R**,*R**)-bis(spiropyrazolone)cyclopropanes in good to excellent yields (76–96%). This aqueous reaction exhibits very high chemoselectivity, and the products were obtained by simple Büchner filtration without chromatographic isolation procedure.

Cyclopropane moiety plays a prominent role in synthetic chemistry because the strained structure and unique bonding characteristics of the three-membered ring determine a variety of organic transformations.[1] Among different types of cyclopropane fragments, spirocyclopropyl moiety has been attracting much attention due to its biological activities and pharmacological properties.[2] Especially, a spirocyclopropyl moiety jointed with a heterocyclic counterpart has attracted particular attention due to its synthetic utility and wide range of pronounced pharmacological applications.[3] For example, some fused spirocyclopropyl heterocycles have been recognized as α-L-fucosidase,[4] β-lactamase and HIV-1 non-nucleoside reverse transcriptase inhibitors as well as diagnostic markers for early detection of colorectal and hepatocellular cancer.[5] On the other hand, as an important class of spiro-heterocycles, spiropyrazolone motifs are also ubiquitous in significantly bioactive compounds, such as antimicrobial agent,[6] anti-inflammatory agent,[7] antitumor agent,[8] analgesic agent,[9] RalA inhibitor[10] and 4-phosphodiesterase inhibitor.[11] As a special kind of spiral compounds bearing both spiro-connected cyclopropane and pyrazolone scaffolds, bis(spiropyrazolone)cyclopropanes have great potential

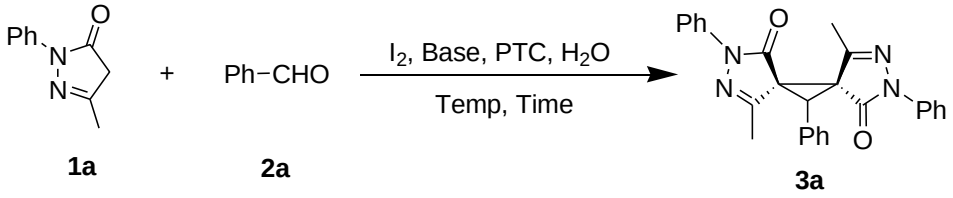
applications in various fields including organic synthesis, biological, medicinal and pharmacological chemistry. For example, they can be used as effective pesticide against fungi *P. oryzae* and *H. oryzae* responsible for rice crop diseases,[12] or as advanced glycation end product (AGE) formation inhibitors to treat human schizophrenia.[13,14] Therefore, the synthesis and investigation of bis(spiropyrazolone)-cyclopropanes is of great importance and has attracted broad attentions. The common synthetic approach to such spirocyclopropanes involves the direct oxidation of 4,4′-(arylmethylene)bis(1*H*-pyrazol-5-ols) by molecular halogen[15] or indirect electrochemical oxidation of them mediated by sodium bromide in an undivided cell,[16,17] the cascade cyclization of bromo-pyrazolone to 4-arylidene-2,4-dihydro-3*H*-pyrazol-5-ones,[18] and direct transformation of aldehydes and two molecules of pyrazolin-5-one into the corresponding spirocyclopropane by analogous electrocatalytic cascade process.[19] Most recently, a column chromatography-free protocol based on NBS induced cyclization has also been developed.[20] Considering our experience and continued interest in the synthesis of spiro heterocyclic compounds,[21] we attempted to develop a new and more environmental method for the facile synthesis of bis(spiropyrazolone)cyclopropanes directly from benzaldehydes and pyrazolin-5-ones via molecular iodine-mediated cascade reactions in aqueous medium. As we know, molecular iodine-mediated reactions are highly efficient, atom-economical, easy to control, eco-friendly protocol rather than transition metal-catalyzed reactions. But most of I_2-catalyzed/promoted reactions involve the use of organic solvents, which is a major concern in terms of environmental issues. Therefore, iodine-catalyzed or promoted reactions performed in an aqueous medium to avoid environmental hazardous, is a thrust area to modern synthetic chemists.[22]

Initially, we chose the reaction of pyrazolin-5-one **1a** with benzaldehyde **2a** as the model reaction to optimize the reaction conditions for the synthesis of the corresponding spirocyclopropane **3a** by fixing on I_2 as the promoter and water as the solvent. The mechanism for the formation of **3a** from **1a** and **2a** is classical and mature as shown in Scheme 1, which involves the following steps: (i) condensation between **1a** and **2a** to give intermediate **A**; (ii) subsequent Michael addition of another molecule of **2a** with **A** to afford the adduct **B**; (iii) iodination of **B** by I_2 to form iodide **C**; (iv) cyclization via intramolecular nucleophilic substitution of **C** to afford product **3a**. From the reaction mechanism it can be plausibly anticipated that the employment of a base would facilitate the desired reaction. On the other hand, phase transfer catalyst (PTC) is generally beneficial to heterogeneous aqueous reactions. Therefore, we systematically investigated the effects from base and PTC besides the usage amount of I_2, reaction temperature and time, and the results are summarized in Table 1.



