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An approach toward oxidopyrylium ylides using Rh(II)-catalyzed cyclization chemistry

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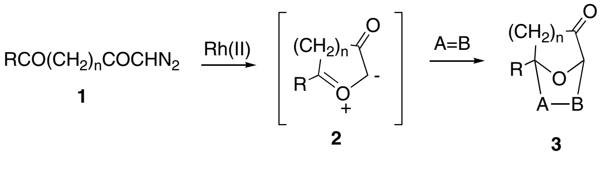
Abstract—The Rh(II)-catalyzed reaction of the *E*-isomer of 2-diazo-3,6-dioxo-6-phenyl-hex-enoic acid methyl ester was carried out in the presence of various carbonyl compounds and was found to give 1,3-dioxoles in moderate to good yield. In an attempt to prepare the starting α-diazo substrate, an unexpected pseudo-dimerization reaction was encountered when 5-phenyl-furan-2,3-dione was heated in the presence of sodium methoxide.

In recent years, a widespread upsurge of activity in the application of carbonyl ylide dipoles to new synthetic transformations has occurred.[1,2] This research has also stimulated interest in the use of carbenes and carbenoids as reactive intermediates for the generation of other types of ylides.[3] A diverse range of chemistry has already surfaced.[1–4] In 1986, work started in the Padwa laboratory to synthesize bridged oxa-substituted bicycloalkanes from the Rh(II)-catalyzed cyclization cascade of α-diazo carbonyl compounds.[5a] The domino reaction was shown to proceed by the formation of a rhodium carbenoid intermediate and a subsequent transannular cyclization of the electrophilic carbon onto an adjacent carbonyl group to generate a cyclic carbonyl ylide dipole.[5–7] This was followed by a 1,3-dipolar cycloaddition reaction with an added dipolarophile A = B (Scheme 1).



Scheme 1.

Our ongoing interest in this procedurally simple methodology led us to focus on the cycloaddition behavior of the related oxidopyrylium dipole **5**, where the extra double bond contained within the ring would not only allow for the formation of the [5 + 2]-dipolar cycloadduct **6**, but also could produce the isomeric cycloadduct **7**. The [5 + 2]-cycloaddition of 3-oxidopyrylium ylides is a well-precedented reaction and has been used for the rapid access of functionalized seven-membered ring structures.[8] Henderson and Farina originally discovered that [5 + 2]-cycloadditions can be carried out by heating acetoxy-pyranones such as **8** and a dipolarophile at 130 °C to afford up to 69% of cycloadduct **10**.[9] This reaction was further developed by Sammes, who found that electron rich dipolarophiles were more reactive toward dipole **9** and that the reaction can also be carried out using Et_3N to generate the oxypyrylium zwitterion at room temperature.[10] Substituted allenes[11] and dienes[12] have also been successfully engaged as dipolarophiles in intra and intermolecular reactions. The rapid generation of molecular complexity in a relatively easy manner has made this cycloaddition reaction extremely useful for the synthesis of seven-membered ring containing natural products. Notably, Wender and co-workers have successfully applied this strategy, in an intramolecular fashion, to the total synthesis of the natural products phorbol and resiniferatoxin.[13] Further examples of intramolecular [5 + 2]-cycloadditions of pyranones of type **11** for natural product synthesis have also been reported by Heathcock,[14] Ohmori,[15] Magnus,[16] and Williams[17] (see Scheme 3).

