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One-Pot Construction of Medium- and Large-Sized Ring Substituted Furans. Efficient Conversion to Dibenzofurans, Coumestans, and 4-Pyrones

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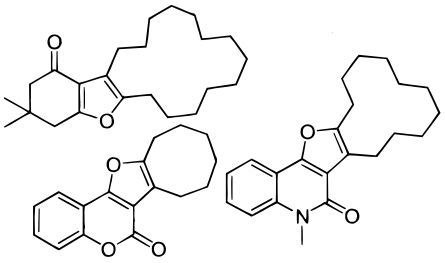
ABSTRACT



New efficient synthesis of medium- and large-sized ring substituted furans is achieved by 1,3-dicarbonyl compounds with vinyl sulfides in the presence of Ag_2CO_3/Celite (Fétizon's reagent) in a one-pot procedure. The synthesized furans can be further converted to biologically interesting compounds such as dibenzofurans, coumestans, benzofuroquinolinone, and 4-pyrone.

Furans are among the most important heteroaromatic compounds with widespread occurrence in nature.[1] They are frequently found in many natural products arising from plants and marine organisms.[2] Possessing a variety of biological activities, they are used as commercially pharmaceutical agents, flavor, fragrance compounds, insecticides, and antileukemic agents.[3] Their important biological activities and usefulness have prompted a search for better methods of the synthesis of furans. Although numerous synthetic methods for the preparation of furans have been reported, single-step annulation approaches still remain scarce.[4] We recently reported that Ag(I)/Celite is a simple and convenient reagent for dihydrofuran formation.[5] We expand this work to the synthesis of a variety of medium- and large-ring substituted furans. We describe here the efficient one-pot synthesis of substituted furans starting from 1,3-dicarbonyl compounds and a variety of vinyl sulfides in the presence of Ag_2CO_3/Celite (Fétizon's reagent).

1,3-Dicarbonyl compounds used in this study include commercially available cyclohexane-1,3-diones **1**−**4**, 4-hydroxycoumarins **5**−**8**, and 4-hydroxyquinolone **9**.

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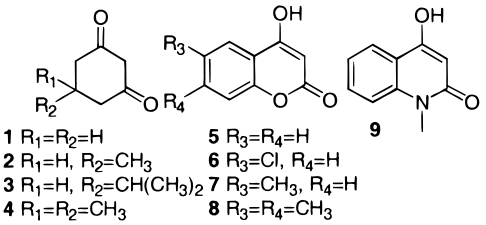
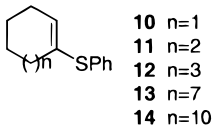
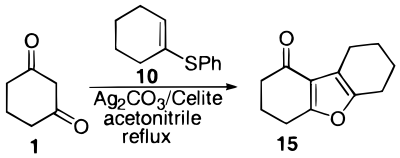


The vinyl sulfides **10**−**14** used to react with the above dicarbonyl partners were readily prepared by using Villemin's method in 50−80% yields.[6]



Treatment of 1,3-cyclohexanedione (**1**) with vinyl sulfide **10** in the presence of 3 equiv of Ag_2CO_3/Celite in refluxing acetonitrile afforded furan **15** in 51% yield (Scheme 1). The

Scheme 1



formation of **15** is supported by the observation of a peak in the IR spectrum at 1671 cm^{-1} (enone C═O) and the expected chemical shifts associated with the three methylene groups of the allylic position in ^1H NMR spectrum. This result provides a concise synthetic entry into the substituted furans as a one-pot reaction.

Next, several additional oxidative cycloadditions of 1,3-dicarbonyl compounds **1**−**4** with a number of vinyl sulfides, **10**−**14**, were investigated in the presence of 3 equiv of Ag_2CO_3/Celite. When 5,5-dimethyl-1,3-cyclohexanedione (**4**) was treated with seven-membered ring **11** in refulxing acetonitrile, furan **18** was obtained in 60% yield. In the case of vinyl sulfide **12** with an eight-membered ring, the expected furan **19** was also produced in 69% yield. More interestingly, with large-sized rings such as **13** and **14**, furan annulation was also successful. Treatment of 5,5-dimethyl-1,3-cyclohexanedione (**4**) with the 12-membered ring **13** gave furan **20** in 48% yield, while treatment with 15-membered ring **14** afforded **21** in 45% yield. In view of our results, reactions with medium-sized ring substituted vinyl sulfides resulted in better yields than large ones.

On the other hand, reaction of 4-hydroxycoumarins **5**−**8** with vinyl sulfides gave the biologically interesting furocoumarins **22**−**27** in 48−71% yields. Compounds **22**−**27** have been clearly shown to be angular by their spectral

