Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

A Fast and Efficient Synthesis of Flavanones From Cinnamic Acids

Kibrom Gebreheiwot Bedane, Runner R. T. Majinda & Ishmael B. Masesane

To cite this article: Kibrom Gebreheiwot Bedane, Runner R. T. Majinda & Ishmael B. Masesane (2016): A Fast and Efficient Synthesis of Flavanones From Cinnamic Acids, Synthetic Communications, DOI: 10.1080/00397911.2016.1228110

To link to this article: http://dx.doi.org/10.1080/00397911.2016.1228110

A fast and efficient synthesis of flavanones from cinnamic acids

Kibrom Gebreheiwot Bedane[1], Runner R. T. Majinda[1], Ishmael B. Masesane[1]

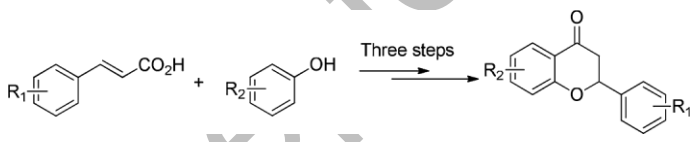
[1]Department of Chemistry, University of Botswana, Gaborone, Botswana

Corresponding author Ishmael B. Masesane E-mail: masesane@mopipi.ub.bw

Abstract

A fast and efficient synthesis of flavanones from cinnamic acids in three steps has been developed. First the cinnamic acid was converted to cinnamyol chlorides using $SOCl_2$. The acid chlorides were then treated with substituted phenols in $BF_3.OEt_2$ to furnish corresponding chalcones in 42%–75% yields. Base catalyzed cyclization of the chalcones at room temperature afforded corresponding flavones in 85%–95% yields. The conversion of the cinnamic acid derivatives to corresponding chalcones was found to be sensitive to the position and nature of the substituents on the aromatic rings.

Graphical Abstract



KEYWORDS: acylation; cinnamic acid; chalcone; flavanone

INTRODUCTION

Natural and synthetic flavanones attract the attention of researchers because of their interesting biological activity including antioxidant,[1–4] antibacterial, antifungal,[5–7] antivirial,[8] anti-inflammatory[9,10] and antihypertensive.[11,12] As part of our broader

interest on flavonoids, we have isolated a number of bioactive flavanones from *Erythrina livingstoniana*.[13,14] In continuation of our interest in flavanones, we explored a simple and easy synthetic method for the basic skeleton of these compounds starting with cinnamic acid or its derivatives.

Most of the reported synthetic methods for the synthesis of flavanones involve the preparation of the key intermediate 2'-hydroxychalcones of type **3** *via* the condensation reaction of 2-hydroxyacetophenones of type **1** and aldehydes of type **2** in the presence of a base. Subsequent cyclisation of intermediates of type **3** in either basic or acidic medium afforded flavanones of type **4** in moderate to high yields, Scheme 1.[15–20]

It is important to note that the synthesis of the key 2'-hydroxychalcone of type **3** through a Lewis acid catalysed aromatic acylation reaction is also possible and has been reported for the synthesis of flavones.[21–23] In continuation of our interest on flavanones, we set out to investigate the preparation of 2'-hydroxychalcone intermediate of type **3** from the reaction of phenols with cinnamyol chloride and subsequent cyclisation of the intermediate chalcones to give flavanones.

RESULT AND DISCUSSION

The first two steps were performed without the isolation of any intermediates. Thus, a reaction of cinnamic acid **5** and $SOCl_2$ under reflux for 2 hours to give intermediate acid chloride **6**. The progress of the reaction was monitored by TLC. Excess $SOCl_2$ was then removed under reduced pressure and resorcinol and $BF_3.OEt_2$ were added to the residue.

The mixture was then refluxed for 30 minutes to give chalcone **7** in 72% yield together with coumarin **8** in 4%, Scheme 2. The two products were easily separable by column chromatography. Having achieved the expedient synthesis of chalcone intermediate **7**, we were in a position to address its cyclisation to the corresponding flavanone. Although it is conceivable that chalcone **7** could cyclized to the corresponding flavanone under acidic conditions, all attempts at the use of H_3PO_4 acid under a variety of conditions failed to give the flavanone. Attention was then turned to bases and Na_2CO_3 failed under different reaction conditions to facilitate the cyclisation of chalcone intermediate **7**. Gratifyingly, when a solution of chalcone **7** in methanol was stirred in the presence of KOH at room temperature for four hours, flavanone **9** was isolated in 95% yield[24] (Scheme 2). Both chalcone **7** and flavanone **9** were characterized using NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectral features worth mentioning are signal for a chelated proton at δ_C 13.44 in chalcone **7**'s spectrum and the ring C protons signals at δ_H 2.77, 3.05 and 5.59 for the spectrum of flavanone **9**.

