ORGANIC
LETTERS

2012
Vol. 14, No. 12
3170–3173

Design, Preparation, X-ray Crystal Structure, and Reactivity of *o*-Alkoxyphenyliodonium Bis(methoxycarbonyl)methanide, a Highly Soluble Carbene Precursor

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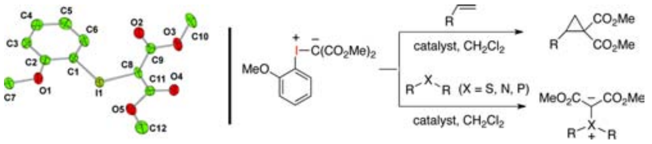
Received May 8, 2012

ABSTRACT



The preparation, X-ray structure, and reactivity of new, highly soluble, and reactive iodonium ylides derived from malonate methyl ester and bearing an *ortho* substituent on the phenyl ring are reported. These new reagents show higher reactivity than common phenyliodonium ylides in the Rh-catalyzed cyclopropanation, C–H insertion, and transylidation reactions under homogeneous conditions.

Within the rapidly growing field of hypervalent iodine chemistry,[1] phenyliodonium ylides[2] occupy a special and important place as efficient carbene precursors, alternative to the diazo compounds,[3] but without major drawbacks, such as explosiveness and toxicity. Phenyliodonium ylides (**1**, Figure 1) are prepared by the reaction of C–H acidic compounds (e.g., 1,3-dioxo derivatives) with hypervalent iodine(III) reagents such as $PhI(OAc)_2$. The nitrogen analogs of phenyliodonium ylides, phenyliodonium imides **2**, are synthesized similarly from arylsulfonamides and $PhI(OAc)_2$.

Under catalytic, thermal, or photochemical conditions, both reagents **1** and **2** serve as excellent progenitors for generation of singlet carbene (or carbenoid)[4] and nitrene

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10.1021/ol301268j

1 phenyliodonium ylides

2 phenyliodonium imides

X = CO_2Me, **1a**; COR; SO_2R; or other electron-withdrawing group

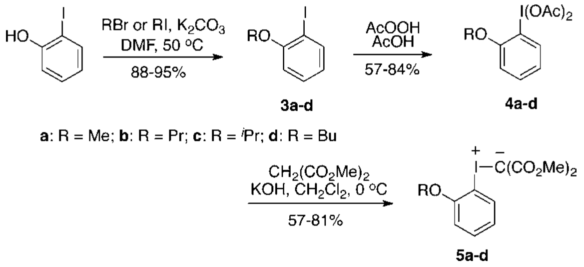
Figure 1. Phenyliodonium ylides and imides.

species, respectively. Particularly important and well-developed are the nitrene transfer reactions using imides **2** in the presence of Cu(I) or Rh(II) catalysts.[5] In contrast, similar catalytic carbene (or carbenoid) transfer reactions using ylides **1** have been less investigated due to the following reasons: ylides **1** usually are unstable and difficult to purify, and many of them, especially the acyclic compounds, have very low solubility in common organic solvents. For example, phenyliodonium bis(methoxycarbonyl) methanide **1a**, a most common iodonium ylide derived from malonate methyl ester, has found synthetic applications in the cyclopropanation of alkenes,[6] C−H insertion reactions,[7] epoxidation,[8] and asymmetric synthesis.[9] However, despite its importance, **1a** is not a perfect reagent. The main challenges are its poor solubility (insoluble in most organic solvents except DMSO) and low stability (should be stored −20 °C).[2,6c,6d] In view of the innocuous and eco-friendly attributes of iodonium ylides, the quest for modified ylides **1** that are more stable and soluble in common organic solvents is particularly attractive.

Recently, we have found that the solublility and reactivity of phenyliodonium imides **2** can be significantly improved by the introduction of an *o*-alkoxy group in the phenyl ring of the phenyliodonium moiety.[10a] Herein, we report the design, preparation, structural investigation, and reactivity of new highly soluble and stable iodonium ylides **5**, which are derived from *o*-alkoxyiodobenzene and malonate methyl ester. The choice of this structural motif is based on our previous research[10] and that of Protasiewicz et al.[11]

