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Synthesis of oxygen heterocycles

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Abstract—A generalised scheme for the synthesis of flavones, flavonones and chromones involving 3-acyl-γ-pyrone intermediates has been developed. Convenient synthesis of other oxygen heterocycles using similar procedure have been outlined.

1. Introduction

There has been considerable interest[1] in recent years in the area of flavonoids, which are known to be kinase inhibitors. They also show activity in apoptosis, which is implicated in cancer chemotherapy. In addition they are known to be antioxidants and also show activity against P-gp 170, a multiple drug resistant gene product. We therefore decided to explore chemistry in this area with an idea of making a library of compounds for biological testing. We decided to synthesise these compounds using Baker–Venkataraman (B–V)[2] reaction and during our study we made an unusual observation.[3a] We observed that Baker–Venkataraman reaction under our experimental condition did not yield the expected γ-pyrones instead we obtained 3-acyl-γ-pyrones.[3b]

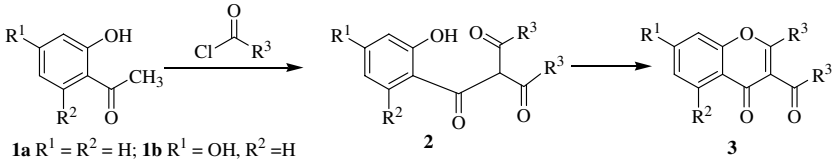
Thus when compounds **1a**–**d** were treated with aliphatic or aromatic acid chlorides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and pyridine they yielded 3-acyl-γ-pyrones. We speculated that the formation 3-acyl-γ-pyrones involved the intermediacy of the triketones **2** (Scheme 1).

2. Present work

In our present work we have explored this reaction further thus making it possible to prepare a library of flavonoids for biological testing. In addition we have discovered a novel approach for the synthesis of other oxygen heterocycles.

In Scheme 2 a brief summary is presented of the acid chlorides used in the above reaction and the products[5,6] obtained. It should be noted that excepting in the case of the 3-substituted acid chlorides wherein a single product was isolated in all the other cases both the possible compounds were obtained. We have already reported that the treatment of the phenolic 3-acyl-γ-pyrones with aqueous potassium carbonate yield γ-pyrones. Thus the combination of the above reactions will provide a library of flavonoids for biological testing.

We also explored whether 3-acyl-γ-pyrones could be a source for the preparation of flavonones. Thus we have reduced **11a** with sodium borohydride to the *trans*-dihydro compound **13**. The methyl ether **14** obtained from **13** was in turn converted to the oxime **15** by treatment



1a $R^1 = R^2 = H$; **1b** $R^1 = OH$, $R^2 = H$
1c $R^1 = OCH_3$, $R^2 = H$; **1d** $R^1 = R^2 = OH$

Scheme 1.

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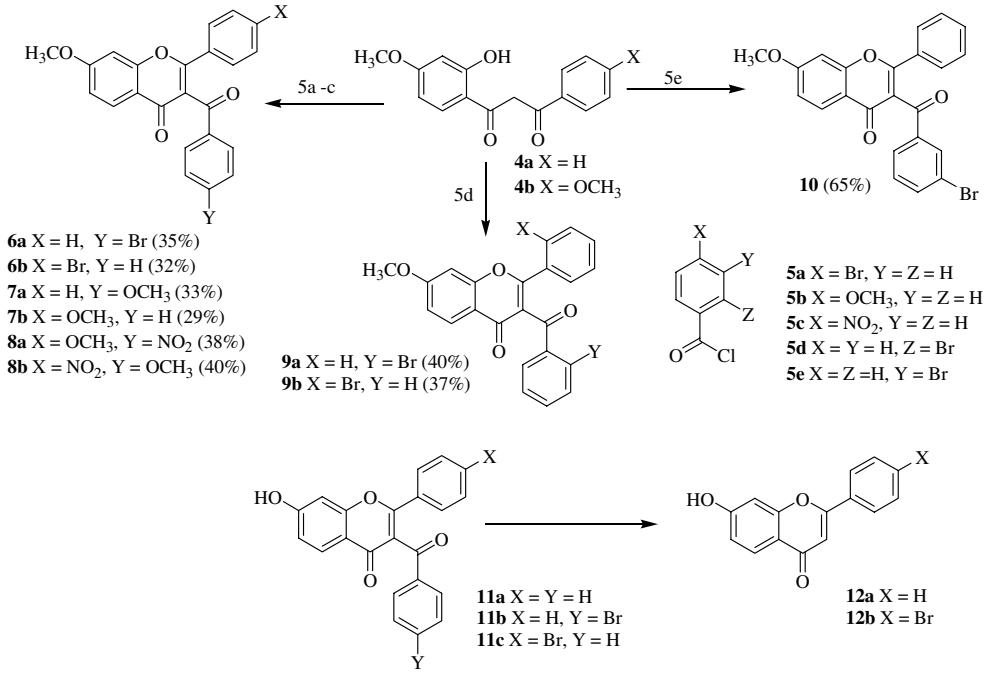
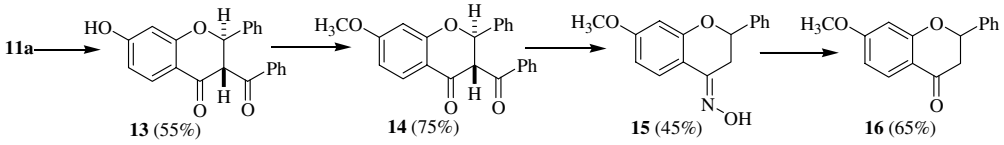
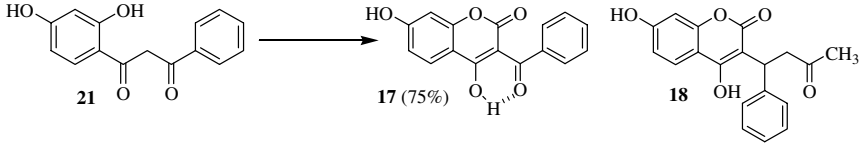


