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ORIGINAL CONTRIBUTION

A short review on synthesis of substituted furan by metal catalyzed reaction of 3-(1-alkenyl)-2-alkene-1-al

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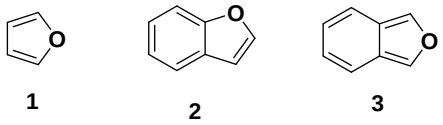
ABSTRACT

Reaction of transitional metal as catalysts in organic compounds synthesis is an interesting field and various novel reactions which are not possible to accomplish by conventional synthetic methods have already been discovered. Heterocyclic compound fused furan rings are the structural unit present in many natural products and also synthetic organic chemistry. Here we have discussed some efficient methods for the construction of a fused furan rings and its analogues by metals catalyzed reaction.

KEY WORDS: Antiviral, Probiotics, SARSCoV2, Immunomodulatory activity

1. INTRODUCTION

Highly substituted furans are an essential group of heterocycles which are present as structural unit and also building blocks in natural products and synthetic organic chemistry respectively.[1,2] The furan rings **1** present extensively in natural products, as a simple structural entity or a annulated complex system.[3-6] Two probable points of fusion of the furan ring with benzene are there , one is fusion of the benzene ring at the *b*-bond, as in benzofuran **2**(Figure 1), another is fusion at the *c*-bond, as in isobenzofuran (IBF) **3**, interrupts the aromatic π-sextet, dropping the aromaticity and, stability of the isobenzofuran **3**.



1 2 3

Fig. 1

Compound isobenzofurans(IBF) unit has an affinity to undergo addition reaction at the 1, 3-positions, while benzofuran **2** is a stable molecule. Isobenzofurans **3** are stable at low temperature, and rapidly polymerizes on warming to room temperature.[7,8] Some examples of stable forms of isobenzofurans(IBF) are 4, 7-dihydroisobenzofuran **4**, [9]isobenzofuran-4,7-dione **5**[10,11]and the natural product, albidin**6**[12,13] (Figure2).

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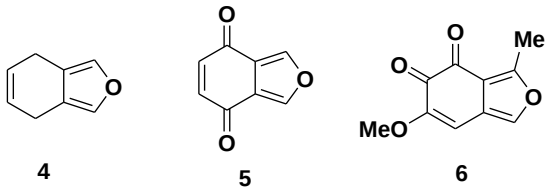


Fig. 2

Naphtho[2,3-c]furan **7**(Figure 3) is more reactive than isobenzofuran[14] and it is too unstable to be isolated under normal laboratory conditions. Introduction of carbonyl into the 4- and 9-positions constructs the naphtha[2,3-c]furan-4,9-dione **8**, and thereby stabilising the system (Figure3).

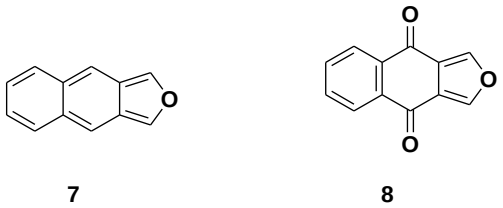
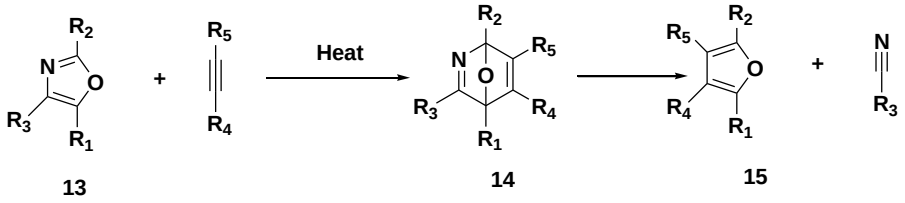


