

Rhodium(II) catalysed three-component coupling: a novel reaction of in situ generated iodonium ylides

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Abstract—Cyclic ethers are cleaved in the presence of nitromethane, a base, a hypervalent iodine compound and a Rh(II) catalyst to give nitromethoxy acetates in up to 71% isolated yields. The reaction is a three-component coupling of an ether with a nitromethane derived carbenoid and a carboxylate group originating from the hypervalent iodine compound.

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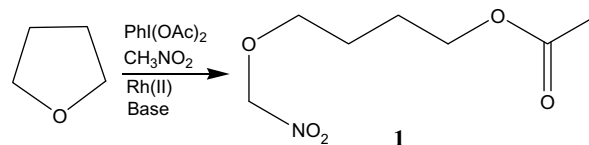
Iodonium ylides are a class of hypervalent iodine compounds that can be used as precursors to metal carbenoids.^{1–6} Iodonium ylides are prepared from an active methylene compound and a hypervalent iodine precursor, and they have gained interest as synthetic equivalents to diazo compounds.⁷ Traditionally, they have been prepared from active methylene compounds with two electron-withdrawing groups, due to the higher stability of the corresponding ylides.⁵ In the studies and utilisation of in situ generated iodonium ylides, focus has so far been mainly on cyclopropanation reactions.^{1–4,6,8–11} Single reports of C–H insertion¹¹ and a rearrangement through intramolecular generation of an oxonium ylide¹² have also been published.

The reaction of a carbene or carbenoid with an ether can have different outcomes. The area has not yet been thoroughly studied, but in addition to C–H insertion and various rearrangements,¹³ there are descriptions of both ether polymerisation^{14,15} and ether cleavage by photolysis,¹⁶ as well as examples of Rh(II) catalysed ether cleavage employing an alkylideneiodonium salt.¹⁷ We recently described a method for cyclopropanation with an in situ generated iodonium ylide flanked with only one electron-withdrawing group.¹⁸ We now report how this iodonium ylide, prepared from nitromethane, may also be utilised in a novel reaction with cyclic ethers.

We discovered that treatment of THF with nitromethane, bis(acetoxy)iodobenzene (PhI(OAc)₂), a base,

and a rhodium catalyst, afforded 4-(nitromethoxy)butyl acetate **1** (Scheme 1).

We started investigating this unprecedented three-component coupling reaction by doing a broad screening, exploring the effects of different bases and catalysts on the reaction (Table 1). In these experiments, PhI(OAc)₂ (1.0 equiv), THF (10.0 equiv), a base, a rhodium(II) catalyst and a large excess of nitromethane (neat) were added simultaneously and the reaction allowed to stir at room temperature for 3 h. All reagents were used as received. We found that the yield of **1** was highly dependent on the choice of base, with potassium fluoride and potassium acetate giving the best yields. Furthermore, in all the reactions, independent of base, **1** was the main product. The acetate group in **1** must originate from bis(acetoxy)iodobenzene since PhI(OAc)₂ was the only source of acetate available in the reaction mixture when non-acetate bases were used. To the best of our knowledge, this is the first example of an iodonium ylide reaction where the carboxylate ligand on PhI(OAc)₂ participates as a reactant and is incorporated in the product.



Scheme 1.

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Table 1. Initial screening

Entry	Catalyst	Catalyst loading (mol %)	Base	Equiv of base	Yield of 1 ^a (%)
1	Rh ₂ (esp) ₂	2.5	KF	1.0	75
2	Rh ₂ (esp) ₂	2.5	KOAc	1.0	69
3	Rh ₂ (esp) ₂	2.5	NaOAc	1.0	32
4	Rh ₂ (OOct) ₄	2.5	KF	2.2	55
5	Rh ₂ (OOct) ₄	2.5	Na ₂ CO ₃	2.2	43
6	Rh ₂ (OOct) ₄	2.5	K ₂ CO ₃	2.2	26
7	Rh ₂ (OOct) ₄	2.5	MgO	2.2	0
8	Rh ₂ (OAc) ₂	10	KF	2.2	42
9	Rh ₂ (OAc) ₂	10	K ₃ PO ₄	2.2	34
10	Rh ₂ (OAc) ₂	10	K ₂ CO ₃	2.2	33
11	Rh ₂ (OAc) ₂	10	CsF	2.2	12
12	Rh ₂ (OAc) ₂	10	CsCO ₃	2.2	10

^a Measured by internal standard (1,3,5-trimethoxy benzene) in ¹H NMR analysis of crude reaction mixture.

