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Digest paper

Substrate and catalyst effects in C–H insertion reactions of α-diazoacetamides

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ABSTRACT

Intramolecular C–H insertion reactions of α-diazocarbonyl compounds typically proceed with preferential five-membered ring formation. However, the presence of a heteroatom such as nitrogen can activate an adjacent C–H site towards insertion resulting in regiocontrol issues. In the case of α-diazoacetamide derivatives, both β- and γ-lactam products are possible owing to this activating effect. Both β- and γ-lactam products are powerful synthetic building blocks in the area of organic synthesis, as well as a common scaffold in a range of natural and pharmaceutical products and therefore C–H insertion reactions to form such compounds are attractive processes.

Contents

Introduction

α-Diazocarbonyl compounds act as precursors to carbenes, neutral species which possess a divalent carbon [1–3]. Formation of these species can occur through decomposition of α-diazocarbonyl precursors via thermolytic or photolytic means, and the resulting carbenes can partake in a number of reactions; however, these processes tend to be unselective and difficult to control and, as a result, of little synthetic value [1,2]. Complexation of the α-diazocarbonyl substrates with transition metal catalysts leads to forma-

Abbreviations: acam, acetamidate; cap, caprolactamate; esp, α,α,α′,α′-tetramethyl-1,3-benzenedipropionate; 4(*S*)-MACIM, methyl 1-acetyl-2-oxoimidazolidine-4(*S*)-carboxylate; 4(*S*)-MEOX, methyl 2-oxazolidone-4(*S*)-carboxylate; 5(*S*)-MEPY, methyl 2-pyrrolidone-5(*S*)-carboxylate; oct, octanoate; pfb, perfluorobutyrate; PTTL, *N*-phthaloyl-*tert*-leucinate.

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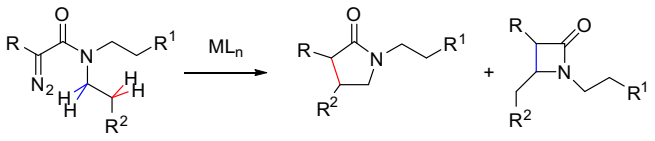


Scheme 1. 1,5- and 1,4-C–H insertion.

tion of metal-carbenoids which retain the synthetic versatility of free carbenes, while also exhibiting enhanced chemo-, regio- and stereoselectivity.

For a given substrate, several reaction pathways may be available, and the chemoselectivity of such processes is dependent on the nature of both the substrate and the catalyst. The C–H insertion process is an important reaction as it functionalises unreactive C–H bonds resulting in formation of a new C–C bond [4–8]. The intramolecular version of this transformation can, depending on the substrates, lead to the formation of carbocyclic and heterocyclic compounds. The focus of this review will be intramolecular C–H insertion reactions of α-diazoacetamides which allow formation of lactams through C–H functionalisation. The area of rhodium (II)-catalysed intramolecular C–H insertion reactions of α-diazoacetamides was reviewed by Afonso and co-workers in 2004 [9], and thus this review will focus predominantly on developments since 2004 with inclusion of only the most significant examples prior to 2004. A very recent review has covered the selective synthesis of β-lactams via C–H insertion reactions [10].

A major challenge for the synthetic development of C–H insertion reactions remains control of insertion chemo- and/or regioselectivity [1,4,6,11–13]. Taber's seminal work in the 1980s showed intramolecular C–H insertion reactions generally proceed with preferential formation of five-membered carbocycles [14–19]. However, addition of a heteroatom such as nitrogen to the α-diazocarbonyl substrate can facilitate four-membered ring formation owing to the activating effect of the heteroatom (Scheme 1). Thus competitive 1,4- and 1,5-C–H insertion can be observed for these types of compounds, although 1,5-C–H insertion is typically observed as the major pathway [4].

This review will be divided into two sections; section one will deal with the impact of the substrate structure on the C–H insertion reaction, while the second section will focus on the catalyst effect and ultimately the importance of catalyst choice for these reactions.

