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Synthesis of pyran-4-ones from isoxazoles

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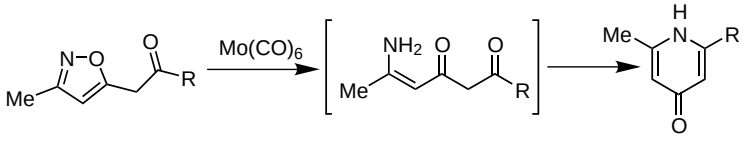
Abstract—A synthesis of mono-, di- and tri-substituted pyran-4-ones from isoxazoles is reported. The isoxazoles can be synthesized from readily available starting materials and undergo a reductive cleavage reaction with $Mo(CO)_6$ to generate enamino ketone intermediates, which are then cyclized to pyran-4-ones under acidic conditions. © 2002 Published by Elsevier Science Ltd.

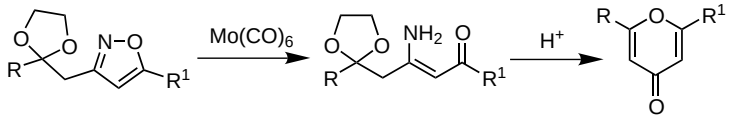
Isoxazole is a versatile heterocycle and has been demonstrated to be a very useful synthetic intermediate.[1,2] One of the key features of this heterocycle is the reductive ring opening to provide 1,3-dicarbonyl compounds. Under other conditions, isoxazole is quite stable because of properties associated with aromaticity. Therefore, chemical reactions that are not normally compatible with 1,3-dicarbonyl compounds can be carried out with isoxazoles. Isoxazole can be synthesized from readily available or easily prepared starting materials[1] and synthetic applications of isoxazole in the synthesis of natural products and other heterocycles are well documented.[1,2]

Nitta has reported that an isoxazole bearing a 2-oxoalkyl side chain at the 5 position was converted to pyridin-4-one in situ under reduction with $Mo(CO)_6$ (Scheme 1).[3] We have found that if the 2-oxoalkyl side chain was at the 3-position of the isoxazole, the corresponding enamino ketone intermediate could be isolated after reduction with $Mo(CO)_6$. This enamino ketone intermediate would then be cyclized to the corresponding pyran-4-one under appropriate acidic conditions (Scheme 2). Herein, we report our application of this strategy to the synthesis of substituted pyran-4-ones.

The isoxazole intermediates could be synthesized from a 1,3-dipolar cycloaddition reaction of nitrile oxides with acetylenes.[1,2] The nitrile oxide precursors, nitro compounds, and acetylenes were easily prepared from well established methodologies. The nitrile oxide intermediate was generated in situ under Mukaiyama's dehydration conditions[4] with phenyl isocyanate from



Scheme 1.



Scheme 2.

Keywords: pyran-4-ones; isoxazoles; 1,3-dipolar cycloaddition reactions; nitrile oxides.

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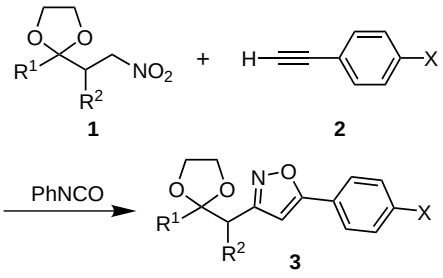
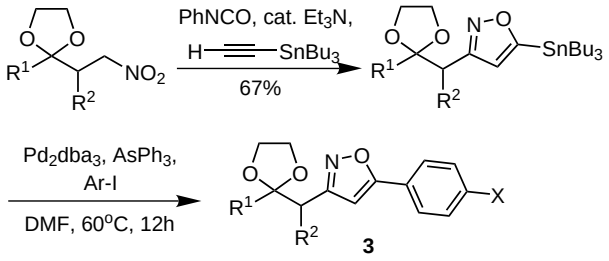
the corresponding nitro compound and then cyclized with the acetylene to give the isoxazole intermediate (Table 1). As an alternative, a 5-stannyl isoxazole intermediate was prepared and then submitted to Stille coupling with various substituted aryl iodides to provide the desired isoxazoles[5] in moderate yields (Table 2). This approach has the potential to easily prepare a large number of different 5-substituted isoxazoles from a common intermediate. $Mo(CO)_6$ in moist acetonitrile[6] was found to be an excellent reagent for the reductive ring opening of the isoxazoles and furnished the enamino ketone intermediates in good yields (Table 3). Other conditions such as Raney Nickel afforded complex mixtures for some substrates. Several acid conditions have been evaluated for the conversion of the enamino ketones to pyran-4-ones. The best results were obtained with 80% aqueous formic acid at 60°C for 12 h and the desired pyran-4-ones were produced in good yields (Table 4).

