Chapter 7
Comparative Review of the Synthesis of Flavanones *via* the Reaction of Cinnamic Acids and Phenols and the Reaction of 2-Hydroxyacetophenones and Benzaldehydes

Ishmael B. Masesane, Kenamile Rabasimane, and Kibrom G. Bedane

Abstract This review compares the efficiency of a three-step procedure developed by the authors for the synthesis of flavanones that relied on the boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$)-mediated reaction of cinnamic acid and phenols to the one-step or two-step procedures reported in literature involving the reaction of 2-hydroxyacetophenones and benzaldehydes. The three-step procedure was found to give the flavanones in comparable yields to both the one-step and the two-step literature methods.

7.1 Introduction

The isolation and characterization of flavonoids from medicinal and economically relevant plants has been the main focus of research in the Department of Chemistry, University of Botswana since the 1980s. These research endeavors have contributed several novel flavonoid structures and promising biological activities of these isolated compounds [1]. It however became evident that the limited quantities of compounds that are isolated from plants made it difficult to develop them further into useful chemicals.

In an effort to subvert the quantity problem mentioned above, we develop a synthetic method for the preparation of flavanones from the reaction of cinnamic acids and phenols. Flavanones are a class of flavonoids that has attracted our interest because of their presence in the genus *Erythrina*. The genus *Erythrina* has been at the centre of our phytochemical work for over a decade [2–4]. In this review, our cinnamic acid method for the synthesis of flavanones will be compared

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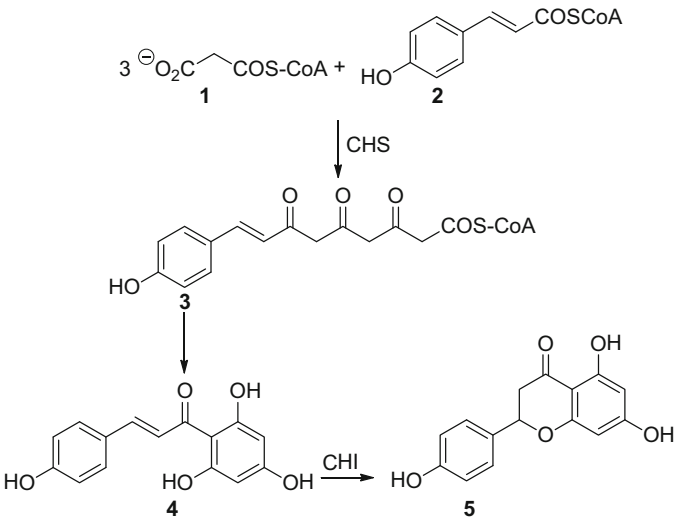


Scheme 7.1 Biosynthesis of flavanones

to the conventional methods that rely on the reaction of 2-hydroxyacetophenones and benzaldehydes.

At this juncture, it is instructive to draw attention to the fact that our cinnamic acid route for the synthesis of flavanones was inspired by the biosynthetic pathway. Flavanones biosynthesis involves the chalcone synthase(CHS)-catalyzed condensation of three molecules of malonyl-CoA **1** and one molecule of p-coumaroyl-CoA **2** to give the polyketide intermediate **3** that cyclizes and aromatizes to afford chalcone **4**. The chalcone is then cyclized to the corresponding flavanone **5** in a reaction catalyzed by the enzyme chalcone isomerase (CHI), as shown in Scheme 7.1 [5].

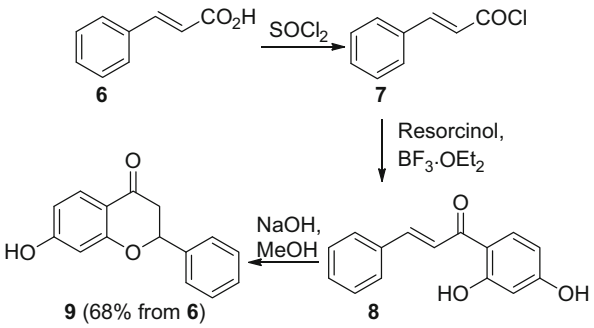
Section 7.2 of this chapter will discuss the authors' procedure for the synthesis of flavanones *via* the reaction of cinnamic acid derivatives with phenols. Section 7.3 will review the literature methods for the synthesis of flavanones *via* the reaction of 2-hydroxyacetophenone derivatives with benzaldehydes and compare the efficiency of these methods to the authors' procedure.

