

Transition-Metal-Catalyzed Ring Expansion of Diazocarbonylated Cyclic *N*-Hydroxylamines: A New Approach to Cyclic Ketonitrone

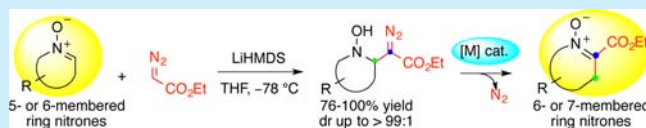
Evelyn Lieou Kui, Alice Kanazawa,* Jean-François Poisson, and Sandrine Py*

Univ. Grenoble Alpes, DCM, F-38000 Grenoble, France

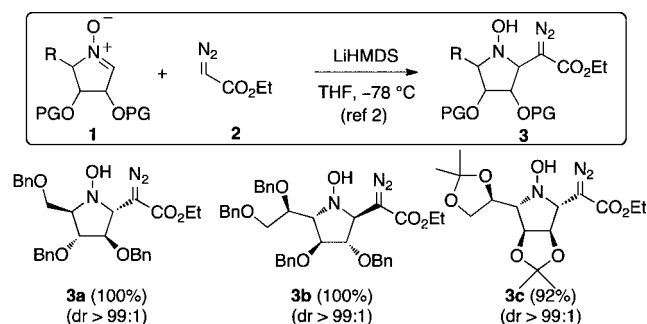
CNRS, DCM, F-38000 Grenoble, France

S Supporting Information

ABSTRACT: Novel C-ethoxycarbonyl cyclic ketonitrone are synthesized from the Ag- or Cu-catalyzed ring expansion of β -diazo cyclic hydroxylamines. The latter are themselves easily obtained by the addition of lithiated ethyl diazoacetate onto cyclic nitrones. The regioselective metal-catalyzed rearrangement of β -diazo cyclic hydroxylamines proved highly efficient and resulted in a synthetically useful ring expansion to produce 6- or 7-membered ring functionalized nitrones. The outcome of the two steps, i.e. nucleophilic addition of α -diazoesters to nitrones and ring expansion, is a formal nitron homologation.



Diazo compounds are highly versatile intermediates in organic synthesis. In particular, they are precursors of metal carbenoids that can undergo powerful synthetic transformations.¹ We recently reported the synthesis of β -diazo *N*-hydroxylamines by addition of lithiated α -diazoesters on a variety of nitrones.² From carbohydrate-derived cyclic nitrones **1**, the expected *N*-hydroxypyrrolidines **3a–c** were obtained in high yields and excellent diastereoselectivities (Scheme 1).

Scheme 1. Previous work²

Intrigued by the reactivity of these novel highly functionalized diazoester derivatives, we decided to investigate their transformation in the presence of metal catalysts. We report herein an extension of the scope of preparation of cyclic β -diazo *N*-hydroxylamines from nitrones and the first study on their transformation in the presence of metal catalysts, granting access to novel, homologated cyclic nitrones conjugated to an ester function.

Various substituted cyclic nitrones³ were treated with ethyl lithiodiazoacetate (1.5 equiv) in THF at $-78\text{ }^{\circ}\text{C}$ (Table 1), according to our reported protocol. From nitron **1d**⁴ or **1e**,⁵ the corresponding β -diazo *N*-hydroxypyrrolidines **3d** and **3e** were readily obtained in good yields, as single *trans* diastereomers (Table 1, entries 1 and 2).⁶ In contrast, a

mixture of diastereomeric hydroxylamines **3f** and **3g** (*trans/cis* = 60:40) was obtained from nitron **1f**,⁷ albeit in excellent overall yield (93%) (Table 1, entry 3). The noncarbohydrate nitron **4**⁸ (MiPNO, Table 1, entry 4) was readily converted into **8** in good yield and with excellent diastereoselectivity (76%, *dr* >99:1), in line with the total diastereocontrol previously observed in the addition of Grignard reagents to this nitron.⁹