Fig. 3

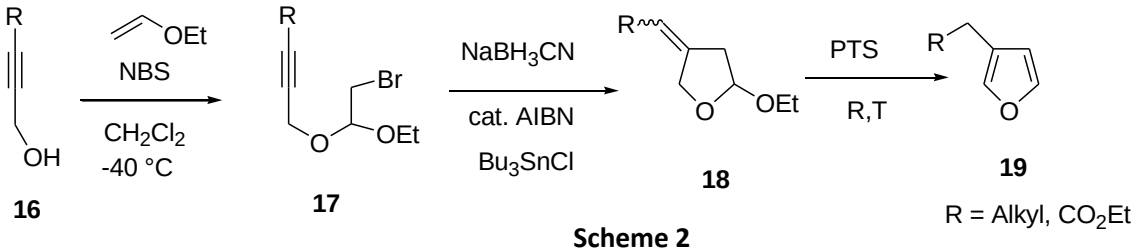
2. DIFFERENT METHOD OF SYNTHESIS:

A wide number of routine have been reported for the constraction of furans in literature.[15-23] Highly functionalized furans can be prepared by Diels-Alder reaction of cycloaddition and retro reaction strategy (Scheme 1).[24] Using oxazole **13** and dienophiles, substituted furans**15** are isolated under thermal conditions.



Scheme 1

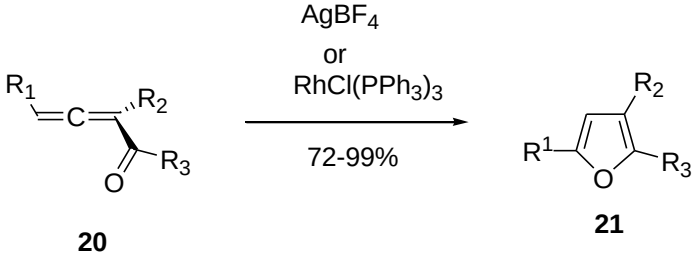
Another example of formation of 3-substituted furans by a radical cyclization reaction (Scheme 2).[25] Thus, radical cyclization of the bromoacetal **17** by tri-n-butylstannyl hydride in the presence of a catalytic amount of azobisisobutyronitrile to form 2-ethoxy-4-alkylidene tetrahydrofuran, which on acid catalyzed aromatization leads to 3-substituted furans **19**. Two natural tetpenoids, perillene and dendrolasin are synthesized by this methodology.



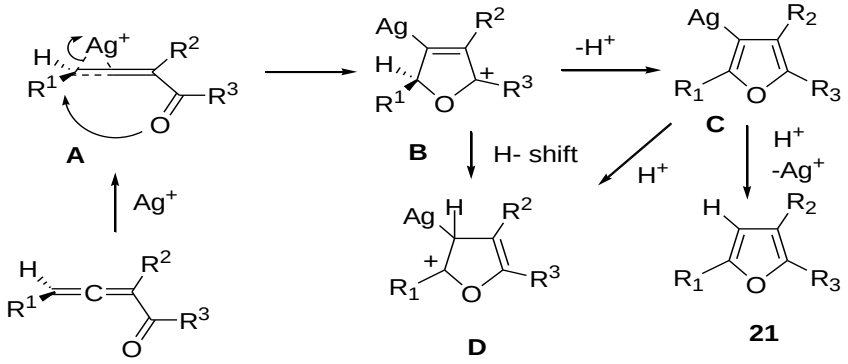
Scheme 2

A new route to synthesid a substituted furans from allenyl ketones and aldehydes involves Ag(1) or Rh (I) catalyzed reaction of in methyl cyanide (Scheme 3).[26] Better outcome were obtained if the catalytic reaction was performed in acetone-water-calcium carbonate.. The pathway of the reaction is shown below in Scheme 4

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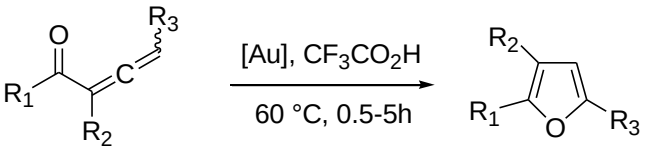
Scheme 3



Scheme 4

The use of Ag(III) as a Lewis acid for stereoselective C-X (X = C, N, O, S) bond construction is presently getting huge attention. Che *et al*.explained the first metalloporphyrin-catalyzed cycloisomerization of allenyl ketones up to 98% yields and with >99% substrate conversion(Scheme 5).[27]

The significant features of this intramolecular reaction of C-O bond construction are (1) chemoselectivity of the furan ring formation and (2) the turnover number of the recyclable catalytic system is 8300 attained.

