

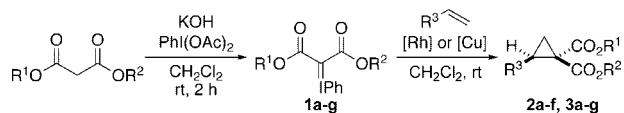
General Method for the Synthesis of Phenyliodonium Ylides from Malonate Esters: Easy Access to 1,1-Cyclopropane Diesters

Sébastien R. Goudreau, David Marcoux, and
André B. Charette*

Département de chimie, Université de Montréal,
P.O. Box 6128, Station Downtown, Montréal,
Québec, Canada H3C 3J7

andre.charette@umontreal.ca

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A general method to access phenyliodonium ylides from malonates has been developed. These ylides provide easy access to a variety of useful 1,1-cyclopropane diesters using rhodium or copper catalysis. Moreover, the iodonium ylide of dimethyl malonate was obtained in 78% yield using improved conditions that involve a simple filtration step to isolate the desired product. This ylide was shown to be a safer and convenient alternative to the corresponding diazo compound and a very efficient way to 1,1-cyclopropane diesters when used with a catalytic amount of $\text{Rh}_2(\text{esp})_2$.

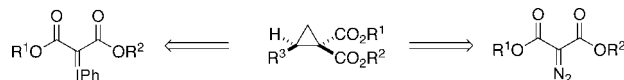
The cyclopropane moiety is found in many molecules of biological and pharmaceutical interest. Their reactivity also allows cyclopropanes to be versatile intermediates in the synthesis of complex molecules. In this regard, activated cyclopropanes represent an important class of synthons acting as electrophiles^{1,2} or can be involved in cycloaddition reactions.³ The most straightforward and convergent approach to these cyclopropanes remains the reaction of olefins with metal carbenes, which come from the decomposition of diazo compounds or iodonium ylides (Scheme 1).^{4,5} In the case of the synthesis of 1,1-cyclopropane diesters, the decomposition of diazomaltonates is well-known and has been proven to be

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SCHEME 1. Synthesis of 1,1-Cyclopropane Diesters



efficient.⁶ However, diazomaltonates display low reactivity and, at ambient temperature, only rhodium dimers can be used for their decomposition.⁵¹

Recently, the employment of iodonium ylides in this chemistry has shown interesting complementary reactivity to that of diazo compounds.⁵ Indeed, the higher reactivity of iodonium ylides versus diazo compounds has allowed cyclopropanation reactions to be performed under milder conditions, leading to the development of more enantioselective methods.^{5a,d,f-h} This strategy was also used in our group for the synthesis of nitrocyclopropylesters.^{5b} However, the main challenge associated with iodonium ylides derived from malonates is their low stability. Consequently, very few have been efficiently isolated.^{5g,h,i,m,o,p,7,8} To overcome this problem, the in situ generation of iodonium ylides has been used. Although this can be an effective alternative, higher catalyst loading and lower yields were observed in cyclopropanation reactions using dimethyl malonate (vide infra). The basic oxidative conditions required to generate the ylide in situ are relatively harsh and sometimes not compatible with the cyclopropanation catalyst. Therefore, in many successful reactions where iodonium ylides have been used, the iodonium ylide was preformed and isolated.^{5k,p,7,9}

Our efforts to develop an enantioselective cyclopropanation reaction to form 1,1-cyclopropane diesters with copper catalysis led to the observation that the use of preformed iodonium ylides was necessary to achieve good conversions. Quite surprisingly,

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SCHEME 2. Attempted Synthesis of the Iodonium Ylides from Malonate Esters Using Previously Reported Conditions

TABLE 1. Optimization of the Synthesis of the Iodonium Ylide from Diisopropyl Malonate

entry	base	solvent	diisopropyl malonate (equiv)	yield (%) ^{a,b}	workup ^c
1	KOH	MeCN	1.0	0	A
2	KOH	CH ₂ Cl ₂	1.0	40	A
3	KOH	CH ₂ Cl ₂	1.0	54	B
4	KOH	CH ₂ Cl ₂	1.2	76 ^d	B
5	KOH	MeCN	1.2	64	B
6	KOH	Et ₂ O	1.2	35	B
7	KOH	hexane	1.2	37	B
8	NaOH	CH ₂ Cl ₂	1.2	55	B
9	MgO	CH ₂ Cl ₂	1.2	7	B
10 ^e	KOH	CH ₂ Cl ₂	1.2	63	B
11 ^f	KOH	CH ₂ Cl ₂	1.2	72	B

^a Average of two experiments. ^b Unless otherwise stated, yields were determined by ¹H NMR with an internal standard. ^c Workup A: Extraction in DCM. Workup B: Filtration on cotton plug. ^d Isolated yield. ^e PhI=O was used instead of PhI(OAc)₂. ^f Performed at 0 °C.

only the iodonium ylide of dimethyl malonate was accessible using known methods.^{5,7} Indeed, treating diethyl, diisopropyl, and di-*tert*-butyl malonates under the standard conditions to form the corresponding iodonium ylide did not yield to any of the desired products (Scheme 2).

