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A Chemoselective Rhodium(II) Mediated Solid Phase 1,3-Dipolar Cycloaddition and its Application to a Thermally Self-Cleaving Furan Scaffold

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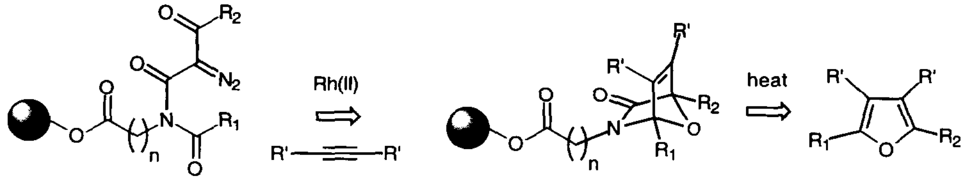
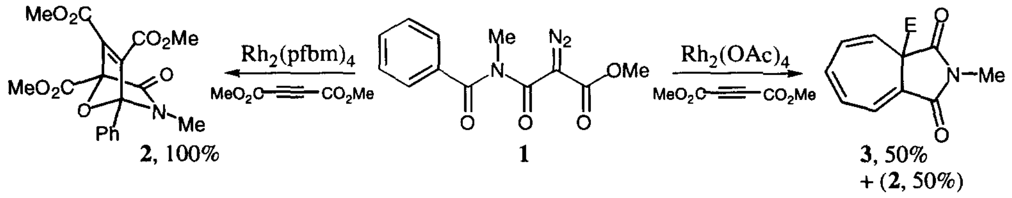
Abstract: A chemoselective rhodium(II) mediated 1,3-dipolar cycloaddition reaction on solid-phase for the construction of a template-directed scaffold is described. In this paper, the reaction of acetylenes with isomünchnones is presented as a general methodology for the combinatorial formation of a furan based library. Additionally, through the development of a novel thermolytic cleavage step, this furan synthesis yields pure product from the solid-phase in a temperature dependent manner. © 1997 Elsevier Science Ltd.

The 1,3-dipolar cycloaddition reaction is becoming increasingly popular as a diversity strategy in the development of solid-phase combinatorial libraries.[1-5] This is due, in large part, to the inherent facile formation of heterocyclic products. The rhodium(II) mediated 1,3-dipolar cycloaddition reaction on solid-phase has not been reported, although a rhodium mediated O-H insertion has been described.[6] We believed that, with proper catalyst selection to control carbenoid selectivity,[7] rhodium carbenes could prove very useful in a solid-phase format. Herein, we describe the use of a rhodium(II) perfluorobutyramide catalyst for the chemoselective construction of a template-directed scaffold.[8,9] In this example, the reaction of acetylenes with isomünchnones is presented as a general methodology for the combinatorial formation of a furan based library. Additionally, through the development of a novel thermolytic cleavage step, this furan synthesis yields pure product from the solid phase in a temperature dependent manner.

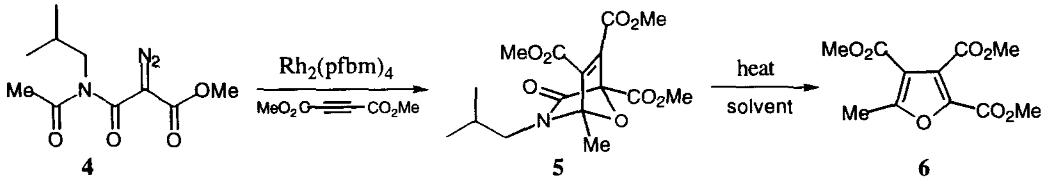


The cycloaddition of isomünchnones with dimethylacetylene dicarboxylate (DMAD) gives a transient cycloadduct, which subsequently undergoes a facile cycloreversion to a tetra-substituted furan and an isocyanate.[10] This thermolytic cycloreversion of diactivated alkyne cycloadducts is described as a one-pot procedure at elevated temperatures. However, to take full advantage of this cycloreversion on solid phase, the initial cycloadduct is synthesized and isolated at ambient temperature, with a subsequent discrete cleavage step under thermally elevated conditions. This approach is advantageous because it eliminates the need for purification of the furan since the unreacted starting materials are removed by filtration after each step. Only pure product is obtained, regardless of cycloaddition yield, since the isocyanate and unreacted synthesis intermediates remain attached to the solid-phase resin.

Initial decomposition experiments of α-diazo ketone **1** with rhodium(II) acetate [$Rh_2(OAc)_4$] at room temperature proved sluggish and showed no selectivity for dipole formation, yielding an equal mixture of the desired cycloadduct **2** and a [7,5]-bicyclic imide **3** in the presence of DMAD. Undesired imide **3** is presumably formed via an aromatic ring cyclopropanation/ring-opening sequence. Recently, Prein and Padwa[11] reported that rhodium(II) perfluorobutyramide [$Rh_2(pfbm)_4$] was selective for five- over six-member ring 1,3-dipole formation. We sought to investigate further the chemoselectivity of this catalyst for 1,3-dipole formation over this apparent cyclopropanation reaction.



