Synthesis of Thiepin-annulated Pyrone and Coumarin Heterocycles by Grubbs' Second Generation Catalyst Mediated Enyne Metathesis

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Synthesis of thiepin-annulated pyrone and coumarin derivatives has been achieved by the ring-closing enyne metathesis using the second generation Grubbs' catalyst under a nitrogen atmosphere.

Coumarin and 2-pyrone are important heterocyclic compounds because these nuclei are found in many natural products.[1] Coumarins fused with other heterocycles have interesting biological and photodynamic properties.[2] Several natural[3] and synthetic[4] 2-pyrones exhibit remarkable biological activity. Recently, we have demonstrated the synthesis of pyrone and coumarin-annulated heterocycles by the application of the Claisen rearrangement[5] and radical cyclization.[6] However there is no report on the thiepin-annulated coumarin and pyrone derivatives. In recent years, the metathesis[7] (ring-closing metathesis or ring-closing enyne metathesis) strategies have been found to be practical methods for the synthesis of medium-sized rings,[8] spirocyclic and polycyclic systems,[9] and several natural products.[10] Metathesis reactions on substrate bearing diverse functionalities and heteroatoms are fully documented.[7b,7c] Surprisingly, however very limited examples of substrates containing sulfur atom have so far been reported. The limited number of examples of metathesis with sulfur containing substrates can be partly explained by the fact that middle to late transition metals used as catalyst may interact favorably with soft sulfur atom.

Tungsten,[11] molybdenum,[12] and titanium[13] catalysts were until lately the only three catalysts to display efficiency in metathesis reactions on substrate bearing sulfur atom. Literature report reveals that Grubbs' catalyst **A** (Figure 1)[14] and several modified recyclable catalysts[15] can promote metathesis reactions on substrate containing sulfonyl groups but these are inactive towards the corresponding diene sulfides with a few exceptions.[16] Catalyst **B** was also found to be effective for the ring-closing metathesis (RCM) of sulfonyl substrates.[17] Only limited examples of the RCM of diene sulfides by the catalyst **B**[18] and **C**[19] are reported in the literature but there is only one example of intermolecular enyne metathesis of sulfur containing alkyne with ethylene using catalyst **B** is known.[20] So far there is no report of successful application of catalyst **B** in intramolecular enyne metathesis of sulfur-containing heterocyclic substrates. This prompted us to investigate the metathesis reactions using catalyst **B** on the substrates 2-pyrone and coumarin containing sulfur atoms to verify the compatibility and effectiveness of the catalyst **B** towards the sulfur-containing substrates to achieve the synthesis of some hitherto unreported thiepin-annulated heterocyclic systems of interest. Herein, we report our results.

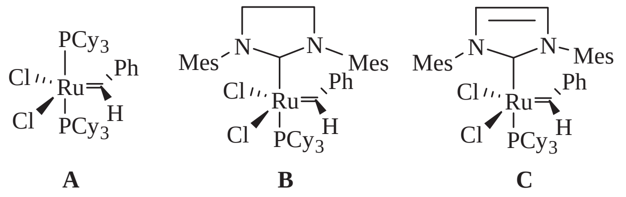


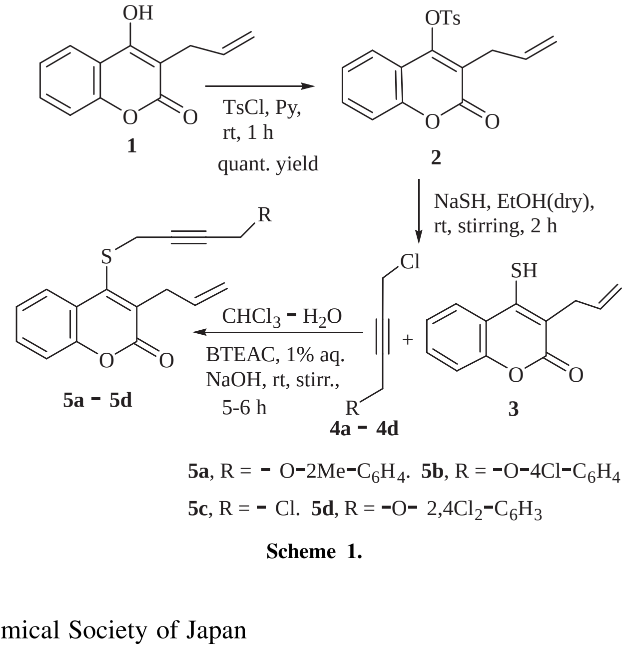
Figure 1.

Compounds **5a**–**5d** were prepared by the treatment of 4-sulfanylbenzopyran-2-one **3** with 1-aryloxy-4-chlorobut-2-ynes (or 1,4-dichlorobut-2-yne) **4a**–**4d** at room temperature for 5–6 h under phase transfer catalyzed condition using benzyltriethylammonium chloride (BTEAC). Compound **3** in turn was synthesized by the reaction of 3-allyl-4-tosyloxybenzopyran-2-one **2** with NaSH in dry ethanol at room temperature for 2 h under nitrogen atmosphere (Scheme 1).

