



[3+2]-Cycloaddition reactions of 2-phenyliodonio-5,5-dimethyl-1,3-dioxacyclohexanemethylide

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Abstract

Iodonium ylide **2**, derived from dimedone, undergoes thermal [3+2]-cycloaddition with acetylenes and nitriles with $\text{Rh}_2(\text{OAc})_4$ to form the corresponding furans and oxazoles, respectively. Photochemically **2** reacts with various alkenes to form *E*-dihydrofuran derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

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The transition-metal catalyzed decomposition of diazo compounds has tremendous potential in organic synthesis.¹ The in situ formation of metallo carbenoids and the transfer of the carbene moiety to a suitable acceptor has found widespread application in the total synthesis of natural products. However, a major drawback of this methodology is the use of diazo compounds, which are potentially explosive, toxic, and/or carcinogenic.

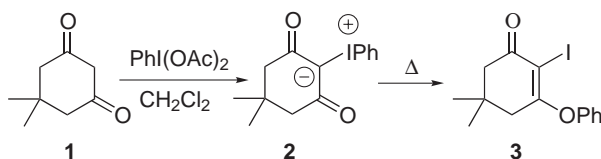
Alternatively, iodonium ylides² have been recognized as synthetic equivalents of the corresponding diazo compounds without major drawbacks, except for the fact that an active methylene compound is required for their facile preparation.³ The photochemical and/or metal-catalyzed decomposition of these stable iodonium ylides affords⁴ products typical of carbenoid reactions, although the involvement of carbenes (or carbenoids) in these reactions has been questioned.⁵

Following our studies directed towards the development of new synthetic applications of iodonium ylides,^{3b,5f,6} we thought that substituted furans and oxazoles could be easily obtained from the reaction of a β -dicarbonyl iodonium ylide with alkynes and nitriles. In fact, the isolation of an oxazole from the reaction of 2-phenyliodonio-5,5-dimethyl-1,3-dioxacyclohexanemethylide and acetonitrile has been reported.^{6b} However, this thermal Cu-catalyzed cyclization was later questioned.^{5c} Thus, we reasoned that we had to re-examine this useful reaction

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and undertake a more systematic investigation. Indeed, we now wish to report the preliminary results of the synthesis of furans, oxazoles and dihydrofurans by the reaction of iodonium ylide **2** with alkynes, nitriles, and alkenes.

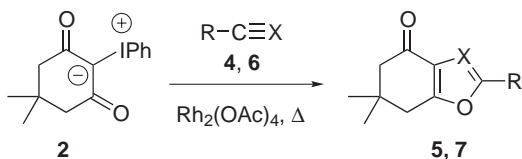
Iodonium ylide **2** had been prepared in 95% yield from the reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1**) and diacetoxyiodobenzene (Scheme 1) employing Koser's method.⁷



Scheme 1.

Although iodonium ylide **2** is stable at -30°C for a prolonged period of time, it isomerized into iodo ether **3** upon heating in various solvents.^{2a,8} This iodo ether is the major product in all the non-catalyzed thermal reactions or a minor by-product of all the thermal Cu- and Rh-catalyzed reactions of iodonium ylide **2**.

Without solvent and an inert atmosphere, heating at reflux, a suspension of iodonium ylide **2**, alkyne **4a**, and catalytic amounts of $\text{Rh}_2(\text{OAc})_4$ for 15 min afforded,⁹ after the usual work-up, furan **5a** in 47% yield (Scheme 2). The reaction was extended to a variety of other terminal alkynes **4b–d** as well as nitriles **6a–e**, affording the corresponding furans **5** and oxazoles **7** in moderate yields (Table 1).



Scheme 2.

The employment of $\text{Cu}(\text{AcAc})_2$ as a catalyst leads to lower yields of the desired product and to greater amounts of the iodoether; when the reactions with alkynes were repeated photochemically much lower yields of the desired products were isolated from complex reaction mixtures.¹⁰

It is noteworthy that the cycloaddition proceeds without the use of an inert atmosphere. The reaction also exhibits high regioselectivity. The oxygen atom of the iodonium ylide added exclusively onto the more substituted carbon atom of the triple bond, i.e. terminal acetylenes, afforded 2-substituted furans exclusively, the other possible regioisomer was not detected at all.

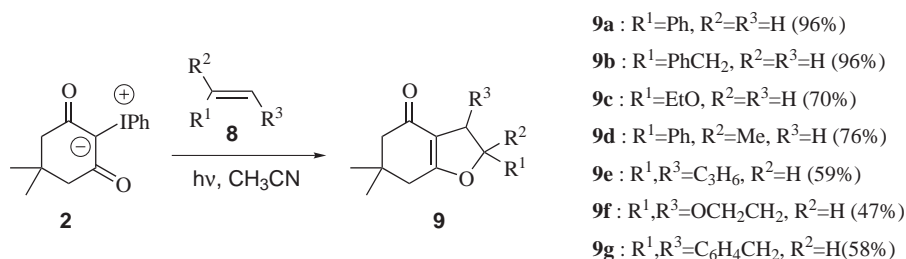
It is clear from the results listed above that variation in the reaction conditions have a profound influence on the product distribution. The best yields (thermally) that we have achieved so far have come from the treatment of iodonium ylide with an Rh-catalyst. Bearing this in mind, we turned our attention to the cycloaddition reaction with alkenes. Although the $\text{Rh}_2(\text{OAc})_4$ catalyst, as well as PdCl_2 , works better than $\text{Cu}(\text{AcAc})_2$ or $\text{Hg}(\text{OAc})_2$, the photochemical conditions (400 W medium pressure Hg lamp) in CH_3CN were superior. The irradiation of a suspension of iodonium ylide **2** and styrene (excess) **8a** in CH_3CN leads to the isolation of dihydrofuran **9a** in 96% yield, while the corresponding Rh-catalyzed thermal reaction yields **9a** in 75% yield only (Scheme 3).