7.2 Preparation of Flavanones *via* the Reaction of Cinnamic Acids and Phenols

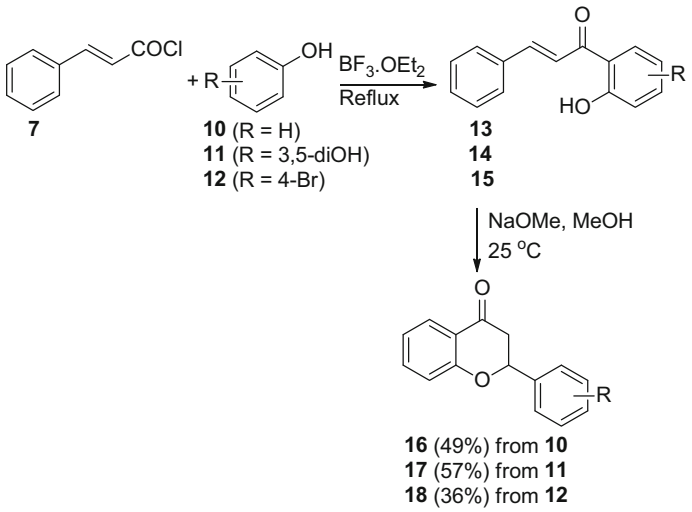
The preparation of flavanones that involves $BF_3{\cdot}OEt_2$-mediated reaction of cinnamoyl chlorides and phenols was recently reported by our group [6]. The procedure involved conversion of cinnamic acids into the corresponding cinnamoyl chlorides using thionyl chloride, reaction of the cinnamoyl chlorides with phenols

in the presence of $BF_3{\cdot}OEt_2$ to give chalcones and finally cyclisation of chalcones in the presence of a base to give the flavanones. For example, the reaction of cinnamic acid **6** with thionyl choride ($SOCl_2$) gave cinnamoyl chloride **7** which was not isolated. Excess $SOCl_2$ was removed under vacuum and cinnamoyl chloride **7** was reacted with resorcinol in the presence of $BF_3{\cdot}OEt_2$ under reflux to give chalcone **8** in 72% yield (Scheme 7.2). Cyclisation of chalcone **8** in the presence of NaOH gave flavanone **9** in overall yield of 68% [6].

Further reactions involving cinnamoyl chloride **7** and phenols **10**, **11** and **12** in the presence of $BF_3{\cdot}OEt_2$ followed by cyclisation using NaOMe instead of KOH gave flavanones **16**, **17** and **18** in 49, 57 and 36% yields respectively (Scheme 7.3) [6]. It is important to note that 4-nitrophenol and 3-nitrophenol failed to react with cinnamoyl chloride **7** to give the corresponding chalcones. The nitro group is a strongly electron-withdrawing group that deactivates the aromatic ring against



