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Tetrahedron Letters 46 (2005) 5399–5402

Tetrahedron Letters

Formation of the unexpected 3-alkylated flavonoids in the alkylation of B-ring substituted 5,7-dihydroxy flavones

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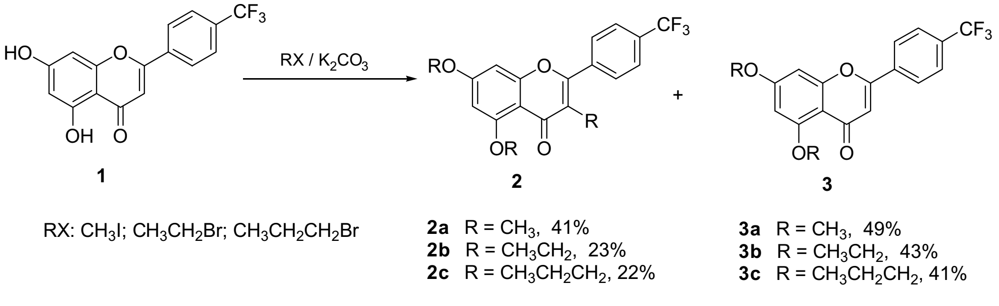
Received 19 April 2005; revised 27 May 2005; accepted 30 May 2005
Available online 22 June 2005

Abstract—Treatment of B-ring substituted 5,7-dihydroxy flavones with alkyl halides in the presence of potassium carbonate gave unexpected 3-alkylated flavonoids. Related experiments were carried out to explain the formation of 3-alkylated flavonoids and a ring opening followed by alkylation and ring closure mechanism was proposed.

Flavonoids have been found to exhibit a broad range of pharmacological properties.[1] In recent years, there has been a growing interest in the search for anti-tumor flavonoids with high efficacy and low toxicity.[2] It is known that fluorine is the most electronegative element and the van der Waals radius of fluorine is close to that of hydrogen. The introduction of the trifluoromethyl (CF_3) or *gem*-difluoromethylene (CF_2) group into organic molecules often changes their physiological, physical and chemical properties dramatically, without extra steric demand.[3] We have recently reported that introduction of CF_3 group into the A- and B-ring of flavonoids molecule can enhance their anti-cancer activities.[4,5] When CH_3I, CH_3CH_2Br and $CH_3CH_2CH_2Br$ were used as alkylating agents for the alkylation of B-ring trifluoromethylated flavonoid **1**, unexpected 3-alkylated products **2** were formed along with the expected compounds **3** (Scheme 1).[5] This result aroused our interest. So a series of experiments have been carried out to explain the formation of 3-alkylated flavonoids.

Under the same reaction conditions, when bulky alkyl halides such as benzyl chloride and heptyl chloride were used, only compounds **3** were obtained, no 3-alkylated flavonoids were found (Scheme 2).

Treatment of compounds **3** (R = CH_3, C_2H_5, $CH_3CH_2CH_2$) with CH_3I, CH_3CH_2Br and



Scheme 1.

Keywords: Flavonoids; Fluorinated compounds.

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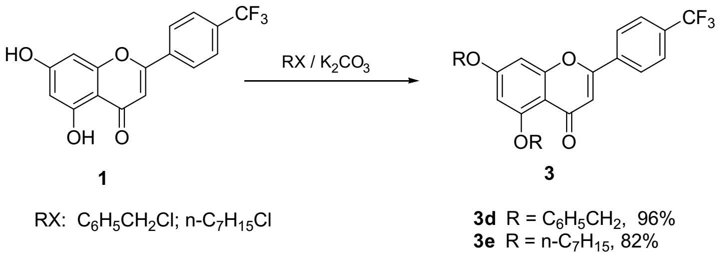
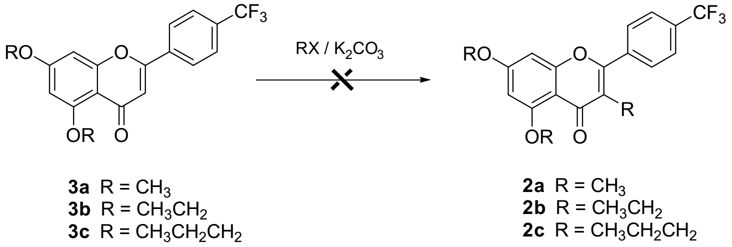
doi:10.1016/j.tetlet.2005.05.144



