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Study of New Diazo Ketones Synthesis from Higher Diazo Alkanes

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ABSTRACT

Diazo group transfer reactions are transformations in which an intact diazo unit is transferred from a donor to an acceptor molecule <67AG786, 67AG(E)733, 72S351>. This is undoubtedly the most versatile class of reactions for the synthesis of α-diazo carbonyl and α-diazo β-dicarbonyl compounds.

The most useful substrates for diazo group transfer are those possessing active methylene groups. For example, diazo transfer to β-dicarbonyl compounds from sulfonyl azides is performed in the presence of tertiary amine bases . Because of the mildness, simplicity and reliability of this reaction, it has replaced amine diazotization as the method of choice for the preparation of α-diazo β-dicarbonyl compounds. In most cases, diazo group transfer to an active methylene compound proceeds via an intermediate triazine which is formed by attack on the azide by the anion of the active methylene compound. Spontaneous decomposition of this intermediate, accompanied by a proton shift, then leads to the product diazo compound. A wide variety of azides, including tosyl azide <67AG786, 67AG(E)733, 90CC652>, methanesulfonyl azide <86JOC4077>, p-carboxybenzenesulfonyl azide <68JOC3610> and azidotris(diethylamino)phosphonium bromide <90TL4987>, have been used as diazo transfer reagents in this reaction.

KEYWORDS: *diazo ketones, alkanes, synthesis, compounds, transformations*

INTRODUCTION:-

In organic chemistry, the diazo group is an organic moiety consisting of two linked nitrogen atoms at the terminal position. Overall charge-neutral organic compounds containing the diazo group bound to a carbon atom are called diazo compounds or diazoalkanes[a] and are described by the general structural formula $R_2C{=}N^+{=}N^-$. The simplest example of a diazo compound is diazomethane, CH_2N_2. Diazo compounds ($R_2C{=}N_2$) should not be confused with azo compounds (R–N=N–R) or with diazonium compounds (R–N+2).

A limitation of diazo transfer reactions of this type is the requirement of two electron-withdrawing substituents to activate the methylene group. This problem can be circumvented by temporary activation with a formyl group, which can be introduced by Claisen condensation and is lost during diazo group transfer. The reaction can be performed in a one-pot sequence by using the alkali salt formed during Claisen condensation directly in the diazo group transfer reaction <67TL739, 68CB2622>.

Deformylative diazo group transfer is very useful for the synthesis of α-diazo ketones, α-diazo aldehydes, α-diazo esters and α,β-unsaturated diazo ketones <68CB2622, 70LA(739)174>, [1,2,3]and can proceed by two possible pathways .In the first pathway (a), a triazoline intermediate is formed which decomposes to give the sulfonylformamide and the α-diazo ketone product. In the alternative mechanism (b), an intermediate triazine is formed, and loss of the formyl group occurs by alcoholysis. When the diazo transfer reaction of a formyl ketone is performed in dichloromethane in the presence of triethylamine, there is evidence that the reaction proceeds by way of a triazoline intermediate <67TL739, 68CB2622>. The formation of a triazoline intermediate can be a problem during diazo group transfer to some types of α-formyl cycloalkanones, and may lead to formation of a β-keto amide rather than the α-diazo cycloalkanone <67TL739, 68CB1263>.

Other proton-activating groups can be employed to achieve temporary activation of the methylene group during the formation of α-diazo ketones. For example, the benzoyl group has been used as an activator in the synthesis of steroidal α-diazo ketones <80TL15>, and the alkoxyoxalyl group has been used as an activator during the synthesis of α,β-unsaturated diazo ketones <68CB2622, 74S577>. A useful new diazo group transfer method for the synthesis of α-diazo ketones has been developed. In this procedure, trifluoroacetylation of a ketone enolate, followed by treatment of the resulting β-diketone with methanesulfonyl azide in the presence of triethylamine affords the α-diazo ketone (Scheme 58) <90JOC1959>. This protocol is especially useful for diazo group transfer to α,β-unsaturated ketones which are poor substrates for deformylative diazo group transfer. Yields are superior to those obtained by deformylative diazo group transfer in many other cases.

