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LETTERS

Palladium-catalysed cascade molecular queuing-cycloaddition, cyclocondensation and Diels–Alder reactions

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Abstract

The locked *s-cis* enone system present in 3-methylenequinol-4-ones and chroman-4-ones offers substantial further synthetic opportunities as illustrated by the ability to function as a 2π-component in 1,3-dipolar cycloaddition reactions, or as a 2π- or 4π-component in Diels–Alder reactions. Cascade molecular queuing-cycloadditions/cyclocondensations are reported. © 2000 Elsevier Science Ltd. All rights reserved.

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In the preceding paper[1] we discussed the synthesis of 3-methylenequinol-4-ones and chroman-4-ones via palladium-catalysed termolecular queuing processes and the potential of the locked *s-cis* enone system in these quinolones and chromanones for accessing γ-aminoalcohols via Michael additions and subsequent stereoselective reductions. The conformationally locked *s-cis* enone system can also function as 2π-component in 1,3-dipolar cycloadditions, or as a 2π- or 4π-component in Diels–Alder reactions.

Spiro-fused 6/5-heterocycles were created via 1,3-dipolar cycloaddition reactions. The azomethine ylide cycloaddition makes use of our recently developed Ag_2O/base[2] catalytic system. Cycloadditions of (**1**)[3] with 3-methylenechroman-4-ones or quinol-4-ones (**2**) proceeded stereo- and regiospecifically in toluene at room temperature to afford *syn–endo*[4] cycloadducts (**3a–e**) in good yields (Scheme 1). The stereochemistry of (**3a–e**) is based on the usual facial selectivity and *endo*-transition state observed for metallo-azomethine ylide cycloadditions.[4]

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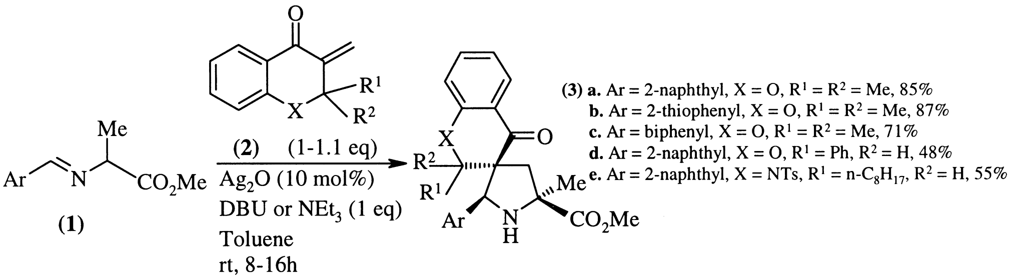
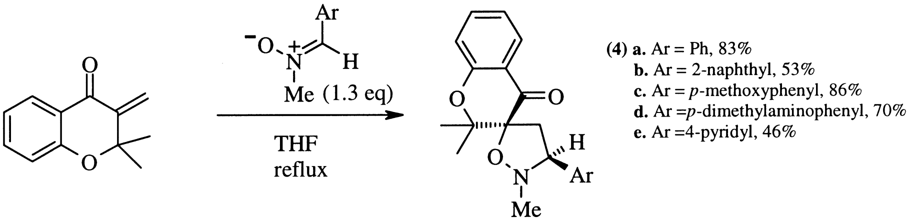


(3) **a.** Ar = 2-naphthyl, X = O, $R^1 = R^2$ = Me, 85%
b. Ar = 2-thiophenyl, X = O, $R^1 = R^2$ = Me, 87%
c. Ar = biphenyl, X = O, $R^1 = R^2$ = Me, 71%
d. Ar = 2-naphthyl, X = O, R^1 = Ph, R^2 = H, 48%
e. Ar = 2-naphthyl, X = NTs, R^1 = n-C_8H_{17}, R^2 = H, 55%

Scheme 1.