Scheme 7.2 Synthesis of flavanone **9** from cinnamic acid **6**

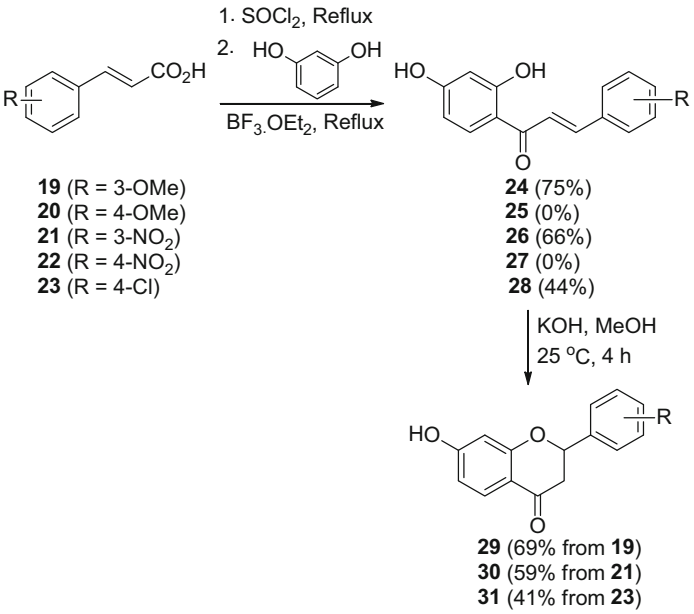


Scheme 7.3 Synthesis of flavanones **16**–**18**

electrophilic substitution reactions, therefore these results were not surprising. However, bromophenol **12**, a phenol with a less electron-withdrawing bromo group, reacted with acid chloride **7** to give chalcone intermediate **15** in lower yield of 42%. Cyclisation of chalcone **15** afforded flavanone **18** in 36% overall yield.

The effects of both electron donating and withdrawing groups attached to the cinnamic acid on the efficiency of the reaction were also investigated. Thus, 3-methoxycinnamic acid **19** was converted to its acid chloride using $SOCl_2$, reacted with resorcinol to give chalcone **24** in 75% yield and then cyclized using KOH to give flavanone **29** in 92% yield (Scheme 7.4) [6]. Interestingly, subjection of 4-methoxycinnamic acid **20** to the same reaction conditions failed to give the corresponding chalcone **25**. Similarly, 3-nitrocinnamic acid **21** was converted to chalcone **26** in 66% yield and chalcone **26** was subsequently cyclized in the presence of KOH to afford flavanone **30** in 90% yield. However, attempts to convert 4-nitrocinnamic acid **22** to the corresponding chalcone **27** under the same reaction conditions failed. 4-Chlorocinnamic acid **23**, on the other hand was successively converted to its acid chloride and reacted with resorcinol in the presence of $BF_3{\cdot}OEt_2$ to give chalcone **28** in lower yield of 44%. Cyclisation of chalcone **28** afforded flavanone **31** in 93% yield.

The logical explanation for the similar effect of 4-OMe and 4-NO_2 groups is that $BF_3{\cdot}OEt_2$ 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



Scheme 7.4 Synthesis of flavanones **29**–**31**

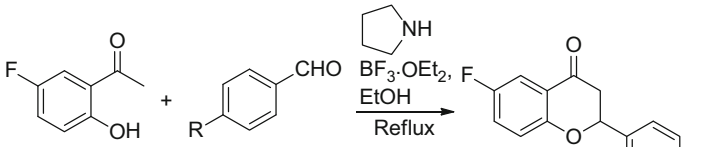
3-NO_2 substituted cinnamic acid substrates because of lack of conjugation between the substituents and the acid carbonyl group.

To the best of the knowledge of the authors, this is the only method in the literature for the synthesis of flavanones from cinnamic acids. Flavanones were prepared in three steps in overall yields of 36–69%.

7.3 Preparation of Flavanones *via* the Reaction of 2-Hydroxyacetophenones and Benzaldehydes

Unlike the preparation of flavanones from the reaction of cinnamic acids and phenols described above, the synthesis of flavanones through the reaction of 2-hydroxyacetophenones and benzaldehydes has been reported extensively in the literature. The synthesis of flavanones through this route can be achieved either by a one-step process or a two-step procedure. Zhou and co-workers achieved the one-step synthesis of flavanones **37**–**40** in 54–68% yields from acetophenone **32** and benzaldehydes **33**–**36** in the presence of catalytic amount of pyrrolidine and $BF_3{\cdot}OEt_2$ (Scheme 7.5) [7]. The benzaldehydes **34**, **35** and **36** with electron-withdrawing groups afforded the corresponding flavanones in lower yields when compared to the benzaldehyde **33**. This procedure afforded flavanones with electron-withdrawing groups on ring B in better yields that the authors' procedure described in Sect. 7.2.