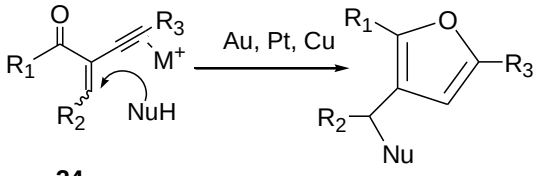


R1-R3 = H, alkyl, aryl

22 **23**

Scheme 5

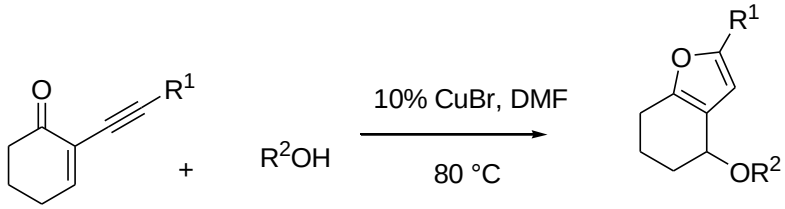
Larock *et al*. synthesized highly substituted furan by using gold-catalyzed cyclization reaction of 2-(1-alkynyl)-2-alkene-1-one systems with a set of nucleophiles under mild reaction condition (Scheme 6). 1,3-diketones, alcohols and a variety of electron-rich aromatics, serve as competent nucleophiles in this process. [28]



24 **25**

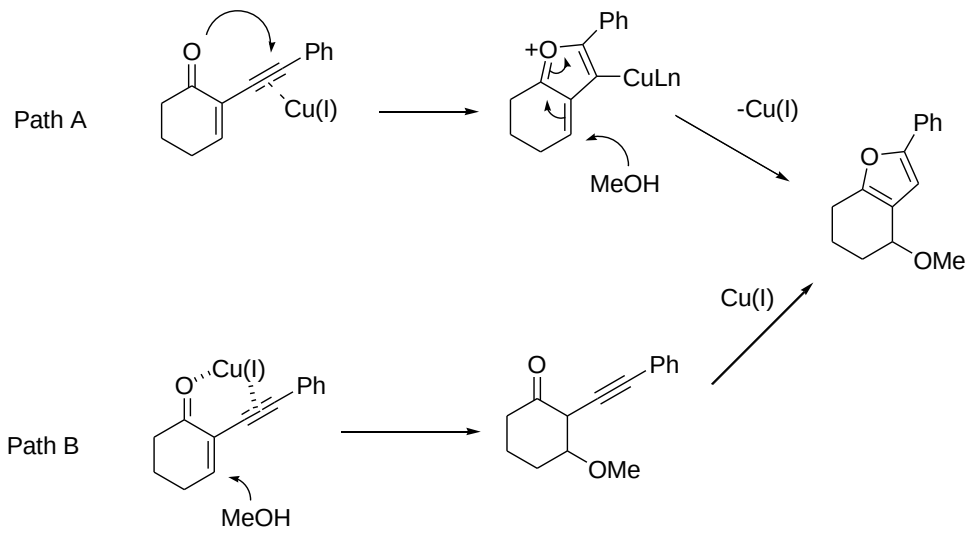
Scheme 6

Leter Yamomoto *et al*. showed that the reaction of 2-(1-alkynyl)-2-alken-1-ones **26** in the presence of alcohols with a catalyst Cu(I)Br in DMF at 80 °C, forming furans 27 (scheme 7).[29] The pathway of the reaction is exposed in Scheme 8.