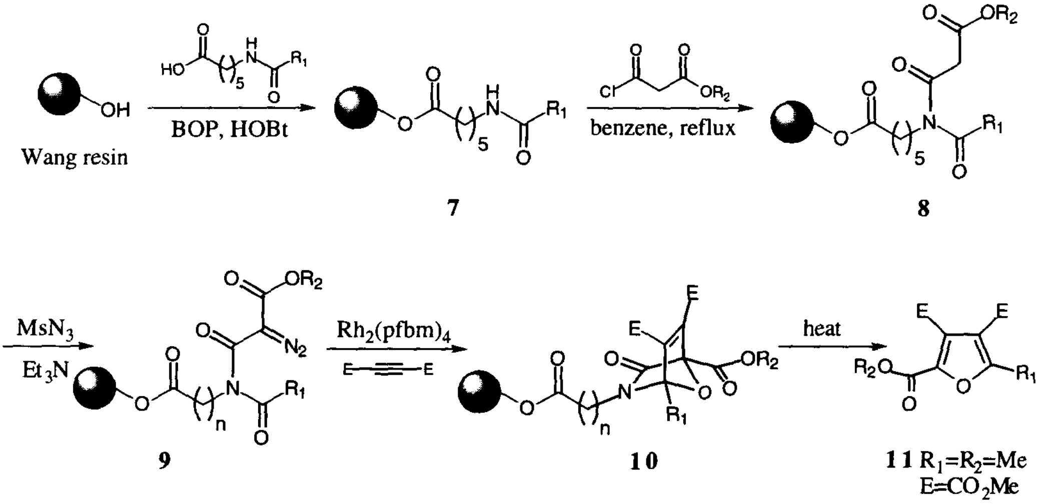
Treatment of α-diazo ketone **1** with $Rh_2(pfbm)_4$ at room temperature, in the presence of DMAD, gave exclusively cycloadduct **2** in quantitative yield, without any observable imide **3**. Similar treatment of α-diazo ketone **4** with $Rh_2(pfbm)_4$, lead exclusively to cycloadduct **5**, with no observable methine C-H insertion. The selectivity of this catalyst for 1,3-dipole formation will prove useful in the synthesis of combinatorial libraries containing potentially reactive functionality.



In order to demonstrate the feasibility of the thermally cleavable system, a solution phase model system **5** was evaluated. The thermal cleavage reaction was then investigated in a range of solvents at various temperatures to give the methylfuran tricarboxylate trimethyl ester **6** (see table). Cleavage of the furan was carried out in polar aprotic, polar protic and non-polar aprotic solvent and appears to be somewhat solvent dependent. The cleavage rate from the solid support, at similar temperatures, is highest in polar protic solvents (see table), which should allow for the cleavage to be carried out directly into aqueous media. It has not escaped our attention that this cleavage rate is amenable to the *in vitro* growth rate of many cell culture systems.

Solvent	Temperature	Cycloreversion
chloroform-d	23 °C	50% in 5.5 days
chloroform-d	37 °C	50% in 24 hours
methanol-d_4	37 °C	50% in 12 hours
benzene-d_6	37 °C	50% in 22 hours
benzene-d_6	79 °C	100% within 1 hour

The solid-phase synthesis began with the esterification of Wang-resin[12] with *N*-acyl protected aminocaproic acid to give amide **7**. The acylation of amide **7** with alkyl malonyl chloride in benzene at reflux temperature provided the imide **8**, and was followed by diazotransfer (MsN_3, Et_3N) to result in the diazoester **9**. Decomposition of the diazoester **9** with $Rh_2(pfbm)_4$ and cycloaddition with dialkylacetylene dicarboxylate at room temperature afforded the cycloadduct **10** on the solid support[13] without any observable cycloreversion product, furan **11**. The formation of cycloadduct **10** represents, to the best of our knowledge, the first solid-phase rhodium(II)-catalyzed 1,3-dipolar cycloaddition reaction. Furan **11** was then thermally cleaved from the solid support (benzene, 79°C, 1h) in 70% yield (based on the initial loading) and isolated in over 98% purity (^1H-NMR and GC/MS spectroscopy) directly from cleavage of the solid support.



7

8

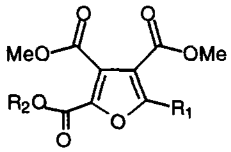
9

10

11 $R_1=R_2=Me$
$E=CO_2Me$

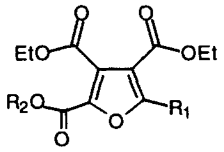
This solid-phase chemistry has been extended to a split-pool synthesis of a combinatorial furan library (3x3x2), from commercially available starting materials, with diversity being incorporated into the amides (R_1= Me, i-Pr and Ph), esters (R_2= Me, Et and t-Bu) and the cycloaddition dipolarophiles (E= CO_2Me and CO_2Et). The final cycloaddition reactions were not recombined, yielding two nine-member pools (**A** & **B**). Reverse phase HPLC and ^1H-NMR analysis confirmed that, in both pools, all nine furan-triesters were formed in good yield and very high library purity (93-96%). The use of the rhodium(II) perfluorobutyramide catalyst allows for the incorporation of both alkyl- and aryl-substituted furans, as can be seen by the formation of the benzamide

(R_1= Ph) and isopropyl (R_1= i-Pr) library members, pathways otherwise excluded by our initial rhodium(II) acetate studies.



Pool A

R_1=Me, i-Pr, Ph
R_2=Me, Et, t-Bu



Pool B

In summary, we have reported the first rhodium(II) mediated 1,3-dipolar cycloaddition reaction carried out on solid support. In addition, we have attempted to show the importance of chemoselectivity in the application of this technique to chemical diversity. An extension of this sequence to a more extensive library synthesis and the application of this thermally assisted self-cleaving scaffold is currently underway. In particular, we are interested in applying this approach to the removal of compounds from the solid-phase resin, at physiologically relevant temperatures, without the need for the photolytic, acidic or basic cleavage conditions.

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13. The degree of reaction completion was determined via direct IR spectroscopy of the resin material, ground into a KBr disk, and monitored at 2100 cm^{-1} (diazo stretch).

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