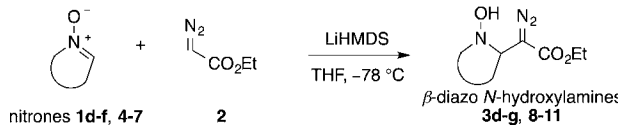
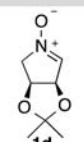
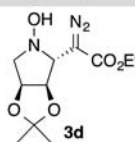
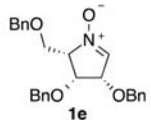
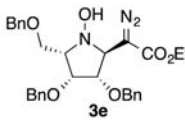
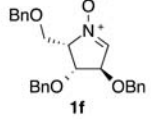
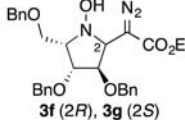
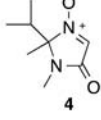
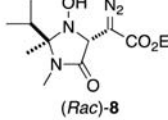
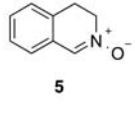
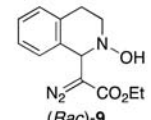
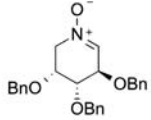
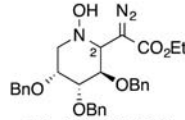
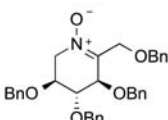
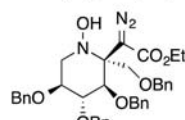
The addition of ethyl lithiodiazoacetate was next extended to six-membered-ring nitrones. From 3,4-dihydroisoquinoline *N*-oxide **5**¹⁰ the expected β -diazo *N*-hydroxylamine **9** was obtained in 78% yield.¹¹ In the case of the arabinopyranose-derived nitron **6**¹² the nucleophilic addition was also found to proceed efficiently (97% yield), although in a 64:36 ratio of diastereomers (Table 1, entry 6). The *cis* *N*-hydroxypiperidine **10a** was the major diastereomer, in contrast with previous reports on organometallic additions on this nitron, yielding preferentially *trans* hydroxylamines.^{3d,e,13} Interestingly, the cyclic ketonitrone **7**¹⁴ was smoothly transformed into the corresponding α -quaternary β -diazo *N*-hydroxypiperidine **11**, in good yield (79%) and excellent diastereoselectivity.⁶ This represents a unique example of organometallic addition on a 6-membered ring ketonitrone.¹⁵

The reactivity of β -diazo hydroxylamines has not been reported to date. As they could represent excellent precursors of oxazetidines¹⁶ by intramolecular O–H-insertion of a transient carbenoid, we studied their reactivity in the presence of metal catalysts. A variety of metal complexes are known to induce decomposition of the diazo functionality, with extrusion of gaseous dinitrogen and formation of highly reactive metal carbenoids. The latter can evolve through different processes including X–H insertion,¹⁷ 1,2-hydride shift, and 1,2-C \rightarrow C or 1,2-X \rightarrow C bond migration (e.g., X = O, N, S, Si). Although

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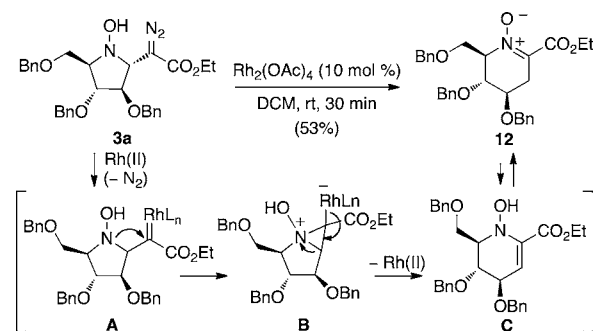
Table 1. Scope of Nucleophilic Addition of Ethyl Diazoacetate on Cyclic Nitrones

					
entry	cyclic nitron	β -diazo N-hydroxylamine	time (h)	yield (%) ^a	dr ^b
1			1.5	93	> 99:1
2			3	78	> 99:1
3			1.5	93	60:40
4			1.5	76	> 99:1
5			3	78	-
6			1.5	97	64:36
7			3.5	79	> 99:1

^aIsolated yield after column chromatography. ^bDetermined by integration of representative signals in ¹H NMR.

examples of chemo- and regioselective rearrangements of carbenoids generated from diazo compounds have been reported,¹⁸ most often several processes compete, leading to mixtures of products.¹

Dirhodium tetraacetate, the most popular catalyst for carbenoid formation,^{1a,19} was tested first on *N*-hydroxypyrrolidine **3a**. The six-membered ring nitron **12** was the only isolated product, with no trace of oxazetidine. The formation of the nitron **12** can be explained by generation of the Rh(II) carbenoid **A**, from which 1,2-migration of nitrogen would take place to afford an ammonium ylide intermediate **B** (Scheme 2). Then, ring enlargement would occur producing a six membered-enehydroxylamine **C** that tautomerizes to **12**.²⁰ A concerted mechanism for the conversion of metalcarbenoid **A** to intermediate **C** is also plausible.

