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ARTICLE

Hypervalent-iodine (III) Oxidation of Hydrazones to Diazo Compounds and One-pot Nickel (II)-Catalyzed Cyclopropanation

Received 00th January 20xx,
Accepted 00th January 20xx

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DOI: 10.1039/x0xx00000x

A one-pot process for catalytic cyclopropanation of various alkenes with unsubstituted hydrazones is described. Iodosobenzene (PhI=O) was found to be a competent oxidant of hydrazone to diazo compound. Ni(OH)₂ was chosen as an effective and cheap metal catalyst. The cyclopropane products can be generated efficiently (5 min-4 h) in moderate to good yields (42-91%) at mild (80 °C) and neat conditions.

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Introduction

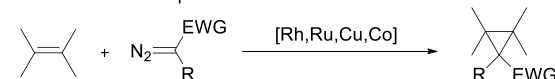
Cyclopropyl moiety is ubiquitous in the structure of natural occurring compounds.¹ As the smallest strained cycloalkane, cyclopropane arouses chemists' interest in many aspects including theoretical study of bonding,² potential synthetic transformations³ and the structure importance of it in drugs and enzyme inhibitors.⁴ Consequently, a variety of synthetic routes to cyclopropanes have been developed.⁵ Among them, transition metal catalytic decomposition of diazo compounds in the presence of alkenes is a classic and common method.⁶ The active metal complexes include rhodium,⁷ ruthenium,⁸ copper,⁹ and cobalt,¹⁰ while only scattered reports concern nickel catalyst.¹¹ And the investigations have been restricted to diazo esters or diazo ketones (Scheme 1a). Diazo compounds are toxic, irritating and sometimes explosive. In order to broaden substrate scopes and to avoid handling of diazo compounds, protocols that combine in situ generation of diazo compounds and carbene addition to alkenes are most desirable. Either base elimination of tosylhydrazones or the oxidation of hydrazones is a choice of generating diazo compounds in situ. The first strategy has been extensively scanned using aromatic aldehyde tosylhydrazones or substituted acetophenone tosylhydrazones as substrates with a wide range of olefins (Scheme 1b).¹² However, this strategy involves using strong base or high temperature and a relatively long reaction time is often needed. The latter strategy faces more challenge since it is hard to tolerate alkenes in an oxidation environment. Conventionally, the oxidizing agents used to oxidation of hydrazones to diazo compounds have been mercuric oxide,¹³ manganese dioxide,¹⁴ silver oxide¹⁵ and lead tetraacetate.¹⁶ Manganese dioxide was chosen to operate cyclopropanation from hydrazones in some reports, but excess

amount of the oxidant was used and the reaction had to be operated in a two-step manner, means long reaction times and tedious work-up procedures.¹⁷

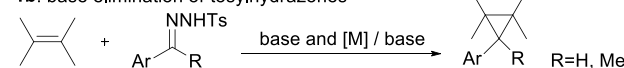
On the other hand, the wide application of hypervalent iodine reagents in modern synthesis has been well-documented.¹⁸ Cyclopropanation of alkenes can be achieved by formation of iodonium ylide derived from active methylene compound and subsequent carbene transfer.¹⁹ However, the strategy of in situ generating diazo species mediated by hypervalent iodine reagent was only applied in one-pot esterification reactions using benzophenone hydrazones or *N*-*tert*-butyldimethylsilyl hydrazones with carboxylic acid.²⁰ In these esterification reactions, since both the active intermediate (diazo compound) and the substrate (hydrazone) were tended to decomposition, low temperature (-78 °C or -10 °C) had to be used. We intended to broaden the application of this strategy by exploring new catalytic systems that would compatible to new reaction types. Also, in order to continue our research on hypervalent iodine reagent²¹ and circumvent the existing shortcomings in cyclopropanation. We present here a one-pot cyclopropanation from hydrazones and alkenes, which is highly efficient and adapts to general hydrazones (Scheme 1c).

