

Diazocarbonyls

Versatile Intermediates in Chemical Synthesis

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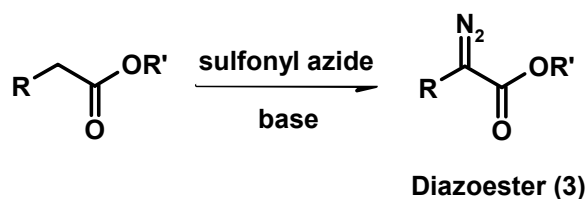
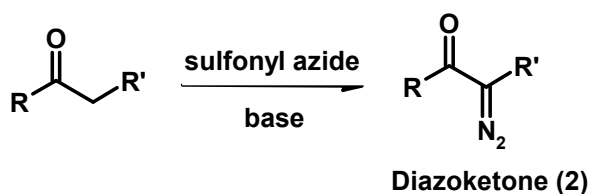
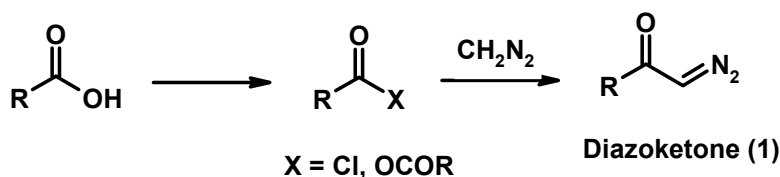
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Introduction

Although more than a century has passed since the German chemists Curtius and Buchner began their systematic study of the reactions of ethyl diazoacetate with organic substrates, modern organic synthesis continues to benefit from the unique versatility of diazocarbonyl intermediates in a broad range of transformations, including alkene and alkyne cyclopropanation, homologation of carboxylic acids, aromatic substitution, alkane C-H insertion, cycloaddition, and heterocycle formation (ref 1).

Almac Sciences and Phoenix Chemicals have been involved for several years in exploiting the potential of diazocarbonyls in the synthesis of intermediates and building blocks with applications in pharmaceutical products. It is our hope that our experiences, highlighted in this article, will provide an attractive starting point for anyone interested in developing new or improved routes to bioactive molecules.

The diazocarbonyls of particular interest are those with the diazo group located alpha to a carbonyl group in a monosubstituted (1) or a disubstituted diazoketone (2) or a diazoester (3). All three types are accessible via diazo transfer methods, the first involving the use of diazomethane and the latter two using a sulfonyl azide.





Most of our exploratory work has been with terminal diazoketones (type 1) which are readily prepared from diazomethane and an activated acyl derivative such as an acid chloride or an anhydride.

Although diazomethane is used extensively in the discovery laboratory, its toxicity and explosive nature have, until relatively recently, precluded the scaling up of such work. However, through the use of *continuous processing technology*, Phoenix Chemicals has developed novel and patentable processes for producing and using high purity diazomethane safely on a commercial scale that maintains the process inventory of diazomethane at very low levels at all times. The plant, which incorporates reliable monitoring, control, and safety systems, is capable of producing > 60 metric tonnes of diazomethane per annum. It supplements the Company's pilot facility, the design and operating details of which have been described elsewhere (ref. 2). The pilot plant is capable of producing diazomethane on a range of scales from a gram to 1 kilogram/day.

Diazoketone reactions

Some of the most important applications of diazoketones in synthesis are accessed through a range of reactions involving the loss of nitrogen in a controlled manner.

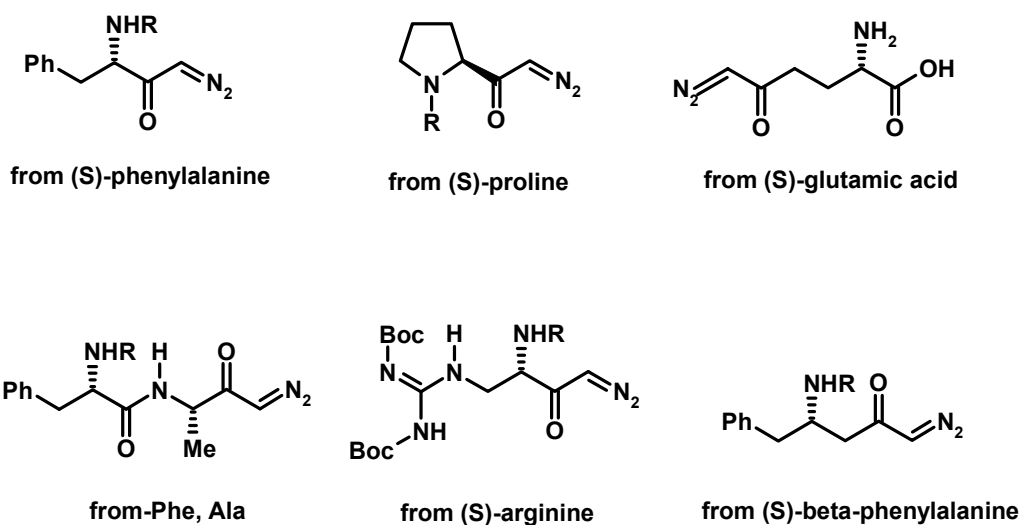
These include :

