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Hypervalent Iodine(III) Reagents as Safe Alternatives to α-Nitro-α-diazocarbonyls

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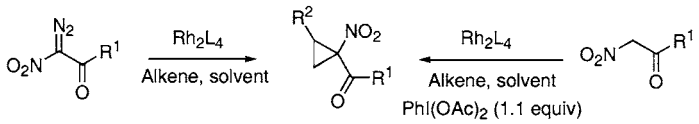
ABSTRACT



A cyclopropanation reaction involving iodonium ylides generated in situ allows for efficient preparation of substituted 1-nitro-1-carbonyl cyclopropanes. This robust cyclopropanation reaction can be performed in organic solvents, biphasic aqueous media, or under solvent-free conditions with alkene substrates. The iodonium ylides generated in situ display some surprising differences in reactivity when compared to α-nitro-α-diazocarbonyl compounds. They do not undergo O–H insertion reactions and exhibit reduced reactivity with certain alkenes.

We recently reported a facile and efficient diazo transfer reaction involving trifluoromethanesulfonyl azide for the preparation of α-nitro-α-diazo-carbonyls.[1] In our research program involving the asymmetric synthesis of unnatural amino acids,[2] these substrates could represent an amino acid equivalent upon reduction of the nitro group. Additionally, cyclopropanes derived from these substrates could serve as useful synthons.[3]

Of particular interest, however, was the development of an efficient and expedient method for the synthesis of cyclopropane amino acids[4] via reduction of the nitro group.[5] Transition metal-catalyzed cyclopropanation of alkenes with diazo compounds represents a direct approach for cyclopropane preparation.[6] However, the instability of α-nitro-α-diazoacetate reagents precludes their use for the large-scale preparation of cyclopropane amino acids.[7]

Attempts to circumvent the potential drawbacks of diazo chemistry have led to the development of in situ diazo generation procedures.[8] Hypervalent iodine(III) reagents have also been gaining in popularity as synthetic equivalents to diazo compounds.[9]

These iodine(III) reagents represent an attractive alternative for acidic hydrogen containing substrates **1** due to their ease of preparation. They also exhibit similar reactivities when

(1) (a) Charette, A. B.; Wurz, R. P.; Ollevier, T. *J. Org. Chem.* **2000**, *65*, 9252. (b) Charette, A. B.; Wurz, R. P.; Ollevier, T. *Helv. Chim. Acta* **2002**, *85*, 4468.

(2) See, for example: (a) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721. (b) Charette, A. B.; Mellon, C. *Tetrahedron* **1998**, *54*, 10525. (c) Charette, A. B.; Gagnon, A.; Janes, M.; Mellon, C. *Tetrahedron Lett.* **1998**, *39*, 5147. (d) Charette, A. B.; Gagnon, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1961.

(3) (a) As a source of nitrocyclopropanes, see: O'Bannon, P. E.; Dailey, W. P. *J. Org. Chem.* **1990**, *55*, 353. (b) Vettiger, T.; Seebach, D. *Liebigs Ann. Chem.* **1990**, 195. (c) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J. P. *J. Org. Chem.* **1991**, *56*, 6258. (d) Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727. (e) Seebach, D.; Häner, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507.

(4) Davies, H. M. L.; Cantrell, W. R., Jr. *Tetrahedron Lett.* **1991**, *32*, 6509. (c) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. See also ref 8d.

(5) For reduction of the nitro group in the unsubstituted nitro cyclopropane carboxylate, see: Seebach, D.; Häner, R. *Chimia* **1985**, *39*, 356.

(6) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; Wiley: New York, 1998. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(7) Methyl α-nitro-α-diazoacetate explodes when heated (see ref 1), but ethyl diazoacetate is quite stable upon heating. For the preparation of ethyl diazoacetate on a 1000 mol scale, see: Scott, J. W. *Abstracts of Papers*, 223rd National Meeting of the American Chemical Society, Orlando, FL, April 7−11, 2002; American Chemical Society: Washington, DC, 2002; Abstract 186.

(8) (a) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2002**, *4*, 4531. (b) Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem.* **2001**, *66*, 8260. (c) Aggarwal, V. K.; de Vincente, J.; Bonnert, R. V. *Org. Lett.* **2001**, *3*, 2785. (d) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433.

(9) For a review on hypervalent iodonium reagents, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Müller, P.; Boléa, C. *Helv. Chim. Acta* **2001**, *84*, 1093. (c) Müller, P.; Boléa, C. *Synlett* **2000**, 826. (d) Müller, P.; Fernandez, D. *Helv. Chim. Acta* **1995**, *78*, 947.