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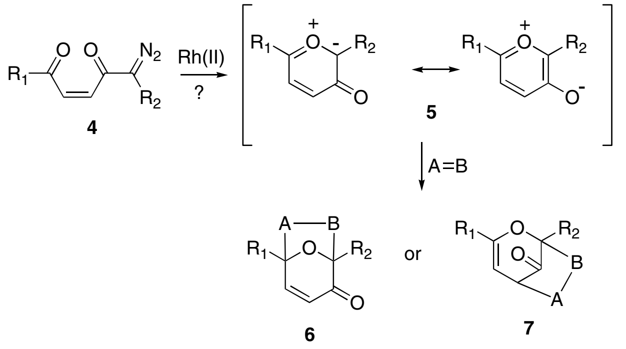
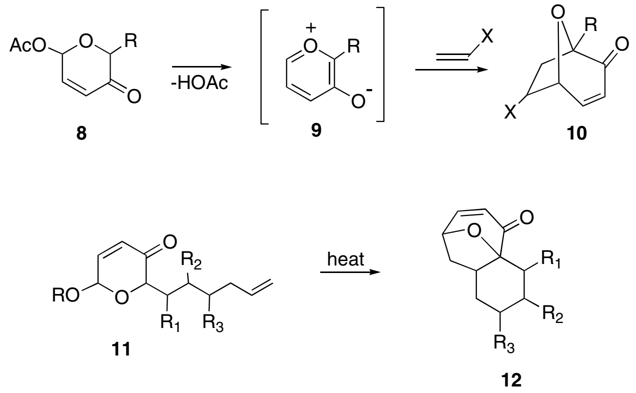
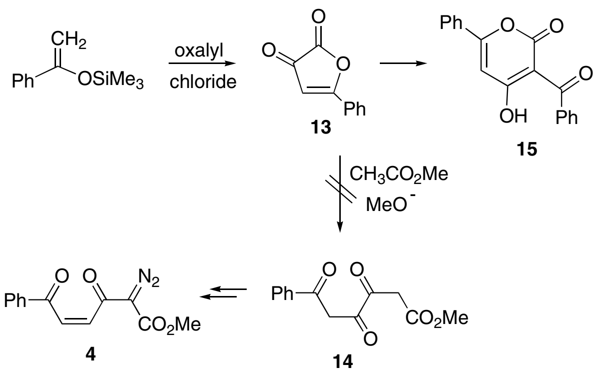


Scheme 2.



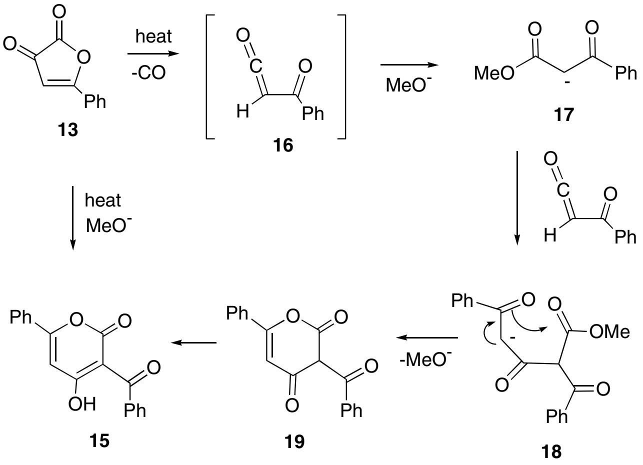
Scheme 3.

Since we were interested in using the Rh(II)-catalyzed reaction of α-diazo ketoesters such as **4** as a way to generate various oxidopyrylium ylides (Scheme 2), we undertook a study of several methods to synthesize the required precursor α-diazo ketoesters. To this end, 5-phenylfuran-2,3-dione (**13**) was prepared in 80% yield by reacting trimethyl (1-phenylvinyloxy)silane with oxalyl chloride.[18] Our intention was to heat **13** with methyl acetate in the presence of sodium methoxide with the hope that we should be able to prepare methyl 3,4,6-trioxo-6-phenylhexanoate acid (**14**), which would then be transformed into the corresponding α-diazo ketoester **4** (Scheme 4).



Scheme 4.