Scheme 1. The reaction mechanism for the formation of **3a** from **1a** and **2a**

Table 1. Optimization of the reaction conditions[a]



Entry	I_2 (equiv.)	Base (equiv.)	PTC (equiv.)	Temp (°C)	Time (h)	Yield[b] (%)
1	-	-	-	rt	5	0
2	1.0	-	-	rt	5	25
3	1.0	-	-	rt	10	32
4	1.0	-	-	40	5	42
5	1.0	-	-	60	5	34
6	1.0	NaOH (1.0)	-	rt	5	46
7	1.0	Na_2CO_3 (1.0)	-	rt	5	58
8	1.0	K_2CO_3 (1.0)	-	rt	5	63
9	1.0	K_2CO_3 (1.0)	-	rt	10	67
10	1.0	K_2CO_3 (1.2)	-	rt	10	67
11	1.2	K_2CO_3 (1.0)	-	rt	10	73
12	1.2	K_2CO_3 (1.0)	TBAB (1.0)	rt	10	84
13	1.2	K_2CO_3 (1.0)	TBAI (1.0)	rt	10	94
14	1.2	K_2CO_3 (1.0)	TBAI (1.0)	rt	5	94
15	**1.2**	**K_2CO_3 (1.0)**	**TBAI (0.4)**	**rt**	**5**	**94**
16	1.2	K_2CO_3 (1.0)	TBAI (0.3)	rt	5	88
17	1.2	K_2CO_3 (1.0)	TBAI (0.3)	rt	10	89

[a] Reaction conditions: a mixture of **1a** (1.0 mmol), **2a** (0.5 mmol), I_2, base and PTC was vigorously stirred in H_2O (8 mL deionized water) at the given temperature. [b] Isolated yield based on **1a**.

The results clearly demonstrated that the employment of a base and a PTC can obviously facilitate this aqueous reaction, in which K_2CO_3 as the base and tetrabutylammonium iodide (TBAI) as the PTC

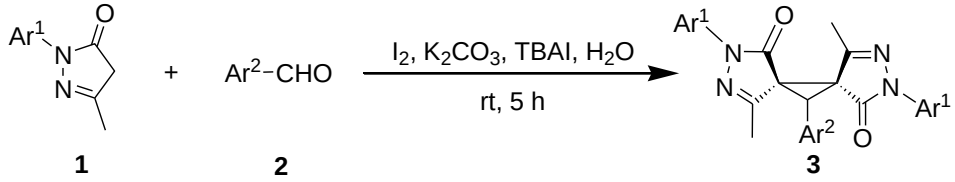
exhibited the best efficiency. As to the usage amount of I_2, 20 mol% of excess is necessary to ensure a full completion of the reaction. Interestingly and excitingly, the reaction achieved the best chemoselectivity at room temperature, and side reactions occurred under higher temperature. For example, when the reaction was carried out at 40 or 60 ^oC for 5 hours, TLC analysis on the reaction mixture showed several obvious byproducts, though the reactants were almost completely consumed. Therefore, the product **3a** had to be isolated by conventional column chromatography in only 42% (Entry 4) and 34% (Entry 5) yield, respectively. The usage amount of TBAI was further optimized to 0.4 equivalent. After comprehensive analysis and judgment of these results, the optimal reaction conditions for the I_2-promoted aqueous synthesis of bis(spiropyrazolone)cyclopropane **3a** from **1a** and **2a** are: I_2 (1.2 equiv.), K_2CO_3 (1.0 equiv.), TBAI (0.4 equiv.), at room temperature for 5 hours (Entry 15, Table 1). Under the conditions, **3a** was synthesized in almost quantitative isolated yield (94%), which was obtained just by simple Büchner filtration without chromatographic isolation procedure.

Using the optimal condition for synthesis of **3a** as the standard conditions, various substituted pyrazolin-5-ones and aldehydes were employed, and a series of bis(spiropyrazolone)cyclopropanes were obtained in good to excellent yields. The results are outlined in Table 2.