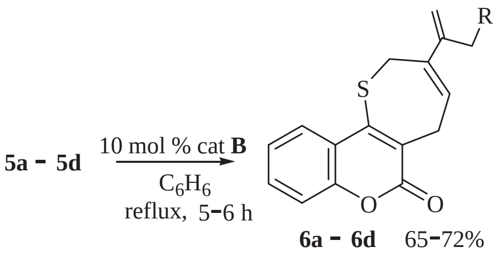
Attempts to carry out the metathesis reaction of the substrates **5a**–**5d** with Grubbs' catalyst **A** in dichloromethane, benzene, and toluene proved unsuccessful. Only decomposition of the catalyst was observed. This observation supports earlier reports that the sulfide substrates poison the catalyst **A**. We then decided to use the ruthenium catalyst **B** for the enyne metathesis of the sulfur-containing substrates. Accordingly the substrate **5a** in the presence of 10 mol % catalyst **B** was refluxed for 6 h in benzene. Cyclized product **6a** was obtained in 65% yield. Other substrates **5b**–**5d** were similarly treated with catalyst **B** to give **6b**–**6d** in 65–72% yields, respectively (Scheme 2).

Once we are successful with the cyclization of the enynes bearing coumarin sulfides, we have also investigated the potentiality of catalyst **B** in case of enyne bearing 2-pyrone sulfide. Compounds **10a**, **10c**, **10d** and **11a**, **11b** were prepared according to the above mentioned procedure (Scheme 3).

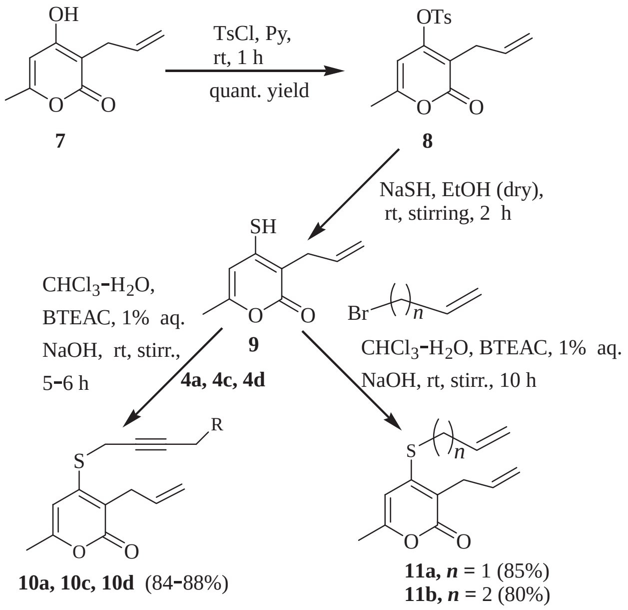
Compound **10a** and 10 mol % of catalyst **B**, were refluxed in



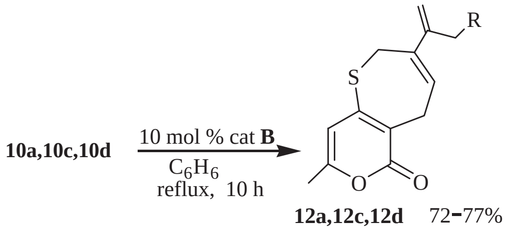
Scheme 1.



Scheme 2.



Scheme 3.

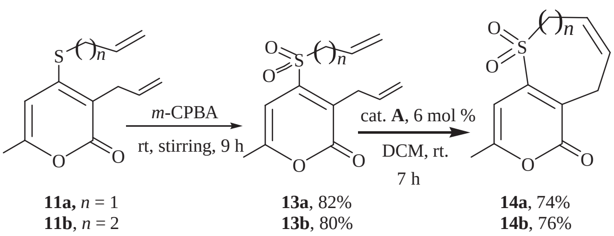


Scheme 4.

benzene for 10 h, under nitrogen atmosphere to give **12a** in 77% yield. Other substrates **10c** and **10d** were similarly treated to afford the cyclized products **12c** and **12d** in 72 and 75% yields respectively (Scheme 4).

The literature report reveals that the sulfonyl oxygen can coordinate with the ruthenium in catalyst **A**.[21] The sulfonyl group is less likely to induce poisoning of the catalyst. With this presumption compounds **13a** and **13b** were prepared according to the standard *m*-CPBA oxidation procedure at room temperature in dichloromethane for 9 h (Scheme 5) and subjected to the RCM reaction. Diallyl sulfone **13a** and allyl–homoallyl sulfone **13b** underwent facile RCM utilizing 6 mol % of catalyst **A** to yield the corresponding medium-sized cyclic sulfones **14a** and **14b** in 74 and 76% yields respectively.

In conclusion metathesis reaction of enyne sulfides of different heterocyclic systems have been successfully carried out for the first time by the catalyst **B** in good yield. In addition, with the advent of well-defined metathesis catalyst we have achieved the synthesis of structurally unique thiepin-annulated pyrone and coumarin heterocycles which may exhibit potential biological activity.



Scheme 5.

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