1. Formation of α -halo ketones by reaction with hydrogen halides, mainly HCl or HBr;
2. Cycloaddition to unsaturated substrates, notably alkenes, alkynes and nitriles;
3. Arndt-Eistert Homologation of carboxylic acids via Wolff rearrangement;
4. X-H Insertion where X = C, O, N and S groups ;
5. Oxidation to α -ketoaldehyde intermediates suitable for heterocycle formation.

Almac Sciences and Phoenix have been particularly active in applying some of these processes to diazoketones derived from amino acids and C-terminal peptides of the type shown in Table 1.

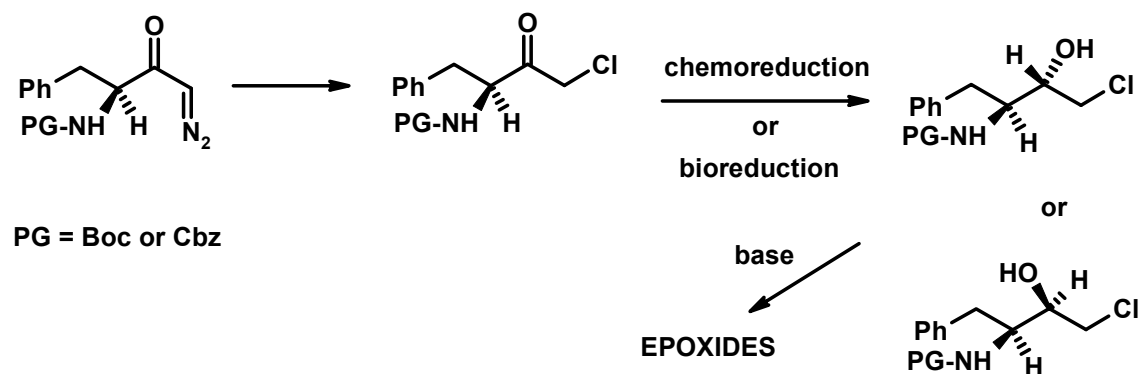
Amino acids and C-terminal peptides with suitable N-protection, (most commonly Boc or Cbz), are readily transformed into α -diazoketones via treatment of an acyl chloride or mixed anhydride intermediate with diazomethane. With the possible exception of phenylglycine, this conversion is usually racemization free.

Table (1). Some Amino-Acid Derived Diazoketones (R = Cbz or Boc)



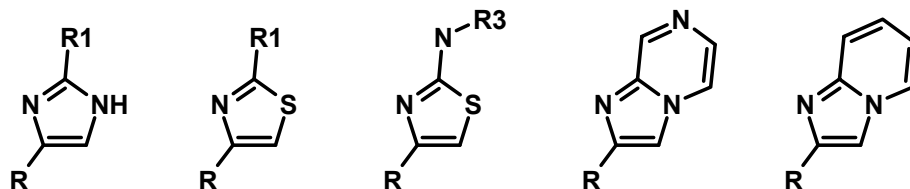
The transformation of diazoketone into α -halomethyl ketone is a classic clean reaction involving slow addition of the hydrogen halide, HCl or HBr, to a solution of the diazo ketone at room temperature: nitrogen evolution occurs over the addition period and the product can be used as a solution for further reactions or recovered in a high state of purity by removal of solvent. α -Fluoromethyl ketones are also accessible in this way, though this reaction is much less developed; the reaction is not generally applicable to the formation α -iodomethyl ketones. The reaction of the phenylalanine derived diazoketone with hydrogen chloride (Scheme 1) has been used extensively by us to produce the chloromethyl ketone in enantiopure form. These products are valuable intermediates for the production of chiral alcohols via reduction which in turn provide access to chiral epoxides via cyclisation in base.