Table 1. Synthesis of isoxazoles



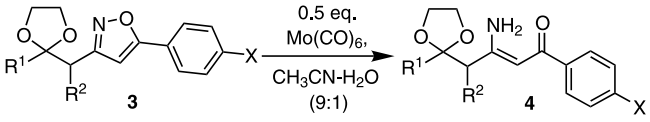
R^1	R^2	X	Product	Yield (%)
Me	H	H	**3a**	75
Me	H	CO_2Me	**3b**	45
Me	H	OMe	**3c**	52
Me	H	Br	**3d**	53
H	Me	H	**3e**	78
H	Me	CO_2Me	**3f**	90
H	Me	OMe	**3g**	49
H	Me	Br	**3h**	64
H	H	H	**3i**	68
H	H	Co_2Me	**3j**	76
H	H	OMe	**3k**	45
H	H	Br	**31**	73

Table 2. Alternative synthesis of isoxazoles



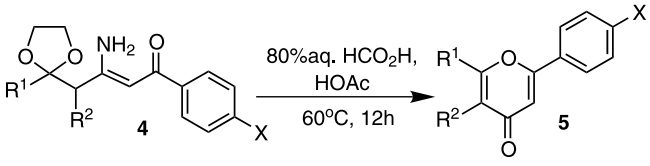
R^1	R^2	X	Product	Yield (%)
Me	H	H	**3a**	31
Me	H	CO_2Me	**3b**	60
Me	H	OMe	**3c**	57
Me	H	Br	**3d**	42

Table 3. Reductive cleavage of isoxazole intermediates



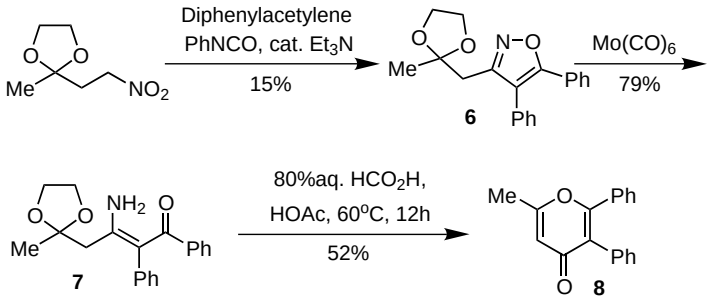
R^1	R^2	X	Product	Yield (%)
Me	H	H	**4a**	80
Me	H	CO_2Me	**4b**	87
Me	H	OMe	**4c**	68
Me	H	Br	**4d**	77
H	Me	H	**4e**	74
H	Me	CO_2Me	**4f**	74
H	Me	OMe	**4g**	54
H	Me	Br	**4h**	95
H	H	H	**4I**	86
H	H	CO_2Me	**4j**	76
H	H	OMe	**4k**	80
H	H	Br	**4l**	89

Table 4. Cyclization of enamino ketone intermediates



R^1	R^2	X	Product	Yield (%)
Me	H	H	**5a**	65
Me	H	CO_2Me	**5b**	68
Me	H	OMe	**5c**	74
Me	H	Br	**5d**	64
H	Me	H	**5e**	70
H	Me	CO_2Me	**5f**	49
H	Me	OMe	**5g**	74
H	Me	Br	**5h**	71
H	H	H	**5i**	70
H	H	CO_2Me	**5j**	75
H	H	OMe	**5k**	72
H	H	Br	**5l**	90

Extension of this strategy to the synthesis of trisubstituted pyran-4-ones was also briefly investigated. One approach was the use of disubstituted acetylenes for the 1,3-dipolar cycloaddition. However, two regioisomers could be produced if unsymmetrical acetylenes were used and also the 1,3-dipolar cycloaddition reaction could become more sluggish because of increasing steric hindrance. To simplify the chemistry, this approach was demonstrated with diphenyl acetylene (Scheme 3). An alternative approach was to introduce the substituent in the isoxazole intermediate. This was demonstrated with isoxazole intermediate **3a**. Therefore, the ketal was removed under acidic conditions and the ketone intermediate was alkylated with benzyl bromide under basic conditions.[7] The monoalkylated product was separated