Next, a more reactive phenol, phloroglucinol, was used in the preparation of the intermediate chalcone instead of resorcinol. In the event, cinnamic acid was treated with $SOCl_2$ as described above to give the acid chloride. Once excess $SOCl_2$ was removed, the reaction mixture was treated with phloroglucinol and $BF_3.OEt_2$ and refluxed for 2 hours to give chalcone **10** in 63% yield together with coumarin **11** in 6% yield, Scheme 3. Subjection of chalcone **10** to the KOH-mediated cyclisation conditions gave flavanone **12** in 90% yield.

The reactions that were described thus far involved phenols that we activated towards electrophilic substitution reactions in the synthesis of the chalcone intermediates. It was therefore of interest to investigate if less active phenols would participate in the reaction. Thus, treatment of the acid chloride that was prepared by reaction of cinnamic acid with $SOCl_2$ with phenol and $BF_3.OEt_2$ and refluxing for 2 hours gave chalcone intermediate **13** in 55% yield. Surprisingly, attempts to cyclise chalcone **13** in the presence of NaOH were not successful. However, subjection of chalcone **13** to a stronger base NaOMe led to its cyclisation to give flavanone **14** in 87% yield, Scheme 4.

In a parallel sequence of reactions, a mixture cinnamic acid and $SOCl_2$ was refluxed for 4 hours and then treated with 4-bromophenol in the presence of $BF_3.OEt_2$. The mixture was further refluxed for 2 hours and chalcone intermediate **15** was isolated in 42% yield. Subsequent treatment of chalcone **15** with NaOMe gave flavanone **16** in 85% yield, Scheme 5. It is important to note that the aromatic acylation reaction failed when 4-nitrophenol was used instead of 4-bromophenol. This was not surprising bearing in mind that the nitro group withdraws electrons from the aromatic by both resonance and inductive effect thereby making the ring less nucleophilic and less reactive to the acyl group. The bromo substituent on the other hand only withdraws electrons from the aromatic ring by inductive effect.

Lastly, the effects of electron donating and electron withdrawing substituents attached to cinnamic acid on the yields of reactions involved in this procedure were investigated. To this end, 3-methoxycinnamic acid **17** and 3-nitrocinnamic acid **19** were converted to their

acid chlorides using $SOCl_2$ and reacted with resorcinol in the presence of $BF_3.OEt_2$ to give chalcones **22** and **24** in 75% and 66% yields respectively, Scheme 6. Consequent cyclization of chalcones **22** and **24** afforded flavanones **27** and **28** in 92% and 90% respectively. Interestingly, 4-methoxy and 4-nitrocinnamic acids **18** and **20** under the described conditions failed to undergo the aromatic acylation reaction and only the corresponding esters where detected in the reaction mixture. However, 4-chlorocinnamic acid **21** was successively converted to its acid chloride and reacted with resorcinol to give chalcone **26** in 44% yield. Chalcone **26** was thereafter subjected to the cyclisation conditions to give flavanone **29** in 93% yield.

It is instructive to draw attention to the fact that the aromatic acylation reaction is dependent on the position and nature of the substituent on the cinnamic acid. While C-4 attached substituents that either withdraw or donate electrons by resonance (-OMe and $-NO_2$) shut down the aromatic acylation reaction, a C-4 attached substituent that withdraws electrons by inductive effect (-Cl) allows the reaction to proceed. The logical explanation for the similar effect of 4-OMe and 4-NO_2 groups is that $BF_3.OEt_2$ coordinates with the oxygen atom of the methoxy group and turns it into an electron withdrawing group. The effect is less pronounced for 3-OMe and 3-NO_2 substituted cinnamic acid substrates because of lack of conjugation between the substituents and the acid carbonyl group.

