Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 46 (2005) 4119–4121
Tetrahedron Letters

Synthesis and properties of 3-acyl-γ-pyrones, a novel class of flavones and chromones

A. K. Ganguly,[a,*] S. Kaur,[a] P. K. Mahata,[a] D. Biswas,[a] B. N. Pramanik[b] and T. M. Chan[b]

[a]*Stevens Institute of Technology, Hoboken, NJ 07030, USA*
[b]*Schering-Plough Research Institute, Kenilworth, NJ 07033-1300, USA*

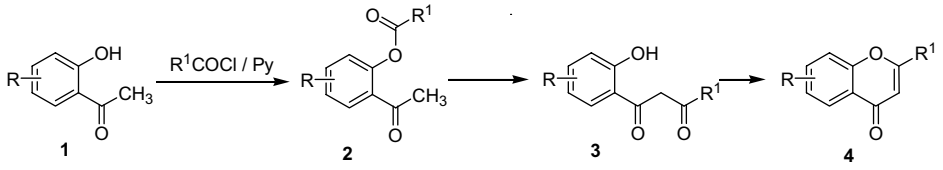
Received 10 March 2005; accepted 1 April 2005
Available online 19 April 2005

Abstract—Using modified Baker–Venkataraman reaction a novel class of 3-acyl flavones and chromones have been synthesised. Reaction mechanism for their formation have been elucidated. The properties of 3-acyl flavonoids indicate them to be precursors for the synthesis of flavones.

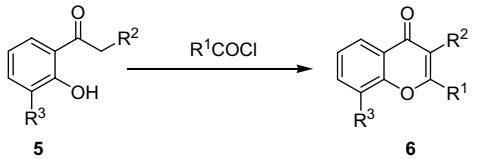
1. Introduction

Flavonoids are a well known class of natural products and have been known for a long time to possess antioxidant properties. Recent reports[1] suggesting their possible use in cancer chemotherapy involving kinase inhibition or apoptosis attracted our attention and we decided to investigate whether a library of flavonoids could be synthesised conveniently for biological testing.

To achieve this objective we performed solution chemistry following Baker–Venkataraman reaction[2] for the synthesis of flavonoids. In Baker–Venkataraman reaction substituted 2-hydroxy acetophenones **1** are converted to esters **2**, which undergo rearrangement in the presence of potassium hydroxide and pyridine to the diketones **3**, which then undergo cyclisation to **4** under rather harsh conditions for example treatment with concentrated sulfuric acid or heating with glacial acetic acid.



Over a period of years several groups have investigated and improved upon the experimental conditions of Baker–Venkataraman reaction amongst which the work[3] of Riva and colleagues attracted our attention. In their procedure compounds such as **5** were heated with acyl chlorides in the presence of 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) and pyridine to obtain compounds of general structures **6**.



$R^2 = CH_3$ or H; R^3 = esters or olefins;
R^1 = aliphatic, aromatic or alicyclic groups

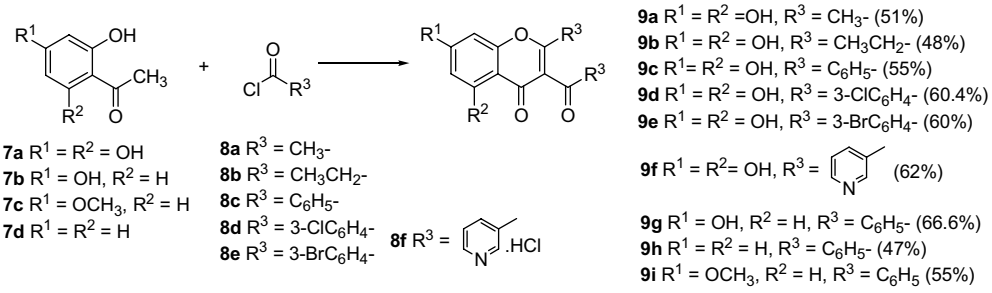
Keywords: Synthesis; Heterocycles.
* Corresponding author. Tel.: +1 201 216 5540; fax: +1 201 216 8240; e-mail: akganguly1@aol.com

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.04.010

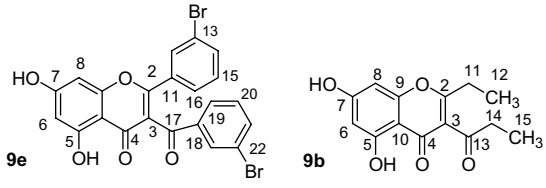
2. Present work

As we were interested in synthesising compounds, which resembled naturally occurring flavonoids we repeated the above work with 2′,4′-dihydroxy and 2′,4′,6′-trihydroxy acetophenones and made an unexpected observation. In our hands this reaction yielded 3-acyl-γ-pyrones, which to the best of our knowledge have never been reported in the literature. In this communication we wish to disclose our preliminary results including the properties of 3-acyl-γ-pyrones and the mechanism of their formation. Some comments on Baker–Venkataraman reaction are also being presented. We also believe that 3-acyl-γ-pyrones are versatile intermediates for the preparation of substituted flavones.