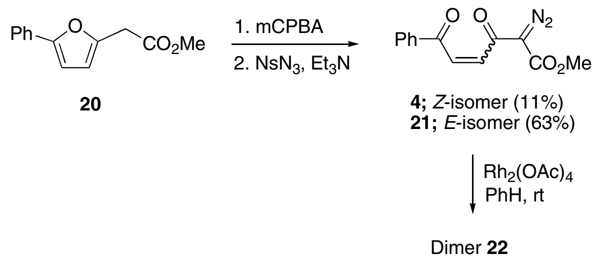
However, in our attempts to convert furandione **13** into **14**, we encountered a rather unusual reaction. The major (80%) and unexpected product obtained from the thermal reaction of **14** under basic conditions was identified as 3-benzoyl-4-hydroxy-6-phenyl-2*H*-pyran-2-one (**15**) on the basis of its spectral data[19] and by the procurement of an X-ray crystal structure. The pseudo-dimerization of **13**–**15** can be accounted for by an initial thermal extrusion of carbon monoxide from **13** to give benzoyl ketene **16** as a transient species. Attack of methoxide anion at the electrophilic ketene center in **16** generates the stable anion **17**, which in turn reacts with another molecule of the ketene to furnish 1,3-dicarbonyl anion **18**. Cyclization of **18**–**19** followed by tautomerization to the more stable enol form nicely accounts for the formation of pyranone **15** (Scheme 5).



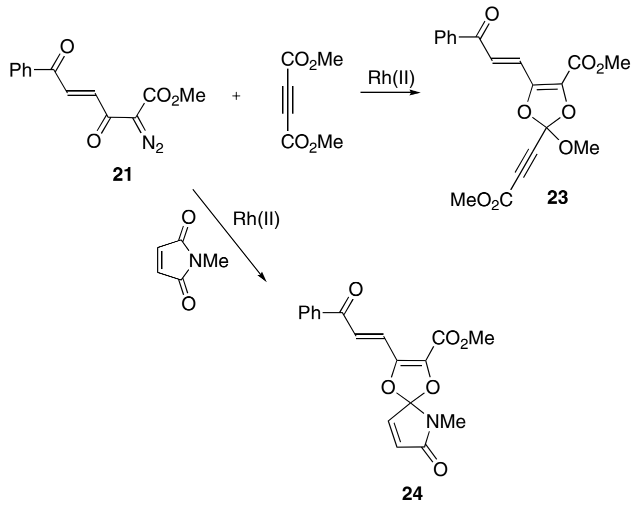
Scheme 5.

In an alternate approach that we next employed for the preparation of α-diazo ketoester **4**, we made use of an oxidation reaction of furan **20**.[20] Thus, methyl 2-(furan-2-yl)acetate (**20**) was treated with mCPBA at 0 °C in CH_2Cl_2 and this resulted in a 6:1-stereomeric mixture of the expected ring-opened butene-diones, which were immediately converted to the corresponding α-diazo ketoesters (i.e. **4** and **21**) using *p*-nitrobenzenesulfonyl azide and Et_3N according to the standard Regitz protocol.[21] The two isomeric α-diazo compounds were separated by fractional recrystallization. Treatment of the minor *Z*-isomer **4** with a catalytic quantity of rhodium(II) acetate in benzene at 25 °C afforded an unknown dimer (i.e. **22**) in 45% yield. Unfortunately, all of our attempts to trap an oxidopyrylium ylide intermediate from the *Z*-isomer **4** using various trapping agents failed to afford any signs of a [5 + 2]-cycloadduct. The only compound detected in these reactions was dimer **22**[22] (see Scheme 6).

We also studied the Rh(II)-catalyzed behavior of the major *E*-diazo isomer **21**. This isomeric α-diazo ketoester cannot undergo internal cyclization to give a carbonyl ylide dipole and we were curious as to what pathway would be followed with this system. Toward this end, **21** was added to a benzene solution containing DMAD and a catalytic amount of $Rh_2(OAc)_4$ under an argon atmosphere at 80 °C. The reaction was monitored



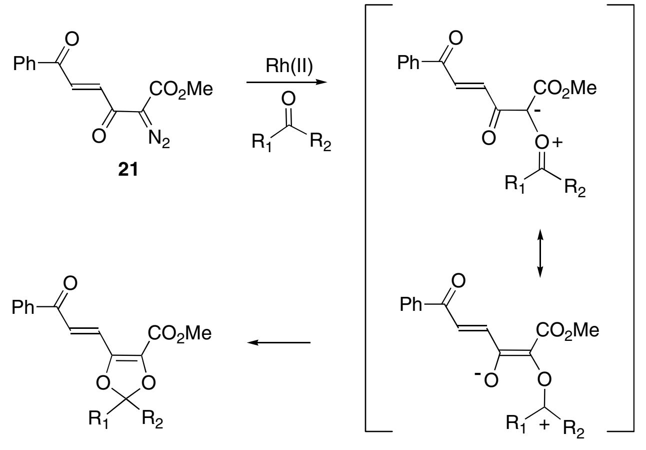
Scheme 6.



