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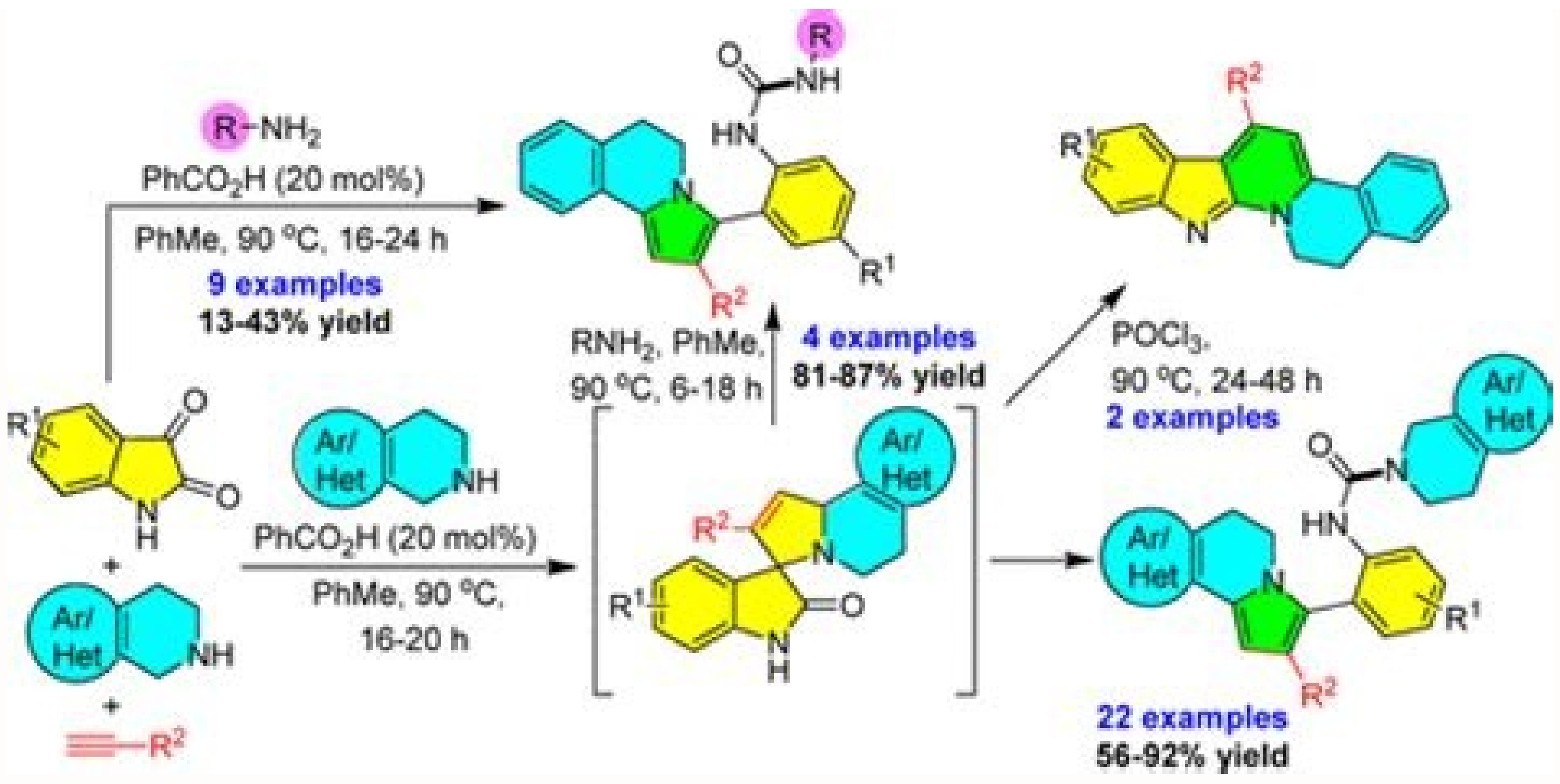