Scheme (1). Stereochemically-Defined Alcohols and Epoxides from Phenylalanine-Derived Diazoketone



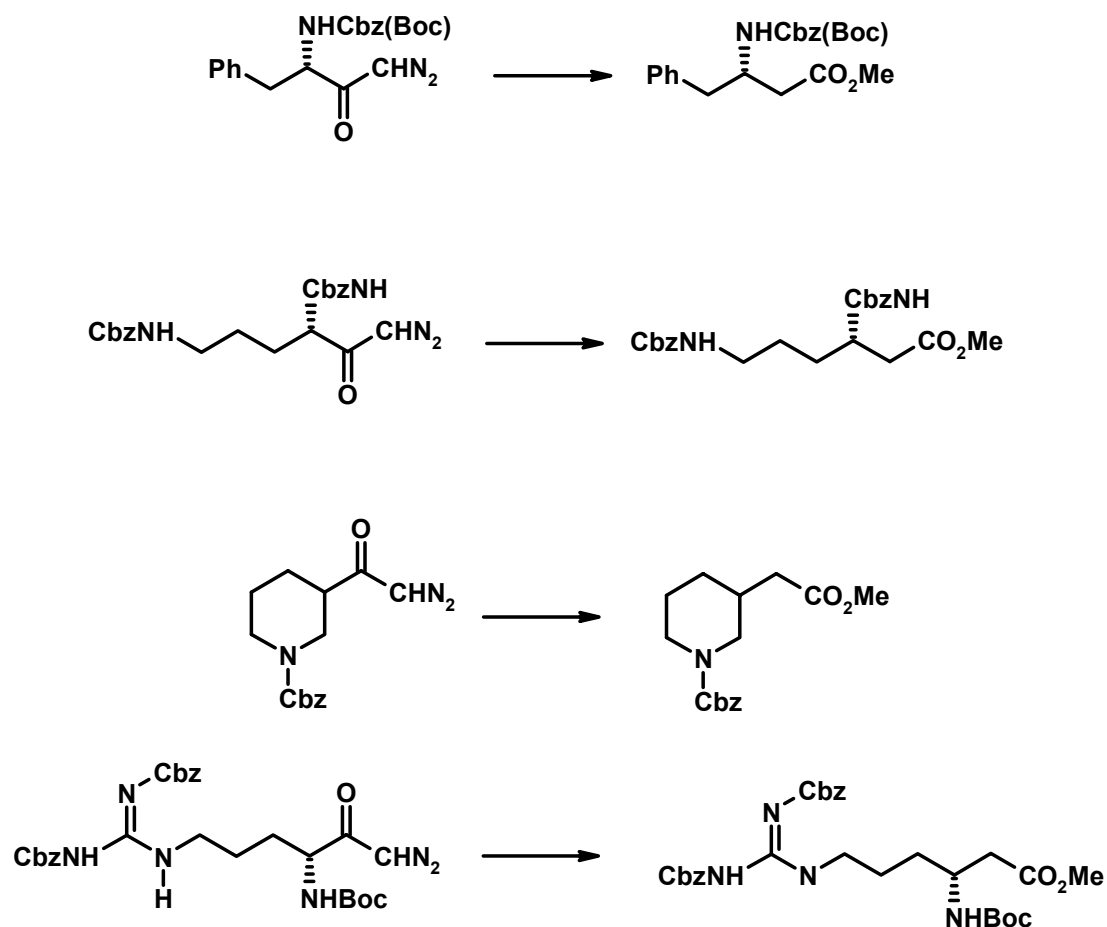
□ Halomethyl ketones and □ ketoaldehydes (see below) also provide direct routes to a range of heterocycles, including imidazoles, thiazoles, aminothiazoles, imidazopyridines and various fused pyridines. Several examples are shown below in Table 2.

Table 2 : some heteroaromatic rings accessible from α -haloketones and α -ketoaldehydes.