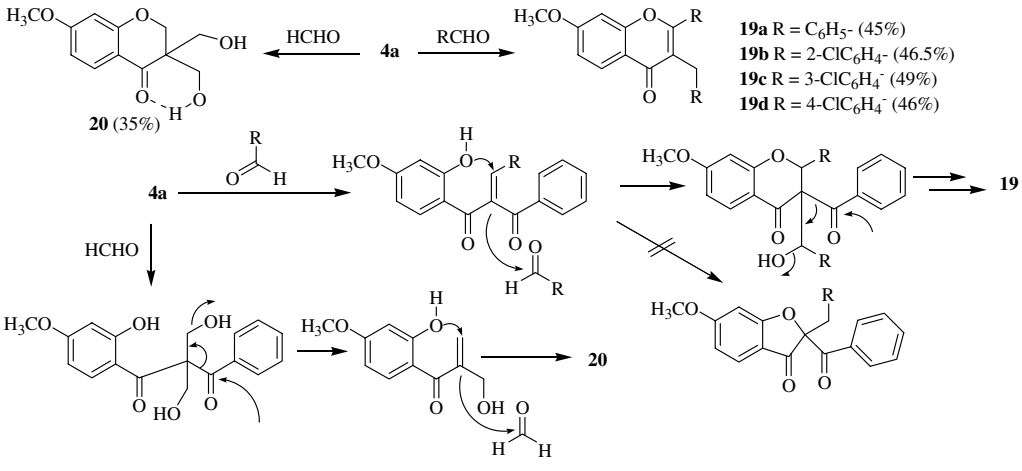
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

with hydroxylamine hydrochloride/KOH in ethanol. The oxime **15** was converted to the flavonone **16** by reacting with nitrous acid (Scheme 3).

To extend further our synthesis of 3-acyl-γ-pyrones we treated **21** with carbonyl diimidazole and DBU/pyridine and obtained in good yield the 4-hydroxy coumarin derivative **17**, which has been previously synthesised[4] using a multistep procedure. 4-Hydroxy coumarins possess important biological activity, for example, warfarin **18** is a well known anticoagulant (Scheme 4). As diketones such as **21** are easily synthesised the above reaction could be extended further to make analogues.

Interestingly when the diketone **4a** was treated with aromatic aldehydes it gave **19a**–**d** and on treatment with formaldehyde it yielded **20**. The possible mechanisms involved in these conversions are summarised in Scheme 5. Using diketones with different substitutions on the phenolic ring and various aromatic and aliphatic aldehydes we are in the process of making a library of compounds.

3. Conclusion

Using our modified experimental condition of Baker–Venkataraman reaction we have developed convenient synthetic procedures, which will allow preparation of libraries of compound containing flavones, flavanones, coumarines and other oxygen heterocycles.

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5. NMR and high-resolution mass spectra of all the compounds described in this paper were consistent with the assigned structures. Assignments were further confirmed using HMBC, HSQC and COSY experiments.
6. All compounds described in this letter were crystalline. Crystals were obtained from dichloromethane–hexane or ethylacetate. The melting points of compounds **6a**,**b**, **7a**,**b**, **8a**,**b**, **9a**,**b**, **10**, **11a**–**c**, **12a**,**b**, **13**–**17**, **19a**–**d** and **20** were 182–183, 203–204, 158–159, 196–197, 176–177, 196–197, 186–187, 144–146, 166–167, 270–271, 268–269, 287–288, 241–242, 282–283, 220–221, 175–176, 139–140, 62–63, 263–264, 123–124, 171–172, 112–113, 152–153 and 129–130 °C. Yields are indicated in the parenthesis.