

# DOWNLOAD PDF N-ALKYLATION OF NITROGEN AZOLES PAUL A. BENJES AND M. ROSS GRIMMETT

## Chapter 1 : Imidazole and Benzimidazole Synthesis - PDF Free Download

*alkylation, arylation, dealkylation, dearylation, C-acylation, olefination* Abstract ChemInform is a weekly Abstracting Service, delivering concise information at a glance that was extracted from about leading journals.

Aromatic Substitution Approaches to Synthesis Chapter 8. Synthesis of Specifically Substituted Imidazoles and Benzimidazoles Index of Compounds and Methods Dedication To my wife, Anne, whose support and understanding has made it possible for me to take on a succession of such projects, and to those stalwarts of Heterocyclic Chemistry, Ken Schofield and Alan Katritzky, who have been my catalysts over many years. Foreword This is the second book in the sub-series of Best Synthetic Methods "Key Systems and Functional Groups and is particularly close to my heart. This stated that given the right number of carbons and nitrogens, any starting material would ultimately end up as a benzimidazole! A good example is shown below: PPA hfc NHCOMe The imidazole and benzimidazole ring systems are, of course, not just interesting and a source of endless research pleasure but are key systems both in nature such as the amino acid histidine, vitamin B12, a component of DNA base structure and purines, histamine, biotin, etc. To underline this ubiquity of their medicinal applications, over one third of the pages of the excellent compilation of the Drug Compendium in Volume 6 of Comprehensive Medicinal Chemistry Pergamon Press, contain imidazole or benzimidazole units. Other important uses of these systems include high temperature polymer products and dyestuffs. Ross Grimmett is an established master in the field, having compiled several authoritative reviews of these systems. I hope you will enjoy it as much as I have. Methyl 1-methylimidazoline-4-carboxylate Methyl 1-methylimidazolecarboxylate. U From three-membered rings. General procedure for 1-arylimidazoles and 1-arylbenzimidazoles Phase transfer method. Indeed, it is necessary to consider a number of widely divergent processes each time a synthesis is contemplated. For this reason I have divided the synthetic approaches arbitrarily into methods which make specific bonds in the imidazole product, those which transform another heterocycle, and those which start with the preformed imidazole ring. With such a myriad of methods it has not been possible to check many of the actual syntheses included, although an endeavour has been made to cross check among different publications, and our experiences in the laboratory at Otago University have been drawn on extensively in assessing methods included I have provided an index which should help lead research workers to specifically substituted products, so that comparisons can be made of the possible approaches. In addition, care has been taken to ensure that the referencing is sufficiently detailed. Other review material has been less heavily oriented towards synthesis [1, 2]. When making use of the synthetic details included one needs to be aware of modern safety considerations. In consequence, it may be advisable to seek alternatives to solvents such as benzene, chloroform, carbon tetrachloride and hexane used in the methods described. Some earlier examples quoted could profitably be improved by the use of more modern separation and purification techniques. Yields quoted are those from the original publications; in our experience these have sometimes been shown to be optimistic. My thanks are due to the University of Otago who granted me a short period of study leave, part of which was devoted to this work, and to the staff of the Chemistry Department at the Open University, Milton Keynes, UK, where I was able to work with few distractions in a friendly environment. I also owe much to Julie Leith, Andrea Krause and Diane Watson who so expertly did most of the word processing and preparation of diagrams at the University of Otago. Hofmann, in *77ie Chemistry of Heterocyclic Compounds. Imidazole and its Derivatives, Part 1* ed. Day, in *Heterocyclic Compounds* ed. New York, , Vol 5. Preston, in *Benzimidazoles and Congeneric Tricyclic Compounds* ed. Interscience-Wiley, New York, Grimmett, in *Comprehensive Heterocyclic Chemistry* ed. Pergamon Press, Oxford, , Vol. Grimmett, in *Comprehensive Heterocyclic Chemistry*. R, Katritzky and C. TrantsL 35, Karri t7ky and J. Lagowski, *Chemistry of Heterocyclic ti-Oxides*. Academic Press, New York,