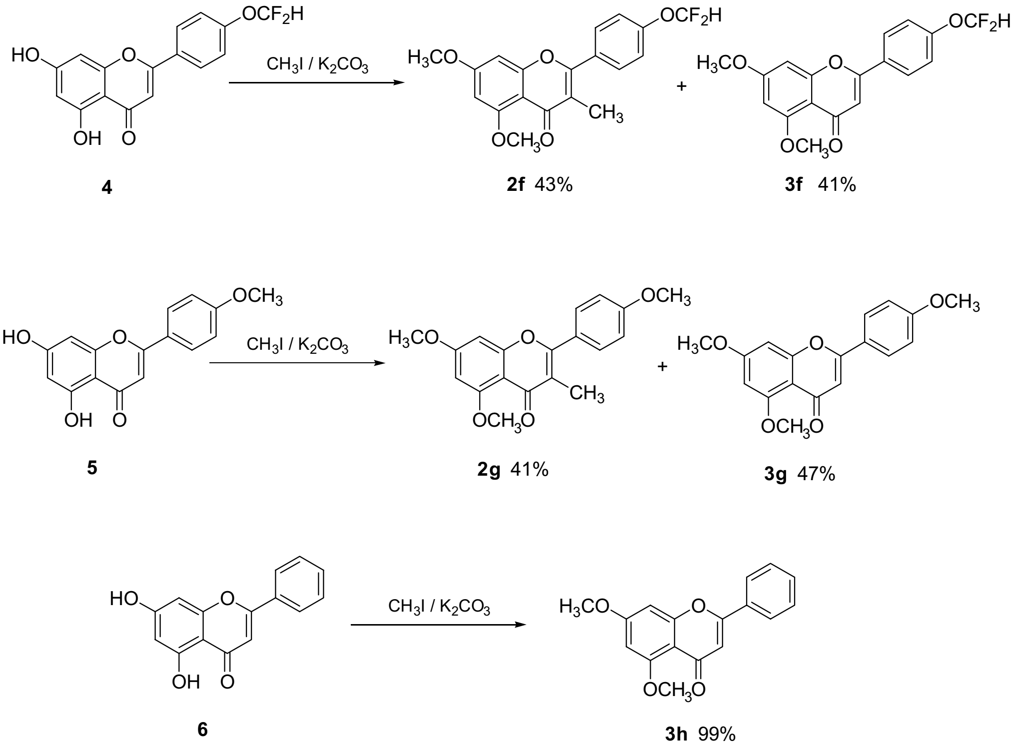
Scheme 2.



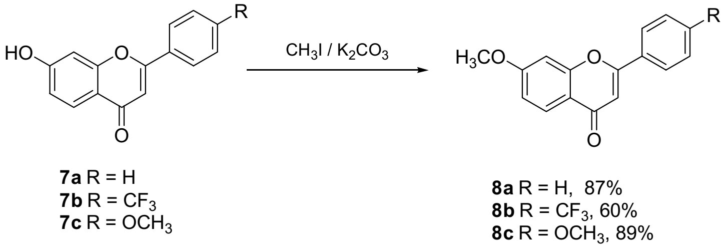
Scheme 3.

$CH_3CH_2CH_2Br$, respectively, in the presence of K_2CO_3 failed to give 3-alkylated products **2** (Scheme 3). These results showed that compounds **2** were not formed from the further alkylation of compounds **3**.