It was clear from the initial screening that the ligands on the dirhodium core of the catalyst had a substantial effect on the outcome of the reaction. Hence, the effect of different catalysts and catalyst loadings was systematically examined (Table 2). Potassium fluoride was chosen as the base for these and the following optimisation experiments. Whereas Pd(OAc)₂ and Cu(acac)₂ failed to catalyse the formation of **1** (entries 12 and 13), all the Rh(II) catalysts tested provided **1**. Ether cleavage did not occur in the absence of catalyst. The bridged catalyst Rh₂(esp)₂ was the catalyst of choice in the previously described cyclopropanation reaction with nitromethane.¹⁸ Once again, this catalyst proved the most efficient, allowing for a rather low catalyst loading while still giving good yields (entries 1–4). Reducing the catalyst loading to only 1 mol % still gave a yield of 64% (entry 4).

These factors having been established, we started investigating the effects of other parameters on the reaction. Initially, all experiments were performed at room temperature. However, more satisfactory results were obtained when the temperature was increased to 30 °C. The reaction showed a slight temperature dependence;

Table 2. Effect of catalyst and catalyst loading

Entry	Catalyst	Catalyst loading (mol %)	Yield of 1 ^a (%)
1	Rh ₂ (esp) ₂	10	71
2	Rh ₂ (esp) ₂	5	74
3	Rh ₂ (esp) ₂	2.5	75
4	Rh ₂ (esp) ₂	1	64
5	Rh ₂ (OOct) ₄	10	63
6	Rh ₂ (OOct) ₄	5	55
7	Rh ₂ (OOct) ₄	2.5	55
8	Rh ₂ (OOct) ₄	1	31
9	Rh ₂ TMA ₄	10	57
10	Rh ₂ (OAc) ₂	10	42
11	Rh ₂ TFA ₄	10	11
12	Pd(OAc) ₂	10	0
13	Cu(acac) ₂	10	0

^a Measured by internal standard (1,3,5-trimethoxy benzene) in ¹H NMR analysis of crude reaction mixture.

results seemed to be more reproducible at 30 °C than at room temperature. A reaction time of 3 h, as chosen to begin with, proved to be sufficient. Increasing the reaction time to 7, 15 or 24 h had no effect on yields. A reaction time of 1 h gave a 66% yield of **1**, compared to 75% after 3 h. Rigorously dry conditions did not increase yields, whereas 0.3 equiv of added water prevented completely the reaction. We originally believed that 2 equiv of base was necessary. It did, however, become apparent that the reaction was in fact catalytic with regards to base, and as little as 0.6 equiv of potassium fluoride was sufficient to obtain high a yield of **1** (Table 3, entry 2). Since both nitromethane and THF are inexpensive and readily available, both were initially used in a rather large excess. Experiments showed that the amounts of THF and nitromethane could be decreased to 5 equiv and 10 equiv, respectively, without significant effect on the yields (Table 3, entries 6–8). The amounts of all three reagents could not be reduced simultaneously without lowering the yield (Table 3, entry 12). To reduce the equivalents of THF and nitromethane, the amount of potassium fluoride had to be at least 1.0 equiv.

Having established a satisfactory set of reaction conditions, we then proceeded to investigate the effect of other hypervalent iodine compounds. The experiments were performed at 30 °C, using a catalyst loading of 2.5 mol % and reagent amounts as shown in Table 3, entry 8. PhI(OPiv)₂ gave a 57% yield of 4-(nitromethoxy)butyl pivalate, the analogous product to **1**. This result confirmed that the carboxylate group in the product originated from the hypervalent iodonium source. With PhI(TFA)₂ as the hypervalent iodine compound, no formation of the TFA-derivative of **1** was observed. Iodosylbenzene, having no carboxylate substituent on iodine, gave a complex product mixture.