Thus when compounds **7a**–**d** were treated[4] with acyl chlorides **8a**–**f** in the presence of DBU and pyridine they yielded **9a**–**i**. In some instances in addition to the 3-acyl-γ-pyrones we have noticed the formation of the corresponding phenolic esters.



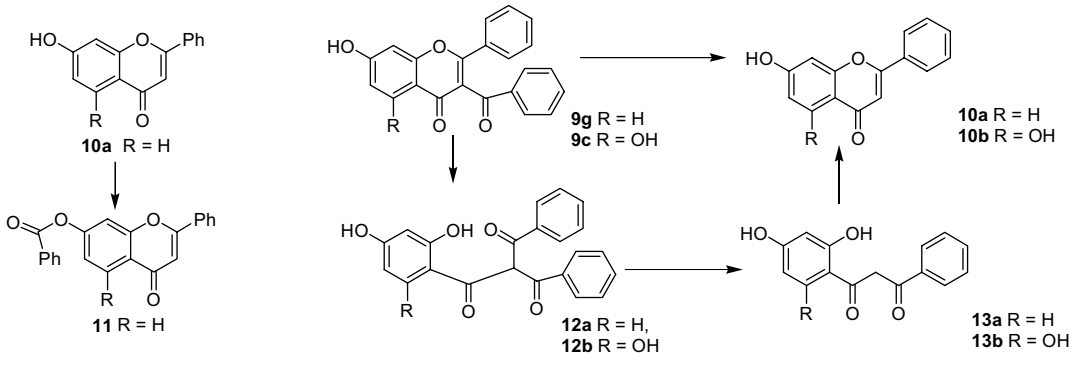
The structures[5] of 3-acyl-γ-pyrones were solved using high resolution mass spectrometry and by the application of 2-D NMR spectroscopy. We wish to summarise the NMR assignments of relevant protons and carbons with compounds **9e** and **9b**.



Compound **9e**, $C_{22}H_{12}O_5Br_2$, shows H_6 at δ 6.28 and H_8 at δ 6.54, which are mutually meta coupled. The signal for H_3 proton, which appears at $\delta \sim 6.64$ in flavonoids is missing in **9e** and the ^{13}C NMR spectrum shows the presence of carbonyl groups at δ 179.6 and δ 191 assigned to C_4 and C_{17}, respectively. NMR spectra of **9e** also shows the presence of two exchangeable phenolic hydroxyl groups at δ 11.1 and δ 12.1 assigned to the OH groups at 7- and 5-positions, respectively, and a total of 10 aromatic protons out of which H_6 and H_8 have already been identified. Compound **9b**, $C_{14}H_{14}O_5$ shows H_6 at δ 6.2 and H_8 at δ 6.4, which are mutually meta coupled. The signal for H_3 is missing and ^{13}C NMR spectra shows the presence of two carbonyl groups at δ 202 and δ 180 assigned to C_{13} and C_4, respectively. There are two triplets at δ 1.0 and δ 1.2 assigned to H_{15} and H_{12}, respectively. The two $-CH_2$ groups appear as quartets at δ 2.6 (H_{11}) and δ 2.8 (H_{14}).

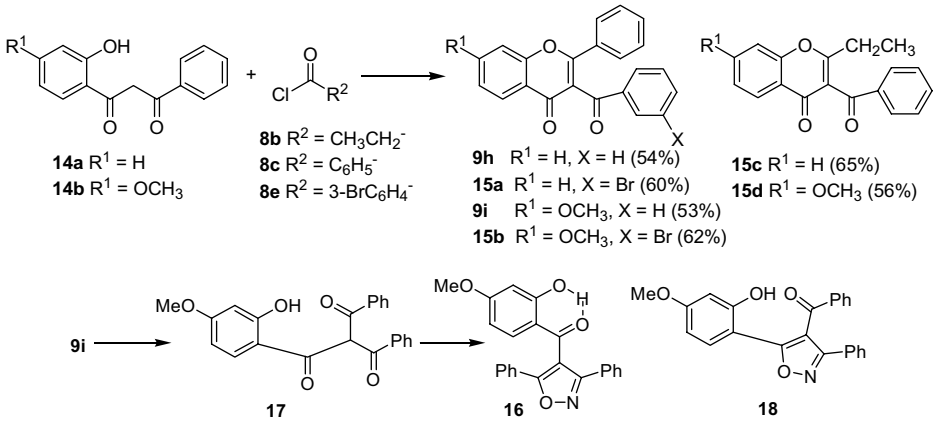
Intrigued by the above observation we decided to explore the mechanism involved in the formation of 3-acyl flavonoids. Thus we treated **10a** with benzoyl chloride in the presence of DBU and pyridine under identical condition[4] used for the preparation of 3-acyl flavones and obtained[5,6] only **11** and not **9g** thus establishing that the 3-acyl flavones were not formed by acylation of flavones.