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## Chapter 2 : Imidazole and Benzimidazole Synthesis (Best Synthetic Methods) - PDF Free Download

*Reactions of importance in synthesis. [J M Coxon;] N-alkylation of nitrogen azoles / Paul A. Benjes and M. Ross azoles / Paul A. Benjes and M. Ross Grimmett.*

This stated that given the fight number of carbons and nitrogens, any starting material would ultimately end up as a benzimidazole! A good example is shown below: To underline this ubiquity of their medicinal applications, over one third of the pages of the excellent compilation of the Drug Compendium in Volume 6 of Comprehensive Medicinal Chemistry Pergamon Press, contain imidazole or benzimidazole units. Other important uses of these systems include high temperature polymer products and dyestuffs. Ross Grimmett is an established master in the field, having compiled several authoritative reviews of these systems. I hope you will enjoy it as much as I have. Methyl-N-[2-[[ methylamino phenylmethylene ]amino]- 1 -cyclohexen- 1-yl]benzamide. General method f o r preparing imidazoles or 1-imidazolamines N- 2-Aminophen yl - 1 H-pyrroll-amine Hydrolysis o f the 2-cyano or 2-carbethoxy group. Oxidative cyclization o f acylated N,N-diakyllo-aminoanilines Preparation f r o m ot-aminoacetals. N- 2, 2-Dimethoxyethyl dichlo roacetamide. General method f o r cyclization o f an enaminone. Ethyl Z -N- 2-amino- 1,2-dicyanovinyl formimidate Z - N- 2-A mi no- 1 , 2-di c yano vin y l formamide Z - N 3- 2-Amino- 1 , 2-dicyano vin y l formamidrazone Oxidation o f N-phenylphenylacetamide; 2-benzylbenzimidazole. N, N - D i m e t h y l - 1 - t - b u t y l - 3 , 3 - b i s [ d i methylamino]azapropenyliden ammonium perchlorate Benzimidazolone -- method B General procedure f o r preparation o f benzimidazoles. General method f o r synthesis o f to-acylamides. Methyl E - and Z Bromo2-isocyanocinnamate. General procedure f o r synthesis o f imidazoles. Typical hydrolysis procedure to a-aminoketone hydrochloride. Ethyl 2-amino- 1-methylimidazolecarboxylate hydrochloride. General procedure for 1,4-disubstinted imidazoles using formamide. General procedure for 1-alkyl- and 1-aryl2-methylthioimidazoles. General method for 1-substituted 5-aminoimidazolenitriles. General method for synthesis of 4-acylimidazoles. Conversion o f a 4-tosyloxazoline into a 1, 4-disubstituted imidazole. General procedure method B. Aromatization o f 5,5-disubstituted 2-imidazolines. General procedure for 2,4,5-triarylimidazoles. References