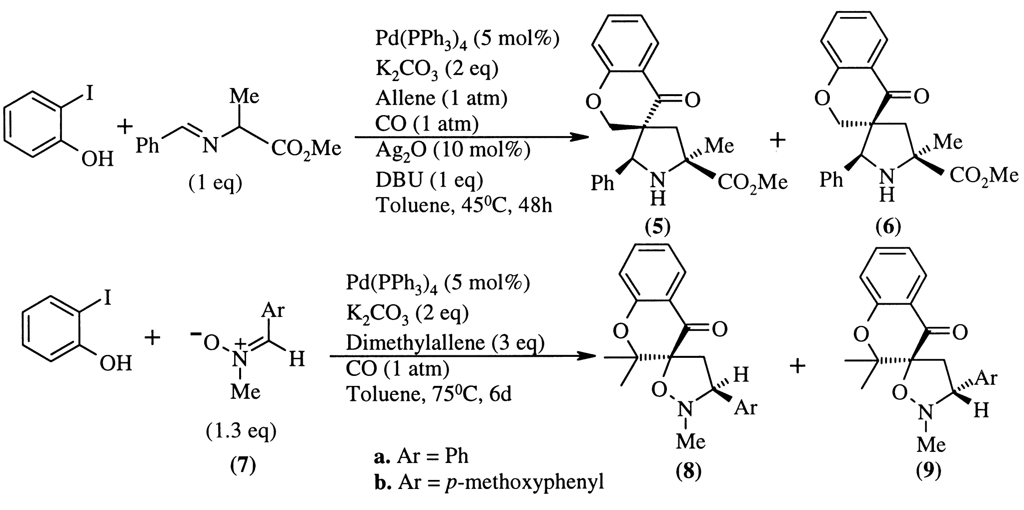
A range of aldonitrones[5] underwent cycloadditions to 3-methylenechroman-4-one (**2**, X = O, $R^1 = R^2$ = Me) in boiling THF with excellent regioselectivity and a high degree of diastereoselectivity[6] (Scheme 2). *exo*-Isoxazolidines (**4a**–**e**) were obtained in good yield together with traces of *endo*-isomers.



(4) **a.** Ar = Ph, 83%
b. Ar = 2-naphthyl, 53%
c. Ar = *p*-methoxyphenyl, 86%
d. Ar = *p*-dimethylaminophenyl, 70%
e. Ar = 4-pyridyl, 46%

Scheme 2.

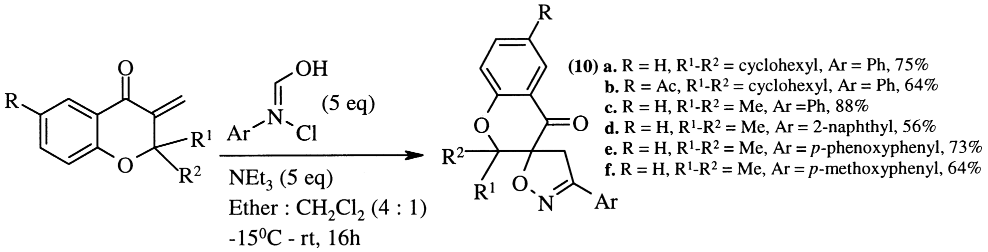
Cascade reactions incorporating both palladium-catalysed termolecular queuing processes[1] and 1,3-dipolar cycloaddition reactions were designed and their synthetic viability explored (Scheme 3). One-pot chromanone synthesis–azomethine ylide cycloaddition was performed using *o*-iodophenol, CO, allene and imine (**1**, Ar = Ph). Reaction occurred at 45°C in toluene in the presence of



Scheme 3.

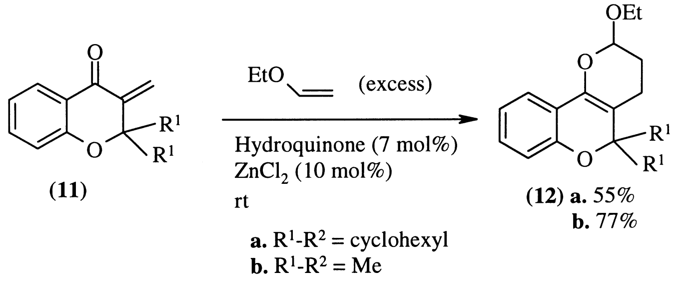
$Pd(PPh_3)_4$ and K_2CO_3, Ag_2O and DBU to give a 1:1 mixture of *exo*- and *endo*-cycloadducts[4] (**5**) and (**6**) in 60% combined yield. The nitrone (**7a**) upon stirring in toluene at 75°C in the presence of $Pd(PPh_3)_4$ and K_2CO_3, *o*-iodophenol, CO and dimethylallene reacted to afford a 6:1 diastereomeric mixture[6] of isoxazolidines (**8a**) and (**9a**) in 78% combined yield, whilst an analogous cascade employing nitrone (**7b**) resulted in isoxazolidine (**8b**) in 83% yield as a single isomer.[6]

1,3-Dipolar cycloadditions of aryl nitrile oxides (generated in situ from aryl chlorooximes[7] in the presence of NEt_3) with chromanones proceeded in good yield in a regiospecific manner to afford isoxazolines (**10a–f**)[8] (Scheme 4). These results are in accordance with the majority of literature cases involving 1,1-disubstituted olefins, in which the oxygen of the nitrile oxide becomes attached to the more sterically hindered end of the double bond.[9]



Scheme 4.