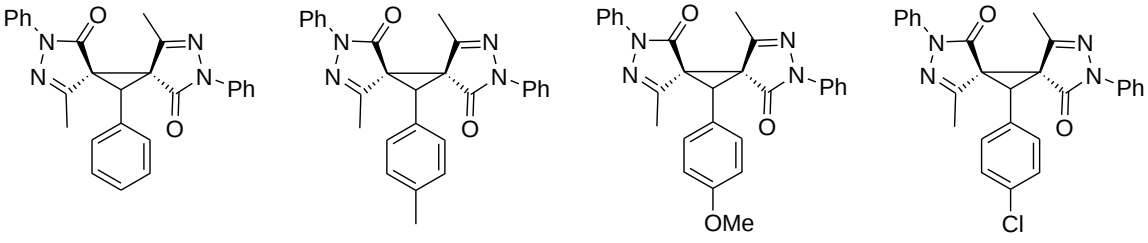
From Table 2, it can be seen that benzaldehydes bearing either electron-donating or -withdrawing groups could afford efficiently the corresponding products. In contrast, electron-withdrawing groups exhibited higher efficiency than electron-donating groups. The reactions with bulky aldehydes such as *ortho*-substituted benzaldehydes and naphthyl aldehyde bring about the slight decrease in the yield. When the Ar^2 group was changed into another aromatic group such as naphthyl, the corresponding product **3q** was also obtained in a moderate 76% yield. To further extend the scope of substrates, some aliphatic aldehydes were attempted. Unfortunately, the corresponding reactions didn't work well, thus the desired products were not obtained by this method. As to the substrates of pyrazolin-5-ones **1**, only those with Ar^1 as phenyl and tolyl groups were performed, because pyrazolin-5-ones with Ar^1 as other substituents and especially aliphatic groups were not available and can hardly be prepared using conventional methods. It should be noted that all the obtained products **3** adopt as (*R**,*R**)-diastereomers on the basis of NMR spectra and previous relevant literatures,[19,20] exhibiting an exclusive diastereoselectivity of the present reaction.

To inspect the practicability of this method in organic synthesis, we further amplified the reaction to a gram-scale taking the synthesis of **3a** as an example. Satisfactorily, the reaction still delivered **3a** in a comparable 95% yield even if it was scaled up to five times (5 mmol), only that the reaction time needed to be extended to 10 hours (Scheme 2). This result demonstrated that the present protocol could be feasibly adopted for large-scale synthesis of (*R**,*R**)-bis(spiropyrazolone)cyclopropanes.

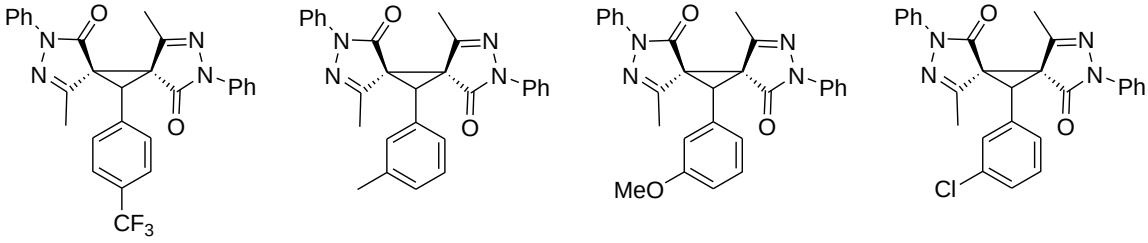
Table 2. Iodine-promoted synthesis of (*R**,*R**)-bis(spiropyrazolone)cyclopropanes **3** in water[a,b]



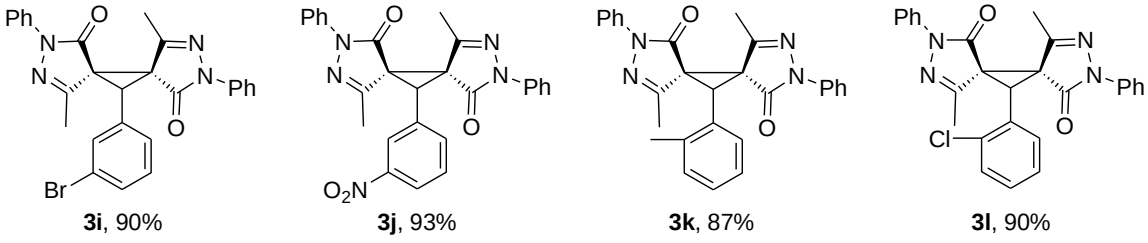
1 **2** **3**



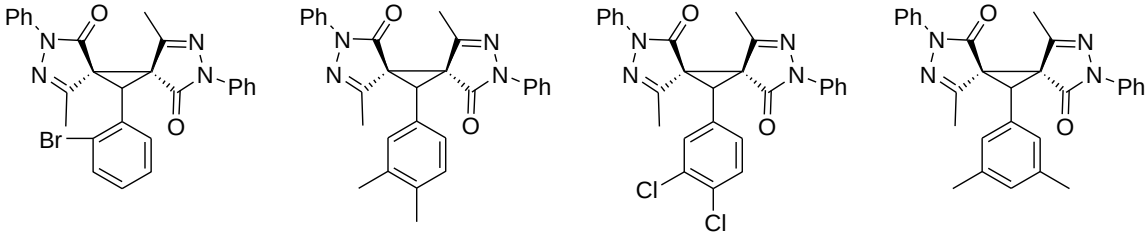
3a, 94% **3b**, 90% **3c**, 87% **3d**, 96%