Phase transfer conditions can be employed in cases where deformylative diazo group transfer cannot be used. Tosyl azide is usually utilized as the diazo group transfer reagent, but azidinium salts have also been used. When p-carboxybenzenesulfonyl azide is used as the diazo transfer reagent, excess azide and the product sulfonamide can be removed from the product by treatment with aqueous base. This can be advantageous in cases where incomplete reaction complicates purification of the α-diazo carbonyl product <68JOC3610>.

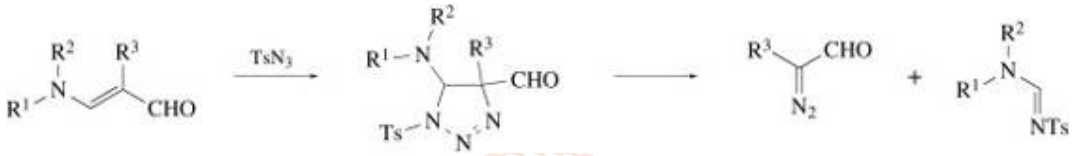
In some cases it is possible to accomplish diazo group transfer from diazo compounds rather than sulfonyl azides. For example, reaction of 1,1-dimethylcyclohexane-3,5-dione with ethyl diazo-nitroacetate affords the product of diazo group exchange[4,5,6]

The electronic structure of diazo compounds is characterized by π electron density delocalized over the α-carbon and two nitrogen atoms, along with an orthogonal π system with electron density delocalized over only the terminal nitrogen atoms. Because all octet rule-satisfying resonance forms of diazo compounds have formal charges, they are members of a class of compounds known as 1,3-dipoles. Some of the most stable diazo compounds are α-diazo-β-diketones and α-diazo-β-diesters, in which the electron density is further delocalized into an electron-withdrawing carbonyl group. In contrast, most diazoalkanes without electron-withdrawing substituents, including diazomethane itself, are explosive. A commercially relevant diazo compound is ethyl diazoacetate ($N_2CHCOOEt$). A group of isomeric compounds with only few similar properties are the diazirines, where the carbon and two nitrogens are linked as a ring.

DISCUSSION

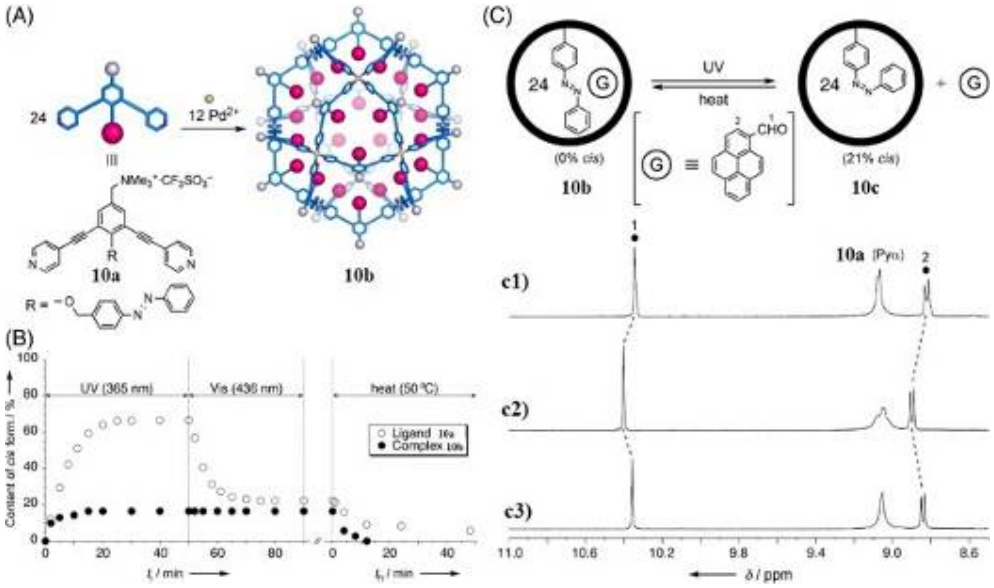
α-Diazo ketones can be prepared by diazo group transfer from azidinium compounds to activated substrates under acidic or neutral conditions rather than basic conditions <61LA(647)11>. This reaction can also be accomplished under acidic or neutral conditions using azidochloromethylene-dimethylammonium chloride <80AG754, 80AG(E)716>.