EXPERIMENTAL

Laboratory grade chemicals and solvents were procured from Sigma-Aldrich and used without any further purification. Reactions were monitored by TLC, which was carried out on 0.25 mm layer of Merck silica gel 60 F_{254} pre-coated on aluminium sheets. Melting points measurements were determined on a Stuart melting point apparatus SMP1 (UK) and are uncorrected. Infra-red spectra were recorded neat on a Perkins Elmer FT-IR spectrophotometer. Mass spectra were recorded on a GCT Premier spectrometer (Waters) and an ionization energy of 70 eV. NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer using standard pulse sequences and referenced to residual solvent signals.

Typical Procedure For The Synthesis Of Chalcone Intermediates

Cinnamic acid **1** (1.48 g, 10 mmol) was suspended in $SOCl_2$ (2 ml) and refluxed for 2 hours and monitored by TLC. Excess $SOCl_2$ was then removed under pressure and to the remaining residue was added resorcinol (1.0 g, 9 mmol) and $BF_3.OEt_2$ (2.0 ml). The mixture was refluxed for 4 hours, and then quenched with water (25 ml) and extracted three times with ethyl acetate (25 ml x 2). The organic layers were combined and dried under pressure. The residue was subjected to column chromatography eluting with petroleum ether:ethyl acetate (8:2) to give chalcone **3** in 72% yield and coumarin **4** in 4%.

2',4'-dihydroxychalcone (**3**): yellow solid, 72% yield, mp 156-158 °C; IR (neat) ν: 3248, 1610, 1552, 1587 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): δ 7.46-7.49 (3H, *m*, H-3,4,5), 7.84-7.88 (2H, *m*, H-2,6), 6.43 (1H, *d*, 2.5 Hz, H- 3'), 6.52 (1H, *dd*, 8.5, 2.5 Hz, H- 5'),

8.18 (1H, *d*, 8.5 Hz, H- 6'), 7.90 (1H, *d*, 15.6 Hz, H-α), 7.96 (1H, *d*, 15.6 Hz, H-β). ^{13}C NMR (75 MHz, acetone-d_6): δ 135.0 (C-1), 128.7 (C-2 and 6), 128.9 (C-3 and 5), 130.5 (C-4), 113.6 (C-1'), 165.9 (C-2'), 103.9 (C-3'), 167.7 (C-4'), 108.0 (C-5'), 132.7 (C-6'), 192.0 (C=O), 120.8 (C-α), 143.9 (C-β). HRMS-ES (m/z) calcd for [$C_{15}H_{12}O_3$ + H]: 241.0865; found, 241.0872.

Typical Procedure For The Synthesis Of Flavanones

Chalcone **3** (0.24 g, 1.0 mmol) was dissolved in a solution of KOH (0.24 g, 1.0 mmol) in methanol (25 ml) and the mixture was stirred at room temperature. The reaction mixture was then acidified with HCl (2 M) and then extracted three times with ethyl acetate. The organic extracts were combined and concentrated under pressure to give flavanone **5** in 95% yield.

7-hydroxyflavanone (**5**): yellow solid, 95% yield, mp 180-182 °C; IR (neat) ν: 3675, 2988, 2905, 1656, 1601, 1552 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6): δ 5.58 (1H, *dd*, 12.8, 3.0 Hz, H-2), 2.77 (1H, *dd*, 16.7, 3.0 Hz, H-3$_{eq}$), 3.05 (1H, *dd*, 16.7, 12.8 Hz, H-3$_{ax}$), 7.77 (1H, *d*, 8.7 Hz, H-5), 6.62 (1H, *dd*, 8.7, 2.3 Hz, H-6), 6.49 (1H, *d*, 2.3 Hz, H-8), 7.65 (1H, *m*, H-2', 6'), 7.40-7.50 (3H, *m*, H-3', 4', 5'). ^{13}C NMR (75 MHz, acetone-d_6): δ 79.7 (C-2), 43.9 (C-3), 189.3 (C-4), 128.7 (C-5), 110.5 (C-6), 163.5 (C-7), 102.9 (C-8), 164.4 (C-9), 114.4 (C-10), 139.6 (C-1', 6'), 126.3 (C-2', 5'), 128.5 (C-3'), 128.3 (C-4'). HRMS-ES (m/z) calcd for [$C_{15}H_{12}O_3$ + H]: 241.0865, found, 241.0862

The following chalcones and flavanones that were prepared are known compounds and were characterised on the basis of data that matched literature data: Chalcones **3**[25], **6**[26], **10**[27], **12**[28], **19**[29], **21**[30] and **23**[31]; Flavanones **5**[32], **8**[33], **11**[34,35], **13**[36], and **25**[37].