Previous reports:

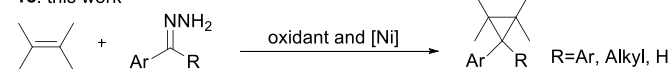
1a: from diazo compounds



1b: base elimination of tosylhydrazones



1c: this work



Scheme 1. Cyclopropanation strategies.

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Results and Discussion

We began our investigations by using benzophenone hydrazone (**1a**) as a model substrate. Treating the substrate with hypervalent iodine reagent such as (diacetoxyiodo)benzene (DIB), hydroxy(tosyloxy)iodobenzene (HTIB), [bis(trifluoroacetoxy)iodo]benzene (PIFA), and 2-iodoxybenzoic acid (IBX) in chloroform at room temperature, only decomposition products could be isolated which is consist with the literature.²² When iodosobenzene was used as oxidant, the accumulation of diphenyldiazomethane was visible by the outstanding red-violet color spot on the thin layer chromatography (TLC) plate. Adding methanol before GC-MS analysis and (methoxymethylene) dibenzene could be examined in 35% yield. The parent ketone was found in 40% yield formed by decomposition of the starting hydrazone in solution and reaction with oxygen. The conversion of the starting material is 85% after 10 minutes. With the initial findings, we continued our study by using styrene to trap the in situ generated diphenyldiazomethane, the desired cyclopropane product (**3a**) was formed in 35% yield at 80 °C after 20 hours (Table 1, entry 1). Styrene was used in excess to depress side reactions of the starting hydrazone.

In order to accelerate the reaction, various metal catalysts were then scanned at similar reaction conditions, to

our delight, Ni(OAc)₂·4H₂O exhibited catalytic activity and **3a** could be obtained in 46% yield (Table 1, entries 2-5). The attempt to improve product yield by additives like surfactant, ligand and base only got inferior results (Table 1, entries 6-10). We then tended to survey Ni (II) salts with different counter ions, the reaction greatly speeded up when using NiF₂·4H₂O or Ni(OH)₂ as catalyst (Table 1, entries 11-13). As GC-MS analysis showed byproducts result from the solvent, we ran the reaction under neat conditions and the product yield climbed to 72% (Table 1, entry 14). Carefully screen of alkene equivalents showed that 4 equivalents of styrene (with regard to hydrazones) is optimal (Table S1 in ESI). The cumbersome of running the reaction under argon had little effect on the yield of **3a** (Table 1, entry 15). But in this case, the in situ generated diazo compound was decomposed by disproportionation to give the symmetrical azine as the main byproduct. Lowering the reaction temperature to 60 °C led to a drop in reaction performance (Table 1, entry 16). It is worth to note that an acceptable yield (62%) could also be obtained when decreased the catalyst loading to 10 mol%, only longer reaction time was needed (Table 1, entries 17-18).