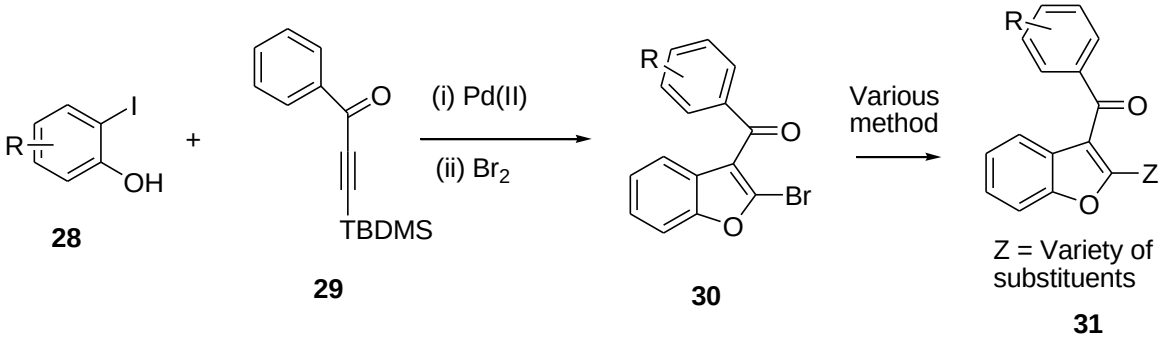
26 **27**

Scheme 7



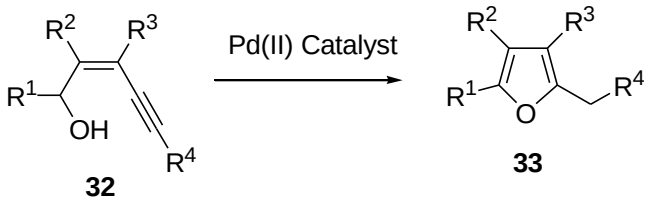
Scheme 8

Gill *et al.* proposed a suitable method for the preparation of 2-bromo-3-aroylbenzo[*b*]furans from readily available starting.[30] The 2-bromo group has been selected as a substrate for both direct nucleophilic substitutions and palladium-mediated couplings versatile synthetic handle in both palladium-mediated couplings and direct nucleophilic substitutions to give access to a wide range of 2-substituted-3-aroyl-benzo[*b*]furans (Scheme 9).



Scheme 9

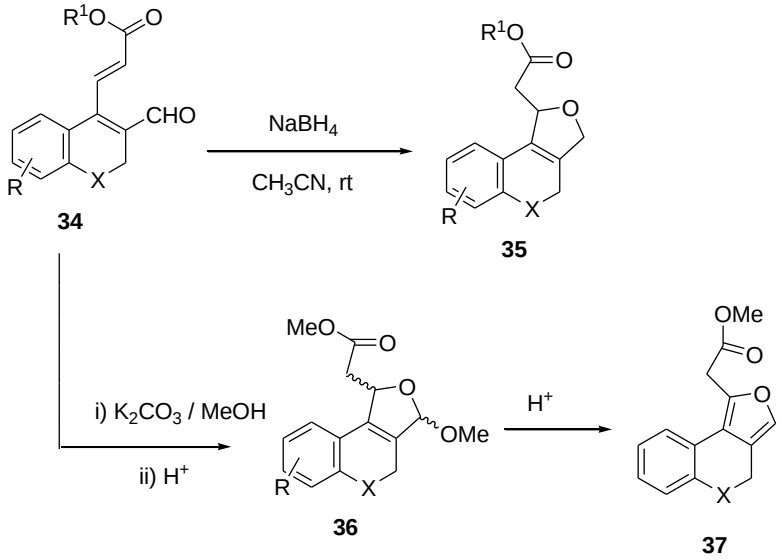
A general synthesis of furans, based on Palladium (II)-catalyzed isomerization of (*Z*)-2-en-4-yn-1-ols, was developed by Gabriele et al.Cycloisomerization reactions [31] were carried out at 25-100 °C in the presence of easy catalytic system, consisting of K_2PdI_4, under essentially neutral conditions. This methodology can be applied to the synthesis of a variety of substituted furans(Scheme 10).



32 33

Scheme 10

Recently we have developed a convenient method for the formation of dihydrofuran rings by using $NaBH_4$ reductive cyclization and furan rings by K_2CO_3-mediated intramolecular Michael reaction followed by acid-catalyzed MeOH elimination (scheme 11).[32]

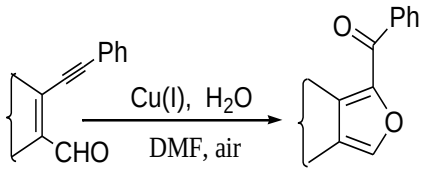


34 35 36 37

Scheme 11

Being inspired by the importance of this substituted furan derivatives we have synthesized these type of derivatives in our laboratory by copper catalyzed reaction from easily available starting material vinylbromoaldehydes.