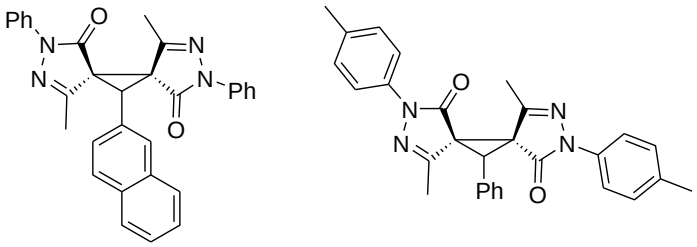
3e, 95% **3f**, 88% **3g**, 86% **3h**, 92%



3i, 90% **3j**, 93% **3k**, 87% **3l**, 90%

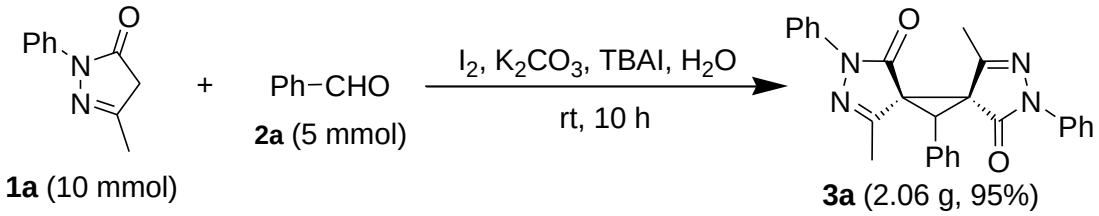


3m, 89% **3n**, 86% **3o**, 94% **3p**, 91%



3q, 76% **3r**, 89%

[a] Reaction conditions: a mixture of **1** (1.0 mmol), **2** (0.5 mmol), I_2 (152.3 mg, 0.6 mmol), K_2CO_3 (69.0 mg, 0.5 mmol) and TBAI (73.8 mg, 0.2 mmol) was vigorously stirred in H_2O (8 mL deionized water) at room temperature for 5 h. [b] Isolated yields based on **1**.



Scheme 2. Gram-scale synthesis of **3a**

In conclusion, we have explored and found that a variety of substituted bis(spiropyrazolone)-cyclopropanes could be efficiently synthesized from benzaldehydes and pyrazolin-5-ones in good to excellent yields using molecular iodine as the promoter in aqueous media. The use of water as reaction media, mild reaction conditions, high yields, and the facile separation of the products by simple Büchner filtration make this protocol convenient, effective and environmentally friendly for the synthesis of bis(spiropyrazolone)cyclopropane derivatives.

EXPERIMENTAL

All reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded on a 500 MHz NMR spectrometer (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR). ^{1}H NMR chemical shifts were determined relative to internal TMS at δ 0.0 ppm. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ at δ 77.16 ppm. Data for ^{1}H NMR and ^{13}C NMR are reported as follows: chemical shift (δ, ppm) and multiplicity (s = singlet, d = doublet, t = triplet and m = multiplet). All melting points were determined on a XT-4 binocular microscope melting point apparatus. High-resolution mass spectra (HRMS) were measured with ESI-TOF in the positive mode.

Starting Materials. All chemicals used in this study were commercially available.

Typical Procedure for the Preparation of Products 3. (5*R, 6*R**)-11-(4-Chlorophenyl)-4,10-dimethyl-2,8-diphenyl-2,3,8,9-tetraazadispiro[4.0.4.1]undeca-3,9-diene-1,7-dione (3d).** Light yellow solid, 96% yield, mp 143–144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H), 7.44 (t, J = 7.9 Hz, 2H), 7.40 (t, J = 8.2 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.26–7.19 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H), 4.37 (s, 1H), 2.52 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.6, 165.5, 155.9, 154.9, 137.84, 137.77, 134.9, 131.4 (2C), 129.14 (2C), 129.07 (2C), 129.0 (2C), 126.7, 125.8, 125.7, 119.09 (2C), 119.07 (2C), 51.2, 50.1, 42.3, 20.4, 18.5; HRMS (ESI-TOF) calcd for $C_{27}H_{22}{}^{35}ClN_4O_2$ $[M + H]^+$ 469.1431, found 469.1440.

Characterization data of other synthesized bis(spiropyrazolone)cyclopropanes and copies of NMR spectra for all products are available in the Supporting Information.

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