CONCLUSION

In conclusion, a convenient straightforward and efficient synthesis of flavanones starting from cinnamic acid in three steps has been developed. The first two steps were performed without solvents and without purification of intermediates. In the final step base-catalysed cyclisation of the 2'-hydroxychalcones at room temperature afforded the flavanones in consistent yields of over 85%. The aromatic acylation reaction was found to be highly sensitive to the type and position of the substituents on both phenol and cinnamic acid.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed from the publisher's website.

ACKNOWLEDGEMENTS

Kibrom G. Bedane gratefully acknowledges German Academic Exchange Service (DAAD) for a doctorial scholarship through NAPRECA. We thank Mr S. M. Marape (University of Botswana) for NMR experiments.

REFERENCES

[1] Cioffi, G.; Morales, Escobar, L.; Braca, A.; De Tommasi, N. *J. Nat. Prod*. **2003**, *66*, 1061-1064.

[2] Heo, H. J.; Kim, D. O.; Shin, S. C.; Kim, M. J.; Kim, B. G.; Shin, D. H. *J. Agric. Food Chem*. **2004**, *53*, 1520-1525.

[3] Sharma, M.; Akhtar, N.; Sambhav, K.; Shete, G.; Bansal, A. K.; Sharma, S. S. *Curr. Top. Med. Chem*. **2015**, *15*, 187-195

[4] Di Majo, D.; Giammanco, M.; La Guardia, M.; Tripoli, E.; Giammanco, S.; Finnoti, E. *Food Res. Int*. **2005**, *38*, 1161-1166.

[5] Fareza, M. S.; Syah, Y. M.; Mujahidin, D.; Juliawaty, L. D.; Kurniasih, I. *Z. Naturforsch C*. **2014**, *69*, 375-380.

[6] Wachter, G. A.; Hoffmann, J. J.; Furbacher, T.; Blake, M. E.; Timmermann, B. N. *Phytochemistry*, **1999**, *52*, 1469-1471.

[7] Iinuma, M.; Tsuchiya, H.; Sato, M.; Yokoyama, J.; Ohyama, M.; Ohkawa, Y.; Tanaka, T.; Fujiwara, S.; Fujii, T. *J. Pharm. Pharmacol*. *1994*, *46*, 892-895.

[8] Paredes, A.; Alzuru, M.; Mendez, J.; Rodríguez-Ortega, M. *Biol. Pharm. Bull.* **2003**, 26, 108-9.

[9] Njamen, D.; Mbafor, J. T.; Fomum, Z. T.; Kamanyi, A.; Mbanya, J. C.; Recio, M. C.; Giner, R. M.; Máñez, S.; Ríos, J. L. *Planta Med*. **2004**, *70*, 104-107.

[10] Domínguez-Villegas, V.; Domínguez-Villegas, V.; García, M. L.; Calpena, A.; Clares-Naveros, B.; Garduño-Ramírez, M. L. *Nat. Prod. Commun*. **2013**, *8*, 177-180.

[11] Oh, J. S.; Kim, H.; Vijayakumar, A.; Kwon, O.; Choi, Y. J. Huh, K. B.; Chang, N. *Nutr. Res. Pract*. **2016**, *10*, 67-73.

[12] Chanet, A.; Milenkovic, D.; Manach, C.; Mazur, A.; Morand, C. *J. Agric. Food Chem.* **2012**, *60*, 8809–8822.

[13] Bedane, K. G.; Kusari, S.; Eckelmann, D.; Masesane, I. B.; Spiteller, M.; Majinda, R. R. T. *Fitoterapia* **2015**, *105*, 113–118.

[14] Bedane, K. G.; Kusari, S.; Masesane, I. B.; Spiteller, M.; Majinda, R. R. T. *Fitoterapia* **2016**, *108*, 48–54.

[15] Deodhar, M.; Wood, K.; Black, D. S.; Kumar, N. *Tetrahedron Lett.* **2012**, *53*, 6697–6700.

[16] Sirin, O. Z.; Demirkol, O.; Akbaslar, D.; Giray, E. S. *J. of Supercritical Fluids* **2013**, *81* 217– 220.