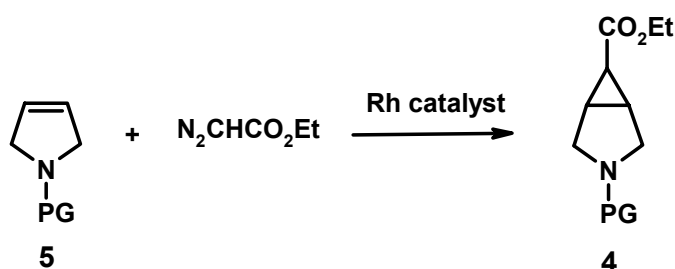
The Arndt-Eistert synthesis is a well-established method of homologation of a carboxylic acid. It consists of treating the diazoketone with a silver catalyst in the presence of a nucleophile such as water, an alcohol or a primary secondary amine. The reaction can also be promoted photochemically in the absence of catalyst. We have found it particularly useful in converting amino acids and C-terminal peptides into amino acid homologues, some examples of which are shown below in Table (3).

Table (3). Amino Acid Derivatives via Arndt-Eistert Homologation



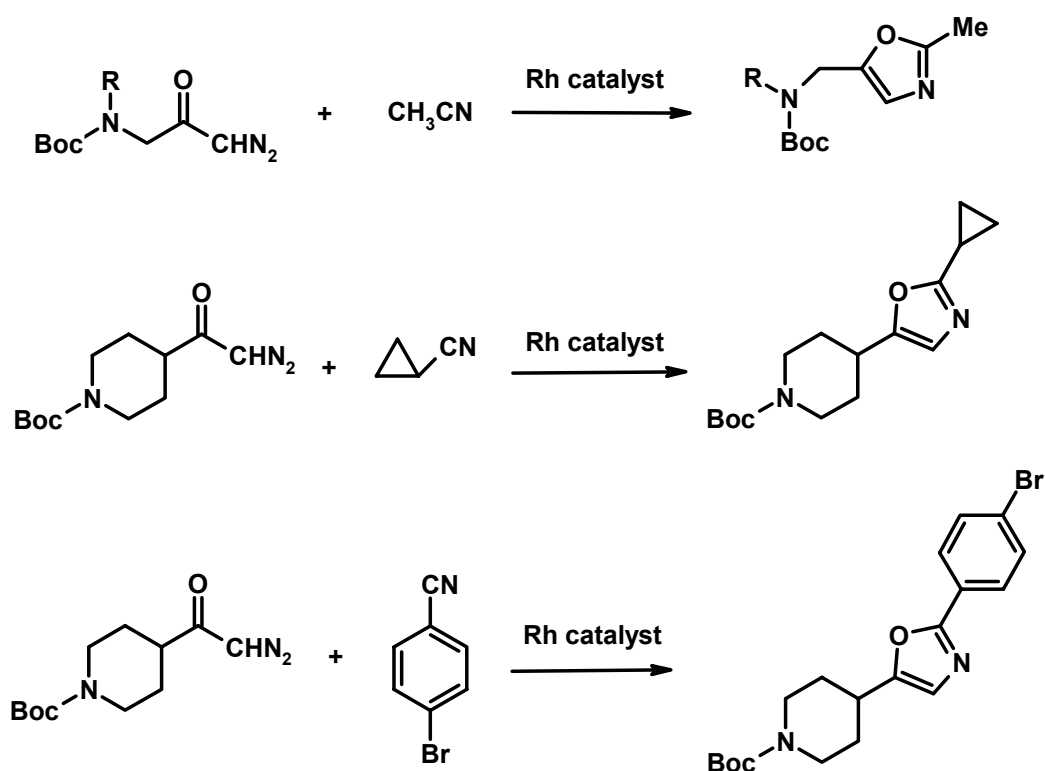
Among other important uses of diazocarbonyls as building blocks in synthesis is their ability to undergo cycloaddition to unsaturated substrates. Perhaps the best known reaction in this category is cyclopropanation of alkenes using ethyl diazoacetate, for example the formation of adduct (4) from alkene (5) (Table 4).