Scheme 7.

by TLC and column chromatographic purification of the crude reaction mixture afforded cycloadduct **23** as the only isolable product in 42% yield. A related cycloadduct (i.e. **24**) was isolated when *N*-methyl maleimide was used as the trapping dipolarophile (Scheme 7). When *N*-methyl succinimide, benzaldehyde, cyclohexanone, or acetone were used as the trapping agents, the analogous cycloadducts **26**–**29** were obtained in 25–80% yield. Ethyl acetate turned out to be a very efficient trapping agent producing cycloadduct **30** in 80% yield. The overall cycloaddition can be rationalized by an initial reaction of α-diazo ketoester **21** with the Rh(II)-catalyst to first generate an electrophilic metallo carbenoid. This species then reacts with the nucleophilic carbonyl oxygen atom of the added dipolarophile to furnish the highly reactive carbonyl ylide intermediate **25**. The presence of the adjacent enone carbonyl group facilitates an intramolecular [1,5]-electrocyclization that leads to the corresponding 1,3-dioxole derivatives **26**–**30**.[23] A resonance structure of carbonyl ylide with the negative charge on the oxygen atom of the enone carbonyl group and a positive charge on the carbonyl C-atom of the added dipolarophile contributes significantly to the resonance hybrid of the transient ylide **25**, thereby favoring the [1,5]-electrocyclization pathway (Scheme 8).

In summary, we have investigated the Rh(II)-catalyzed reaction of the *Z*-isomer of 2-diazo-3,6-dioxo-6-phenyl-hex-4-enoic acid methyl ester and found that a dimer was formed as the major product. We have also shown that the Rh(II)-catalyzed reaction of the related *E*-isomer in the presence of various carbonyl compounds undergoes cyclization to give substituted 1,3-dioxoles as the major products. An unexpected pseudo-dimerization process was also encountered when the thermolysis of 5-phenyl-2,3-dione was carried out in the presence of sodium methoxide.



25

26; $R_1 = CH_2CH_2$; $R_2 = N(CH_3)CO$ (25%)
27; $R_1 = Ph$; $R_2 = H$ (25%)
28; $R_1 = R_2 = (CH_2CH_2)$ (45%)
29; $R_1 = R_2 = CH_3$ (80%)
30; $R_1 = OC_2H_5$; $R_2 = CH_3$ (80%)

Scheme 8.

Acknowledgements

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22. The reaction of **4** with a number of Rh(II) catalysts in several solvents and at different concentrations using diverse trapping agents only led to varying quantities of dimer **22** together with a tarry residue, which resisted purification. Our attempts to obtain an X-ray crystal structure of dimer **22** also failed due to the amorphous nature of the solid.
23. For some examples of 1,3-dioxole formation during the decomposition of diazocarbonyl compounds in the presence of simple aldehydes and ketones, see: (a) Weigand, F.; Dworschak, H.; Koch, K.; Konstas, S. *Angew. Chem.* **1961**, *73*, 409; (b) Alonso, M. E.; Jano, P. *J. Heterocycl. Chem.* **1980**, *17*, 721; (c) Huisgen, R.; De March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4952; (d) Huisgen, R.; Fisera, L.; Giera, H.; Sustmann, R. *J. Am. Chem. Soc.* **1995**, *117*, 9671; (e) Russell, A. E.; Brekan, J.; Gronenberg, L.; Doyle, M. P. *J. Org. Chem.* **2004**, *69*, 5269; (f) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933.