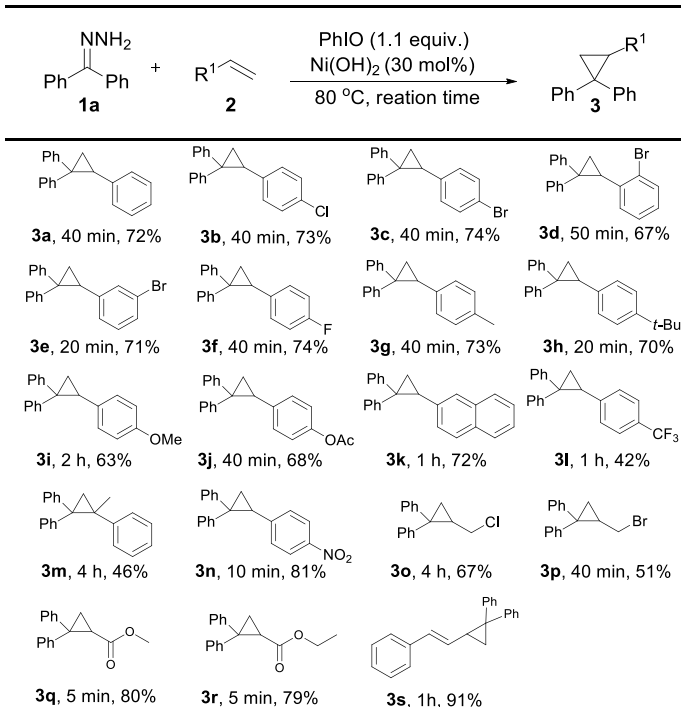
With the optimized conditions in hand (Table 1, entry 14), the scope of this protocol was examined for the reaction of benzophenone hydrazone (**1a**) with a series of substituted alkenes (Table 2). The reactions proceeded smoothly to afford the target cyclopropanes in moderate to good yields. For 4-substituted styrenes in which the substituent is halogen and alkyl group (**2b**, **2c**, **2f-2h**), the protocol was applicable without significant differences in product yields (**3b**, **3c**, **3f-3h**). When 2-bromostyrene was used as substrate, the yield of product was a bit reduced compared with 3- and 4-bromostyrene which shows an influence of steric effect (**3c-3e**). The presence of moderate electron-donating group (-OAc) or strong electron-donating group (-OMe) on the benzene ring of styrene gave the products (**3j**, **3i**) in slightly lower yields. When we employed 4-nitrostyrene as the substrate, the corresponding product (**3n**) was achieved in 81% yield, suggesting that styrene with strong electron-withdrawing group is favored in this transformation. But unexpectedly, trifluoromethyl-substituted product (**3l**) was only isolated in 32% yield, which may be attributed to the highly volatility of 4-(trifluoromethyl) styrene. The protocol was also applicable to α -methylstyrene and 2-vinylnaphthalene, affording the desired products (**3m**, **3k**) in 46 and 72% yields, respectively. Aliphatic alkenes were also examined. To our delight, allyl chloride and allyl bromide could react and afforded the desired cyclopropanes in moderate yields (**3o**, **3p**). Halogen containing products were highly meaningful since halogen enables further functional group manipulations to more complex structures. Meanwhile, this kind of product can't be synthesized from tosylhydrazones, because, under basic conditions, the known N-alkylation of tosylhydrazones with alkyl halide will be a dominant side reaction.²³ Alkyl acrylates such as methyl acrylate and ethyl acrylate can react with benzophenone hydrazone efficiently and generated the corresponding cyclopropanes in 80% and 79% yields, respectively (**3q**, **3r**). Unfortunately, acyclic internal alkenes show no reactivity

Table 1. Optimization of the reaction conditions^a

Entry	Catalyst	Additive	Solvent	Time	Yield (%) ^b
1	—	—	CHCl ₃	20 h	35
2	CuBr ₂	—	CHCl ₃	20 h	—
3	VO ₂ ·xH ₂ O	—	CHCl ₃	20 h	—
4	BiCl ₃	—	CHCl ₃	20 h	—
5	Ni(OAc) ₂ ·4H ₂ O	—	CHCl ₃	20 h	46
6	Ni(OAc) ₂ ·4H ₂ O	TBAC	CHCl ₃	20 h	26
7	Ni(OAc) ₂ ·4H ₂ O	SDS	CHCl ₃	20 h	32
8	Ni(OAc) ₂ ·4H ₂ O	Ph ₃ P	CHCl ₃	20 h	28
9	Ni(OAc) ₂ ·4H ₂ O	TMEDA	CHCl ₃	20 h	22
10	Ni(OAc) ₂ ·4H ₂ O	K ₂ CO ₃	CHCl ₃	20 h	35
11	Ni(acac) ₂	—	CHCl ₃	20 h	40
12	NiF ₂ ·4H ₂ O	—	CHCl ₃	4 h	55
13	Ni(OH) ₂	—	CHCl ₃	1 h	58
14	Ni(OH) ₂	—	—	40 min	72
15 ^c	Ni(OH) ₂	—	—	1 h	73
16 ^d	Ni(OH) ₂	—	—	20 h	25
17 ^e	Ni(OH) ₂	—	—	1 h	67
18 ^f	Ni(OH) ₂	—	—	2 h	62