o-Alkoxyphenyliodonium bis(methoxycarbonyl) methanides **5a**−**d** were synthesized according to the procedure shown in Scheme 1. Reaction of commercially available 2-iodophenol with appropriate alkyl bromide or alkyl iodide afforded 2-iodophenol ethers **3a**−**d** in excellent yields. Subsequent oxidation to diacetoxyiodo derivatives **4a**−**d** was accomplished using freshly prepared peracetic acid. At last, diacetates **4a**−**d** were converted to the final *o*-alkoxyphenyliodonium bis(methoxycarbonyl) methanides **5a**−**d** by treatment with malonate methyl ester under basic conditions. Products **5** are relatively stable at rt and can be stored for several months in a refrigerator without significant degradation, which is clearly advantageous in comparison to the original **1a**. All ylides **5a**−**d** have good solubility in dichloromethane, chloroform, or acetone (e.g., the solubility of **5b** in dichloromethane is 0.56 g/mL). Thus, the new ylides **5** have a significant advantage over previously known iodonium ylides.

Scheme 1. Synthesis of Iodonium Ylides **5a**−**d**



All new ylides **5a**−**d** were identified by NMR spectroscopy, IR, and elemental analysis, and the structure of **5a** was unambiguously established by a single crystal X-ray diffraction analysis. To the best of our knowledge, this is the first single crystal X-ray analysis of a malonate ester derived iodonium ylide since the discovery of this class of ylides in 1965.[12] The X-ray crystal structure of **5a**, showing

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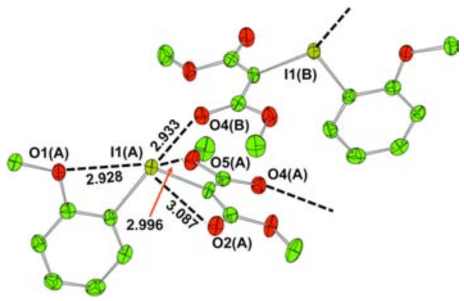
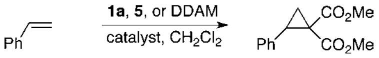


Figure 2. X-ray crystal structure of **5a** showing intra- and intermolecular interactions with the hypervalent iodine center.

Table 1. Comparison of Rectivity of **5**, **1a**, and Dimethyl 2-Diazomalonate (DDAM) in Cyclopropanation of Styrene[a]



DDAM = dimethyl 2-diazomalonate, $(MeO_2C)_2CN_2$

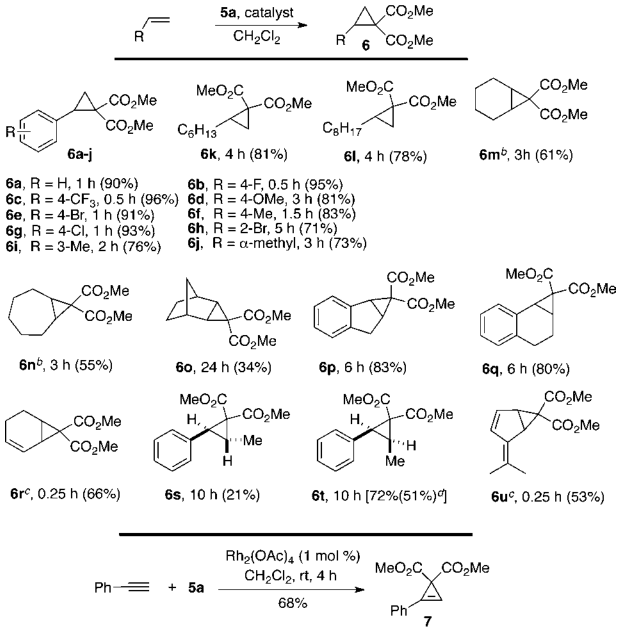
entry	reagent	catalyst	temp (°C)	time (min)	yield (%)[b]	ref
1	**1a**	$Rh_2(OAc)_4$	rt	30	80	6c
2	**1a**	$Rh_2(esp)_2$[c]	rt	120	91	6c
3	**1a**	$Rh_2(OAc)_4$	120	1	80	6f
4	DDAM	$Rh_2(OAc)_4$	rt	–[d]	39	6c
5	**5a**	$Rh_2(OAc)_4$	rt	60	90	
6	**5b**	$Rh_2(OAc)_4$	rt	60	88	
7	**5c**	$Rh_2(OAc)_4$	rt	60	74	
8	**5d**	$Rh_2(OAc)_4$	rt	60	72	
9	**1a**	CuOTf	rt	–[d]	57	6c
10	DDAM	CuOTf	rt	–[d]	5	6c
11	**5a**	CuOTf[e]	rt	120	77	
12	**1a**	$Cu(acac)_2$	80	10	57	6f
13	**5a**	$Cu(acac)_2$	80	10	74	
14[f]	**4a**	$Rh_2(OAc)_4$	rt	300	27	