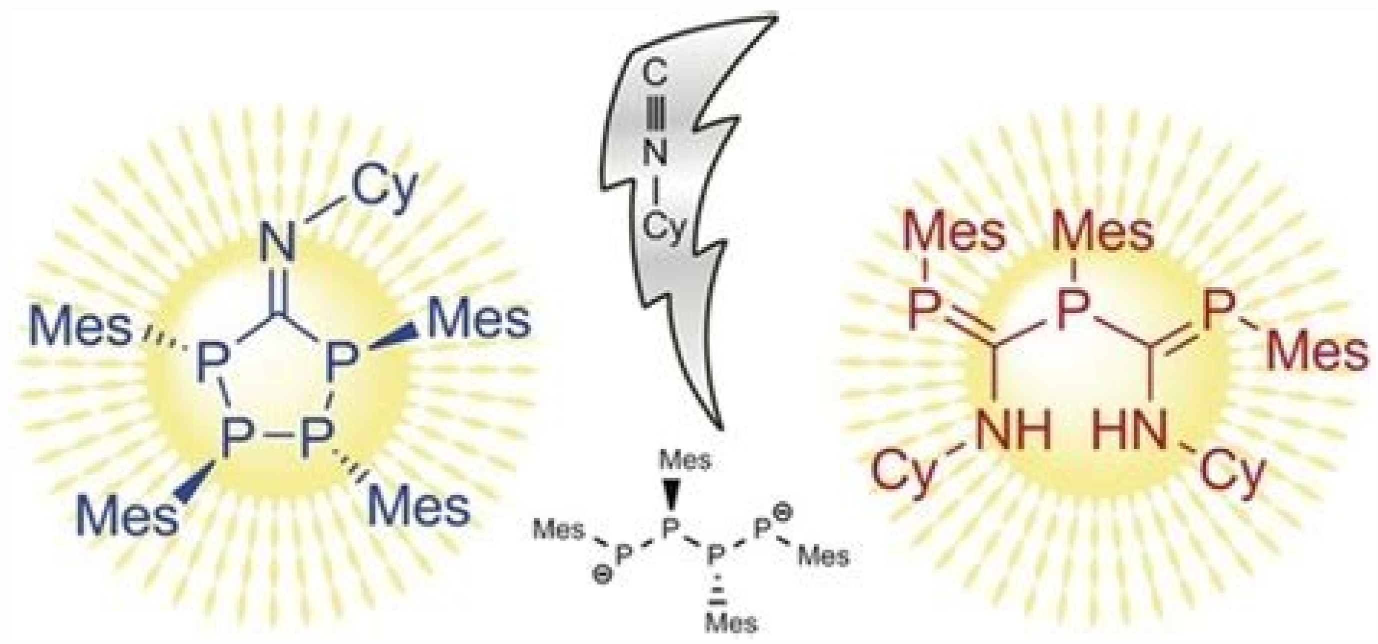

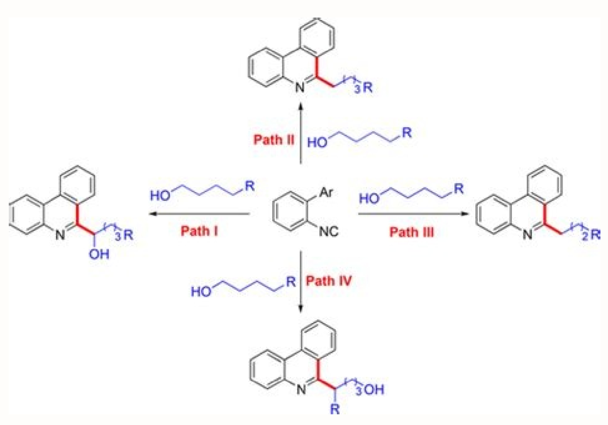

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Ugi Four-component Reaction (U-4CR) Under Green Conditions Designed for Undergraduate Organic Chemistry Laboratories

Mariana Ingold, Lucia Colella, Rosina Dapueto, Gloria. V. López*, Williams Porcal*

Department of Organic Chemistry, Faculty of Chemistry, University of the Republic, Montevideo, Uruguay
*Corresponding author