[17] Bhaskar, N.; Reddy, M. K. *J. Chem. Pharm. Res*. **2011**, *3*, 759-765.

[18] Zhou, Y.; Huang, W.; Song, Z.; Tao, D. *Catal. Lett.* **2015**, *145*, 1830–1836.

[19] Rostamizadeh, S.; Zekri, N.; Tahershamsi, L. *Chemistry of Heterocyclic Compounds* **2015**, *51*, 526–530.

[20] Rajesh, U. C.; Sunny Manohar, S.; Rawat, D. S. *Adv. Synth. Catal.* **2013**, *355*, 3170 – 3178.

[21] Huang, W.-H.; Chien, P.-Y.; Yang, C.-H.; Lee, A.-R. *Chem. Pharm. Bull.* **2003**, *51*, 339–340.

[22] Li, Z.-Y.; Cao, X.; Wang, X.; Guo, Q.-L.; You, Q.-D. *Org. Prep. Proced. Int.* **2009**, *41*, 327–330.

[23] Kim, S.; Sohn, D. W.; Kim, Y. C.; Kim, S. A.; Lee, S. K.; Kim, H. S. *Arch Pharm Res* **2007**, *30* (1), 18–21.

[24] Vatkar, B. S.; Pratapwar, A. S.; Tapas, A. R.; Butle, S. R.; Tiwari, B. *Int. J. ChemTech Res.* **2010**, *2*, 504–508.

[25] Passalacqua, T. G.; Torres, F. A. E.; Nogueira, C. T.; de Almeida, L.; Del Cistia, M. L.; dos Santos, M. B.; Regasini, L. O.; Graminha, M. A. S.; Reinaldo Marchetto, R.; Zottis, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3564–3568.

[26] Das, S.; Mitra, I.; Batuta, S.; Alam, M. N.; Roy, K.; Begum, N. A. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5050–5054.

[27] Tiecco, M.; Germani, R.; Cardellini, F. *RSC Adv*. **2016**, *6*, 43740–43747.

[28] Kakade, K. P.; Kakade, S. P.; Deshmukh, S. Y. *World Journal of Pharmacy and Pharmaceutical Sciences*, **2015**, *4*, 1591-1597.

[29] Naveenkumarb, R. K. A.; Madhavaraoa, V. *World Journal of Pharmaceutical Research* **2014**, *3*, 380-388.

[30] Murti, Y.; Ashish Goswami, A.; Mishra, P. *International Journal of Pharm. Tech. Research* **2013**, *5*, 811-818.

[31] Narsinghani, T.; Sharma, M. C.; Bhargav, S. *Med. Chem. Res*. **2013**, *22*, 4059–4068.

[32] Kshatriya, R. B.; Nazeruddin, G. M. *Orient. J. Chem*. **2014**, *30*, 857-862.

[33] Yenjai, C.; Wanich, S.; Pitchuanchom, S.; Sripanidkulchai, B. *Arch. Pharm. Res.* **2009**, *32*, 1179-1184.

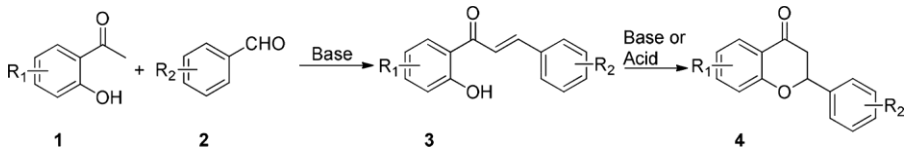
[34] Patil, S. S.; Sonawane, M. V.; Chaudhari, S. B.; Sonawane, J. P. *World Journal of Pharmaceutical Research* **2015**, *4*, 909-914.

[35] Kulkarni, P.; Wagh, P.; Zubaidha, P. *Chemistry Journal* **2012**, *2*, 106-110.

[36] Bovicelli, P.; Bernini, R.; Antonioletti, A.; Mincione, E. *Tetrahedron Lett*. **2002**, *43*, 5563-5567.