[a] Reactions were performed by stirring styrene (5 equiv) with appropriate catalyst (0.05 equiv) in CH_2Cl_2 unless otherwise noted. [b] Isolated yields. [c] esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropanoate. [d] Reaction time is not provided in the reference. [e] $(CuOTf)_2 \cdot C_6H_6$ was used as the source of CuOTf. [f] In situ formation of the ylide **5a** using **4a**, dimethyl malonate, MgO, and 4 Å molecular sieves.

intra- and intermolecular interactions with the hypervalent iodine center, is given in Figure 2. In the solid state **5a** has a polymeric, asymmetrically bridged structure with a hexacoordinated geometry around the iodine centers formed by two short C–I bonds [2.117 Å for I–C(Ph) and 2.039 Å for I–C(malonate)] and two relatively long I–O intramolecular interactions between I–O1 (2.928 Å) and I–O2 (3.087 Å). In addition, a relatively weak intermolecular I–O4 secondary interaction (2.933 Å) is also present in the solid state structure of **5a**. Because the intermolecular interaction between molecules of **5a** is weak, this compound is highly soluble in organic solvents.

The reactivity of iodonium ylides **5** was tested in a cyclopropanation reaction with styrene using various catalysts in comparison with reactions of the common carbene precursors, ylide **1a** and dimethyl 2-diazomalonate (Table 1). In general, the reactions of ylides **5** with alkenes proceed under mild conditions and afford higher yields of cyclopropanation products compared to ylide **1a** and dimethyl malonate, which can be explained by the better solubility of **5a**.

Scheme 2. Cyclopropanation Reactions of Alkenes[a] and Phenylacetylene Using **5a**

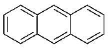
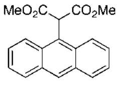
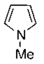
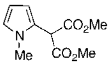
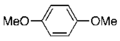
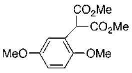


[a] The cyclopropanation of alkenes was conducted in CH_2Cl_2 at rt by stirring **5a** (1 equiv), alkene (5 equiv), and $Rh_2(OAc)_4$ (0.05 equiv) unless otherwise noted. [b] $Cu(acac)_2$ was used instead of $Rh_2(OAc)_4$ under reflux conditions. [c] The reaction was conducted under reflux conditions. [d] The yield shown in parentheses corresponds to the use of **5c** instead of **5a**.

With the aim to develop and define the scope and limitation of the reactions, the new ylide **5a** was first tested as a reagent in typical Rh-catalyzed cyclopropanations with a wide range of unsaturated compounds, including benzylic, allylic, heterocyclic, alicyclic, aliphatic alkenes, dienes, and an alkyne (Scheme 2).

Diversely substituted styrene-type derivatives underwent smooth cycloaddition to afford the corresponding cyclopropanedicarboxylates in excellent yields without any evidence of C–H insertion at the benzylic positions (**6a**–**6j**). Cyclic, alicyclic, and aliphatic alkenes also reacted smoothly rendering cyclopropanation adducts in moderate to good yields (**6k**–**6o**). Interestingly, the outcome of the reaction of β-methylstyrenes depended on the stereochemistry of the alkene. The *cis*-isomer afforded exclusively the *cis*-cyclopropane product in high yield, while the *trans*-isomer led to a complex mixture of products, from which the *trans*-cyclopropane was isolated in only 21% yield (**6s** vs **6t**). This very high degree of stereospecificity indicates that the steric hindrance effect is much more important than the influence of electronic effect in the present system. The cyclopropanation seems to be electrophilic in nature, but the steric factor is dominant, which

Table 2. C−H Insertion Reactions Using Iodonium Ylide **5a**

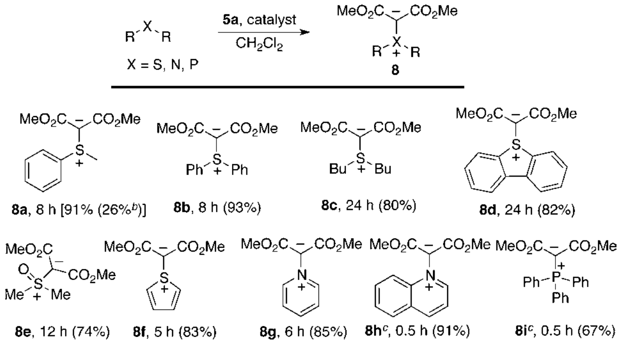
entry	substrate	product	method[a]	time (h)	yield (%)[b]
1			A	0.25	0
2			B	1.0	<5(0[c])
3			C	24	51
4			D	3.0	37
5			A	0.5	39
6			B	1.0	27
7			C	24	48
8			D	1.5	54
9			A	0.25	0
10			B	1.0	0
11			C	24	62
12			D	48	32[d]