Although diazo group transfer to enamines is usually employed to prepare diazo alkanes which do not possess adjacent carbonyl groups, the reaction can also be used to synthesize α-diazo carbonyl compounds, and is especially useful for the preparation of α-diazo aldehydes. Treatment of a formyl enamine with tosyl azide gives the corresponding α-diazo aldehyde in good yield (Scheme 60) <66TL1109, 67CC299, 70CCC3618>. Ethyl diazoacetate and various diacyldiazomethanes have been prepared from their respective enamines in this fashion <70LA(734)70>.



The diazo group is one of the most well-studied functional groups for its photochromic behavior. Therefore, several research groups have developed numerous SCC containing diazo moiety at various locations of the macromolecules.

Fujita and coworkers [22] have reported a new type of 3D large metallacage 10b by reacting a 120° azo dipyridyl donor 10a containing appended diazo group and by treating it with palladium nitrate in a 2:1 ratio (Fig. 7.10). The very large metallacage contained 12 Pd centers and 24 ligands. The azo groups were strategically located with an inward orientation. The formation of the 10b was characterized by a change in ^1H NMR of the ligand and was further established by CSI-MS analysis. Finally, suitable single-crystals of 10b were obtained and the single-crystal X-ray diffraction study established the structure of the macro cage. The azobenzene-based cage displayed two peaks at 365 and 436 nm in the absorption spectra which were assigned to the π–π* and n–π* transition in the ligand. When exposed to the 365 nm UV radiation a 17% conversion from trans to cis-azobenzene metallacage 10c was observed and after further irradiation at 436 nm 20% total conversion was observed. The cis-azobenzene is thermally unstable and as a result, when the cis-isomerized metallacage was heated at 50°C the cis isomer transformed into the more stable trans form.[7,8,9] The trans azobenzene ligand is nonpolar but the cis-azobenzene is more polar due to high dipole moment, therefore the interior of the 10b is hydrophobic but the interior of 10c is hydrophilic. Therefore using light as external stimuli the interior of the metallacage can be changed between hydrophobic and hydrophilic. This unique behavior was exploited by the research group in the light-induced encapsulation and release of hydrophobic guest molecules inside the cage. The pyrenealdehyde is well known as a hydrophobic guest molecule and is well studied for encapsulation in macrocyclic systems. When the pyrenealdehyde was added to the acetonitrile: water solution of the cage 10b, an upfield shift in the guest ^1H NMR was observed indication encapsulation and more shielding, but when the guest encapsulated cage was irradiated with UV light, the cage interior transformed into more hydrophilic nature and the guest was released from the molecular capsule. When the isolated guest and cage were heated at 50°C the cage became hydrophobic due to cis to trans isomerization and an upfield shift in the guest proton was obtained



Several methods exist for the preparation of diazo compounds.[4][5]

From amines

Alpha-acceptor-substituted primary aliphatic amines R-CH_2-NH_2 (R = COOR, CN, CHO, COR) react with nitrous acid to generate the diazo compound.

From diazomethyl compounds

An example of an electrophilic substitution using a diazomethyl compound is that of a reaction between an acyl halide and diazomethane,[6] for example the first step in the Arndt-Eistert synthesis.

By diazo transfer

In diazo transfer certain carbon acids react with tosyl azide in the presence of a weak base like triethylamine or DBU. The byproduct is the corresponding tosylamide (p-toluenesulfonamide). This reaction is also called the Regitz diazo transfer.[7] Examples are the synthesis of tert-butyl diazoacetate[8] and diazomalonate.[9] Methyl phenyldiazoacetate is generated in this way by treating methyl phenylacetate with p-acetamidobenzenesulfonyl azide in the presence of base.[10][11]

The mechanism involves attack of the enolate at the terminal nitrogen, proton transfer, and expulsion of the anion of the sulfonamide. Use of the β-carbonyl aldehyde leads to a deformylative variant of the Regitz transfer, which is useful for the preparation of diazo compounds stabilized by only one carbonyl group.[13]

