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# Rhodium(II)-catalyzed reactions of 3-diazo-2,4-chromenediones. First one-step synthesis of pterophyllin 2

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## Abstract

Rhodium(II)-catalyzed reactions of 3-diazo-2,4-chromenediones **1–3** with a variety of substrates are described. Reactions of **1** with nitriles, isocyanates, and ketones give the corresponding 5-membered heterocycles in moderate yields, whereas those of **1** with acid chlorides afford α-chloroenones in moderate yields. Reactions of **1** with electron-rich and -deficient olefins such as vinyl ethers and allyl iodide give dihydrofurocoumarins as a single compound, whereas those of **3** with vinyl esters afford either angular dihydrofurocoumarin and a linear product or a rearranged product as an isomer. Furthermore, this novel method has been applied to the synthesis of the natural pterophyllin 2 isolated from *Ekebergia pterophylla*. © 1999 Elsevier Science Ltd. All rights reserved.

The rhodium-catalyzed decomposition of diazocarbonyl compounds has become an important method in organic and natural product synthesis.[1] The rhodium(II)-catalyzed reactions of acyclic and cyclic diazodicarbonyl compounds with several substrates such as olefins, nitriles, isocyanates, carbon disulfides, furans, benzofurans, thiophenes, and pyrroles have been extensively studied by many groups.[2] The reactions include C-H and X-H insertion,[3] cyclopropanation,[4] ylide formation,[5] and cycloaddition.[6] However, little study has been made of the reactions of 3-diazo-2,4-chromenedione **1–3** to substrates. We have been interested in reactions of 2-diazo-1,3-dicarbonyl compounds with several substrates.[7] As an extension of our work, we have investigated the rhodium-catalyzed carbenoid reactions of 3-diazo-2,4-chromenediones with substrates to synthesize the skeletons of naturally-occurring coumarins and dihydrofurocoumarins.[8] They are reported to show various biological activities such as anticoagulant, insecticide, anthelminthic, hypnotic, antifungal, phytoalexin, and provide HIV protease inhibition.[9] This wide range of biological properties has stimulated the development of the new synthetic methods for the construction of coumarins and dihydrofurocoumarins.

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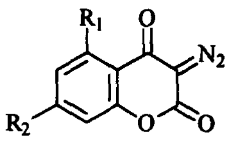
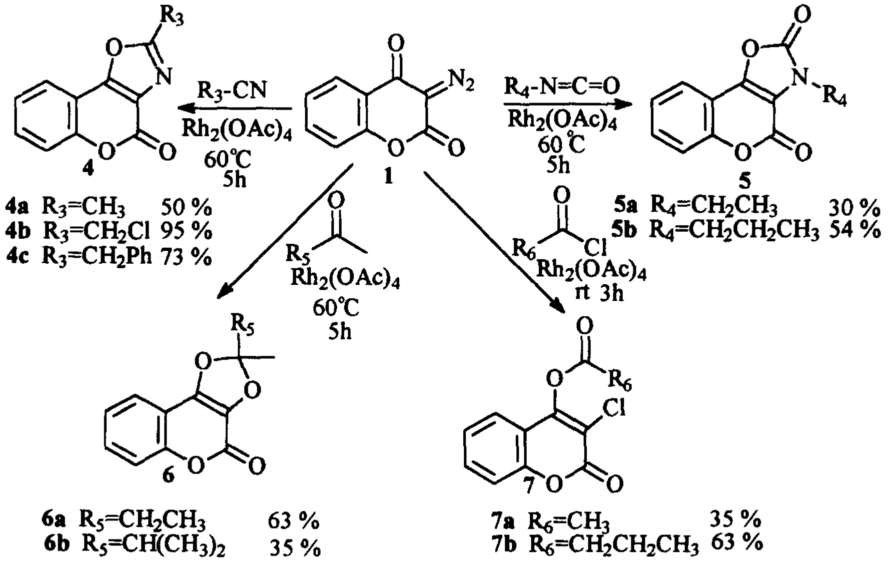