The next question we wished to address was whether 3-acyl flavones were precursors to the formation of flavones. On heating under reflux with an aqueous solution of 5% potassium carbonate compound **9g** and **9c** yielded **10a** (58%) and **10b** (53%), respectively.



Although we have not isolated the triketones **12a** and **12b** in these conversions, it appears entirely possible that **10a** and **10b** arose via **12a** and **12b** that is the triketones are converted to the diketones **13a** and **13b** (which are similar to the Baker–Venkataraman reaction intermediates) followed by cyclisation to the flavones **10a** and **10b**. However it should be noted that the condition of our experiment is very different than that used in Baker–Venkataraman reaction.

To confirm the above hypothesis we have treated the diketones **14a** and **14b** with acyl chlorides **8b**, **8c** and **8e**, respectively in the presence of DBU and pyridine under our experimental condition[4] and obtained **9h**, **9i**, **15a**, **15b**, **15c** and **15d**. It should be noted that when **14a** or **14b** were treated with acyl chloride **8b** or **8e** we obtained only one product and their formation perhaps indicates that the less bulkier carbonyl groups in the triketone intermediates cyclise with the phenolic hydroxyl group followed by dehydration to yield the corresponding 3-acyl-γ-pyrones. Thus suggesting that the 3-acyl flavonoids are formed via the triketones such as **12a** and **12b** and not through acylation of flavones. Interestingly when the 3-acyl flavone **9i** was treated with hydroxylamine it yielded **16**. The formation of **16** perhaps also involves the triketone intermediate **17**. The presence of the hydrogen bonded phenolic hydroxylic group in **16** ruled out the alternative structure **18** for the isoxazole.



3. Conclusion

Using a modified Baker–Venkataraman reaction we have synthesised a novel class of 3-acyl-γ-pyrones. The reaction mechanism for their formation and the properties of 3-acyl-γ-pyrones have been elucidated. 3-Acyl-γ-pyrones have been shown to be the precursors for the formation of γ-pyrones.

Acknowledgements

One of us (P.K.M.) would like to thank Stevens Institute of Technology for the award of a postdoctoral fellowship. We would also like to thank Schering-Plough Research Institute for generous financial assistance.

References and notes

1. (a) Marchand, L. L. *Biomed. Pharmacother.* **2002**, *56*, 296; (b) Sausville, E. A.; Zaharvitz, D.; Gussio, R. *Pharmacol. Ther.* **1999**, *83*, 285; (c) Matsui, J.; Kiyokawa, N.; Takenouchi, H.; Taguchi, T. *Leukemia Res.* **2005**, *29*, 573.
2. (a) Baker, W. *J. Chem. Soc.* **1933**, 1381; (b) Mahal, H. Si.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767.
3. (a) Riva, C.; De Toma, C.; Donadd, L.; Boi, C.; Pennini, R.; Motta, G.; Leonardi, A. *Synthesis* **1997**, 195, and references cited therein; (b) Hirao, I.; Yamaguchi, M.; Hamada, M. *Synthesis* **1984**, 1076.
4. In a typical experiment an acyl chloride (8.88 mmol) was added dropwise under N_2-atmosphere to a solution of hydroxy acetophenone (2.69 mmol) in anhydrous pyridine. Finally DBU (10.71 mmol) was added dropwise to the reaction mixture and it was heated at temperature of 80–90 °C for 6–7 h (monitored by TLC). The reaction mixture was dissolved in dichloromethane, washed with ice water, acidified until pH 3–4 using dil HCl, and finally washed with water again, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by silica-gel column chromatography using hexane–EtOAc (60:40) as eluent. The compound crystallised from hexane–dichloromethane or ethanol.
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 paper were crystalline. Crystals were obtained from dichloromethane-hexane or ethanol. The melting points of compounds **9a**, **9b**, **9c**, **9d**, **9e**, **9f**, **9g**, **9h**, **9i**, **10a**, **10b**, **11**, **15a**, **15b**, **15c**, **15d** and **16** were 250–251, 144–145, 193–194, 224–225, 215–216, 304–305, 270–271, 121–122, 162–163, 241–242, 284–285, 151–152, 126–127, 100–102, 64–65, 132–133 and 150–151 °C. Yields were indicated in the parenthesis.