From N-alkyl-N-nitroso compounds

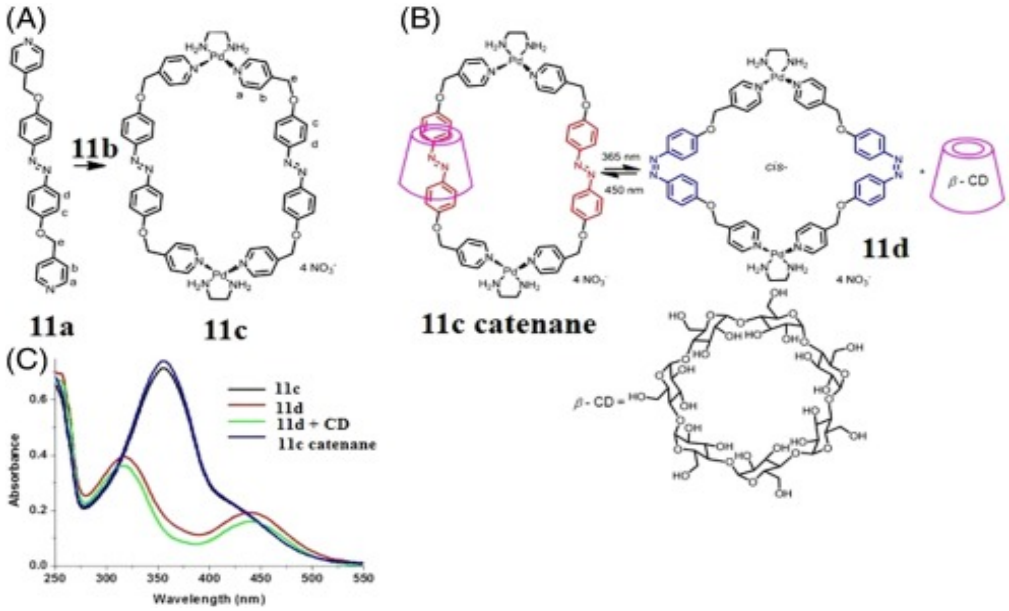
Diazo compounds can be obtained in an elimination reaction of N-alkyl-N-nitroso compounds,[14] such as in the synthesis of diazomethane from Diazald

From hydrazones

Hydrazones are oxidized (dehydrogenation) for example with silver oxide or mercury oxide for example the synthesis of 2-diazopropane [fr] from acetone hydrazone.[16] Other oxidizing reagents are lead tetraacetate, manganese dioxide and the Swern reagent. Tosyl hydrazones RRC=N-NHTs are reacted with base for example triethylamine in the synthesis of crotyl diazoacetate[17] and in the synthesis of phenyldiazomethane from PhCHNHTs and sodium methoxide.[18]