Chapter 3 : Imidazole | Revolv

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Marzari, Nilo Zanatta, Helio G. The reaction time and yields were investigated and this method showed shorter reaction times Keywords: An alter- [1,2], including blockbuster drugs such as Celecoxib [3] and Viagra native synthetic route to obtain N-alkyl pyrazoles would be [4]. Therefore, due to the broad range of activity and impor- absorption, distribution, metabolism, and excretion properties. On the other alky pyrazoles. For example, in the prevalent method, where hand, we have observed that the regioselectivity of the reaction substituted hydrazines react with 1,3-dicarbonyl compounds and also depends on the hydrazine employed. In general, methyl and there is similar reactivity between the two carbonyl groups, the re- phenyl hydrazines have produced mixtures of isomers [13,14]. Re- sult is often a mixture of regioisomers. Another impor- long reaction times and low yields. Finally, we carried out the reaction low product yields was obtained [15]. On the other hand, re- in the absence of base, in [BMIM]BF<sub>4</sub> and acetonitrile, and the cently, there have been several reports of N-alkylation of N-hetero- yields were drastically reduced entries 7 and 8, Table 1 , demon- cycles in ionic liquids [22]. Ionic liquids ILs have attracted strating the importance of the base in this reaction. Although ionic liquids were initially introduced as alternative reaction medium in terms of yields and reaction times entry 3, Ta- green reaction media because of their unique chemical and physi- ble 1. The majority of agent. The results are shown in Scheme 1 and Table 2. There are few reports in the literature on the N-alkylation The <sup>1</sup>H NMR data showed the chemical shift of the methylene reaction of pyrazoles in ionic liquids. Moreover, to the best of our R<sup>x</sup> from the range of d 3. In addition, the EI mass data showed luoromethylpyrazoles until now. Thus, due to our continuous the molecular ion of all N-alkyl pyrazoles. The formation of com- interest in organic reactions in ionic liquids [26,27] as well as pounds 5a g was accompanied by formation of compounds 6a g. The difference in the stability and abundance of frag- 2. The stability of the pyrazole cations was supported by their ener- We started our study from the reaction of butyl bromide with gies obtained by the calculation of minimum energy of the struc- 3,5-dimethyl-1H-pyrazole by evaluating the best reaction condi- ture of pyrazole cations by semi-empirical AM1 method using tions. This method of characterizing isomers was not adequate for in acetonitrile and base [15]. When we switched the base from KOH to to pass from one N to another in the pyrazole ring, generating the K<sub>2</sub>CO<sub>3</sub>, the yields were lower entry 2, Table 1. However, when io- formation of a more stable cation. Thus the use of ionic liquids in these reactions provided a mild Reactions conditions used for N-alkylation reaction. Table 3 Mass spectral data of N-alkyl pyrazoles 5a and 6a. The ability of the ionic liquid to accelerate the ketones were condensed with methyl hydrazine, mixtures of 1,3- reaction is probably a result of the decrease of activation energy of and 1,5-isomers of 3 5 -ethyl carboxylatemethyl-1H-pyrazole the activated complexes, which in turn is most likely due to the were obtained with ratios of between 1: In an interesting study, Bonacorso charged intermediates, such as carbocations or carbanions, and et al. Studies on the effect of ionic liquids in methylmethyl-1H-pyrazole was highly regioselective [14]. SN<sub>2</sub> reactions have shown that it is possible to generally state that, Taking these data on cyclocondensation reactions together with when using ionic liquids for reactions of highly associating anions the results of the present study, we could hypothesize that, like such as halides, reaction rates will probably be greater in ionic liq- the cyclocondensation reaction between alkyl hydrazines and 1,3- uids composed of the least coordinating cations poor hydrogen dielectrophilic systems, the N-alkylations reaction of unsymmetrical bond acids. In fact, the relative rates of reaction can be explained pyrazoles is not chemoselective. However, the formation of a mix- and predicted by the classical Hughes-Ingold approach for exam- ture can be explained by different reasons. In the case of cyclocon- ining solvent effects on organic reactions [32]. The greater propor- ation reactions of unsymmetrical pyrazoles, we studied the che- tion of 1,3-isomers of the products is expected because the substi- moselectivity

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of the reaction by comparing condensation tuted nitrogen in methyl hydrazine is more nucleophilic [34]. On other hand, when a,b-unsaturated group, resulting in the preferential formation of the 1,3-isomer. In addition, we introduced a new Zanatta, M. Yu, nally, we concluded that, although the formation of N-alkyl pyra- G. Hall, *Chimia* 58 News 84 Experimental section [8] T. Kennedy, *Synthesis* 43; b R. The ILs were synthesized according with the methodology de- [13] M. Diethyl ether 3 mL was added, [19] J. Jaskot, *Heterocycles* 45 4. The diethyl ether was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and Zheng, *Synthesis* The structure of compounds 4â€™6 was [25] M. This information is available in Supple- [26] M. The authors thank the Conselho Nacional de Desenvolvimento [30] T. Richardson, *Mechanism and Theory in Organic Chemistry*, second ed. March, *Advanced Organic Chemistry*, fourth ed. Ingold, *Structure and Mechanism in Organic Chemistry*, second ed. Supplementary material Supplementary data associated with this article can be found, in the online version, at doi:

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## Chapter 4 : Advances in Heterocyclic Chemistry, Volume 73 - [PDF Document]

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It is a white or colourless solid that is soluble in water, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and has non-adjacent nitrogen atoms. Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles share the 1,3-CN ring but feature varied substituents. This ring system is present in important biological building blocks, such as histidine and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antifungal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam. It exists in two equivalent tautomeric forms, because hydrogen can be bound to one or the other nitrogen atom. Imidazole is a highly polar compound, as evidenced by its electric dipole moment of 3. Some resonance structures of imidazole are shown below: Amphoterism Imidazole is amphoteric. That is, it can function as both an acid and as a base. As an acid, the pK of imidazole is The acidic proton is the one bound to nitrogen. Deprotonation gives the imidazole anion, which is symmetrical. As a base, the pK of the conjugate acid cited as pK to avoid confusion between the two is approximately 7, making imidazole approximately sixty times more basic than pyridine. The basic site is the nitrogen with the lone pair and not bound to hydrogen. Protonation gives the imidazolium cation, which is symmetrical. Preparation Imidazole was first reported in by the German-British chemist Heinrich Debus, although various imidazole derivatives had been discovered as early as the s. It was shown that glyoxal, formaldehyde, and ammonia condense to form imidazole glyoxaline, as it was originally named. In one microwave modification, the reactants are benzil, benzaldehyde and ammonia in glacial acetic acid, forming 2,4,5-triphenylimidazole "lophine". Many of these syntheses can also be applied to substituted imidazoles by varying the functional groups on the reactants. These methods are commonly categorized by the number of reacting components. Two component The 1,2 and 2,3 bonds can be formed by treating a 1,2-diamino alkane, at high temperatures, with an alcohol, aldehyde, or carboxylic acid. A dehydrogenating catalyst, such as platinum on alumina, is required. The yield of this reaction is moderate, but it seems to be the most effective method of making the 1,4 substitution. Three component This method proceeds in good yields for substituted imidazoles. An adaptation of the Debus method, it is called the Debus-Radziszewski imidazole synthesis. The starting materials are substituted glyoxal, aldehyde, amine, and ammonia or an ammonium salt. This reaction will give substantial yields only if the 1-vinyltetrazole is made efficiently from an organotin compound, such as 2-tributylstannyltetrazole. Imidazole can also be formed in a vapor-phase reaction. This forms a very pure imidazole product. The reaction has later been expanded to a two-step synthesis in which the aldimine is generated in situ: Biological significance and applications Imidazole is incorporated into many important biological molecules. The most pervasive is the amino acid histidine, which has an imidazole side-chain. Histidine is present in many proteins and enzymes and plays a vital part in the structure and binding functions of hemoglobin. Imidazole-based histidine compounds play a very important role in intracellular buffering. Histamine can cause urticaria hives when it is produced during allergic reaction. The relationship between histidine and histamine is shown below: One of the applications of imidazole is in the purification of His-tagged proteins in immobilised metal affinity chromatography IMAC. Imidazole is used to elute tagged proteins bound to nickel ions attached to the surface of beads in the chromatography column. An excess of imidazole is passed through the column, which displaces the His-tag from nickel coordination, freeing the His-tagged proteins. Imidazole has become an important part of many pharmaceuticals. Synthetic imidazoles are present in many fungicides and antifungal, antiprotozoal, and antihypertensive medications. Imidazole is part of the theophylline molecule, found in tea leaves and coffee beans, that stimulates the central nervous system. It is present in the anticancer medication mercaptopurine, which combats leukemia by interfering with DNA activities. A number of substituted imidazoles, including clotrimazole, are selective inhibitors of