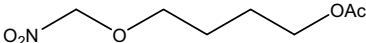
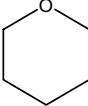
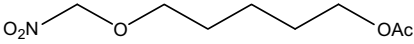
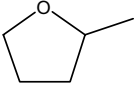
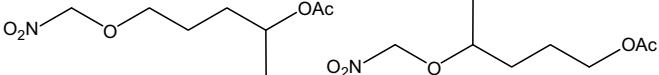
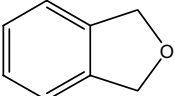
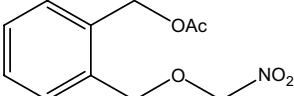
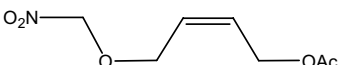
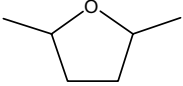
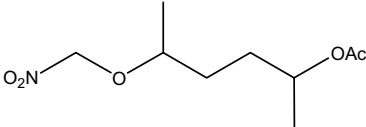
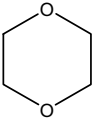
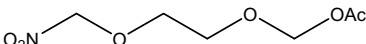
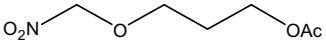
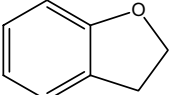
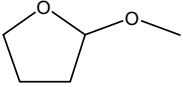
To examine the scope of the three-component coupling reaction, a number of cyclic ethers were exposed to the same reaction conditions as described for the previous experiments. Table 4 shows the results from this examination, in which no steps were taken to optimise the reaction conditions for the substrates in entries 2–10.

Table 3. Effect of varying the amounts of reagents

Entry	KF (equiv)	THF (equiv)	MeNO ₂ (equiv)	Yield of 1 ^a (%)
1	0.5	10	18.6	67
2	0.6	10	18.6	76
3	0.8	10	18.6	76
4	1.0	10	18.6	75
5	1.5	10	18.6	78
6	1.0	5	18.6	71
7	1.0	10	10	73
8	1.0	5	10	71
9	1.0	3	10	58
10	1.0	1	10	33
11	1.0	5	5	67
12	0.6	5	10	59

^a Measured by internal standard (1,3,5-trimethoxy benzene) in ¹H NMR analysis of crude reaction mixture.

Table 4. Scope of different substrates

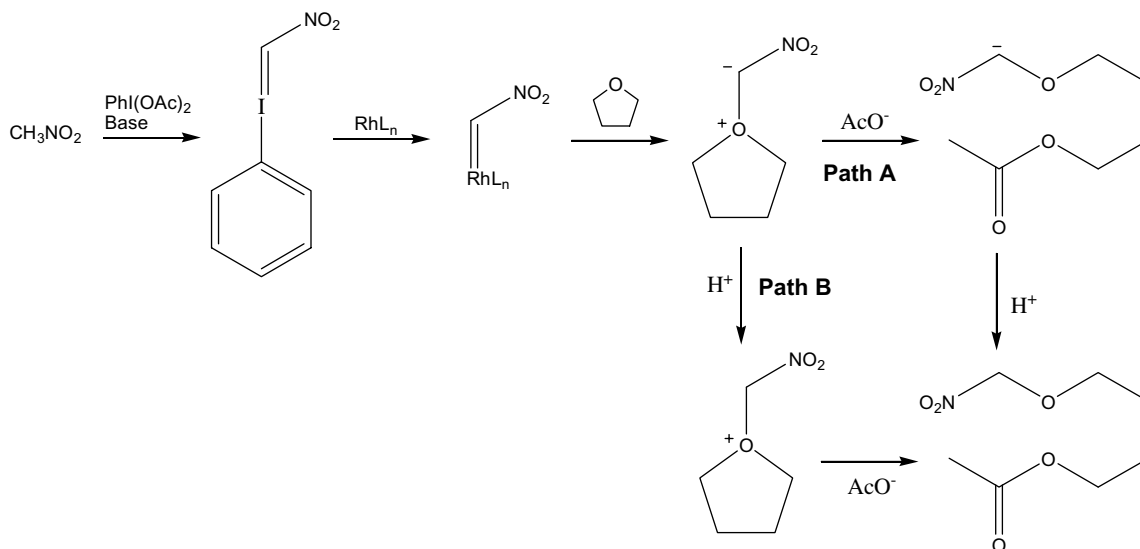
Entry	Substrate	Product(s)	Yield ^a (%)
1			71
2			55
3			45 ^b
4			32
5			28
6			23
7			9
8			7
9		—	0
10		—	0

^a Isolated yield after flash chromatography.^b 1.6:1 ratio favouring the product of attack by AcO[−] at C-2.