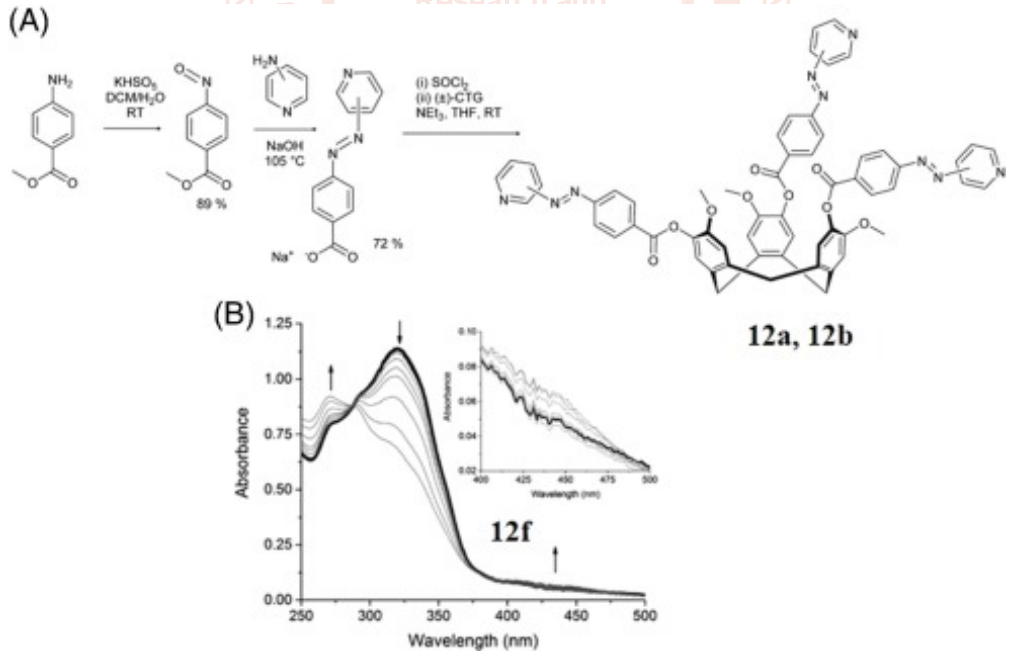
RESULTS

Stang and coworkers [23] have provided a new photochromic palladium metallacycle 11c containing azobenzene-based dipyridyl donor 11a and cis-blocked palladium acceptor 11b .The nitrate salt of the acceptor 11b was treated with the donor 11a with 1:1 a ratio in a methanol–water mixture to afford the final macrocycle 11c. The formation of the macrocycle was established using multinuclear NMR and ESI-MS analysis. When the absorption spectra of the 11c were recorded a sharp peak at 356 nm was observed which was assigned to the trans azobenzene.[10,11,12] But when the macrocycle was exposed to UV irradiation at 365 nm for 60 s, the main absorption peak decreased and a new peak at 442 nm appeared. The new peak was attributed to the formation of a new macrocycle 11d containing cis azobenzene ligand. When the 11d was exposed to visible light at 450 nm for 2 min then the absorption spectra reversed back to the original with the reappearance of the maxima at 356 nm. This cis–trans isomerization was further studied using photoirradiation and ^{1}H NMR. When the trans isomer was irradiated with 365 nm light the original proton peaks of the pyridyl moiety changed from 6.83, and 7.54 to 6.74 and 6.90 ppm, respectively. The radiation of the cis form at 450 nm changed the macrocycle in the original transform. The 11c was further explored for the host–guest inclusion complex formation with β-cyclodextrin (CD). When β-CD was added to a D_2O solution of 11c in a 1:1 ratio, some new peaks appeared in the proton NMR along with the reduced intensity of the previous pyridyl proton peaks. It was proposed that the β-CD formed inclusion complex with only one donor moiety and thus the two pyridyl donor ligands became magnetically nonequivalent which lead to the appearance of multiple proton peaks. The formation of the inclusion complex also enhanced the absorption peak intensity at 356 nm. When treated with β-CD, the cis isomeric macrocycle 11d was not found to display any change in the proton signal indicating the fact that the larger size of the cis linker hindered the host–guest complex formation. Therefore, by using light as the trigger the macrocycle was transformed between 11c and 11d which further controlled the host–guest complex formation capability[13,14,15]



CONCLUSION

Hardie et al. [24] have reported a new set of chiral metallacages based on cyclotriguaiacylene (CTG) units . The four new ligands 12a, 12b, 12c, and 12d contained azobenzene-based tripyridyl donors with para and meta coordination sites. The ligands were combined with a new iridium-based accurate ESI-MS analysis and multinuclear 1D and 2D NMR. Since all the cages exhibited similar photophysical behavior, the authors reported the absorbance, fluorescence, and photochromic behavior of cage 12f. The absorption of the cage was recorded in DC and two ligand-centered peaks were obtained at 274 and 293 nm. When irradiated with UV light of 355 nm, the cage transformed from E isomer to Z isomeric cage 12k. The UV irradiation also reduced the peak associated with the ligand centered π−π* transition. The cages gave very high conversion efficiency from E to Z isomer with a range between 39% and 40%. The transformation of the 12f and 12k was studied by utilizing proton NMR spectra. When the newly formed mixture of E and Z isomeric cages were subjected to an exposure of 450 nm light for 15 min, all the metallacages transformed back to the original E isomeric form, indicating photo-controlled reversible transformation[16]



N-Allylpiperidines with a diazo group in a side chain adjacent to nitrogen gave ylides that rearranged to quinolizidine systems with high levels of diastereocontrol. For instance, treatment of diazoketone **220** with $Cu(acac)_2$ in refluxing benzene afforded a mixture (6:1 or 1:6) of two diastereoisomeric quinolizidines **222** and **224** through a [2,3]-rearrangement of the corresponding ammonium ylides **[16]**

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