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nitric oxide synthase, which makes them interesting drug targets in inflammation, neurodegenerative diseases and tumors of the nervous system. For comparison, another group of azoles is the triazoles, which includes fluconazole, itraconazole, and voriconazole. The difference between the imidazoles and the triazoles involves the mechanism of inhibition of the cytochrome P enzyme. The N3 of the imidazole compound binds to the heme iron atom of ferric cytochrome P, whereas the N4 of the triazoles bind to the heme group. The triazoles have been shown to have a higher specificity for the cytochrome P than imidazoles, thereby making them more potent than the imidazoles. Preventing copper corrosion is important, especially in aqueous systems, where the conductivity of the copper decreases due to corrosion. Imidazoles can also be used as organic structure directing agents to synthesize zeolites. Many compounds of industrial and technological importance contain imidazole derivatives. The thermostable polybenzimidazole PBI contains imidazole fused to a benzene ring and linked to a benzene, and acts as a fire retardant. Imidazole can also be found in various compounds that are used for photography and electronics. Salts of imidazole

Simple imidazolium cation Salts of imidazole where the imidazole ring is in the cation are known as imidazolium salts for example, imidazolium chloride. These salts are formed from the protonation or substitution at nitrogen of imidazole. These salts have been used as ionic liquids and precursors to stable carbenes. Salts where a deprotonated imidazole is an anion are also well known; these salts are known as imidazoles for example, sodium imidazolate, NaCHN. Related heterocycles Benzimidazole, an analog with a fused benzene ring Dihydroimidazole or imidazoline, an analog where 4,5- double bond is saturated Pyrrole, an analog with only one nitrogen atom in position 1 Oxazole, an analog with the nitrogen atom in position 1 replaced by oxygen Thiazole, an analog with the nitrogen atom in position 1 replaced by sulfur Pyrazole, an analog with two adjacent nitrogen atoms Triazoles, analogs with three nitrogen atoms See also 4-Methylimidazole

References Walba, H. Imidazole and Benzimidazole Synthesis. Ring Nitrogen and Key Biomolecules. Heterocycles in Life and Society. Christen, Dines; Griffiths, John H. *Annalen der Chemie und Pharmacie*. David; Howard, Jessica L. "Developing a Mechanism To Explain a Product". US patent 6,, , Arduengo, A. "Base-induced cycloaddition of sulfonylmethyl isocyanides to carbon, nitrogen double bonds. Synthesis of 1,5-disubstituted and 1,4,5-trisubstituted imidazoles from aldimines and imidoyl chlorides". *Journal of Organic Chemistry*. Mechanisms and Process in Physiological Evolution. *Comprehensive Pharmacy Review* 6th ed. Antifungal and Antiviral Drugs". In Riviere, Jim E. *Veterinary Pharmacology and Therapeutics* 9th ed.

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## Chapter 5 : Heterocyclic Chemistry: v.3 (Specialist Periodical Reports) (Vol 3) - [PDF Document]

*Download Citation on ResearchGate | On Jul 5, , P. Benjes and others published ChemInform Abstract: Alkylation of 4(5)-Substituted Imidazoles.*