Scheme 2. Preliminary Result and Proposed Pathway


In order to optimize this unprecedented ring expansion, other catalysts were screened (see Supporting Information for complete screening). Copper and silver complexes²¹ have been described to promote NH-insertion and, in some cases, ring expansion.²² In the present process, they were found to be the most efficient to generate nitron **12** from **3a** in high yields (Table 2). In particular, the tetrakis(acetonitrile)copper(I)

Table 2. Selected Results on Catalyst Screening

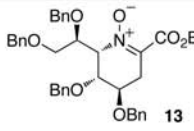
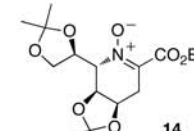
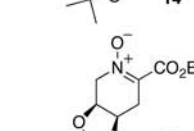
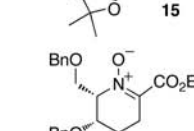
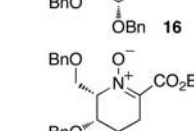
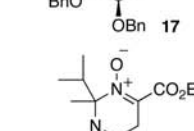
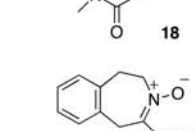
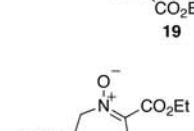
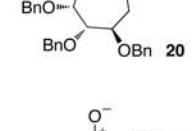
entry	catalyst ^a	solvent	temp	time	yield ^b (%)
1	Rh ₂ (OAc) ₄	CH ₂ Cl ₂	rt	30 min	53
2 ^c	Cu(OTf) ₂	CH ₂ Cl ₂	rt	45 min	77
3	Cu(CH ₃ CN) ₄ BF ₄	CH ₂ Cl ₂	rt	<5 min	86
4 ^d	Cu(CH ₃ CN) ₄ PF ₆	CH ₂ Cl ₂	rt	<5 min	96
6	AgBF ₄	CH ₂ Cl ₂	rt	50 min	82
7	AgOBz	CH ₂ Cl ₂	rt	1.25 h	83
8	AgOTf	CH ₂ Cl ₂	rt	20 min	97
9	no catalyst	CH ₂ Cl ₂	40 °C	120 h	0 ^e
10	no catalyst	PhCF ₃	80 °C	50 min	57

^aThe reactions were performed in the presence of 10 mol % catalyst unless otherwise stated. ^bIsolated yield after column chromatography. ^c15 mol % catalyst. ^dWith 0.5 mol % catalyst, nitron **12** was isolated in 86% yield (40 min). ^eStarting material was totally recovered.

hexafluorophosphate [Cu(CH₃CN)₄PF₆] was an excellent catalyst, producing rapidly the desired nitron **12** in 96% yield (<5 min) with a 10 mol % catalyst loading, and in 86% yield (40 min) with 0.5 mol % catalyst. Catalysis with AgOTf (10 mol %) delivered **12** in 97% yield in 20 min. Thermal decomposition of **3a** was also examined: while no trace of nitron **12** was detected in refluxing CH₂Cl₂ after several days (Table 2, entry 9), the ring-expanded nitron was isolated in 57% yield by heating **3a** at 80 °C during 50 min in trifluorotoluene (Table 2, entry 10).²³

With these results in hand, Cu(CH₃CN)₄PF₆ and AgOTf were selected as catalysts to evaluate the substrate scope (Table 3). As in the case of *N*-hydroxypyrrolidine **3a**, all other five-membered ring β -diazo-hydroxylamines **3** underwent Ag- and Cu-mediated ring expansion to 6-membered ring cyclic nitrones in excellent yields (68–100%) (Table 3, entries 1–13). Nitrones **13**–**17** were isolated as single products and exhibited good stability. The diastereoisomeric *N*-hydroxypyrrolidines **3f** and **3g** were both transformed into the same nitron **17** in good yields, upon Ag- or Cu-catalysis. In general, reactions mediated by Cu(CH₃CN)₄PF₆ catalysis were faster than those mediated by AgOTf. In addition, with 2 mol % copper catalyst the reaction efficiency was maintained (Table 3, entry 9).