Herein, we report a general method to access phenyliodonium ylides from malonate esters, an improved synthesis of the phenyliodonium ylide from dimethyl malonate, and their application in cyclopropanation reactions.

We chose to optimize the reaction conditions using diisopropyl malonate due to its low cost and its bulkier ester groups relative to most other malonates. On the basis of literature precedent,⁵¹ the first set of conditions that were tested involved treating diisopropyl malonate with iodobenzene diacetate and KOH in acetonitrile (Table 1, entry 1). Unfortunately, the desired product could not be isolated. We suspected that, although the desired product was formed, decomposition occurred while concentrating the reaction mixture under reduced pressure at relatively high temperatures (> 40 °C). Gratifyingly, changing the solvent to dichloromethane led to the isolation of the desired product albeit in modest yields. We also observed that the ylide decomposed in the presence of water, so we predicted that higher yields could be obtained if the aqueous workup was omitted. Indeed, filtering the reaction mixture on a cotton plug to remove all the salts' byproduct followed by concentration of the filtrate cleanly gave a 54% yield of the desired ylide (entry 3). The amount of malonate was optimized, and reproducible yields were obtained with 1.2 equiv (entry 4).

Many solvents were screened, but few were compatible with the reaction conditions (entries 4–7). Dichloromethane remained the optimal choice since the salts formed during the reaction precipitated nicely, and its low boiling point makes removal of

TABLE 2. Synthesis of Iodonium Ylides from Malonate Esters

entry	R ¹	R ²	product	yield (%) ^a
1	i-Pr	i-Pr	1a	76
2	Et	Et	1b	38
3	<i>t</i> -Bu	<i>t</i> -Bu	1c	75
4	Bn	Bn	1d	53 ^b
5	Et	<i>t</i> -Bu	1e	73
6	Me	Me	1f	25 ^c
7			1g	70

^a Isolated yields. ^b Unable to isolate analytically pure ylide: yield determined by ¹H NMR. ^c The product was partially soluble in CH₂Cl₂.

the solvent easier under reduced pressure at low temperature.¹⁰ When *t*-BuOK, Al₂O₃, or K₂CO₃ were used, <20% yields were obtained. Surprisingly MgO gave only 7% (entry 9) even though it is known to increase the yield of cyclopropanation reactions where the iodonium ylide of dimethyl malonate is generated in situ.^{5f} The use of NaOH as the base (entry 8) or iodobenzene as the oxidant (entry 10) did not improve the yield. By optimizing the temperature, we found that similar yields were obtained if the reaction was carried out at 0 °C (entry 11). Investigation of the reaction time revealed that 2 h was optimal.

Although the crude ylide was contaminated with small amounts of iodobenzene and malonate dimer, it could be used directly in the cyclopropanation reaction. Alternatively, it could be kept at –20 °C for a week without significant decomposition.¹¹ However, significant decomposition was observed within 1 h when it was kept at room temperature.

The optimized conditions were used to synthesize iodonium ylides derived from other malonate esters. The method proved to be efficient, providing the desired ylides in moderate to good yields (Table 2). The ylides, except the one derived from dibenzyl malonate, were obtained as pure white solids after recrystallization or trituration.¹² In pure form, these ylides decomposed only slowly at room temperature and they could be kept for several weeks at –20 °C.¹³ Surprisingly, a modest 25% yield was obtained with dimethyl malonate (entry 6).¹⁴ Since the ylide **1f** partially precipitated under the optimized reaction conditions, we envisaged that we could improve the preparation of this reagent by isolating the product by filtration rather than by concentration of the filtrate. Gratifyingly, the addition of water to the reaction mixture to dissolve the salts' byproduct followed by filtration led to the desired iodonium ylide in 40% yield (Table 3, entry 1). A further optimization of the base, the reaction temperature, and the solvent led to the

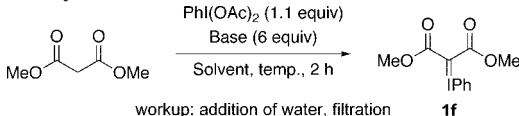
(10) Concentration at higher temperature gave significantly lower yields.