Scheme 3.

and then transformed to the desired trisubstituted pyran-4-one as described before (Scheme 4). Another possibility would be to take advantage of the acidity of the proton at the 4-position of the isoxazole ring and hence, alkyl substituents could potentially be introduced relatively easily.[8]

In summary, we have developed a convenient synthesis of 2-substituted, 2,5-disubstituted and 2,6-disubstituted pyran-4-ones from isoxazole intermediates.[9] The isoxazole intermediates were easily synthesized from readily available starting materials such as nitro compounds and acetylenes. A common intermediate such as the 5-stannyl substituted isoxazole might provide the opportunity to easily synthesize a wide range of pyran-4-one analogs. In addition, it could be further functionalized to provide highly substituted pyran-4-ones.

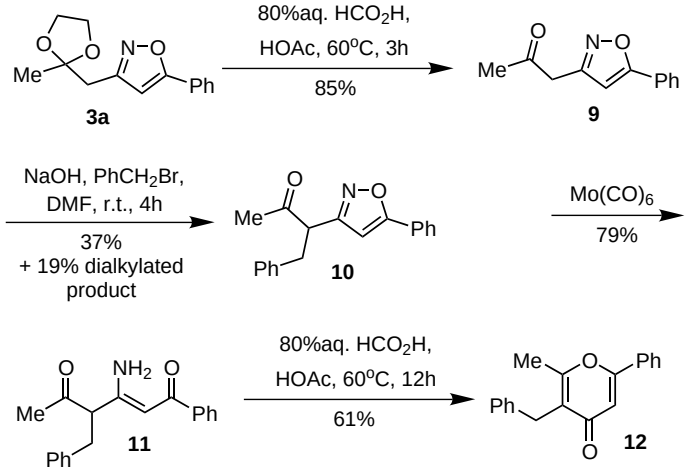
General experimental procedures

All compounds have been characterized by ^{1}H NMR, MS and either HRMS or combustion analysis.

Synthesis of the isoxazole intermediate. To a solution of acetylene (3.0 equiv.) and nitro compound (1.0 equiv.) in benzene (so as to give a 0.2 M solution of the acetylene) was added Et_3N (two drops) and phenyl isocyanate (4.0 equiv.). The mixture was refluxed overnight and cooled to room temperature. Water was added and the mixture was stirred at room temperature for 30 min, filtered through Celite and extracted with EtOAc (2×). The combined EtOAc extracts were washed with saturated aqueous NaCl, dried (anhydrous $MgSO_4$) and concentrated. The crude residue was chromatographed over silica gel and eluted with ~30% EtOAc in hexanes to provide the isoxazole intermediate.

Reductive cleavage of the isoxazole intermediate. To a 0.05 M solution of isoxazole intermediate (1.0 equiv.) in acetonitrile:water (9:1) was added $Mo(CO)_6$ (0.5 equiv.). The mixture was heated under reflux and stirred for 3 h. Solvents were evaporated in vacuo. The residue was chromatographed over silica gel and eluted with 50% EtOAc in hexanes to give the enamino ketone intermediate.

Cyclization of the enamino ketone intermediate. The enamino ketone intermediate (1 mmol) was dissolved in HOAc (1 mL) and diluted with 80% aqueous HCO_2H (4 mL). The mixture was heated to 60°C and stirred overnight. After cooling to room temperature, the mixture was added to water and extracted with EtOAc. The EtOAc extract was washed successively with 1 M aqueous NaOH (3×10 mL, until the washing was not acidic) and brine; dried (anhydrous $MgSO_4$) and concentrated. The residue was chromatographed over silica gel and eluted with EtOAc to give the pyran-4-one product.



Scheme 4.

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7. The alkylation condition has not been optimized.
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9. This strategy is not limited to 2-aryl substituted pyran-4-ones. A 2,6-dialkylated pyran-4-one such as 2-butyl-6-methyl-4*H*-pyran-4-one was prepared in a similar manner from the corresponding nitrile oxide precursor and 1-hexyne.