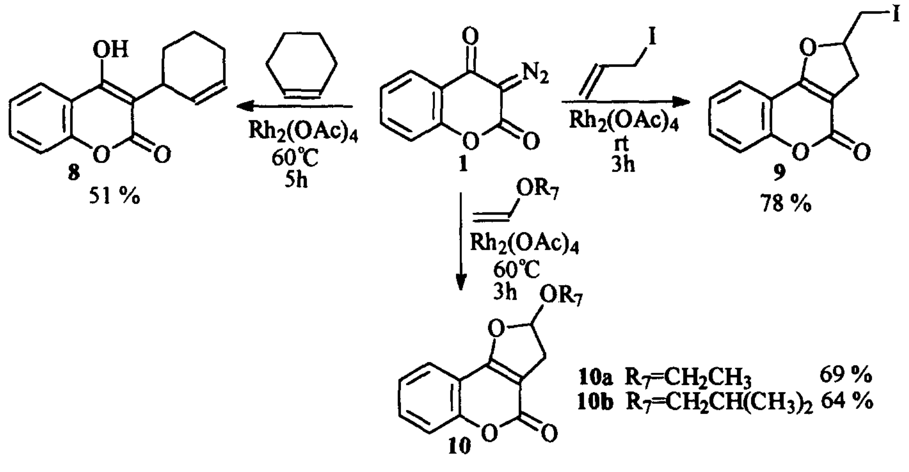
**1** $R_1=R_2=H$
**2** $R_1=CH_3$, $R_2=H$
**3** $R_1=H$, $R_2=CH_3$

3-Diazo-2,4-chromenediones **1–3** were prepared by the diazotransfer reaction of the corresponding 4-hydroxycoumarins with mesyl azide according to Taber's method.[10] 3-Diazo-2,4-chromenediones **1–3** are fairly stable and can be stored in a refrigerator for a long time without any decomposition. In order to check the reactivity of **1** as carbenoid reactions, several nitriles were first used. When acetonitrile was heated at 60°C for 5 h as a solvent and a reactant in the presence of 1 mol% of $Rh_2(OAc)_4$, oxazole **4a** was isolated in a 50% yield (Scheme 1). Under the same conditions, chloroacetonitrile and phenylacetonitrile also afforded oxazoles **4b** (95%) and **4c** (73%) in increased yields. When ethyl isocyanate and propyl isocyanate were used, oxazolones **5a** and **5b** were produced in 30 and 54% yields, respectively, as a single compound. Reactions of **1** with 2-butanone and 3-methyl-2-butanone, 1,3-dioxoles **6a** and **6b** were obtained in 63 and 35% yields, respectively. In particular, there is no direct precedent for Rh(II)-catalyzed reaction of diazodicarbonyl compounds with ketones, so it is noteworthy that reactions of **1** with ketones give the 1,3-dioxoles in moderate yields. In related work, Alonso has reported that the copper(II)-catalyzed reaction of acyclic methyl 2-diazo-3-oxobutyrate with ketones gave 1,3-dioxole adducts in moderate yields.[11] However, reaction of **1** with other carbonyl compounds such as acetyl chloride and propionyl chloride, α-chloroenones **7a** and **7b** were produced in 35 and 63% yields, respectively, without a trace of expected 1,3-dioxole adducts. Support for the structural assignment comes from their spectroscopic analysis. The α-chloroenone **7a** is identified by the $^1H$ NMR peak of the methyl group of the vinyl acetate as a singlet at δ 2.49, and by the two IR carbonyl absorptions of the lactone at 1730 $cm^{-1}$ and the vinyl ester at 1784 $cm^{-1}$.



Scheme 1.

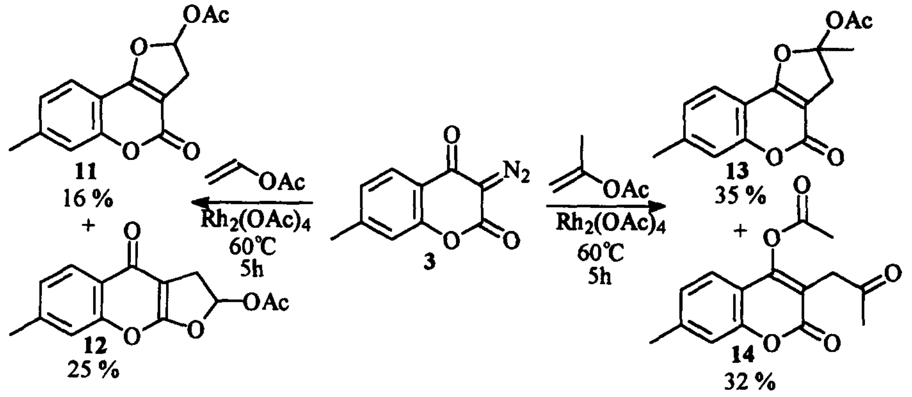
To synthesize the skeletons of naturally-occurring coumarins and dihydrofurocoumarins, additional reactions with several olefins were investigated. Reaction of **1** with an excess of cyclohexene used as a solvent and a reagent, in the presence of 1 mol% of $Rh_2(OAc)_4$ at 60°C for 5 h gave the unexpected rearranged product **8** in a 51% yield (Scheme 2). The two olefinic protons of **8** were observed at $\delta$ 6.29 and $\delta$ 6.04. When allyl iodide with electron-deficient olefin was used, the dihydrofurocoumarin **9** was obtained in 78% yield as a single compound. This result is also in clear contrast to that of Doyle, who reported that the rhodium(II)-catalyzed reactions of acyclic ethyl diazoacetate with allyl iodide afforded the [2,3]-rearranged product without forming the cycloaddition adduct as a single compound.[12] Another approach for dihydrofurocoumarin formation was obtained by using vinyl ethers. On heating neat ethyl vinyl ether and isobutyl vinyl ether in the presence of 1 mol% of $Rh_2(OAc)_4$ for 3 h, dihydrofurocoumarins **10a** and **10b** were produced in 69 and 64% yields, respectively. These results indicate that reactions with more electron-rich and electron-deficient olefins than simple alkenes such as cyclohexene provide an efficient route for synthesizing the dihydrofurocoumarin skeletons.