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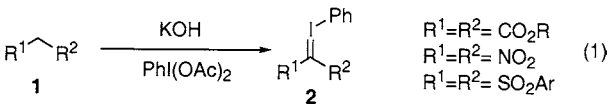
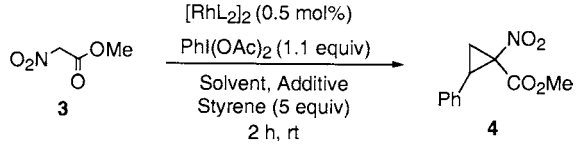
compared to the corresponding diazo substrates. They are generally isolated upon treatment of **1** with methanolic KOH and bis(acetoxy)iodobenzene (eq 1).[10]



Under these reaction conditions methyl nitroacetate (**3**) failed to yield the desired iodonium ylides due in part to solubility problems and/or degradation. Thus, we turned to an in situ approach where the iodonium ylides are generated in the presence of Rh(II) carboxylate catalysts and an olefin substrate.[11] This "one-pot" procedure would avoid isolation of the potentially unstable intermediate. A number of reaction variables, including solvent and base, were tested (Table 1).

Table 1. In Situ Generation of Iodonium Ylides Followed by Cyclopropanation



solvent	catalyst	additive (equiv)	yield of **4** (%)	ratio *E*/*Z*
CH_2Cl_2	$[Rh(OAc)_2]_2$	3 Å MS	20[b,c]	92:8
CH_2Cl_2	$[Rh(OAc)_2]_2$	MgO (5)	52[c]	92:8
CH_2Cl_2	$[Rh(OAc)_2]_2$	Na_2CO_3 (2)	32[c]	90:10
H_2O	$[Rh(OPiv)_2]_2$	Na_2CO_3 (2)	86	93:7
none	$[Rh(OAc)_2]_2$	none	41	90:10
none	$[Rh(C_7H_{15}CO_2)_2]_2$	none	71	91:9
none	$[Rh(OPiv)_2]_2$	none	83	92:8
none	$[Rh(OPiv)_2]_2$	none	67[d]	92:8

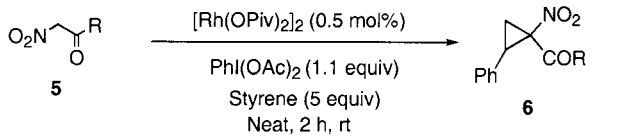
[a] Isolated yields after purification. [b] PhI=O used as a hypervalent iodine source. [c] Reaction time: 6 h in refluxing CH_2Cl_2. [d] Styrene (2 equiv) was used.

In all cases, the reagents were added simultaneously and allowed to stir. Initial attempts in refluxing dichloromethane afforded low to modest yields with a variety of drying agents and bases. When the reaction was performed using water as a solvent and a hydrophobic catalyst,[12] the yields reached acceptable levels. To further simplify the procedure, the reaction was tested in the absence of solvent and additives and found to give optimal yields of cyclopropane **4** in only 2 h at room temperature.

It is noteworthy to mention that although $[Rh(OAc)_2]_2$ and $[Rh(C_7H_{15}CO_2)_2]_2$ catalysts gave inferior yields compared to $[Rh(OPiv)_2]_2$, stirring overnight allowed for isolation of 70 and 81% yields of **4**, respectively. A modest yield of **4** (67%) was maintained when only 2 equiv of styrene was used.

The scope of the cyclopropanation reaction was examined by variation of steric bulk on the α-nitro carbonyl substrate. The results suggest that the reaction is efficient for a variety of α-nitro carbonyl substrates (Table 2). Of particular interest

Table 2. Scope of the Cyclopropanation Reaction



product	R	yield (%)[a]	*E*/*Z* ratio
6a	OAllyl	71	90:10
6b	OBn	83	84:16
6c	O*i*-Pr	64[b]	82:18
6d	Ph	61	9:91
6d	Ph	75[c]	10:90
6e	*c*-C_3H_5	72	72:28

[a] Isolated yields after purification. [b] Reaction time: 3 h. [c] Heated at 40 °C for 3 h.

is the tolerance for alkenes that are part of the α-nitro ester reagent (**5a**), as the reaction proceeded smoothly and exclusively in an intermolecular fashion.[13] The reaction can also be successfully scaled-up with reduced catalyst loadings.[14]

α-Nitro ketones also lead to modest isolated yields in the cyclopropanation reaction, closely approximating that of the diazo substrate except for substrate **5d** in which yields of 74% can be obtained when the diazo is used.[1b]

The yields could be improved to 75% by heating at 40 °C for 3 h. It is noteworthy that this α-nitro ketone substrate allows access to predominantly the (*Z*)-isomer.

Next, a variety of olefinic substrates were tested under the standard conditions (Table 3). We noticed small differences between the reactivities of the in situ-generated iodonium ylides and the diazo compounds.

Cyclopropanation in the presence of alkenes such as indene, para-substituted styrenes, and α-methyl styrene afforded the corresponding cyclopropanes with similar chemical yields to the reaction using the corresponding diazo reagents, while 1,1-diphenylethylene and methylene cyclopentane were problematic under the standard reaction conditions (Table 3). Acceptable yields of the cyclopropanes were obtained when the reaction mixtures were heated to 40 °C for 3 h (condition C) (**8e**,**f**).[15] It is noteworthy to mention

(10) Ochiai, M.; Kitagawa, Y. *J. Synth. Org. Chem. Jpn.* **2000**, 1048.