(11) Since these side products are generally formed in the subsequent reaction, they do not interfere in the cyclopropanation reaction. Indeed, no significant difference in the yields were observed in cyclopropanation when the crude ylide was used.

(12) See Supporting Information.

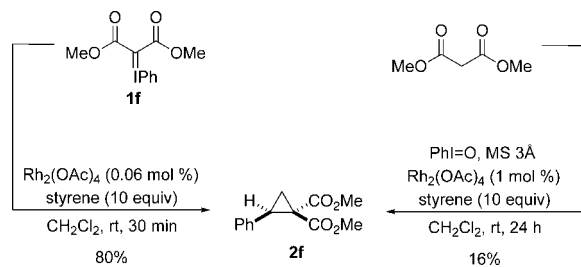
(13) The iodonium ylide of the Meldrum's acid is an exception since it is stable at room temperature for many weeks.

(14) Müller and Hadjarapoglou have reported the synthesis of this iodonium ylide in 56 and 61% yield respectively (see refs 5f and 5o).

TABLE 3. Optimization of the Synthesis of the Iodonium Ylide from Dimethyl Malonate


entry	base	solvent	temp	yield (%) ^a
1	KOH	CH ₂ Cl ₂	rt	40
2	KOH	MeOH	rt	0
3	KOH	Et ₂ O	rt	67
4	KOH	MeCN	rt	75
5	KOH	MeCN	0 °C	78
6	NaOH	MeCN	rt	56
7 ^b	KOH	MeCN	rt	68
8 ^{b,c}	KOH	MeCN	rt	58
9 ^d	KOH	MeCN	rt	54

^a Isolated yield (average of two experiments). ^b 1.0 equiv of PhI(OAc)₂ was used. ^c 2.0 equiv of malonate. ^d PhI=O was used instead of PhI(OAc)₂.

SCHEME 3. Preparation of 2f from Dimethyl Malonate: In Situ Method versus Isolated Reagent 1f

optimal use of KOH in acetonitrile at 0 °C. Under these conditions, a satisfying 78% yield of iodonium ylide **1f** was obtained (Table 3, entry 5). A similar yield was observed when the reaction was carried out on a 60 mmol scale.

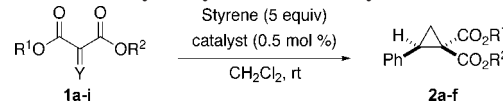
It is important to note that having an easy access to the iodonium ylides from malonate esters can facilitate the preparation of 1,1-cyclopropane diesters and improve the overall yields from malonate esters. For example, the synthesis of **2f** from styrene using the in situ formation of the ylide gave 16% yield¹⁵ with 1 mol % of rhodium acetate dimer (Scheme 3). The same reaction using the preformed ylide gave 80% yield with only 0.06 mol % of the same catalyst. Moreover, a large quantity of molecular sieves is needed for the in situ reaction, which makes this procedure not very convenient on a larger scale.

In order to demonstrate the utility of the iodonium ylides from malonate esters, we tested them in cyclopropanation reactions with styrene using various catalysts and compared the reactions with those using the related diazo reagents (Table 4). As expected, the iodonium ylides were more reactive than the corresponding diazo reagents. This higher reactivity allows the use of lesser reactive copper-based catalysts in these reactions. This advantage is illustrated with the use of diazodiisopropyl malonate (entries 5–8). When Rh₂(OAc)₄ was employed as the catalyst, mainly C–H insertion to form β-lactone was observed,¹⁶ while CuOTf¹⁷ was not able to degrade the diazo compound. However, when the iodonium ylide was used, 61% yield of the corresponding cyclopropane was obtained using CuOTf (entry 8).

(15) Five percent yield was obtained when MgO was added.

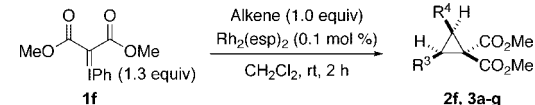
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(17) (CuOTf)₂·C₆H₆ complex was used.