Scheme 2.

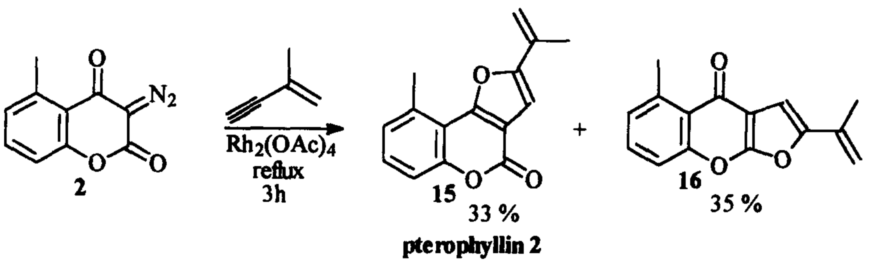
Next, reactions with vinyl acetates were also examined. Reaction of **3** with vinyl acetate at 60°C for 5 h afforded the two regioisomeric cycloadducts **11** and **12** in 16 and 25% yields, respectively (Scheme 3). The two isomers were easily assigned from spectroscopic data. The $^1H$ NMR spectrum of angular dihydrofurocoumarin **11** showed methine peaks at $\delta$ 7.00 as a doublet associated with the dihydrofuran ring, whereas linear adduct **12** showed peaks at $\delta$ 6.87 as a doublet. The clear assignment was based on comparison of IR carbonyl absorption. In angular isomer **11**, there are two C=O peaks stretching at 1753 and 1711 $cm^{-1}$ corresponding to the two ester groups, while in linear isomer **12** the two C=O stretches are shown at 1660 $cm^{-1}$ for an enone and at 1765 $cm^{-1}$ for an ester group. On the other hand, reaction of **3** with isopropenyl acetate afforded angular dihydrofurocoumarin **13** (35%) and rearranged product **14** (32%) as a mixture. Surprisingly, in this case, the expected linear adduct was not detected. These mixtures were easily separated by column chromatography, and the assignment of their structures of **13** and **14** was made on the basis of spectral data. The methylene protons of **14** are observed as a singlet at $\delta$ 3.55, and the two methyl protons of the ester and ketone are shown at $\delta$ 2.43 and $\delta$ 2.41, also as singlets. Further support for the structural assignment of **14** is accomplished from its IR spectrum, which clearly shows the expected three C=O absorptions at 1776, 1730, and 1709 $cm^{-1}$ due to two esters and a ketone.

Finally, in order to extend the utility of these reactions, one-step synthesis of a furocoumarin natural product was attempted. Pterophyllin 2 (**15**) has been isolated from a small evergreen tree of *Ekebergia pterophylla*, found in South Africa.[13] The structure of pterophyllin 2 was established by spectroscopic analysis, but no synthetic methods are known. Reaction of **2** with 2-methyl-1-buten-3-yne (15-fold



Scheme 3.

excess) under 1 mol% of rhodium catalysis at reflux for 3 h afforded pterophyllin 2 (33%) together with linear isomer **16** (35%) as a mixture (Scheme 4). These products were easily separated by column chromatography, and the spectroscopic properties of our synthetic pterophyllin 2 agree well with those reported in the literature.[13]



Scheme 4.

In conclusion, the rhodium(II)-catalyzed reactions of 3-diazo-2,4-chromenedione **1–3** with several substrates is described. This method provides a novel entry into the naturally-occurring biologically active coumarin and dihydrofurocoumarin skeletons, and demonstrates an interesting application of one-step synthesis of the natural product, pterophyllin 2. Further mechanistic studies and applications of these carbenoid reactions are in progress in our laboratory.

## Acknowledgements

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