Insertion reactions of macrocyclic rhodium carbenoids: a novel method for the synthesis of cryptands

Sengodagounder Muthusamy* and Boopathy Gnanaprakasam

School of Chemistry, Bharathidasan University, Tiruchirappalli 620 024, India

Received 29 May 2007; revised 26 June 2007; accepted 5 July 2007
Available online 13 August 2007

Abstract—Reaction of macrocyclic diazocarbonyl compounds and alcohols or diols in the presence of rhodium(II) acetate catalyst led to functionalized macrocyclic di- or tetralactones via O–H insertion. Interestingly, the double O–H insertion reaction with dihydroyx compounds gave cryptands of various ring sizes.

The formation of inter- and intramolecular ether linkages from diazo ketones and alcohols in the presence of rhodium(II) acetate is well studied. The decomposition of diazocarbonyl compounds, predominantly with protic/aprotic and Lewis acids has also been well studied and applied to the synthesis of important natural products. Esterification of acids using diazo-methane is very common, whereas the etherification reaction of alcohols using diazocarbonyl compounds is not widely used despite the fact that they often proceed in good yields via an O–H insertion reaction. Molecular recognition is a powerful technique that can be used to generate noncovalently bound host–guest complexes for a variety of purposes. Macrocycles form a major class of molecules that encompass a wide range of structures and functional groups. They also perform a wide range of functions in areas as diverse as ion transport, gelation and catalysis. Chemists have been fascinated for many years by the inherent physical properties of macrocycles and by the synthetic challenge that these structures represent. Contemporary chemistry, however, is increasingly directed towards the creation of molecules that are tailored to perform a well-defined function. The synthesis of macrocyclic diazocarbonyl compounds and their reactions have not been reported so far. In continuation of our studies on diazocarbonyl compounds and macrocycles, herein report a novel method for the synthesis of functionalized macrocyclic di- or tetralactones and cryptands via the O–H insertion reactions of macrocyclic rhodium(II) carbenoids.

With the aim to develop new ether linked macrocyclic tetralactones via O–H insertion reactions, we have synthesized a series of macrocyclic diazocarbonyl compounds (Scheme 1). The macrocyclic diazocarbonyl compounds 1a–g were synthesized by the reaction of malonyl chloride with dihydroxy compounds to afford macro cyclic lactones. Subsequent diazotransfer reaction of the macro cyclic lactones afforded the corresponding macrocyclic diazocarbonyl compounds (Fig. 1).

Initially, the O–H insertion reaction of macrocyclic diazocarbonyl compounds with alcohol was studied. Thus, the reaction of 1b with DCM containing two drops of water at reflux in the presence of 2 mol % of rhodium acetate afforded O–H insertion product 2a in

Scheme 1. Synthesis of macrocyclic diazocarbonyl compounds. Reagents: p-Acetamidobenzenesulfonyl azide, DBU, DCM.

Keywords: Carbenoids; Cryptands; Diazo ketones; Macrocyclic lactones; O–H insertion; Rhodium(II) acetate.

* Corresponding author. Tel.: +91 431 2407053; fax: +91 431 2407045; e-mail: muthu@bdu.ac.in
90% yield (Scheme 2). Similarly, macrocyclic diazocarbonyl compound 1b was treated with ethanol, methanol, benzyl alcohol and benzene-1,2-dimethanol to afford the corresponding ether functionalized macrocyclic dilactones 2b–e in good yields (Table 1).

Encouraged by this result, we envisaged the formation of two C–O bonds via double O–H insertion. 10 Thus, excess diazocarbonyl compound 1b was refluxed with Rh2(OAc)4 in aqueous DCM to afford ether linked macrocycle 3a in moderate yield (Scheme 3). Similar reactions of 1b with ethylene glycol or 1,8-octanediol afforded the corresponding bis-crown compounds 3b,c having an aliphatic linker (Table 2). The reaction of 1b with 1,2-benzene dimethanol afforded the bis-crown compound 3d having an aromatic linker. Next, the double O–H insertion reaction was investigated with bis-diazocarbonyl compounds. To this end, compounds 1e,f were refluxed with ethanol to afford diethoxy-substituted tetralactones 4a,b in good yields (Scheme 4).
Finally, we investigated the synthesis of the cryptands based on the above successful double intermolecular O–H insertion strategy. To this end, bis-diazocarbonyl compound 1g was refluxed with Rh$_2$(OAc)$_4$ in DCM containing two drops of water to afford the oxygen linked bicyclic system 5a in low yield (Table 3). Product 5a showed a characteristic singlet at 4.85 ppm for the H$_a$-proton and confirms the structure of the O–H insertion product. The formation of cryptand 5a was also confirmed by the mass spectral data. The reaction of an equimolar amount of bis-diazocarbonyl compound 1g and ethylene glycol afforded the corresponding cryptand 5b in 60% yield containing an oxyethylene spacer (Scheme 5). Reaction of bis-diazo macrocyclic compound 1g with 1,8-octane diol afforded cryptand 5c having an alkoxy spacer.