Table (4). Intermolecular and Intramolecular Cyclopropanation

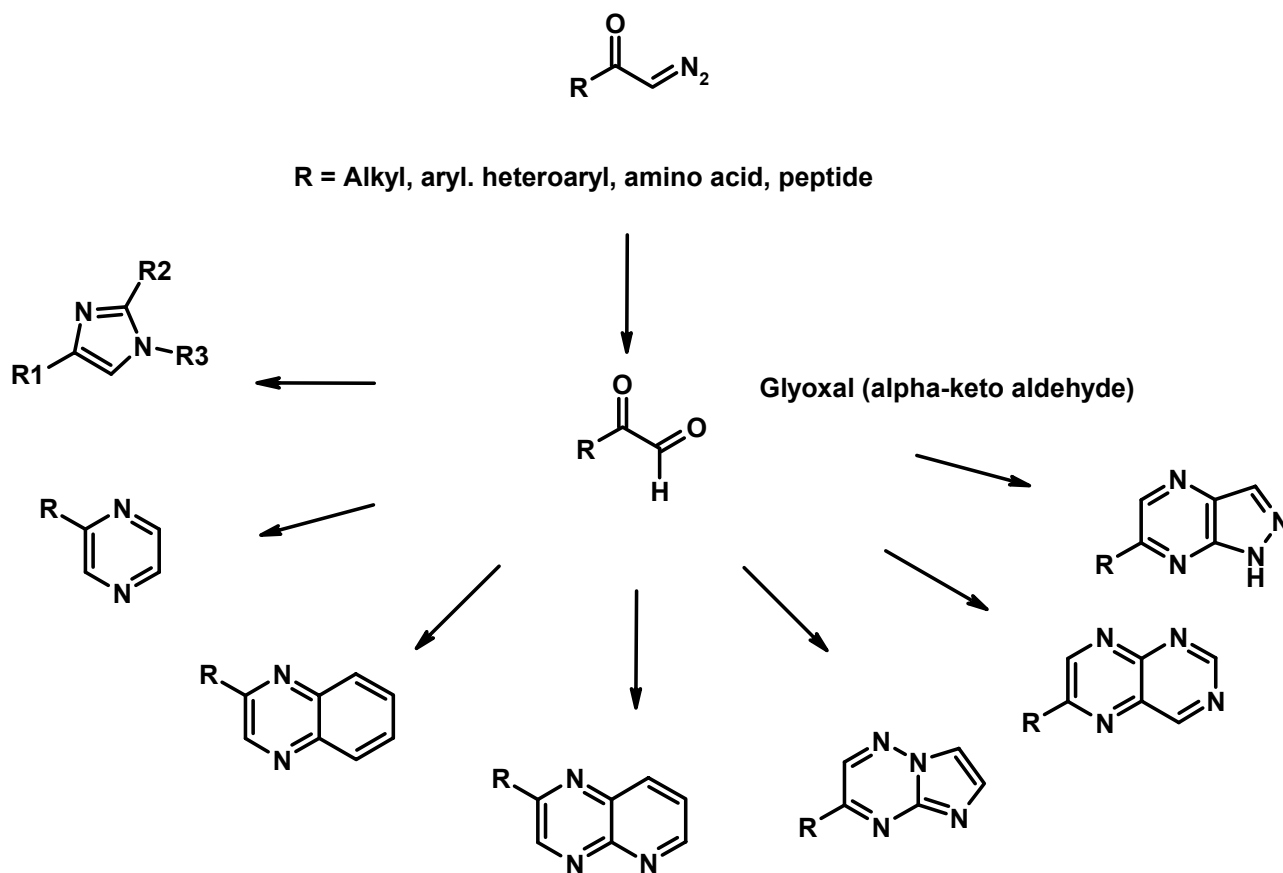


Intermolecular and intramolecular versions of this reaction are available including the use of chiral copper and rhodium catalysts capable of producing chiral cyclopropanecarboxylic acid derivatives with exceptionally high levels of diastereo- and enantioselectivity (ref. 3). Cycloaddition to heteroatomic unsaturated systems, catalysed by copper or rhodium salts, is also an important route to heterocycles. Reaction with nitriles, for example, producing direct access to substituted oxazoles.

Table (5). Intermolecular Cycloaddition of Diazocarbonyls with Nitriles



Scheme (3). Heterocycles Derived from Glyoxals



In summary, we at Almac Sciences and Phoenix Chemicals have explored the chemistry of diazocarbonyls and have demonstrated several useful and efficient applications in the synthesis of a wide variety of heterocycles with potential in medicinal chemistry.

References

1. For a comprehensive survey of the many useful reactions of diazocarbonyl compounds, see "Modern Catalytic Methods for Organic Synthesis with Diazocarbonyl Compounds. From Cyclopropanes to Ylides", M P Doyle, M A McKervey, and Tao Ye, John Wiley and Sons, New York, 652pp
2. Development of a Continuous Process for the Industrial Generation of Diazomethane, L D Proctor and A J Warr, *Org Process Res Develop*, 2002, 6, 884-892
3. For a detailed account of alkene and alkyne cyclopropanation, including the use of chiral rhodium and copper catalysts for asymmetric synthesis, see reference 1, chapters 4 and 5