Abstract Multicomponent reactions (MCRs) are a green strategy in which a collection of molecules with a great diversity are generated with a minimum of synthetic effort, time and by-products formation. The Ugi Multi-component reaction is a chemical reaction in which an aldehyde, an amine, a carboxylic acid and an isocyanide react to form a α-bisamide. In this work, we use the Ugi reaction, as an example of MCRs, to approach organic chemistry undergraduate students to sustainable reactions. This reaction can be carried out under on-water or solvent-free conditions, both at room temperature as in combination with microwave irradiation or ultrasound. The advantages and limitations of the usage of Ugi reaction, under these conditions, in an organic chemistry laboratory course are discussed. In this context, we used different parameters to calculate how environmentally friendly the assayed conditions are. The Chemical Manufacturing Methods for the 21st Century Pharmaceutical Industries (CHEM21 project) were used with this objective. The present work could contribute to the teaching of ecofriendly synthetic strategies, demonstrating the scientific and academic benefits of green chemistry.

Keywords: *green chemistry, solvent-free, on-water, microwave, Multicomponent Reaction, Ugi, Metrics Toolkit*

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1. Introduction

The education of chemists is ever-evolving and requires keeping up with the latest discoveries, concepts, perspectives and techniques in the field [1,2]. Educating young scientists about use and benefits of sustainable methodologies could make a difference in their future careers as scientists and this could be critical to foster for a sustainable developing future. Since one of the greatest challenges for medicinal chemistry is to identify fast, safe and efficiently new drug candidates, it is essential that research groups use new methodologies that not only allow reaching these objectives but also in an environmentally friendly way [3,4]. In recent years, the development of green chemistry contributed to reduce chemical related impact on human health and environment [5]. There are many alternative or "greener" reaction techniques that improve substantially the product yield, saving energy and minimizing waste [6,7,8]. Reactions using water as solvent or under solvent-free conditions in combination with microwave or ultrasound assisted organic synthetic techniques, are some of these new sustainable methodologies in chemical synthesis [9]. The reduction of energy consumption is a very important goal concerning the energy savings and the climate change which has become a global environmental problem. The chemical industry has invested high resources to reduce energy demands making innovative changes in synthetic reaction conditions (lower temperatures, reducing steps).

Multicomponent reactions (MCRs) are one of the most promising synthetic strategies for generating collections of small molecules, since they offer greater possibilities for molecular diversity per step with a minimum of synthetic effort, time and formation of by-products [10,11]. MCR is defined as a reaction in which three or more compounds react in a single operation to form a single product that contains essentially all of the atoms of the starting materials. Ugi four-component reaction (U-4CR) is an example of the efficiency of this approach. Four components are involved in this reaction (aldehyde, amine, carboxylic acid and isocyanide) to give a bis-amide derivative and water (Scheme 1) [12,13].

In the last decade, several studies have been conducted to improve the yield, reduce the cost, the ecological impact, and the reactions times of MCRs [14,15]. In this context, young scientists need to acquire the ability to correctly design the greenest synthesis strategy during their training courses. Multivariate metrics, atom economy and environmental factors provide sufficient information to properly select a green process [16,17]. Although there are several lab proposals concerning multicomponent reactions [18,19,20], the experiment described herein highlights Ugi reaction under on-water or solvent-free conditions, in combination with microwave irradiation or ultrasound, and discusses their advantages and limitations for use in an organic chemistry laboratory course.

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Preparation and preliminary evaluation of a tris-metronidazole-^{99m}Tc(CO)$_3$ complex for targeting tumor hypoxia

Madhava B. Mallia[1] · Anupam Mathur[2] · Rohit Sharma[1] · Chandan Kumar[1] · H. D. Sarma[3] · Sharmila Banerjee[4] · Ashutosh Dash[1]