The reaction of a bis-diazocarbonyl compound having an octane spacer 1e with triethylene glycol afforded the corresponding cryptand 5d in moderate yield. Similarly, the reaction of bis-diazocarbonyl compound 1d with diethylene glycol afforded the corresponding cryptand 5e in 38% yield. All of cryptands 5 (Table 3) obtained by this method were successfully characterized by spectral analysis. Reaction of bis-diazocarbonyl compound 1h under similar conditions was not successful.

In conclusion, we have demonstrated the intermolecular O–H insertion reaction of macrocyclic diazocarbonyl compounds. The intermolecular O–H insertion reaction afforded several ether substituted macrocyclic dilactones. Intermolecular double O–H insertion reaction was also demonstrated with either bis-diazocarbonyl compounds or dihydroxy compounds. The advantage of the double O–H insertion methodology was demonstrated via the synthesis of cryptands possessing oxyethylene or octane spacers for the first time. Supramolecular studies on the synthesized macrocycles is under progress in our laboratory.

Acknowledgements

This research was supported by the Department of Science and Technology, New Delhi. B.G. thanks CSIR, New Delhi for a Senior Research Fellowship.

References and notes


6. (a) Julian, R. R.; May, J. A.; Stoltz, B. M.; Beauchamp, J.


9. General procedure for the O–H insertion reaction: Method A for the synthesis of dilactones 2: A mixture of macrocyclic diazocarbonyl compound 1b (0.5 mmol) and the appropriate alcohol (0.7 mmol) was taken in dry DCM (50 mL) under an argon atmosphere. To the above solution, 2 mol % of rhodium(II) acetate in dry benzene or DCM was added slowly (0.5 mmol) in dry benzene or DCM was added slowly over 1 h using a syringe pump and reflux for 6 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective double O–H insertion products 3. The macrocyclic tetrалactones 4 were synthesized by the reaction of the bis-diazocarbonyl compounds 1d–h (0.5 mmol) and the appropriate dihydroxy compound (5 mmol) was taken in dry DCM (50 mL) under an argon atmosphere. To the above solution, 2 mol % of rhodium(II) acetate dimer catalyst was added and the reaction stirred at reflux for 6 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc or EtOAc) to afford the respective cryptands 5.

10. Method B for the synthesis of dilactones 3: To an oven-dried flask, the appropriate alcohol (0.5 mmol) and 2 mol % of rhodium(II) acetate in dry benzene or DCM (100 mL) were added under an inert atmosphere and the mixture was heated at reflux. To the above refluxing mixture, macrocyclic diazocarbonyl compound 1b (1.2 mmol) in dry benzene or DCM was added slowly over 1 h using a syringe pump and reflux for 6 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc) to afford the respective double O–H insertion products 3. The macrocyclic tetrалactones 4 were synthesized by the reaction of the bis-diazocarbonyl compounds 1d–h (0.5 mmol) with an excess of the respective alcohol (1.5 mmol) in the presence of rhodium(II) acetate in dry benzene or DCM (100 mL) under reflux conditions.

11. Method C for the synthesis of cryptands 5: A mixture of bis-macroyclic diazocarbonyl compound 1d,e,g,h (0.5 mmol) and the appropriate dihydroxy compound (0.5 mmol) was taken in dry DCM (50 mL) under an argon atmosphere. To the above solution, 2 mol % of rhodium(II) acetate dimer catalyst was added and the reaction stirred at reflux for 6 h. The progress of the reaction was monitored by TLC. The solvent was removed under reduced pressure and the resulting residue purified using 100–200 mesh silica gel column chromatography (hexane/EtOAc or EtOAc) to afford the respective cryptands 5.