The best isolated yield, 71%, was obtained with THF. The other substrates gave low to moderate yields. No general trend emerged regarding what types of ethers are more easily cleaved in the reaction. 2-Methyl tetrahydrofuran (Table 4, entry 3) gave the two products of attack at the 2- and 5-position in a ratio of 1.6:1, favouring the product from attack at C-2. The substrate 2,5-dihydrofuran, having a double bond, represented an opportunity to investigate whether ether cleavage or cyclopropanation was the preferred reaction. Even though the reaction conditions were not very different from the conditions we previously used in the cycloprop-

anation of olefins with nitromethane,¹⁸ the reaction resulted in the product of ether cleavage (Table 4, entry 5) and no cyclopropane was observed. The reaction was also tested on THP (Table 4, entry 2) to explore the effect of changing the ring size. THP gave the analogous product to THF in 55% yield. Two compounds failed to undergo a three-component coupling. Neither 2-MeO-tetrahydrofuran nor 2,3-di-hydrobenzofuran gave any analogous products to the rest of the series.

Scheme 2 shows two probable mechanistic pathways for the cleavage of THF with nitromethane and PhI(OAc)₂.



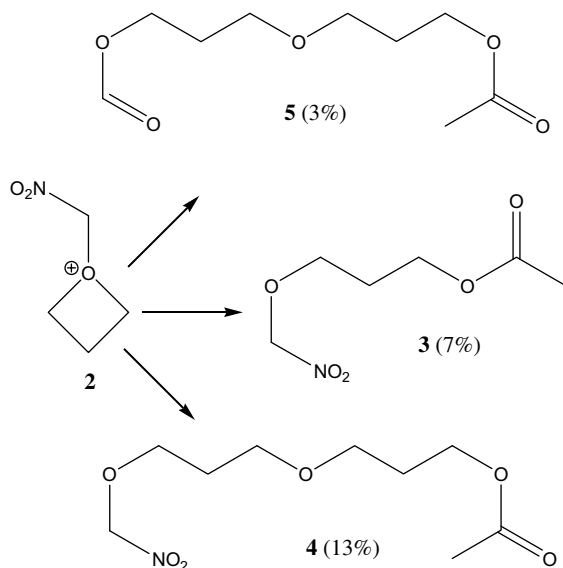
Scheme 2. A plausible reaction mechanism.

Initial formation of an iodonium ylide from nitromethane and $\text{PhI}(\text{OAc})_2$ is followed by $\text{Rh}(\text{II})$ catalysed generation of the analogous ethereal oxonium ylide. Attack on the oxonium ylide, or on the corresponding protonated oxonium ion, by an acetate group then results in ring opening. Considering the weak nucleophilic nature of AcO^- and the presence of KF , competing attack by F^- instead of the acetate ion might have been anticipated. However, the product from such a reaction was not detected.

When oxetane was used as the ether substrate (Table 4, entry 8), three products were isolated and characterised (Scheme 3). Product 3 is the analogous product to the rest of the series, formed by ring opening of the oxonium ylide or oxonium ion by acetate. Product 4 was possibly

generated through ring opening by another molecule of trimethylene oxide, generating a new oxonium ylide or ion that was subsequently attacked by acetate. The formation of product 5 may be explained by a formal Nef reaction of product 4. The formation of products 4 and 5 may be due to the higher ring strain of trimethylene oxide compared to THF, making the ring opening of the trimethylene oxonium ylide or ion favourable enough to allow nucleophilic attack and cleavage by other ether molecules.

In summary, we have developed a novel procedure for cleavage of a range of cyclic ethers, employing nitromethane and a hypervalent iodine compound. The reaction is a three-component reaction, coupling an ether with a nitromethane derived carbenoid and an acetate group originating from the hypervalent iodine compound. This represents the first example where an in situ generated iodonium ylide reacts intermolecularly to generate a cyclic oxonium ylide. Further studies to broaden the scope of the reaction will be reported in due course.



Scheme 3. Products isolated after flash chromatography.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2007.11.021](https://doi.org/10.1016/j.tetlet.2007.11.021).

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