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Rh$_2$(OAc)$_4$-catalyzed reactions of α-diazoimides: a simple and novel synthesis of mono- and bis(2,3-fused perhydrooxazol-4-one) systems†

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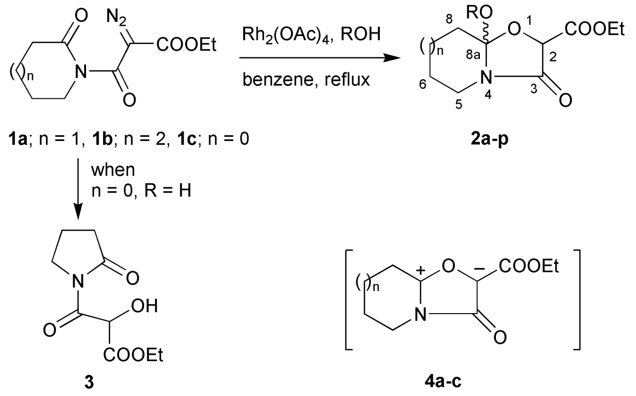
Simply, trapping the intermediate isomünchnone 1,3-dipoles by the external oxygen nucleophiles resulted in new heterocyclic systems and the use of diols led to the formation of four carbon-oxygen bonds in a single operation which eventually delivered bis(2,3-fused perhydrooxazol-4-one) systems.

The synthesis, reactions and biological properties of new heterocyclic systems constitutes a significant part of modern heterocyclic chemistry. The development of a method for novel heterocyclic systems from simple starting materials is attractive from a synthetic point of view. The construction of new heterocycles through selective multiple-bond formation from a single synthetic step is of particular interest in organic synthesis. The metallo-carbenoids generated from diazo carbonyl compounds have been exploited to achieve a range of polycyclic[1] systems through an array of reactions such as cyclopropanation, C–H or heteroatom–H insertion and ylide formation.[2] The intramolecular generation of carbonyl ylides by rhodium(II)-catalyzed decomposition of α-diazo carbonyl compounds and subsequent transformation to diverse products have received enormous attention.[1,2a–d] The chemistry of mesoionic oxazolium ylides (isomünchnones) and its cycloaddition reaction with various dipolarophiles have been well developed in recent years.[2c,3,4] Asymmetric versions[5] of the intermolecular cycloaddition reactions of isomünchnones, further enhancing the synthetic appeal of these intermediates, have also been developed. However, the outcome of the transient intermediate isomünchnones generated by the reaction of diazo carbonyl compounds and rhodium(II) carboxylate catalyst in the absence of any dipolarophiles has scarcely been studied in the literature.[6] Our interest in the chemistry of diazoimides in the presence of rhodium(II) acetate stems from the recent studies[7] on diazoamines and -amides. Inspired by Padwa's pioneering work on isomünchnones[2,3] and taking advantage of our persisting interest in the reactions[8] of diazo carbonyl compounds, we herein report the rhodium(II) acetate catalyzed reactions of α-diazoimides to synthesize a variety of 2,3-fused perhydrooxazol-4-one (bicyclic lactam) as well as bis(2,3-fused perhydrooxazol-4-one) systems *via* tandem process.

Diazoimides **1a–c** were chosen as a test case for the reaction with nucleophiles in the absence of any dipolarophiles because of their easy accessibility and extensive use[3,9] in the construction of complex nitrogen heterocycles using rhodium(II) acetate as a catalyst in the presence of a variety of dipolarophiles.

Our initial efforts were directed towards the trapping of isomünchnones with water. Treatment of α-diazoimide, **1a**, with rhodium(II) acetate (0.3 mol%) at 80 °C in the presence of water yielded fused perhydrooxazol-4-one **2a** as a diastereomeric mixture in the ratio of 43:57. Similar treatment of **1b** delivered the compound **2b**. Unexpectedly, the reaction of diazo carbonyl compound **1c** provided the secondary alcohol **3**. To study this interesting pathway, we decided to expose diazo carbonyl compounds **1a–c** in the presence of a range of alcohols.

To this end, the diazo carbonyl compounds **1a–c** were reacted with an excess amount of methanol which resulted in the formation of methoxy substituted 2,3-fused perhydrooxazole-4-ones **2c–e** in good yields. This reaction was further generalized in the presence of benzyl alcohol, isopropyl alcohol, cyclohexanol, cetyl alcohol and 1-pyrenylmethanol to afford the corresponding 2,3-fused perhydrooxazol-4-ones **2f–p** (Scheme 1, Table 1). Remarkably, the related 5,5- and 5,6-bicyclic lactams are extensively used in the synthesis of an ample range of pyrrolidine and piperidine derivatives of biological and pharmacological interest and further demonstrated to be extremely useful building blocks for a number of natural and non-natural products.[10] Interestingly, pyrene derivatives are



Scheme 1 Reactions of isomünchnones with nucleophiles.