[a] Method A: The reaction was performed by heating a mixture of the iodonium ylide **5a** (1.5 equiv), substrate (1.0 equiv), $Rh_2(OAc)_4$ (0.01 equiv), and CH_2Cl_2 (3 mL) under reflux. Method B: $Cu(acac)_2$ was used instead of $Rh_2(OAc)_4$ in method A. Method C: The reaction was performed using a mixture of the iodonium ylide **5a** (1.5 equiv), substrate (1.0 equiv), $BF_3 \cdot Et_2O$ (3 equiv), and CH_2Cl_2 (3 mL) at 0−5 °C. Method D: Heating a mixture of ylide **5a** (1.5 equiv), substrate (1.0 equiv), and CH_2Cl_2 (3 mL) under reflux. [b] Isolated yield. [c] $Cu(OTf)_2$ was used as catalyst. [d] Reaction was performed at rt.

could be further supported by the fact that using **5c** instead of **5a** in the cyclopropanation of **6t** also led to a lower yield. Heating the ylide **5a** with a diene in the presence of $Rh_2(OAc)_4$ led to the isolation of vinylcyclopropanes in moderate yields (**6r** and **6u**). Again, the reaction with 6,6-dimethylfulvene indicates that the addition of an ylide to a diene is also rather more sensitive to the steric effect than the electronic effect (**6u**). Another remarkable feature of **5a** was observed upon reaction of phenylacetylene, with the corresponding cyclopropene **7** being obtained as the major product.

Next we investigated the direct insertion reactions of reagent **5a** into C−H bonds of aromatic hydrocarbons, which is a challenging synthetic goal that has previously been achieved by using various transition-metal catalysts.[13] We were pleased to find that reagent **5a** readily reacts with hydrocarbons to give the corresponding C−H insertion product under metal-free (method C) or catalyst-free (method D) conditions (Table 2). For example, the reaction with 1,4-dimethoxybenzene proceeds even at rt to afford the product of C−H insertion in 32% yield, without any catalyst, but with a prolonged reaction time (entry 12). Presumably, this reaction proceeds via a cation-radical[7b] (or carbene) pathway rather than a carbenoid pathway. Excellent chemoselectivity was also observed using this system. In the reaction with *N*-methylpyrrole, the α-isomer was the only product; there was no evidence for the formation of the *β*-isomer, which is well-known to form in the reactions using a diazo compound.[14]

Scheme 3. Transylidation Reactions of **5a**[a]



[a] The transylidation was conducted in CH_2Cl_2 at rt using **5a** (1.2 equiv), the appropriate heteroatom nucleophile (1.0 equiv), and $Rh_2(OAc)_4$ (0.01 equiv) unless otherwise noted. [b] The yield shown in parentheses corresponds to catalyst-free reflux conditions. [c] $Cu(acac)_2$ was used instead of $Rh_2(OAc)_4$ under reflux conditions.

We have also found that iodonium ylide **5a** is highly reactive in transylidation reactions with a wide range of heteroatom nucleophiles involving sulfides, sulfoxides, phosphines, and nitrogen heterocycles; the results are summarized in Scheme 3. Structures of sulfonium ylide **8d** and phosphonium ylide **8i** were established by X-ray diffraction (see Supporting Information).

In summary, we have reported the preparation, X-ray structure, and reactivity of new, highly soluble, and reactive iodonium ylides **5** derived from malonate methyl ester and bearing an *ortho* substituent in the phenyl ring. These new reagents afford higher yields of products than common phenyliodonium bis(methoxycarbonyl) methanide **1a** in the Rh-catalyzed cyclopropanation, C−H insertion, and transylidation reactions under homogeneous conditions.

Acknowledgment. C.Z. thanks the China Scholarship Council for supporting his visit to the University of Minnesota Duluth and the Research and Innovation Plan for Graduate Students of Jiangsu Higher Education Institutions for project support (No. CXZZ11_0266). This work was supported by research grants from the NSF (CHE-1009038; MRI CHE-0922366).

Supporting Information Available. Experimental procedures, spectral data for key compounds, and cif files for products **5a**, **8d**, and **8i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.