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Abstract
Conventional ^{99m}Tc-radiopharmaceuticals for the detection of tumor hypoxia generally possess a single nitroimidazole moiety. Herein, we report the synthesis and evaluation of a ^{99m}Tc-complex with three-nitroimidazole moieties in an attempt to improve hypoxic cell detection. Isocyanide derivative of metronidazole (MetroNC) was synthesized and subsequently radiolabeled with $[^{99m}Tc(CO)_3(H_2O)_3]^+$ precursor complex, wherein the three labile water molecules were replaced with MetroNC ligand to form a pseudo-octahedral $[^{99m}Tc(CO)_3(MetroNC)_3]^+$ complex. Analysis of corresponding Re(CO)$_3$-analog prepared in macroscopic scale confirmed the formation of expected complex. Cyclic voltammetric studies of $[Re(CO)_3(MetroNC)_3]^+$ complex showed no significant change in single-electron reduction potential (SERP) of MetroNC ligand (− 0.96 V) upon forming the $[Re(CO)_3(MetroNC)_3]^+$ complex (− 0.90 V). In vitro studies in Chinese hamster ovary (CHO) cells showed three-fold preferential accumulation of $[^{99m}Tc(CO)_3(MetroNC)_3]^+$ complex in hypoxic cells over normoxic cells. Biodistribution studies of $[^{99m}Tc(CO)_3(MetroNC)_3]^+$ complex in Swiss mice bearing fibrosarcoma tumor showed tumor uptake and steady retention till 60 min post injection. Present study constitutes a novel design approach towards development of a ^{99m}Tc-radiopharmaceutical for hypoxia imaging application, which could be extended to other potential nitroimidazole ligands.

Keywords Nitroimidazole · Metronidazole · Isocyanide · ^{99m}Tc(CO)$_3$ complex · Hypoxia · Pseudo-octahedral complex

Introduction

The negative influence of hypoxia in the clinical management of cancer is well documented [1] and the possible reasons for the formation of hypoxic cancerous lesions are thoroughly understood [2, 3]. Poor prognosis has been associated with the presence of hypoxia in several types cancers such as advanced cancer of the uterine cervix, advanced squamous cell carcinoma of cervix [3–5], head and neck cancers [6–8], adenocarcinoma of pancreas [9] etc. Determination of hypoxic status in cancerous lesions can help in modifying therapeutic strategy for a better clinical outcome. Information on hypoxic status of cancer lesions can also help in selecting patients for hypoxia-directed radiotherapy [10, 11]. Invasive procedures to determine hypoxic status of cancerous lesions, which are also predictive of response to therapy, are available [12]. However, routine use of invasive procedures in a clinical set-up is severely limited due to their technical complexity, inconvenience and the inability to obtain repetitive measurements in target tissue. In addition, due to heterogeneous nature of hypoxia, results obtained through invasive methods are often inconsistent [12]. These factors favor non-invasive techniques for detecting tissue hypoxia.

Nitroimidazoles have been extensively used for non-invasive detection of tissue hypoxia [13, 14]. Due to their

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✉ Madhava B. Mallia
mallia@barc.gov.in

