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Preparation and *in situ* use of unstable *N*-alkyl α-diazo-γ-butyrolactams in Rh^{II}-catalyzed X-H insertion reactions

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ABSTRACT

N-Alkyl α-diazo-γ-butyrolactams previously found to be unstable and undergo unproductive dimerization to bis-hydrazones, were successfully converted immediately to various X-H insertion products with alcohols, aromatic amines and thiols *via* an *in situ* Rh^{II}-catalyzed reaction. With aliphatic amines or unreactive, sterically hindered anilines, the reaction tends to yield enamine adducts.

Introduction

Earlier this year, we described the first synthesis and subsequent transformations of a rare type of cyclic α-diazocarbonyl compounds, namely, α-diazo-γ-butyrolactams [1]. In particular, *N*-aryl α-diazo-γ-butyrolactams **1** were efficiently transformed into pyrrolinones **2** on treatment with AgOTf (1 mol%) and into α-alkoxy derivatives **3** *via* $Rh_2(OAc)_4$-catalyzed O-H insertion reaction with various alcohols. In contrast, *N*-alkyl α-diazo-γ-butyrolactams **4** did not enter these reactions typical of α-diazocarbonyl compounds as they rapidly dimerized to give bis-hydrazones **5** (Fig. 1). The instability of *N*-alkyl α-diazo-γ-butyrolactams **4** compared to their *N*-aryl counterparts **1** is most likely related to the reduced electron-withdrawing character of the lactam carbonyl group in the former compared to the latter. This assumption is further supported by the fact that o-substituted *N*-aryl derivatives **1** (in which conjugation of the aromatic ring with the lone pair of the lactam nitrogen atom is reduced due to sterically forced loss of co-planarity between the aromatic ring and the aminocarbonyl moiety) are as unstable as the *N*-alkyl derivatives **4** [1].

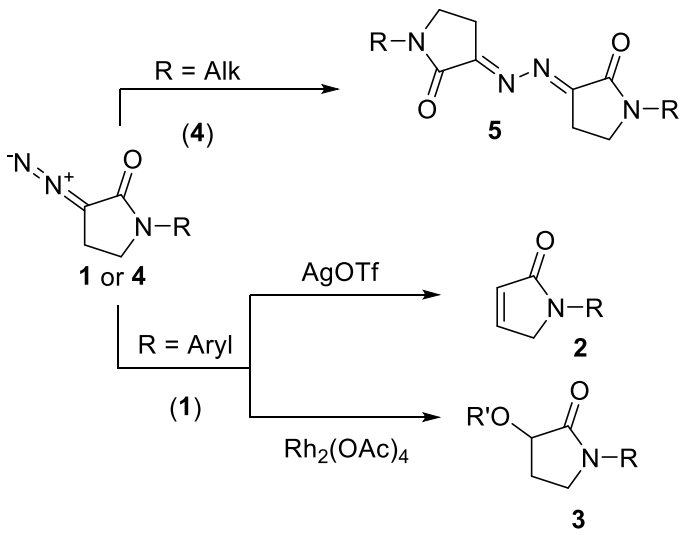


Figure 1. Previously reported uses of α-diazo-γ-butyrolactams.