Table 1 Rhodium(II) acetate catalyzed synthesis of 2,3-fused perhydrooxazol-4-ones **2**

Entry	*n*	R	Yield[a] (%) Product[b] **2**	Diastereomeric ratio
a	1	H	76	43:57
b	2	H	65	30:70
c	0	CH_3	53	30:70
d	1	CH_3	84	34:66
e	2	CH_3	77	24:76
f	0	CH_2Ph	85	40:60
g	1	CH_2Ph	90	44:56
h	2	CH_2Ph	86	30:70
i	0	$CH(CH_3)_2$	85	47:53
j	0	cyclohexyl	81	32:68
k	0	cetyl	64	38:62
l	1	cetyl	63	43:57
m	2	cetyl	61	44:56
n	0	Py[c]	89	46:54
o	1	Py[c]	94	34:66
p	2	Py[c]	83	41:59

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds. [b] Isolated as a mixture of diastereomers and the ratio is based on NMR analyses. [c] Py stands for pyren-1-methyl.

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† Electronic supplementary information (ESI) available: experimental procedure and spectral data for compounds **2a–p**, **3**, **5a–f**. See http://www.rsc.org/suppdata/cc/b2/b211717g/

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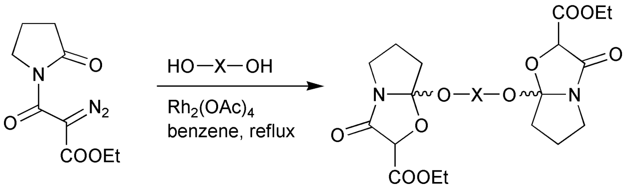
widely used as sensors for a wide variety of analytes including neutral organic compounds and inorganic anions.[11]

The structures of compounds **2** have been evidently characterized from the O–H insertion product **3**, based on the presence of a quaternary carbon atom around δ 110 for carbon-8a (when $n = 1$) and the absence of an amide carbonyl group in ^{13}C NMR.

We further embarked to study this novel reaction in the presence of dihydroxy compounds. For this purpose, an excess amount of diazoimide **1c** with one equivalent of ethane-1,2-diol was characteristically exposed to 0.3 mol% of rhodium(II) acetate at reflux temperature. Interestingly, this reaction provided bis(2,3-fused perhydrooxazol-4-one) compound **5a** in good yield as a diastereomeric mixture. We extended this interesting strategy to other dihydroxy compounds such as propane-1,3-diol, butane-1,4-diol, hexane-1,6-diol, but-2-yne-1,4-diol and benzene-1,4-dimethanol which furnished the corresponding bis(2,3-fused perhydrooxazol-4-one) systems **5b–f** (Scheme 2, Table 2) in good yields. The formation of bis(2,3-fused perhydrooxazol-4-one) products **5** can be explained by the generation of transient isomünchnone dipole **4c**, followed by nucleophilic trapping with both the hydroxy groups of the corresponding diol in a tandem manner. Despite the presence of four chiral centers, NMR analyses showed only the presence of two diastereomers which may be the result of symmetry in compounds **5**.

Based on the reactions of diazo carbonyl compounds,[1] one can envisage the potential formation[2e] of the respective O–H insertion products of type **3**, followed by the intramolecular cyclization may also afford the fused perhydrooxazol-4-ones **2** under our experimental conditions. The literature precedents[3] and the nucleophilic addition of alcohols supported the formation of isomünchnone intermediates **4** rather than the formation of O–H insertion compounds as intermediates in the above reactions. The reason for the formation of secondary alcohol **3** from compound **1c** may be due to a strain present in the 5,5-fused ketal-lactam type **2** (when $n = 0$, R = H) and led to ring opening under the experimental conditions. We did not observe any other products such as β-lactams which can be expected from the possible potential competitive C–H insertion.[12] All these reactions involve the initial tandem ylide formation followed by nucleophilic addition of the hydroxy group to intermediate isomünchnones to furnish the products. It is also known that in the absence of any added trapping agent, the dimerization[13] of carbonyl ylide dipoles takes place; we did not observe any such products from the isomünchnone dipoles. It is relevant to mention that the cyclic diazoimides **1** having an α-hydrogen atom to diazo functionality underwent[7] β-hydride elimination under similar experimental conditions.



1c **5a-f**

Scheme 2 Rhodium(II) acetate catalyzed synthesis of bis(2,3-fused perhydrooxazol-4-one) systems **5**.

Table 2 Synthesis of bis(2,3-fused perhydrooxazol-4-one) systems **5**

		Yield[a] (%)	
Entry	X	Product[b] **5**	Diastereomeric ratio
a	$-(CH_2)_2-$	82	43:57
b	$-(CH_2)_3-$	87	36:64
c	$-(CH_2)_4-$	89	39:61
d	$-(CH_2)_6-$	82	40:60
e	$-CH_2CCCH_2-$	79	44:56
f	$1,4\text{-}(CH_2)_2C_6H_4$	81	38:62

[a] Yields (unoptimized) refer to isolated and chromatographically pure compounds. [b] Obtained as a mixture of diastereomers and the ratio is based on NMR analyses.

In conclusion, the transient isomünchnone intermediates are trapped successfully by nucleophiles to furnish the novel 2,3-fused perhydrooxazol-4-one and bis(2,3-fused perhydrooxazol-4-one) systems, respectively with the option to vary its substituents and ring sizes in good to excellent yields. This forms a facile tandem cyclization–nucleophilic addition process to these new 2,3-fused perhydrooxazol-4-one skeletons and the formation of up to two cyclic rings and four C–O bonds are achieved in a single step. This interesting strategy can also be applicable to other nucleophiles, the investigation in this line is actively being undertaken in our laboratory and will be disclosed in due course.

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