



Reactions of 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes with C,N-diarylnitrones and nitrile oxides

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ARTICLE INFO

Article history:

Received 20 January 2012

Revised 12 March 2012

Accepted 22 March 2012

Available online 29 March 2012

Keywords:

2-Isopropylidene-3-methylenecyclopropanes

Nitrones

Nitrile oxides

3-Methylenepiperidin-4-ones

2,3-Dihydro-3-methylenepyridin-4(1H)-ones, 1,3-dipolar cycloaddition

ABSTRACT

The reactions of unactivated bis(methylene)cyclopropanes with nitrones and nitrile oxides have been investigated. The 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes react with the C,N-diarylnitrones to give a mixture of 2,2-dimethyl-1,6-diaryl-3-(diarylmethylene)piperidin-4-ones and 5-methyl-1-aryl-1-(arylamino)-4-(diarylmethylene)hex-5-en-3-ones. 2,3-Dihydro-3-methylenepyridin-4(1H)-ones are obtained by reaction of 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes with nitrile oxides.

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1,3-Dipolar cycloaddition reactions have long been recognized as important for the synthesis of heterocyclic rings.¹ Nitrones and nitrile oxides are remarkably versatile building blocks in organic synthesis, and are known to take part in 1,3-dipolar cycloaddition reactions with a wide range of dipolarophiles. Cycloadditions of nitrones and nitrile oxides to alkenes are well established reactions in which isoxazolidines and isoxazolines are formed, often with a high degree of stereochemical control.² These cycloadditions have attracted considerable attention due to the potential biological activities of isoxazolines and isoxazolidines.^{1a,b} Isoxazolidines and isoxazolines have also been used as precursors to γ -amino alcohols through the reductive cleavage of the N–O bond, and are potential precursors for the synthesis of natural products such as alkaloids and β -lactam antibiotics.^{2a} The groups of Brandi and de Meijere have systematically studied 1,3-dipolar cycloaddition reactions of methylenecyclopropanes with nitrones and nitrile oxides that afford the exocyclic [3+2] adducts in good yields.^{3,4} Rearrangements of 5-spirocyclopropaneisoxazolines and 5-spirocyclopropaneisoxazolidines have shown potential for the synthesis of functionalized pyridones (Brandi–Guarna reaction)⁵ which are precursors for the synthesis of natural alkaloids.⁶ Recently, Wang

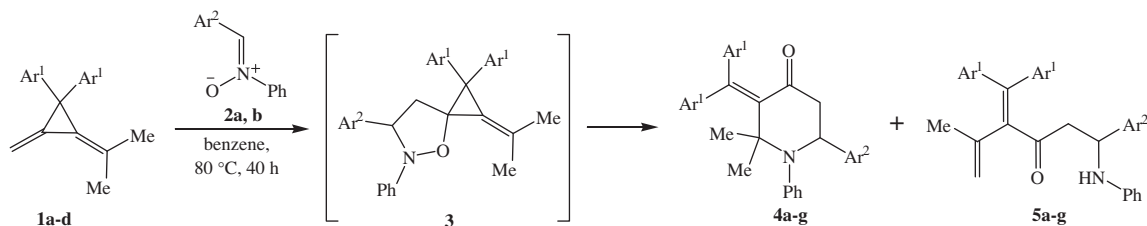
reported the first example of the Yb(OTf)₃-catalyzed formal [3+3] cycloadditions of methylenecyclopropane-dicarboxylates with C,N-diarylnitrones with the formation of substituted 1,2-oxazines in good yields.⁷ The chemistry of methylenecyclopropanes has been explored extensively. Novel intramolecular rearrangements and also cycloaddition reactions with compounds containing carbon–carbon or carbon–heteroatom multiple bonds, such as imines, aldehydes, ketones, and α,β -unsaturated ketones and aldehydes, have been studied.^{2b,d,8} However, reactions of bis(methylene)cyclopropanes with nitrones and nitrile oxides have not been studied. In continuation of our earlier work,⁹ we have studied the reactions of non-activated bis(methylene)cyclopropanes with nitrones and nitrile oxides. The choice of bis(methylene)cyclopropanes **1** as dipolarophiles in this process appeared particularly interesting in order to expand the synthetic utility of this methodology.

The starting 1,1-diaryl-2-isopropylidene-3-methylenecyclopropanes **1a–d** are easily accessible via thermolysis of the corresponding 1-(2-methylpropenylidene)-2,2-diarylcyclopropanes.¹⁰ In earlier studies we investigated the reaction of the C,N-diarylnitron **2a** with bis(methylene)cyclopropane **1a**. Heating of **1a** and nitron **2a** (1.5 equiv) in benzene (80 °C, 40 h) led to a mixture of compounds **4a** and **5a** in 13% and 18% yields, respectively (Table 1, entry 1). 5-spiroisoxazolidine **3** could not be isolated because

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Table 1
Reactions of bis(methylene)cyclopropanes **1a–d** with nitrones **2a–c**