^a Conditions: **1a** (0.5mmol), **2a** (4.0 equiv.), catalyst (30 mol%), additive (20 mol%) in solvent (2 mL) at 80 °C. TBAC = tetrabutylammonium chloride, SDS = sodium dodecyl sulfate, TMEDA = tetramethylethylenediamine. ^b Isolated yield.

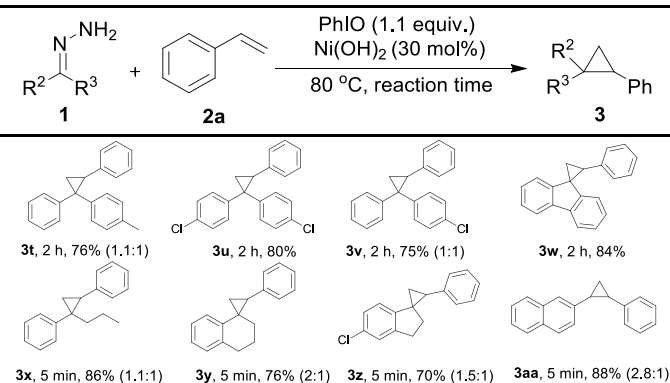
^c Under argon. ^d Reaction was performed at 60 °C. ^e Ni(OH)₂ (20 mol%) was used. ^f Ni(OH)₂ (10 mol%) was used.

Table 2. Reaction of benzophenone hydrazone (**1a**) with alkenes^a

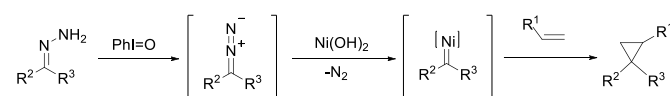
^a Conditions: **1a** (0.5 mmol), **2** (4.0 equiv.), Ni(OH)₂ (30 mol%), PhI=O (1.1 equiv.), at 80 °C. For solid alkenes, chloroform (0.2 mL) was used as solvent. The isolated yields of the products were shown.

under the reaction conditions, only the decomposed products of benzophenone hydrazone (azine and ketone) were detected by GC-MS. (for example 1-chloro-2-butene, (*E*)-stilbene etc. was tested). Cyclic internal alkene as norbornene was used, but 1,3-dipolar cycloaddition product was isolated in 89% yield.²⁴ The product does not exclude molecular nitrogen when contacts with Ni(OH)₂ or heats at 120 °C. When cyclohexene was used, C-H insertion out competes cyclopropanation and C-H insertion product was formed in 47% yield.²⁴ The special reactivity toward allylic C-H insertion product may contribute to both steric and electronic effects.²⁵ For conjugated alkenes, (*E*)-1-phenyl-1,3-butadiene could also smoothly undergo the reaction and the desired product was obtained in 91% yield (**3s**).

Then, the generality of this protocol concerning the hydrazone part was investigated (Table 3). Diaryl ketone hydrazones with chlorine or methyl substituent and 9-fluorenone hydrazone all furnished the corresponding cyclopropanes (**3t-3w**) in satisfactory yields. Furthermore, Aryl-alkyl ketone hydrazones exhibited high reactivity and completed the reactions in 5 min with good product yields (**3x-3z**). Notably, the thermal sensitive aldehyde hydrazone substrate (**3aa**) could undergo this transformation efficiently, and generated the desired product in 88% yield. Products **3t**, **3v**, and **3x-3aa** were isolated as mixtures of diastereoisomers and the *trans/cis* ratios were calculated according to NMR spectras. Compared to diaryl diazo compound, aryl-alkyl diazo compound and aryl diazo compound are even more unstable