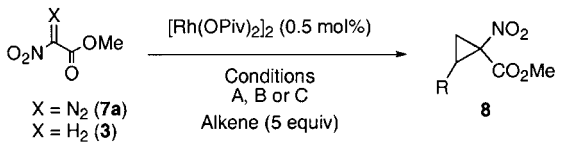
(11) Dauban et al. reports a cyclopropanation involving dimethyl malonate, PhI=O, and $Cu(acac)_2$ as a catalyst affording 55% of cyclopropane; see: (a) Dauban, P.; Sanière, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. For examples involving nitrogen analogues of phenyliodonium ylides, see: (b) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (c) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

(12) Use of hydrophobic catalysts in aqueous reactions is critical for success (see ref 8a).

(13) A variety of intramolecular cyclopropanations can be achieved with the corresponding diazo substrate (see also ref 16).

(14) On a 700 mg scale, 0.1 mol % $[Rh(OPiv)_2]_2$ gave 75% isolated yield (93:7 *E*/*Z* ratio) of **4** upon being heated for 2 h at 40 °C.

Table 3. Diazo vs Iodonium Ylides Cyclopropanation Scope

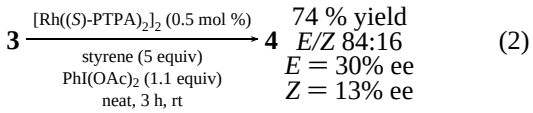


product	alkene	conditions[a]	yield (%)	*E*/*Z* ratio
4	styrene	A	90	90:10
		B	83	92:8
8a	indene	A	84	100:0
		B	91	100:0
8b	4-MeOC$_6$H$_4$CH=CH$_2$	A	91[b]	n/a
		B	82[b]	
8c	4-ClC$_6$H$_4$CH=CH$_2$	A	87	91:9
		B	75	91:9
8d	C$_6$H$_5$C(Me)=CH$_2$	A	91	97:3
		B	80	98:2
8e	Ph$_2$C=CH$_2$	A	97[b]	n/a
		B	0	n/a
		C	63[b]	n/a
8f	methylenecyclopentane	A	80	n/a
		B	0	n/a
		C	73	n/a

[a] A: Diazo (0.5 M in CH_2Cl_2) was added dropwise over 15 min to alkene and then stirred for 2 h. B: $PhI(OAc)_2$ (1.1 equiv), neat, 2 h, rt. C: Same as A, except the reaction was heated at 40 °C for 3 h. [b] Isolated as a mixture of cyclopropane and isoxazoline *N*-oxide.

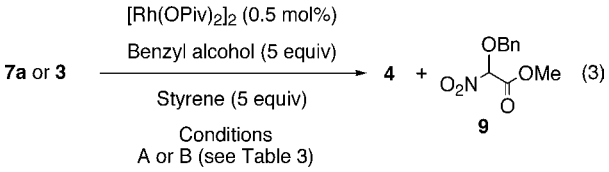
that no dimerization products were observed under any of the reaction conditions tested.

Preliminary work involving asymmetric cyclopropanations[16] was also found to give similar results when compared to its diazo counterpart in organic solvents (eq 2, PTPA = *N*-phthaloylphenylalaninate). In the reaction involving iodonium ylides, the yields and enantiomeric excesses were similar to those in the diazo-mediated cyclopropanation (75% yield in a 86:14 *E*/*Z* ratio; *E* = 30% ee, *Z* = 12% ee).[16]



(2)

Next, a competition experiment was performed with benzyl alcohol and styrene (eq 3). Surprisingly, using an iodonium ylide led to exclusive formation of the cyclopropane product **4** (70% isolated yield). Methyl nitro diazoacetate **7a** gave a mixture of cyclopropane **4** and O−H insertion product **9** in a 1.7:1 ratio (90% overall yield). Mechanistic reasons for the differences in reactivities are presently unknown and will be the subject of future work.



(3)

A variety of other bis(acetoxy)iodobenzene derivatives can be easily prepared,[17] but presently, there appears to be no advantage in using structurally modified iodonium(III) reagents. This report offers a safe alternative to α-nitro-α-diazo carbonyls, although there are advantages and applications for both. Further examination of the implicated mechanism and asymmetric cyclopropanations is being studied and will be reported in due course.

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Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS) and SFC traces for enantioselective cyclopropanations. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Additives such as aqueous KBr solutions, *n*-Bu_4NBr (10 mol %), and small amounts of toluene (to aid solubility) also had a marked accelerating effect. The results in Table 3 are very similar when H_2O was used as a solvent, but the reaction suffers the disadvantage of requiring an extraction.

(16) Charette, A. B.; Wurz, R. P. *J. Mol. Catal. A: Chem.* **2003**, *196*, 83.

(17) McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299.