TABLE 4. Cyclopropanation of Styrene with Iodonium Ylides vs Diazomalones Catalyzed by Rh or Cu Catalysts


entry	R ¹	R ²	Y	catalyst ^a	product	yield (%) ^b
1	Me	Me	N ₂	Rh ₂ (OAc) ₄	2f	39
2	Me	Me	N ₂	CuOTf	2f	5
3	Me	Me	IPh	Rh ₂ (OAc) ₄	2f	80
4	Me	Me	IPh	CuOTf	2f	57
5	iPr	iPr	N ₂	Rh ₂ (OAc) ₄	2a	9
6	iPr	iPr	N ₂	CuOTf	2a	<5
7	iPr	iPr	IPh	Rh ₂ (OAc) ₄	2a	19
8	iPr	iPr	IPh	CuOTf	2a	61
9	Et	Et	IPh	Rh ₂ (OAc) ₄	2b	49
10	<i>t</i> -Bu	<i>t</i> -Bu	IPh	Rh ₂ (OAc) ₄	2c	47
11	Bn	Bn	IPh	Rh ₂ (OAc) ₄	2d	19 ^c
12	Bn	Bn	IPh	CuOTf	2d	25 ^c
13	<i>t</i> -Bu	Et	IPh	Rh ₂ (OAc) ₄	2e	40 ^d

^a Source of CuOTf = (CuOTf)₂·C₆H₆. ^b Isolated yields. ^c Yield over two steps. ^d 85:15 dr: determined by ¹H NMR.

TABLE 5. Scope of the Cyclopropanation Using Rh₂(esp)₂ and 1f


entry	product	yield (%) ^a
1 ^b	2f	91
2	3a	78
3	3b	95
4	3c	95
5	3d	94
6	3e	93
7	3f	69
8 ^c	3g	84

^a Isolated yields. ^b 0.005 mol % of catalyst, 1.0 equiv of styrene, 1.3 equiv of **1f** was used, 5 mmol scale. ^c Reaction time = 16 h.

Recently, it has been shown that Rh₂(esp)₂¹⁸ is a superior catalyst to form 1,1-cyclopropane diesters from dimethyl diazomalones.⁶ Gratifyingly, similar efficiency was obtained using the previously reported conditions while substituting the diazomalone for the iodonium ylide (Table 5). Moreover, we were able to get a 91% yield while lowering the catalyst loading to 0.005 mol % (entry 1).

(18) esp = α,α,α',α'-Tetramethyl-1,3-benzenedipropanoate.

Differential scanning calorimetry (DSC) analyses indicated that the iodonium ylide derived from dimethyl malonate is safer than the corresponding diazo compound.¹² Although it degrades at a lower temperature, the energy released on degradation is significantly less.¹² Another advantage is that, contrary to diazodimethyl malonate, its synthesis does not require the use of an activated azide, which is also known to be explosive.⁴ Overall, the iodonium ylide of dimethyl malonate is a safer alternative to the corresponding diazo compound.

In conclusion, we have developed a general method for the synthesis of iodonium ylides from malonate esters, and we have shown that these ylides could be used in cyclopropanation reactions using rhodium or copper catalysis. We also improved the synthesis of the iodonium ylide derived from dimethyl malonate that requires a simple filtration to isolate the product as a white solid from the reaction mixture. This reagent in presence of a catalytic amount of $\text{Rh}_2(\text{esp})_2$ proved to be a very efficient way to form 1,1-cyclopropane diesters.

Experimental Section

Bis(methoxycarbonyl)(phenyliodinio)methanide 1f. In a 50 mL flask under argon were added KOH (2.00 g, 36.0 mmol), MeCN (20 mL), and dimethyl malonate (693 μL , 6.00 mmol). The heterogeneous mixture was cooled at 0 °C (ice/water bath) and was stirred vigorously for 5 min to produce a milky white suspension. $\text{PhI}(\text{OAc})_2$ (2.13 g, 6.60 mmol) was then added in one portion, and the reaction mixture was stirred vigorously for 2.0 h at 0 °C.

The reaction mixture gradually became a thick creamy mixture. Water (10 mL) was then added, and the mixture was stirred for 1 min. The beige/yellow biphasic solution containing a fluffy white suspension was filtered. The solid was washed with water (2×5 mL). It is important that the solvent be completely removed between each wash. The solid was finally washed with Et_2O (10 mL) then dried under high vacuum to yield **1f** as an off-white solid (1.56 g, 78%): mp 100 °C (decomposition); ^1H NMR (300 MHz, CDCl_3) δ 7.77–7.72 (m, 2H), 7.56–7.50 (m, 1H), 7.44–7.37 (m, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 166.3 (2), 131.6 (2), 131.5 (2), 131.3, 114.3, 52.4 (2); IR (neat) 3081, 2982, 2948, 2899, 1668, 1585, 1575, 1562, 1435, 1425, 1320, 1060, 990 cm^{-1} . Anal. calcd for $\text{C}_{11}\text{H}_{11}\text{IO}_4$: C, 39.54; H, 3.35. Found: C, 39.05; H, 3.34.

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Supporting Information Available: Experimental procedure for the preparation of compounds and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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