Table 3. Scanning of hydrazones^a

^a Conditions: **1a** (0.5 mmol), **2** (4.0 equiv.), Ni(OH)₂ (30 mol%), PhI=O (1.1 equiv.), at 80 °C. For solid alkenes, chloroform (0.2 mL) was used as solvent. The isolated yields of the products were shown. For **3t**, **3v**, and **3x-3aa**, the *trans/cis* ratios of diastereoisomer were shown in bracket.

**Scheme 2.** Proposed mechanisms

and difficult to handle for the lack of one stabilized benzene ring and the electron-donating effect of alkyl- or H- group.²⁶ We believe that the efficient applicable to **3x-3aa** makes this protocol more practical useful and a better choice in this field. Next, when cyclohexanone hydrazone was used, again, only 1,3-dipolar cycloaddition product was obtained in 43% yield.²⁴

Based on the knowledge of transition metal-catalyzed cyclopropanation and the above experiments we explored, we proposed a reaction pathway for this one-pot nickel (II)-catalyzed cyclopropanation of alkenes with hydrazones (Scheme 2). Iodosobenzene functions as the oxidizing agent and in situ oxidize hydrazones to diazo compound. The interaction of diazo compounds with nickel salt generates metal-carbene intermediate and subsequent carbene addition leads to the desired product.

Conclusions

In summary, a new approach to cyclopropane compound has been introduced in this paper. The one-pot and easy operation procedure utilize iodosobenzene as an oxidant to generate non-stabilized diazo compound in situ from unsubstituted hydrazones. There's no need to isolate diazo compound or to run the reaction stepwise. With the aid of nickel catalyst, diazo compound decomposes readily and react with alkene at 80 °C to furnish cyclopropane efficiently (5 min-4 h) and in moderate to good yields (42-91%). The mild protocol is generally applicable to aryl alkenes with different electronic effect substituents (-OMe, -NO₂, -*t*-Bu, -F, etc.), aliphatic alkenes with halogen functional groups, alkyl acrylates and hydrazones derived from diaryl ketone, aryl-alkyl ketone and aldehyde. If lower catalyst loading was used, acceptable yield could also be

obtained and for all reactions the termination can be clearly indicated by the vanishing of the special color of diazo compounds. We concentrated on the synthesis of 1,1-diaryl cyclopropanes for its lack of systemic investigation and a good supplement to the existing methods. The enantioselective version of this protocol through adding chiral ligands or chiral auxiliaries of the substrate, and further exploration of this reliable way of generating diazo intermediate is now in progress in our lab.

Experimental

A screwed tube was charged with the corresponding hydrazone (0.5 mmol), Ni(OH)₂ (30 mol%, 0.014 g) and alkene (4 equiv.). For solid alkenes, chloroform (0.2 mL) was used as solvent. Magnetic stirrer with oil bath was used and pre-heated to 80 °C. The screwed tube was then put to the oil bath and at the same time iodosobenzene (1.1 equiv., 0.121 g) was added. The reaction was stirred at 80 °C until total disappearing of the red-violet color which indicated the completion of the reaction. The reaction mixture was purified by column chromatography using petroleum ether or petroleum ether/ethyl acetate as eluent.

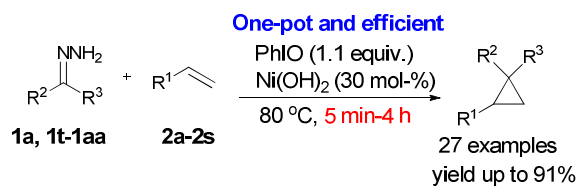
Acknowledgements

We thank the Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). We also thank Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences for testing HRMS.

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A novel and efficient cyclopropanation protocol that can be applicable to general hydrazones and alkenes with broad functionalities.