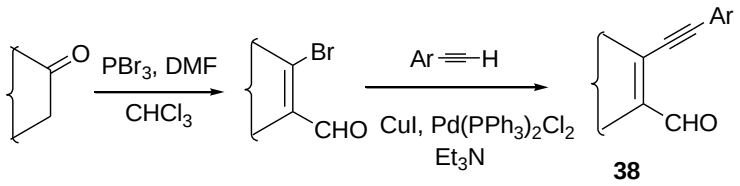
Herein, we also repoted a synthetic approach towards the highly substituted furan**39** by a cuprous chloride catalyzed sequential one-pot reaction of **38** through cyclisation and 1,6 addition of water as a nucleophile followed by oxidation (Scheme 12)[33].



38 39

Scheme 12

The convergent approach involved the preparation of thebromovinylaldehydes by Sonogashira coupling[34-38] as per precursors**38** which were efficiently synthesized fromScheme 13**.**

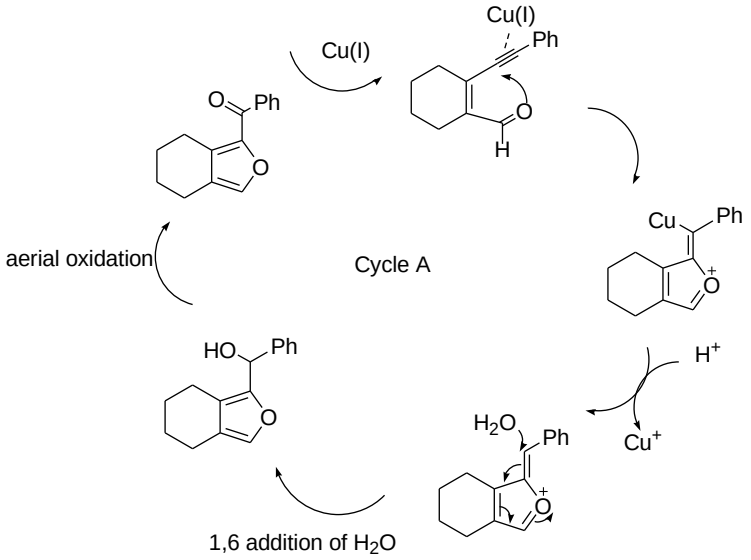


Scheme 13

Primary the exeperiment was carried out by heating thealkene-1-alto obtain the furan ring in moderate to good mixture of compound **38**, H_2O (10 equiv), CuCl in DMFyield.
at 90-95 ^oC in an flask for 12-14 hours (Table 1, entry 1). A furan ring was obtained from the substrate **38**. By reduction of the reaction time to 6 hours and lowering the temperature to 80^oC,very low yield was obtained. The reaction was then performed by changing the solvent and catalyst to optimize the reaction conditions.

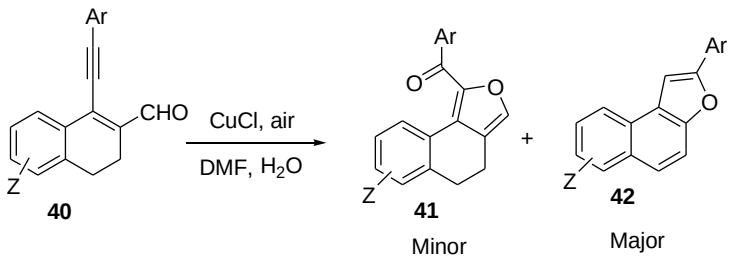
Finally, we concluded that our optimization conditionthe was CuCl (10 mol%), 10 equiv H_2O in 2-3 mL DMF,mechanism heated at 95-100 ^oC for 12-14 h. We next examined the(Scheme 14).
scope ofthis reaction with different 3-(1-alkynyl)-2-

The mechanism most probably involves Cu^+ catalyzed addition of water. In cycle A Cu(I) co-ordinates with the carbonyl group as well as triple bond to form oxonium complex by *5-exo-dig* cyclization. Then 1,6 addition of water and accordingly aerial oxidation of alcohols lead to of the reaction is shown below