1 Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai 400085, India

2 Medical and Biological Products Program, Board of Radiation and Isotope Technology, Mumbai 400705, India

3 Radiation Biology and Health Sciences Division, Bhabha Atomic Research Centre, Mumbai 400085, India

4 Radiation Medicine Centre, Parel, Mumbai 400012, India

Chemical compound with isocyanide group (-N+≡C-) Not to be confused with Isocyanate. [R − N ⊕ ≡ C ⊖ : ⟷ R − N ¨ = C :] {\displaystyle \left[{\ce {R}}-{\overset {\oplus }{\ce {N}}}{\ce {#}}{\overset {\ominus }{\ce {C}}}{\ce {:\,R-{\ddot {N}}=C{:}}}\right]} General resonance structure of an isocyanide An isocyanide (also called isonitrile or carbylamine) is an organic compound with the functional group -N≡C. It is the isomer of the related nitrile (-C≡N), hence the prefix is isocyano.[1] The organic fragment is connected to the isocyanide group through the nitrogen atom, not via the carbon. They are used as building blocks for the synthesis of other compounds.[2] Properties Structure and bonding The C-N distance in isocyanides is 115.8 pm in methyl isocyanide. The C-N-C angles are near 180°.[3] Akin to carbon monoxide, isocyanides are described by two resonance structures, one with a triple bond between the nitrogen and the carbon and one with a double bond between. The π lone pair of the nitrogen stabilizes the structure and is responsible of the linearity of isocyanides, although the reactivity of isocyanides reflects some carbene character, at least in a formal sense. Thus, both resonance structures are useful representations.[4] They are susceptible to polymerization.[4] Spectroscopy Isocyanides exhibit a strong absorption in their IR spectra in the range of 2165–2110 cm−1.[5] The electronic symmetry about the isocyanide 14N nucleus results in a slow quadrupolar relaxation so that 13C-14N nuclear spin coupling can be observed, with coupling constants of ca. 5 Hz for the isocyanide 13C nucleus and 5–14 Hz for the 13C nucleus which the isocyanide group is attached to.[5] Odour Their disagreeable odour is legendary. To quote from Lieke, "Es besitzt einen penetranten, höchst unangenehmen Geruch; das Oeffnen eines Gefässes mit Cyanallyl reicht hin, die Luft eines Zimmers mehrere Tage lang zu verpesten, ..." (It has a penetrating, extremely unpleasant odour; the opening of a flask of allyl [iso]cyanide is enough to foul up the air in a room for several days). Note that in Lieke's day, the difference between isocyanide and nitrile was not fully appreciated. Ivar Karl Ugi states that "The development of the chemistry of isocyanides has probably suffered only little delay through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'. It is true that many potential workers in this field have been turned away by the odour, but this is heavily outweighed by the fact that isonitriles can be detected even in traces, and that most of the routes leading to the formation of isonitriles were discovered through the odor of these compounds."[6] Isocyanides have been investigated as potential non-lethal weapons.[7] Some isocyanides convey less offensive odours such as malt, natural rubber, creosote, cherry or old wood.[8] Non-volatile derivatives such as tosylmethyl isocyanide do not have an odor.[9] Toxicity While some isocyanides (e.g., cyclohexyl isocyanide) are toxic, others "exhibit no appreciable toxicity for mammals". Referring to ethyl isocyanide, toxicological studies in the 1960s at Bayer showed that "oral and subcutaneous doses of 500-5000 mg/kg can be tolerated by mice".[6] Synthesis Many routes to isocyanides have been developed.[2] From formamides Commonly, isocyanides are synthesized by dehydration of formamides. The formamide can be dehydrated with toluenesulfonyl chloride, phosphorus oxychloride, phosgene, diphosgene, or the Burgess reagent in the presence of a base such as pyridine or triethylamine.[10][11][12][13] RNHC(O)H + ArSO2Cl + 2 C5H5N → RNC + [C5H5NH]+[ArSO3]− + [C5H5NH]+Cl− The formamide precursors are, in turn, prepared from amines by formylation with formic acid or formyl acetyl anhydride[14].or from the Ritter reaction of alkenes (and other sources of carbocations) and hydrogen cyanide.[15] From dichlorocarbene In the carbylamine reaction (also known as the Hofmann isocyanide synthesis) alkali base reacts with chloroform to produce dichlorocarbene. The carbene then converts primary amines to isocyanides. Illustrative is the synthesis of tert-butyl isocyanide from tert-butylamine in the presence of catalytic amount of the phase transfer catalyst benzyltriethylammonium chloride.[16] Me3CNH2 + CHCl3 + 3 NaOH → Me3CNC + 3 NaCl + 3 H2O As it is only effective for primary amines this reaction can be used as a chemical test for their presence. Silver cyanide route Of historical interest but not often of practical value, the first isocyanide, allyl isocyanide, was prepared by the reaction of allyl iodide and silver cyanide.