Table 3. Formation of Ketonitrone 13–20 Mediated by Ag(I) and Cu(I) Catalysts^a

entry	β -diazo- <i>N</i> -hydroxylamine [cat.] ^b	reaction time	ketonitrone	yield (%) ^c
1	3b [Ag]	30 min		100
2	3b [Cu]	< 5 min		100
3	3c [Ag]	20 min		99
4	3c [Cu]	< 5 min		88
5	3d [Ag]	130 min		83
6	3d [Cu]	20 min		88
7	3e [Ag]	45 min		95
8	3e [Cu]	< 5 min		89
9	3e [Cu] ^d	< 5 min		93
10	3f/3g [Ag]	30 min		97
11	3f/3g [Cu]	30 min		68
12	8 [Ag]	< 5 min		96
13	8 [Cu]	< 5 min		90
14	9 [Ag]	100 h		36 ^f
15	9 [Ag] ^e	160 min		78
16	9 [Cu]	35 min		60
17	10a [Ag]	70 min		96
18	10a [Cu]	< 5 min		46 ^g
19	10b [Ag]	23 h		64
20	10b [Cu]	20 min		7 ^g
21	11 [Ag] ^e	40 min		0 ^g
22	11 [Cu] ^e	40 min		0 ^g

^aAll reactions were performed in dichloromethane, at room temperature, with 10 mol % catalyst, unless otherwise stated. ^b[Ag]: AgOTf; [Cu]: Cu(CH₃CN)₄PF₆. ^cIsolated yield after chromatography. ^d2 mol % cat. ^e100 mol % cat. ^f24% imine resulting from dehydration of **9** was isolated as a side product. ^gCH-insertion competes favorably with ring expansion (see Supporting Information).

We next turned our attention to the more challenging conversion of *N*-hydroxypiperidines **9**–**11** into 7-membered-ring ketonitrone. When the β -diazo hydroxylamine **9** was treated with 10 mol % AgOTf (Table 3, entry 14) the expected nitrone **19** was isolated in only 36% yield, accompanied by ethyl 2-diazo-2-(3,4-dihydroisoquinolin-1-yl)acetate (24%) arising from dehydration of **9**. However, the 7-membered-ring

nitrone **19** could be obtained in 78% yield, by increasing the amount of silver triflate to 1 equiv (Table 3, entry 15). Using Cu(CH₃CN)₄PF₆ (10 mol %) as the catalyst, nitrone **19** formed in only 35 min (60%, Table 3, entry 16). This result confirms the superiority of the copper catalyst over silver triflate, a trend already observed for the 5 \rightarrow 6-membered ring expansions. Again, when diastereomeric *N*-hydroxypiperidines **10a** and **10b** were treated with the Ag- or Cu-catalysts, the starting materials were consumed much faster with the latter (minutes instead of hours). However, from these β -diazo hydroxylamines, nitrone **20** was isolated in higher yield with the silver catalyst (96% from **10a**, 64% from **10b**). The lower yields in the Cu-catalyzed ring expansion of these *N*-hydroxypiperidines is due to competing insertion of the transient carbenoid in a benzylic C–H bond of the C-3 benzyloxy-substituent in hydroxylamines **10a** or **10b** (see Supporting Information).^{1c,f} Unfortunately, nitrone **21** that was expected to arise from ring expansion of hydroxylamine **11** was not isolated from treatment of **11** with AgOTf or Cu(CH₃CN)₄PF₆, neither with a 10 mol % (not shown) nor with a 100 mol % (Table 3, entries 21, 22) loading. The only products that could be identified from the reaction mixture resulted from CH-insertion (see Supporting Information). This side reaction, which was never observed from β -diazo *N*-hydroxy pyrrolidines, occurs competitively from *O*-benzyl-protected β -diazo *N*-hydroxypiperidines (Table 3, entries 18 and 20–22), as the formation of 7-membered rings is energetically demanding.

In summary, the efficient addition of α -diazo esters to cyclic nitrones, followed by metal-catalyzed ring expansion, results in homologation to new C-ethoxycarbonyl cyclic ketonitrone. In contrast to the well-documented preparation of aldonitrone,³ methods for the preparation of cyclic ketonitrone are scarce and suffer from low yields.^{14,24,25} This novel approach for their synthesis opens new opportunities for development of the rich chemistry of nitrones. Further applications of these novel structures to access cyclic amino acids and bioactive alkaloids are currently ongoing in our laboratory. We are also investigating the factors that influence the selectivity of these reactions depending on the nature of the catalysts.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data, full experimental procedures, and copies of ¹H and ¹³C NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: alice.kanazawa@ujf-grenoble.fr.

*E-mail: sandrine.py@ujf-grenoble.fr.

Notes

The authors declare no competing financial interest.

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