Abramovitch, Clemson, South Carolina A. Balaban, Bucharest, Romania A. Boulton, Norwich, England H. Dorn, Berlin-Bohnsdorj Germany J. Elguero, Madrid, Spain S. Gronowitz, Lund, Sweden E. Lukevics, Riga, Latvia O. Meth-Cohn, Sunderland, England V. Minkin, Rostov-on-Don, Russia C. Scriven, Indianapolis, Indiana D. Black, Kensington, Australia E. Taylor, Princeton, New Jersey M. Tisler, Ljubljana, Slovenia J. No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the Publisher. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale. Copy fees for pre chapters are as shown on the title pages. If no fee code appears on the title page, the copy fee is the same as for current chapters. Theoretical and Structural Aspects Reactions with Carbenes and Nitrenes Oxidation and Reduction Reactions Dipoles of the Propargyl-Allenyl Type Dipoles of the Allyl S p e Part V of Series on Pyrido. Applications and Important Compounds Reactions under Friedel-Crafts Conditions Conversion to Other Heterocycles Thermal and Photochemical Transformations The Literature of Heterocyclic Chemistry. General Sources and Topics Rings with More Than Six Members Heterocycles Containing Unusual Heteroatoms Gramenitskaya , N. Kruchkovskaya , N. Above all, the benzo[c]furans undergo a wide variety of Diels-Alder and other cyclizations, which together with their preparations and other reactions is the subject of a comprehensive overview by Professor W. Heterocyclic seven-membered rings are receiving increasing attention: Nyerges Technical University of Budapest, Hungary in the second chapter of this volume. The chemistry of 1,2,4-triazolo[4,3-a]pyrimidines is covered in the first installment of a general treatment of 1,2,4-triazolopyrimidines isosters of purines by Professor M. Morgaan Alexandria University, Egypt. The final installment of Dr. Parts I through IV appeared in Volumes of our series. Volume 73 closes with Part VI of our ongoing series on the literature of heterocyclic chemistry, which attempts to record all relevant reviews including those not in English in a systematic manner. Part VI, authored by Professor L. Gramenitskaya Zelinsky Institute, Moscow, Russia , covers the three-year period to Isobenzofurans and Benzannulated Derivatives Reactivity of Isobenzofurans in Diels-Alder Reactions. Reactions with Carbenes and Nitrenes. Oxidation and Reduction Reactions. Introduction Benzo[c]furans isobenzofurans 2 constitute a unique class of heterocyclic compounds. They belong to a class of  $\alpha$ -excessive heterocycles 1 Copyright 8 by Academic Press. All rights of reproduction in any form reserved. I1 68MI1 , which can formally be derived from the isoconjugated indenyl anion 1. As they are compounds with an o-quinodimethane structural element 3, they are especially suited for inter- and intramolecular cycloadditions. The following is an updated version of our earlier work 80AHC and covers the literature from mid to the end of , including some references omitted in our earlier review. All these methods have also been applied to the parent system and substituted derivatives 94HOU Because crystal structure determinations for at least two substituted isobenzofurans [4, 86JOC; 5, 94JCS CC ; 95AX C ] have been reported, the computed values can be judged against the experimental data. Several other theoretical studies have been performed for isobenzofurans. For resonance energies see also 91MI2. For an experimental estimation of aromaticity relative to that of benzene see Mitchell et al. Quantum chemical studies of the Elbs reaction on possible isobenzofuran precursors have been performed [92MI1; R 29 ]. A theoretical study of the location of oxygen atoms on the relative thermodynamic stability of polyheterocyclic compounds has been performed 93IZV The intramolecular ring closure of the 2-formyl-benzoyl radical to a 3-phthalidyl radical 1-oxy-isobenzofuran radical has been studied

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computationally 96JOC; see also 94JA,94JA Based on the previously introduced argument that absolute hardness HOMO-LUMO gap is a good measure of aromaticity, the concept of relative hardness has been introduced and applied to a wide variety of cyclic conjugated molecules [e. For a comparison of benzo[b]furan with isobenzofuran see Jursic 98MI4. The electronic density of states of quasi-one-dimensional poly isothionaphthene isobenzofuran lattices has been investigated 90MI2. HMO studies have been performed on the band gap of isobenzofuran polymers 87SM Whether the statement that isobenzofurans have aromatic character relies on a sound experimental basis remains to be established. The synthesis of the parent compound 2 can be traced back to the work 6 7 8 Sec. For the reaction of 2 with 9 see also Meier et al. A The transient existence of both isobenzofuran 2 and its 1,3-dimethyl derivative 19 was proved by Fieser and Haddadin in a further set of experiments. The isolation of the parent compound 2 can be achieved by several methods: A convenient preparation of the tetrazine is described in Russell et al. A prepare larger quantities of pure isobenzofuran. These methodologies have also been used for the preparation of other unstable isobenzofurans, e. FVP of 1-acetoxy-1,4-epoxy-1,2,3,4-tetrahydronaphthalene does not give the corresponding isobenzofuran, but an isomerization product 87AP FVP generation with subsequent thermal rearrangement was also reported for a 1-alkyl-substituted isobenzofuran 97T; see also 98TL

Chapter 6 : Ross Grimmett - [calendrierdelascience.com](http://calendrierdelascience.com)

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