To explain the formation of unexpected compound **2** in the alkylation of compound **1**, the effect of other substitutes on the B-ring of flavonoids was investigated. The alkylation of compound **4** with CH_3I in the presence of K_2CO_3 gave compounds **2f** and **3f**. Compound **5** was treated under the same conditions to give compounds **2g** and **3g**. However, compound **6** only yielded compound **3h** in nearly quantitative yield, no 3-alkylated product was detected (Scheme 4). It was evident that the substituted B-ring was an important factor for the formation of 3-alkylated product, whereas the



Scheme 4.

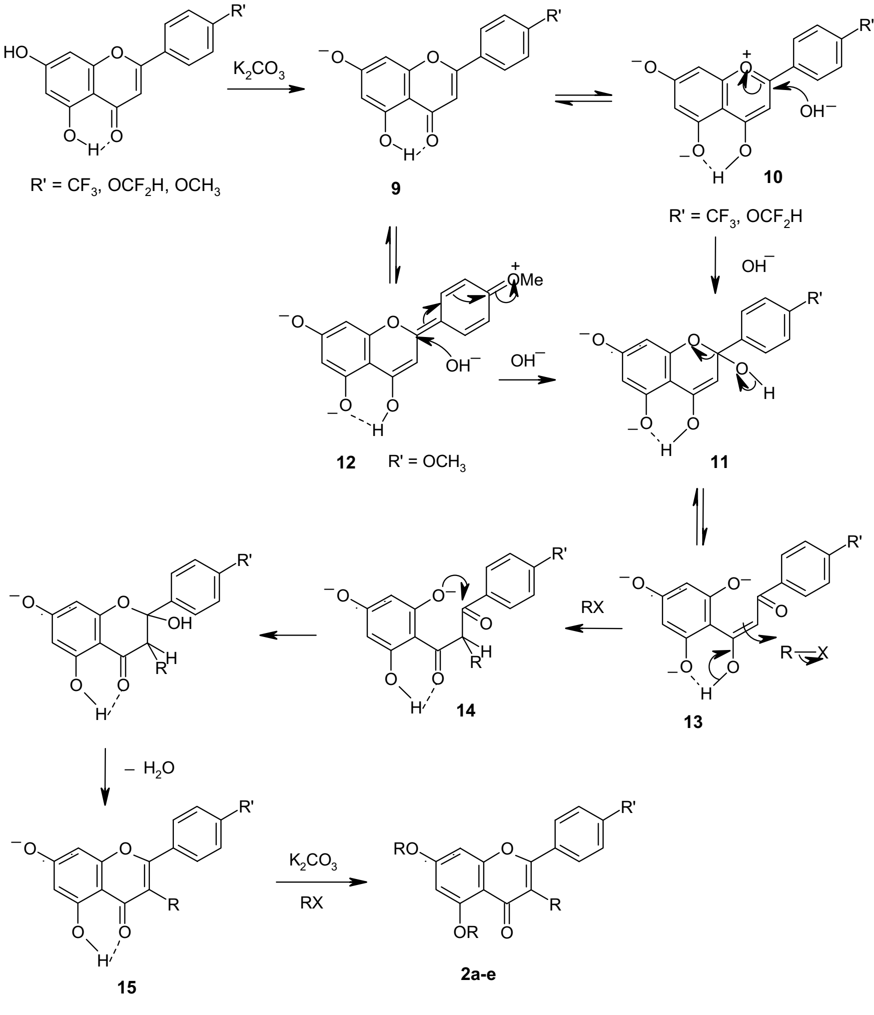


Scheme 5.

electron-withdrawing group (CF_3, OCF_2H) and electron-donating group (OCH_3) of B-ring had no profound effect on the outcome of the alkylation.

Then, we examined the effect of hydroxy groups of A-ring on the formation of 3-alkylated flavonoids. Thus, a series of B-ring substituted 7-hydroxy flavones **7a**–**c** were prepared. The reaction of **7a**–**c** with CH_3I in the presence of K_2CO_3 produced compounds **8a**–**c**, respectively, without the formation of 3-methyl flavonoids (Scheme 5). These results implied that 5-hydroxy group of A-ring played a key role in the formation of 3-alkylated product.