Entry	Ar ¹	Ar ²	Yield of 4 ^a (%)	Yield of 5 ^a (%)
1 ^b	Ph (1a)	Ph (2a)	13 (4a)	18 (5a)
2 ^c	Ph (1a)	4-ClC ₆ H ₄ (2b)	17 (4b)	27 (5b)
3 ^d	4-MeC ₆ H ₄ (1b)	Ph (2a)	16 (4c)	13 (5c)
4 ^e	4-MeC ₆ H ₄ (1b)	4-ClC ₆ H ₄ (2b)	19 (4d)	18 (5d)
5 ^f	4-ClC ₆ H ₄ (1c)	4-ClC ₆ H ₄ (2b)	11 (4e)	19 (5e)
6 ^g	4-MeOC ₆ H ₄ (1d)	Ph (2a)	6 (4f) ^h	43 (5f)
7 ⁱ	4-MeOC ₆ H ₄ (1d)	4-ClC ₆ H ₄ (2b)	8 (4g) ^j	41 (5g)
8 ^k	Ph (1a)	CONHPh (2c)	—	—

^a Isolated yield.

^b 21% of starting material **1a** was recovered.

^c 19% of starting material **1a** was recovered.

^d 23% of starting material **1b** was recovered.

^e 21% of starting material **1b** was recovered.

^f 24% of starting material **1c** was recovered.

^g 19% of starting material **1d** was recovered.

^h Spectral yield.

ⁱ 22% of starting material **1d** was recovered.

^j Spectral yield.

^k Mixture of unidentified products.

rearrangement occurs smoothly under the reaction conditions to give the products **4a** and **5a**. In the ¹H NMR spectrum of the crude reaction mixture the signals due to proposed intermediate **3** were not found. The reaction products were isolated by preparative thin layer chromatography on silica. The compositions and structures of the products were established by elemental and spectral analyses.¹¹ The structures of compounds **4a** and **5a** were confirmed by X-ray diffraction analysis (Figs. 1 and 2).^{12,13} Running the reaction in benzene at 20 °C for 56 h did not lead to the formation of **4** and **5**. The ¹H NMR spectra of the crude reaction mixture contained only signals due to the starting bis(methylene)cyclopropane and nitrone. A similar reaction occurred on the treatment of bis(meth-

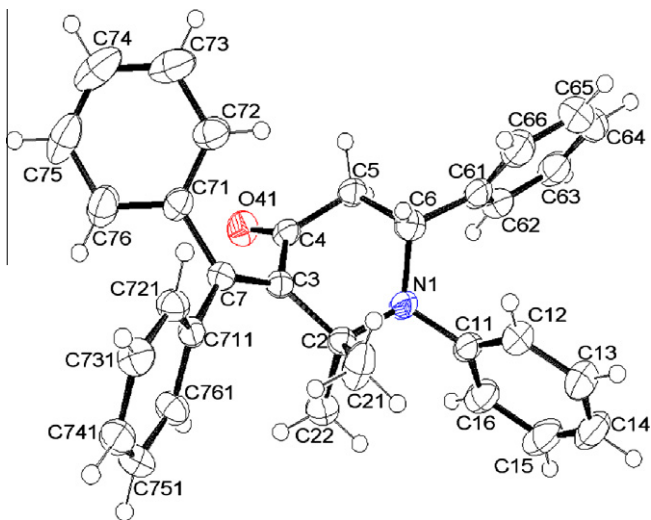


Figure 1. ORTEP representation of **4a**.

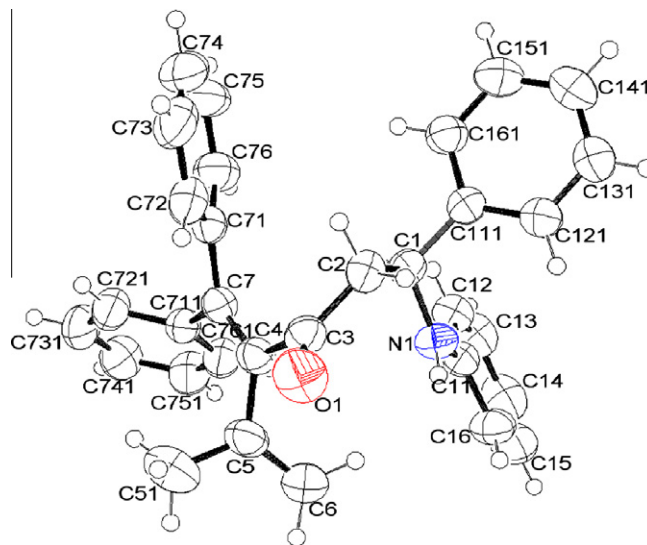


Figure 2. ORTEP representation of **5a**.

ylene)cyclopropane **1a** with nitrone **2b** to give a mixture of compounds **4b** and **5b** in 17% and 27% yields, respectively (Table 1, entry 2). The reactions of bis(methylene)cyclopropanes **1b,c** and nitrones **2a,b** proceed in an analogous manner: mixtures of bis(methylene)cyclopropanes **1b** and **1c**, respectively, and nitrones **2a** or **2b** in benzene afforded, on heating (80 °C, 40 h), mixtures of the corresponding products **4** and **5** (Table 1, entries 3–5). Moreover, increasing the electron density of the aryl functionalities in bis(methylene)cyclopropane **1d** by introducing two electron-donating methoxy groups led to the formation of ketones **5f** and **5g** (41–43%) as the major products (Table 1, entries 6 and 7). Sig-

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