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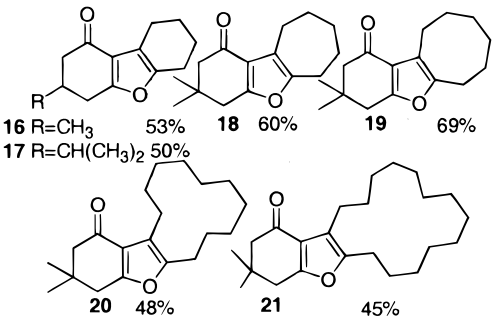
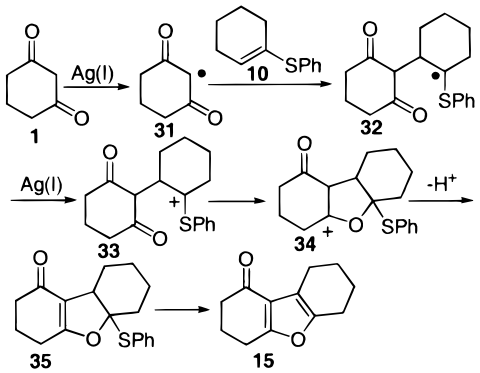


analysis and by comparison with reported data in the literature.[7] Similarly, treatment of 4-hydroxyquinolone **9** with vinyl sulfides also afforded furoquinolinones **28**−**30** in 33−44% yields. In these cases, only single products were seen and no linear regioisomers were found. These reactions also provide a rapid synthetic route toward furocoumarin and furoquinolinone derivatives which are known to have the following biological activities: anticoagulant, anthelminthic, hypnotic, antifungal, phytoalexin, antimicrobial, antimalarial, insecticidal, antineoplastic, antidiuretic, and antiarrhythmic and sedative.[8−98,9]

Although the exact mechanism of the reaction is still not clear, it is best described as shown in Scheme 2. 1,3-

Scheme 2



Dicarbonyl compound **1** is first oxidized by silver(I) to generate α-oxoalkyl radical **31**, which then attacks vinyl sulfide **10** to give radical **32**. Radical adduct **32** now undergoes fast oxidation by another silver(I) to cation **33**. Cyclization of **33** furnishes dihydrofuran **35**, which finally undergoes elimination to give furan **15**.

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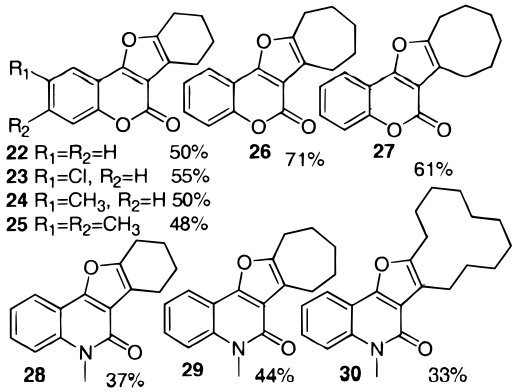
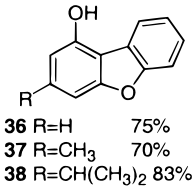
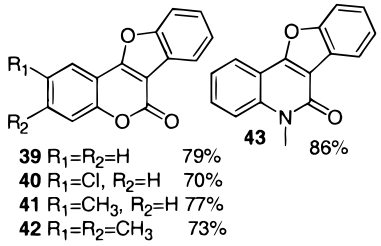


These cycloadducts can be elaborated toward biologically interesting systems. For example, furan adducts **15**−**17** can be readily dehydrogenated to give dibenzofuran derivatives which have been widely found in nature[10] and reported to have biological activities such as antifungal and phytoalexin.[11] Treatment of **15** with Pd/C in phenyl ether at 200 °C for 3 h afforded dibenzofuran **36** in 75% yield. The assignment of **36** is confirmed by ^{1}H NMR analysis of the new aromatic ring. This synthetic method is expected to be used as a simple and rapid route for the preparation of dibenzofuran derivatives.



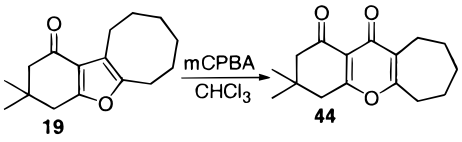
As another application, a new synthetic route to coumestan derivatives was next examined. Coumestan derivatives are widely distributed in nature[12] and are reported to have a wide range of biological properties such as estrogenic, antibacterial, and insecticidal.[13] When **22**−**25** were treated with Pd/C in phenyl ether at 200 °C for 3 h, coumestan derivatives **39**−**42** were produced in 70−79% yields. Although a number of synthetic approaches of coumestan derivatives have been reported by other groups, simple and efficient methods are still few.[14] In view of our result, it is apparent that this reaction provides a concise synthetic entry toward these types of coumestan derivatives. This dehydration is also applied



to the synthesis of biologically active benzofuroquinolinones.[15] When **28** was treated with Pd/C in phenyl ether, **43** was produced in 86% yield. The structural assignment of **43** was easily identified by the new aromatic peaks in the ^{1}H NMR spectrum.

Finally, we turned our attention to the construction of biologically interesting 4-pyrone skeletons by using synthesized furan adducts.[16] The method was carried out by the expansion of the furan ring with mCPBA as shown in Scheme 3. When **19** was treated with 2 equiv of mCPBA in

Scheme 3



chloroform at room temperature for 3 h, **44** was produced in 55% yield. The structural assignment of **44** was based on the expected chemical shifts in the ^{1}H NMR spectrum. Further confirmation of the structure is clearly accomplished from the ^{13}C NMR spectrum, which shows the expected carbonyl peaks at 202.1 and 192.5 ppm due to two ketones.

In conclusion, Ag_2CO_3/Celite-mediated cycloaddition of 1,3-dicarbonyl compounds to vinyl sulfides offers a simple and new strategy for the synthesis of medium- and large-sized ring substituted furans. This methodology provides a rapid route to the preparation of dibenzofurans, coumestans, benzofuroquinolinone, and 4-pyrones.

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Supporting Information Available: Experimental procedures and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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