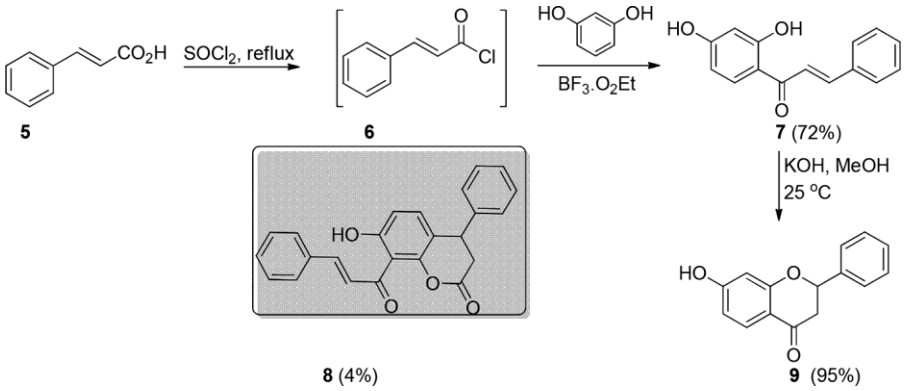
[37] Vatkar, B. S.; Pratapwar, A. S.; Tapas, A. R.; Butle, S. R.; Tiwari, B. *International Journal of Chem. Tech. Research* **2010**, *2*, 504-508.

Scheme 1.



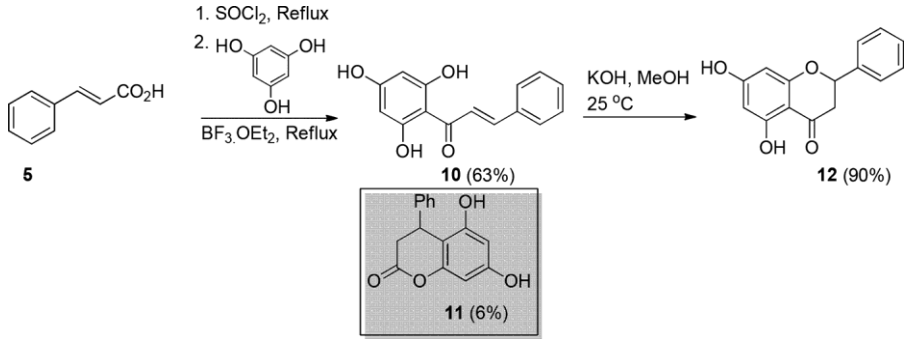
1 2 3 4

Scheme 2.

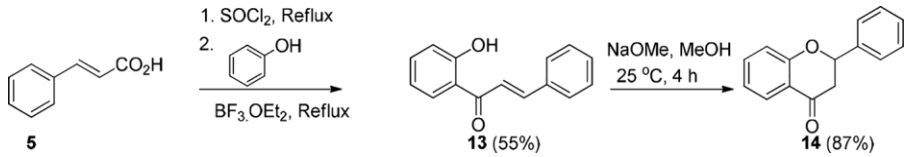


5 **6** **7** (72%) **8** (4%) **9** (95%)

Scheme 3.

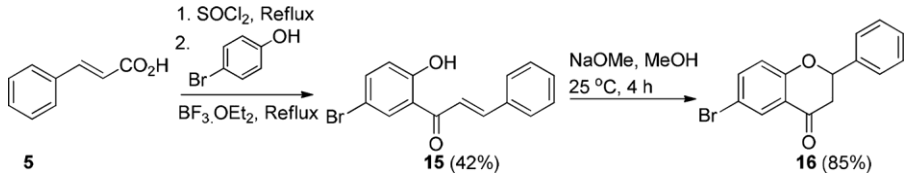


Scheme 4.



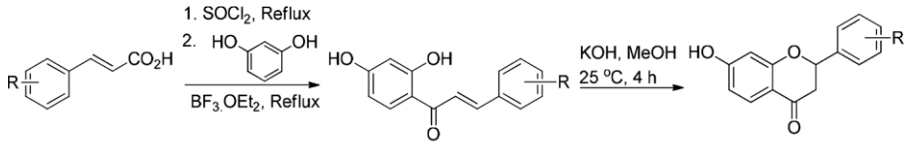
5 **13** (55%) **14** (87%)

Scheme 5.



5 **15** (42%) **16** (85%)

Scheme 6.



17 (R = 3-OMe)
18 (R = 4-OMe)
19 (R = 3-NO_2)
20 (R = 4-NO_2)
21 (R = 4-Cl)

22 (75%)
23 (0%))
24 (66%)
25 (0%)
26 (44%)

27 (92%)

28 (90%)

29 (93%)