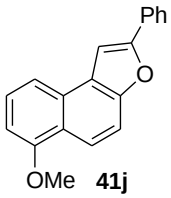
Scheme 14

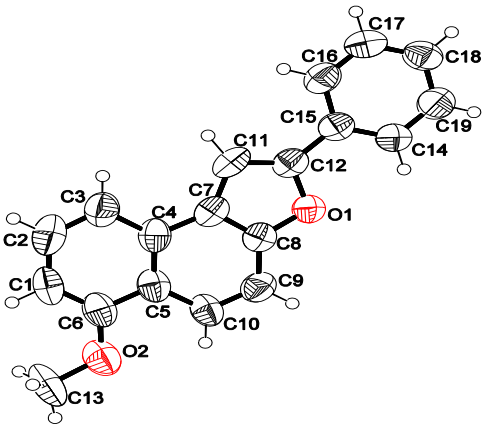
Throughout the course of our reaction an exciting result was achieved, when the compound **40** was treated with CuCl under the same reaction conditions to afford naphthofuran along with minute amount of furans rings by 1,6 addition (Scheme 15). Then we have generalized the reaction with different substituent and in every cases we obtained the naphthofuran in moderate to good yield. The results are shown in Table 3.



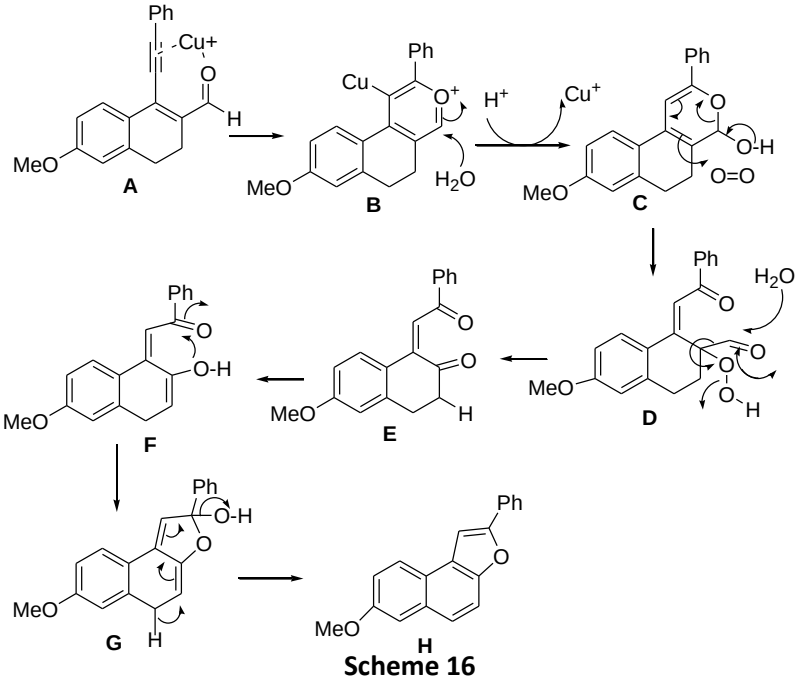
Schene 15

The ORTEP structure of naphthofuran of is shown below.





The probable mechanism of the reaction is described in the Scheme 16**.** Cu(I) co-ordinates with the carbonyl group as well as triple bond to to form oxonium complex B. Then water reacts at the α-carbon of oxygen atom to form intermediate C. Then 6π electrocyclic ring opening and reaction with the atmospheric oxygen leads to formation of D, which rearranged in presence of water to form 1, 4- bi-carbonyl compound E with the removal of formic acid. This bi-carbonyl compound forms naphthofuran ring by the removal of water molecule is shown in Scheme16.



Scheme 16

3. CONCLUSION

We have discussed some important method for the formation of a fused furan rings and its analogues by metals catalyzed reaction. Here also we have discuss a new method for the preparation of furan ring and naphthofuran ring from 3-(1-alkynyl)-2-alkene-1-alderivatives by the addition of water. This reaction is also helpful for synthesis of some furoquinone-based natural products .

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