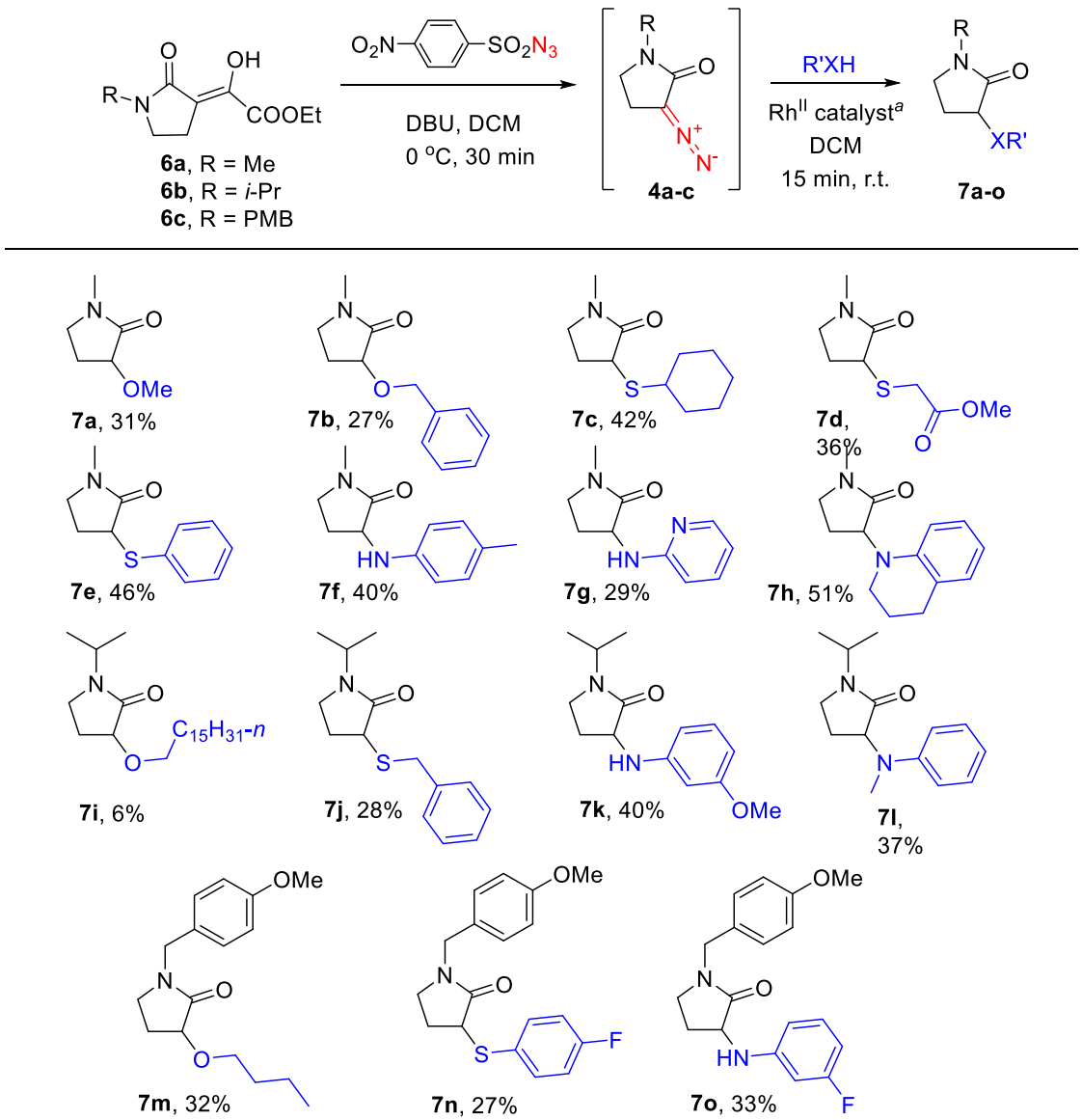
Faced with this serious limitation of the reactivity scope, we set off to investigate the possibility of using unstable compounds **4** *in situ*, promptly after their formation, in various Rh^{II}-catalyzed X-H insertion reactions, particularly, the recently described rhodium carbene insertion into O-H [1], N-H [2] and S-H [3] bonds of alcohols, aromatic amines and thiols, respectively. Herein, we report the results of these studies.