Table 1
Thermal (Rh-catalyzed) reactions^a of iodonium ylide **2**

a/a	Substrate	Substituents		Reaction conditions		Product	Yield (%) ^b
		R	X	Temp. (°C)	Time (min)		
1	4a	CH ₃ OCH ₂	CH	Reflux	15	5a	47
2	4b	CH ₃ CH ₂ CH ₂	CH	Reflux	17	5b	57
3	4c	(CH ₃) ₃ Si	CH	Reflux	20	5c	48
4	4d	C ₆ H ₅	CH	110	3	5d	51
5	6a	CH ₃	N	Reflux	60	7a	68
6	6b	ClCH ₂	N	90–100	30	7b	41
7	6c	C ₆ H ₅ CH ₂	N	90	30	7c	23
8	6d	C ₆ H ₅	N	90–100	30	7d	28
9	6e	<i>p</i> -CH ₃ C ₆ H ₄	N	80–90	30	7e	42

^a All reactions were performed by heating a mixture of iodonium ylide (2.05 mmol), alkyne (excess) or nitrile (excess) and catalytic amount of Rh₂(OAc)₄ at the given temperature for the required time.

^b Isolated yield.



Scheme 3.

Other acyclic as well as cyclic alkenes **8** were found to undergo photochemical cycloaddition in moderate to excellent yields. This cycloaddition reaction also exhibits high regio- and diastereoselectivity, leading to the isolation of one isomer. The oxygen atom of the iodonium ylide added exclusively onto the more substituted carbon of the terminal olefins, i.e. leading to 2-substituted dihydrofurans. The stereochemistry of the double bond was not preserved within the cycloaddition since the stereochemistry of the dihydrofurans **9** was clearly assigned as *E* based upon the absence of signals between the bridged-protons in the ROESY spectrum, i.e. for dihydrofuran **9g** (Fig. 1).

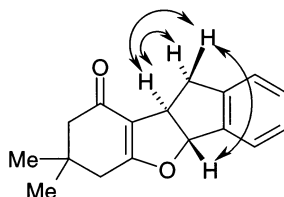


Figure 1. Key ROESY interactions of compound **9g**

Although the exact mechanism of the cycloaddition reaction is still not clear, some points need to be mentioned. (1) The direct formation of the dihydrofuran is suggested since isomerization¹¹ of an initially formed cyclopropane to a dihydrofuran is less likely. (2) The stereochemical outcome suggests a mechanism involving a freely rotating intermediate. A concerted mechanism seems to be ruled out.

In conclusion, thermal metal-catalyzed or photochemical cycloaddition of iodonium ylide to terminal acetylenes, nitriles, and alkenes offers a simple and new strategy for the synthesis of substituted furans, oxazoles, and dihydrofurans. We are currently examining the optimization and application of the methodology described herein towards the total synthesis of natural products.

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- Representative experimental procedure. Synthesis of 5d.** A mixture of iodonium ylide (0.7 g, 2.05 mmol), phenylacetylene (1.0 g, 9.80 mmol) and catalytic amounts of $\text{Rh}_2(\text{OAc})_4$ was heated at 110°C for 3 min. The reaction mixture was subjected to column chromatography (silica gel, $\text{CH}_2\text{Cl}_2 \rightarrow \text{CH}_2\text{Cl}_2/\text{EtOAc}$ 4:1) to afford

- furan **5d**¹⁰ (0.25 g, 47% yield), yellowish crystals: mp 102–103°C (CHCl₃/petroleum ether); IR (KBr) ν 3120, 3040, 3020, 2940, 2910, 2850, 1660, 1610, 1550, 1480, 1445, 1430, 1400, 1360, 1330, 1210, 1155, 1130, 1120, 1040, 1005, 970, 920, 900, 790, 750, 685, 650, 620 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.16 (s, 6H), 2.39 (s, 2H), 2.81 (s, 2H), 6.88 (s, 1H), 7.26–7.42 (m, 3H), 7.63–7.66 (m, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 28.5, 35.2, 37.3, 51.9, 100.6, 121.5, 123.7, 127.9, 128.7, 129.7, 154.4, 165.7, 193.8. **Synthesis of 7a.** A suspension of iodonium ylide (0.7 g, 2.05 mmol), catalytic amounts of Rh₂(OAc)₄ in acetonitrile (10 mL) was refluxed for 60 min. The solvent was removed, and the crude product was purified by column chromatography (silica gel, CH₂Cl₂→CH₂Cl₂/EtOAc 3:1) to afford oxazole **7a** (0.25 g, 68% yield), white crystals: mp 76–77°C (petroleum ether); IR (neat) ν , 2960, 2930, 2870, 1690, 1615, 1590, 1400, 1370, 1340, 1305, 1250, 1205, 1180, 1120, 1050, 1020, 975, 920, 900, 890, 805, 795, 690 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 1.11 (s, 6H), 2.37 (s, 2H), 2.43 (s, 3H), 2.73 (s, 2H); ¹³C NMR (63 MHz, CDCl₃) δ 13.9, 28.5, 35.4, 35.9, 51.5, 133.2, 161.8, 163.1, 190.7; MS m/z 179 (43, M⁺), 164(16), 123(100), 95(44), 43(64); anal. calcd for C₁₀H₁₃NO₂: C, 60.72; H, 7.31; N, 7.82. Found: C, 60.60; H, 7.25; N, 7.70.
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