The impact of substrate structure

Structural aspects of the reacting substrate can dramatically affect the reactivity of the diazo compound, but also various features of the reaction including efficiency, chemo-, regio- and diastereoselectivity. Thus careful design of the α-diazoacetamide framework is imperative in an effort to manipulate and control the ensuing C–H insertion reaction. Features of the α-diazoacetamides which control the reaction outcome in terms of substrate effect include (1) the amide group (2) the α-substituent (Fig. 1).

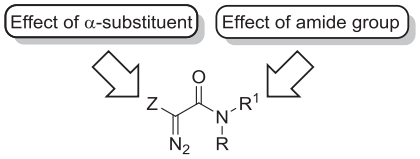


Fig. 1. Aspects of α-diazoacetamide framework which can affect reaction outcome.

Influence of α-substituent

α-Diazocarbonyl compounds can be classified according to their functionality alpha to the diazo moiety. Substrates which bear only one electron-withdrawing group such as a keto, ester or amide group α to the diazo group are precursors to acceptor-substituted metal-carbenoids (Fig. 2) [4]. In this case the α-substituent is a hydrogen atom.

These substrates tend to be more reactive substrates and require mild conditions in order to undergo reaction. However, this increased reactivity can lead to competing side reactions such as homocoupling [4].

This has been effectively demonstrated by Perez and co-workers in their copper-catalysed C–H insertion reactions of acceptor-type *N*-alkyl-α-diazoacetamides [20]. In copper-catalysed reactions of 2-diazo-*N*,*N*-diethylacetamide **1** (Scheme 2), the homocoupling product **4** was typically observed as the major product of the reaction. The reaction was repeated using rhodium(II) acetate and in this case preferential formation of γ-lactam **2** was observed; however, **4** was still observed as a minor product. Perez also investigated reactions of 2-diazo-*N*,*N*-diisopropylacetamide and found C–H insertion was observed as the major reaction pathway for copper and rhodium catalysts [20]. However, in some instances, homocoupling was observed as a minor reaction pathway. Interestingly, homocoupling is not an issue for acceptor-substituted α-diazoacetamides bearing cyclic amido diazo substrates. In these cases, reactions are observed to proceed with high efficiencies for C–H insertion [21].

Introduction of electron-donating groups (or donor groups) such as aryl or vinyl groups as α-substituents can affect the reactivity by reducing the electrophilicity of the derived carbene and thus offering greater selectivity (Fig. 3) [4,22]. Doyle and co-workers recently reported highly regio-, diastereo- and enantioselective

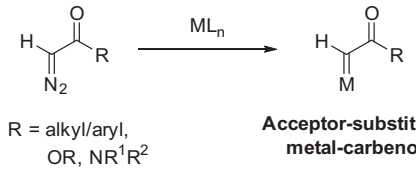
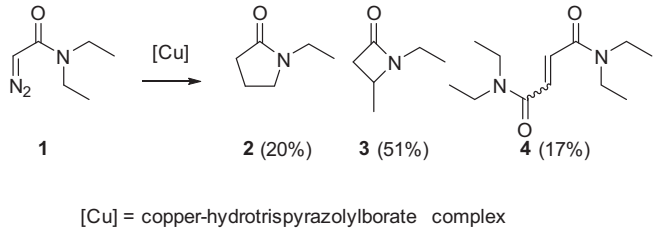


Fig. 2. Formation of acceptor-substituted metal-carbenoids.



Scheme 2. Copper-catalysed reaction of 2-diazo-*N*,*N*-diethylacetamide.

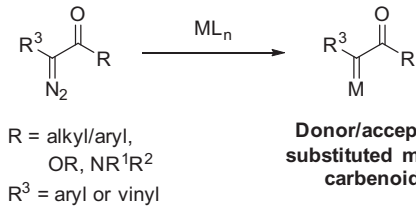


Fig. 3. Formation of donor/acceptor-substituted metal-carbenoids.