Results and discussion

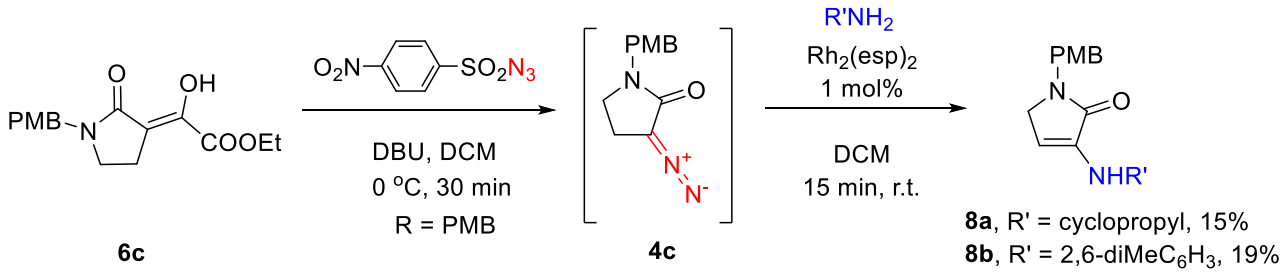
Three *N*-alkyl α-ethoxalyl γ-lactams **6a-c** prepared by oxalylation of the respective γ-lactams as decribed previously [1] underwent a rapid diazo transfer reaction *via* the conventional protocol [4-5] employing 4-nitrobenzenesulfonyl azide and DBU. Quick filtering through a plug of alumina (in lieu of silica gel which decomposed diazo compounds **4a-c**), addition of an alcohol, a thiol or an aromatic amine along with a Rh^{II} catalyst resulted in a rapid insertion reaction and the isolation of the desired α-substituted γ-lactams **7a-o** in modest yields (Scheme 1). It should be noted that, after some experimentation, reactions with alcohols and thiols were found to be efficiently catalyzed by 1 mol% of $Rh_2(OAc)_4$ and to go to completion within 30 min; for aromatic amines, this catalyst proved inefficient and was replaced with 0.5 mol% of $Rh_2(esp)_2$. Attempted change of the catalyst to $Rh_2(esp)_2$ in the reactions with alcohols and thiols (which earlier gave us a marked improvement of the product yield in NH-insertion reactions [2]) resulted in no notable improvement in this case.

The only attempt to employ an aliphatic amine, cyclopropylamine (which would presumably be less reactive in the Rh^{II}-catalyzed insertion reaction [2]) resulted in the formation of a sole identifiable product – enamine **8a** isolated from a complex mixture of unidentified by-products chromatographically. The formation of **8a** (also observed previously, along with the expected,

saturated coupling product in the Rh^{II}-catalyzed reaction of cyclopropylamine with *N*-phenyl α-diazo 2-pyrrolidone [2]) can be rationalized, as proposed previously [2], either by oxidation of diazo lactam **6c** to a respective ketone (a process described in the literature for other α-diazocarbonyl compounds [6]), followed by nucleophilic attack of cyclopropylamine. Alternatively, the formation of the enamine product could be envisaged *via* the reaction of the amine with bis-hydrazone **5** which would form if the N-H insertion pathway was not sufficiently rapid. Both assumptions are in line with the formation of similar enamine coupling product **8b** we observed with 2,6-dimethylaniline. With this unreactive, sterically hindered aromatic amine, **6c** is likely to undergo either the unwanted $N_2 \rightarrow O$ oxidation or dimerize to bis-hydrazone **5**, whereupon the resulting intermediate would be eventually trapped by the aniline to give **8b** (Scheme 2). The viability of either (or both) of these possibilities are currently investigated. It should be noted that a similar $Rh_2(esp)_2$-catalyzed reaction of one of *N*-aryl α-diazo-γ-butyrolactams **1** with 2,6-dimethyl aniline previously gave an excellent yield of the N-H insertion product [2].



Scheme 1. Generation and *in situ* Rh^{II}-catalyzed X-H insertion reactions of diazo compounds - **4a-c** (^{a} Rh^{II} catalyst = 0.5 mol% $Rh_2(OAc)_4$ (for X = O or S) or 1 mol% $Rh_2(esp)_2$ (for X = NR′).



Scheme 2. Formation of enamine coupling products **8a-b**.

Conclusion

We demonstrated that the scope of α-diazo-γ-butyrolactams capable of undergoing Rh^{II}-catalyzed X-H insertions reactions with alcohols, thiols and aromatic amines can be extended to

unstable *N*-alkyl derivatives for which rapid, unproductive dimerization was previously observed. This was achieved through the immediate addition of the X-H insertion partner and a Rh^{II} catalyst to the solution the diazo compound. The reactions are rapid albeit moderately yielding. Despite the latter drawback, the range of 1,3-disubstituted 2-pyrrolidones attainable *via* the intermediate formation of α-diazo-γ-butyrolactams has been substantially expanded thereby making this approach more useful for potential medicinal chemistry exploration of these disubstituted γ-lactams.

Supporting information

Supporting Information File 1

General experimental information, synthetic procedures, analytical data and NMR spectra for the reported compounds.

Acknowledgements

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