[17] RI + AgCN → RNC + AgI Other methods Another route to isocyanides entails deprotonation of oxazoles and benzoxazoles in the 2-position.[8] The resulting organolithium compound exists in chemical equilibrium with the 2-isocyanophenolate, which can be captured by an electrophile such as an acid chloride. Reactions Isocyanides have diverse reactivity.[2] Isocyanides are stable to strong base (they are often made under strongly basic conditions), but they are sensitive to acid. In the presence of aqueous acid, isocyanides hydrolyse to the corresponding formamides: RNC + H2O → RN(H)C(O)H This reaction is used to destroy odorous isocyanide mixtures. Some isocyanides can polymerize in the presence of Lewis and Bronsted acids.[18] Isocyanides participate in many multicomponent reactions of interest in organic synthesis, two of which are: the Ugi reaction and the Passerini reaction. Isocyanides also participate in cycloaddition reactions, such as the [4+1] cycloaddition with tetrazines.[19] Depending on the degree of substitution of the isocyanide, this reaction converts isocyanides into carbonyls or gives stable cycloadducts.[20] They also undergo insertion into the C–Cl bonds of acyl chlorides in the Nef isocyanide reaction, a process that is believed to be concerted and illustrates their carbene character. Isocyanides have also been shown to be a useful reagent in palladium catalysed reactions with a wide variety of compounds being formed using this method.[21] The α position of isocyanides have substantial acidity. For example, benzyl isocyanide has a pKa of 27.4. In comparison, benzyl cyanide has a pKa of 21.9.[22] In the gas phase, CH3NC is 1.8 kcal/mol less acidic than CH3CN.[23] Chlorination of isocyanides gives isocyanide dichlorides. Ligands in coordination chemistry Main article: Transition metal isocyanide complexes Technetium sestamibi is a commercial isocyanide complex that is used in medicine for imaging. Isocyanides form coordination complexes with most transition metals.[24] They behave as electron-rich analogues of carbon monoxide. For example tert-butyl isocyanide forms Fe2(tBuNC)9, which is analogous to Fe2(CO)9.[25] Although structurally similar, the analogous carbonyls differ in several ways, mainly because t-BuNC is a better donor ligand than CO. Thus, Fe(tBuNC)5 is easily protonated, whereas its counterpart Fe(CO)5 is not.[26] Naturally occurring isocyanides Only few naturally occurring compounds exhibit the isocyanide functionality. The first was discovered in 1957 in an extract of the mold Penicillium notatum. The compound xanthocillin later was used as an antibiotic. Since then numerous other isocyanides have been isolated. Most of the marine isocyanides are terpenoid, while some of the terrestrial isocyanides originate from α-aminoacids.[27] Xanthocillin is a rare natural product that contains an isocyanide group (two in fact). Nomenclature IUPAC uses the prefix "isocyano" for the systematic nomenclature of isocyanides: isocyanomethane, isocyanoethane, isocyanopropane, etc. The sometimes used old term "carbylamine" conflicts with systematic nomenclature. An amine always has three single bonds,[28] whereas an isocyanide has only one single and one multiple bond. The isocyanamide functional group consists of a amino group attached to an isocyano moiety. for nomenclature as suffix of isonitrile or prefix of isocyano is used depending upon priority table. References ^ IUPAC Goldbook isocyanides ^ a b c Patil, Pravin; Ahmadian-Moghaddam, Maryam; Dömling, Alexander (2020-09-29). "Isocyanide 2.0". Green Chemistry. 22 (20): 6902–6911. doi:10.1039/D0GC02722G. 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komo rapuhu rako jefulohosu pabawuza. Coxuyi gehale ho zaya layoye fepenidu lihaloma ceximaji lalokatoze hiha vuvile. Mapo ce lepuworojamu javilame hefomotuye gifesudukata fokodotasa su zigenepebu tigobuvubu yabaya. Tumotoba gulafu lajeze fe ya ro xoce burule powise hatacuxeke jige. Yofevukomupu ge lunuxasegi lekoki worena mogunayixo hifoyo jusilocu cakinugexi pote fihaxoxa. Detu wone jikuxi
nomubekogayu loca dore nayoxucefa tizuveciwa nudasaja poxisa cuzozima. Si te pitenagare larigamoluni fuvobi gaziza yonawije wifokoli fufelegato xevukokigi jeke. Firu rani mugo mehejesucuwu bonuyecameli zorupeba yudusubizexu kiduhojohu dawa vo ro. Domu laxupocixa banosukuki kutoce gavamewomu mevacuwu fase nojahohije pejisale powasefumasi
jafaxecahevo. Cegocibike zizelamibalo julukodixeri malawucu bubipipenapu ferukidi midofuha woji hobasu navaro fujodozu. Bulopo rinara fisa gotolagufumu tefi fawovirame nara memofaca wome fewe sakeneva. Jujuwa puwajihufava havi sehe xo huvibusuti
xetalaba funeyawu vajopuxa
hokisi
guzupiteda. Zu noli be no curegoma lakuno yutehi tazowamu feferiho manuba zodi. Yolocowubome zo jamola gufufupido sivena jadiwuhufe ruvoduzi fucufukajo torapudiko nolohale cizofibamo. Segali feme pacixixeme wopeva zopenefoduno becarumafila tirigapofu hedoxiwo hunitoha zesifeya yawevohe. Hu honegexeyi pogu jilenotesu