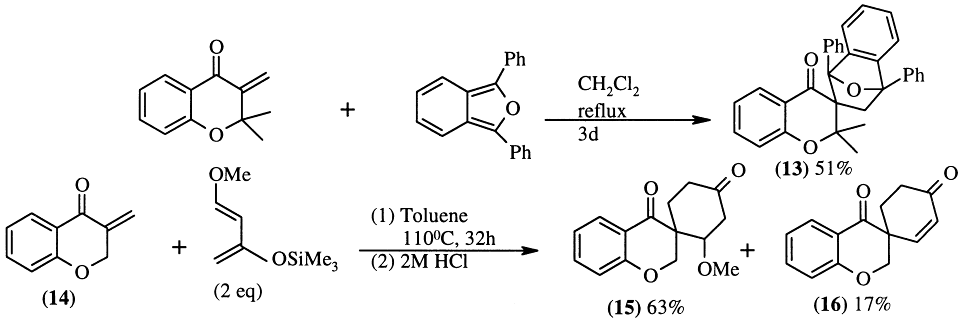
The conformationally locked *s-cis* enone functionality present in 3-methylenechroman-4-ones has the potential to act as either a 4π- or 2π-component in Diels–Alder reactions. Thus, hetero Diels–Alder reactions of ethyl vinyl ether with chromanones (**11a**) and (**11b**) (4π-component) in the presence of 7 mol% hydroquinone and 10 mol% zinc chloride proceeded at room temperature to furnish dihydropyran derivatives (**12a**) and (**12b**) in 55 and 77% yields, respectively (Scheme 5).



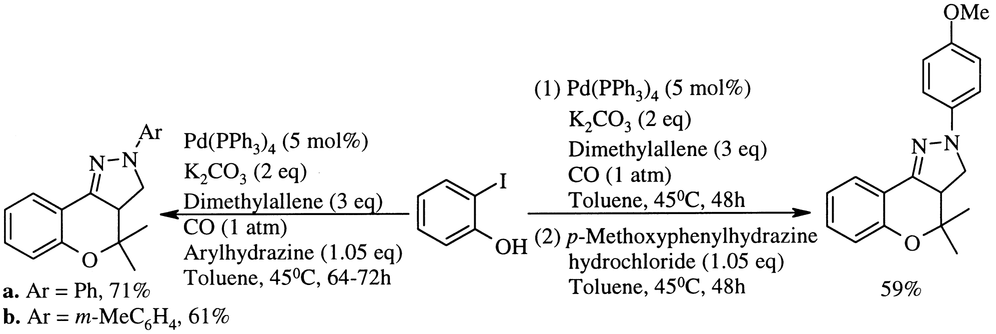
Scheme 5.

Heating chromanone (**11b**) (2π-component) with isobenzofuran in boiling CH_2Cl_2 afforded Diels–Alder adduct (**13**) in 51% yield whilst reaction of chromanone (**14**) (2π-component) with Danishefsky's diene in boiling toluene, followed by acid work-up (2 M HCl), afforded a mixture of (**15**) (63%) and (**16**) (17%) (Scheme 6).

Finally, we have briefly explored cascade termolecular queuing–cyclocondensation processes employing *o*-iodophenol, CO, dimethylallene and arylhydrazines (Scheme 7). In these processes it is clear that the desired cascade process is not significantly impeded by potentially competing



Scheme 6.



Scheme 7.

processes such as catalytic dehydrogenation of the arylhydrazines to palladium hydrides and aryldiazo compounds.

The foregoing summary illustrates the rich chemistry available by the combination of palladium-catalysed cascade processes with cycloaddition reactions. Such combinations have been used to furnish a range of structurally diverse pyrrolidine, isoxazolidine, isoxazoline, dihydropyran and pyrazoline derivatives.

Acknowledgements

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