Based on the above facts, we presumed that the unexpected 3-alkylated compounds **2a**–**g** were formed via a proposed mechanism (Scheme 6). The flavoniods were deprotonated with K_2CO_3 to give anion **9**. When a strong electron-withdrawing group such as trifluoromethyl or difluoromethoxy group was presented at 4′-position such as compound **1** or **4**, the electron density on the oxygen atom at the C-ring decreased, and anion **9** ($R{=}CF_3$, OCF_2H) tended to tautomerize to **10** via a resonance of the lone pair of electrons of oxygen atom and a hydrogen-transfer between 5-hydroxy and 4-carbonyl groups. Under the basic condition, **10** was attacked by a hydroxy anion to form an intermediate



Scheme 6.

11. On the other hand, when a strong electron-donating methoxy group was presented at 4′-position, the intermediate **12** was formed through a resonance of the lone pair of electrons of oxygen atom of methoxy group and the proton switch between 5-hydroxy and 4-carbonyl groups. Under the basic condition, **12** was also attacked by a hydroxy anion to form the intermediate **11**. The intermediate **11** was then ring-opened to give intermediate **13**, which was then alkylated with CH_3I, CH_3CH_2Br or $CH_3CH_2CH_2Br$ to give intermediate **14**, followed by a ring closure and dehydration to give 3-alkylated intermediate **15**. The intermediate **15** was then deprotonated by K_2CO_3 and alkylated with alkyl halides to give 3-alkylated compounds **2a**–**g**. The proton switch between 5-hydroxy and 4-carbonyl groups played an important role in the reaction, and this was supported by the above facts that flavonoids without 5-hydroxy group, such as compounds **7a**–**c** could not give 3-methylated products.

Acknowledgements

We thank the National Natural Science Foundation of China, Ministry of Education of China and Shanghai Municipal Scientific Committee for funding this work.

References and notes

1. (a) Mao, X. S. *Guowai Yixue Yaoxue Fence* **1995**, *22*, 92–96; (b) Liu, Y. L.; Jo, D. K.; Cassady, J. M. *J. Nat. Prod.* **1992**, *55*, 357–363; (c) Kubo, I.; Hori, I. K.; Chaudhuri, S. K.; Kubo, Y.; Sanchez, Y.; Ogura, T. *Bioorg Med. Chem.* **2000**, *8*, 1749–1755; (d) Wang, C. F. *Nutr. Cancer.* **1998**, *31*, 90–100; (e) Comte, G.; Daskiewicz, J. B.; Bayet, C.; Conseil, G.; Uanier, A. V.; Dumontet, C.; Pietro, A. D.; Barron, D. *J. Med. Chem.* **2001**, *44*, 763–768; (f) Liu, P.; Chang, J. B.; Chen, R. F.; Xie, J. X.; Wang, Q. *Acta Pharmaceut. Sinica* **2000**, *35*, 583–586; (g) Wang, G. L. *Shiyong Aizheng Zazhi* **1994**, *9*, 150–151.
2. (a) Kumar, S. K. *J. Med. Chem.* **2003**, *46*, 2813–2815; (b) Wang, Y. Q. *Bioorg. Med. Chem.* **2003**, *11*, 1569–1575; (c) Gao, Y.; Li, D. J.; Keung, W. M. *Bioorg. Med. Chem.* **2003**, *11*, 4069–4081.
3. (a) Dunitz, J. D. *ChemBioChem* **2004**, *5*, 614–621; (b) Jeschke, P. *ChemBioChem* **2004**, *5*, 570–589; (c) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004; (d) *Fluorine in Bioorganic Chemistry*; Welch, J. T., Eswarakrishnan, S., Eds.; Wiley: New York, 1991.
4. Zheng, X.; Meng, W. D.; Xu, Y. Y.; Cao, J. G.; Qing, F. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 881–884.
5. Zheng, X.; Cao, J. G.; Meng, W. D.; Qing, F. L. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3423–3427.