A one-step Julia-Kocienski olefination reaction was used by Kumar and co-workers in the synthesis of an array of flavanones. The reaction involved the refluxing of sulphone **41** with benzaldehydes **33**, **42**, **43** and **44** in the presence of the base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give flavanones **45**, **46**, **47** and **48** respectively in 40–68% yields (Scheme 7.6) [8]. Benzaldehyde **43** with an unprotected hydroxyl group gave the flavanone with the lowest yield. It is important to note that the authors' procedure discussed in Sect. 7.2 tolerated free hydroxyl groups and afforded the corresponding flavanones in better yields.

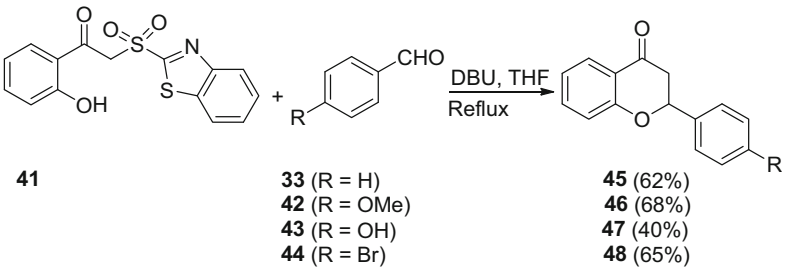


32

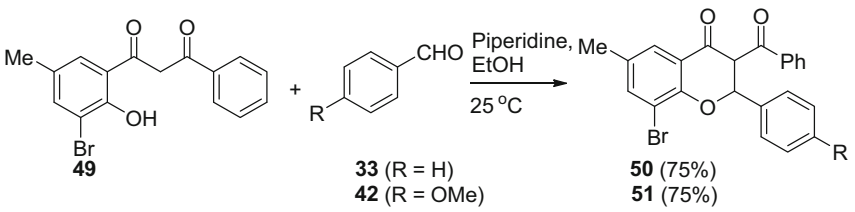
33 (R = H)
34 (R = NO_2)
35 (R = CO_2Me)
36 (R = CHO)

37 (68%)
38 (54%)
39 (60%)
40 (60%)

Scheme 7.5 One-step synthesis of flavanones **37**–**40** from **32**



Scheme 7.6 One-step synthesis of flavanones **45**–**48**



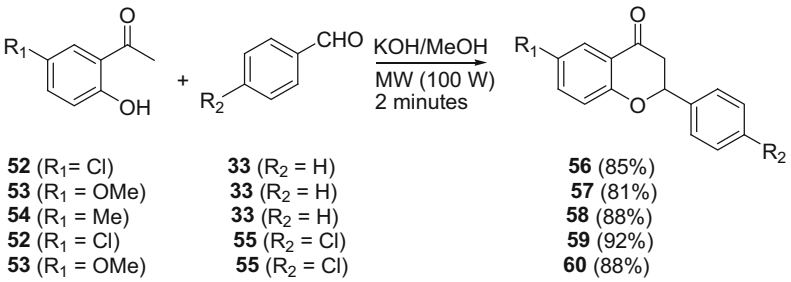
Scheme 7.7 One-step synthesis of flavanones **50** and **51**

In their one-step approach to flavanones **50** and **51**, Mahalle and Khaty relied on the reaction of diketone **49** with benzaldehydes **33** and **42** respectively in the presence of the base piperidine [9]. Thus, flavanones **50** and **51** were prepared in 75% yields by the condensation of diketone **49** with benzaldehydes **33** and **42** respectively in ethanol for two hours in the presence of catalytic amount of piperidine (Scheme 7.7). The products were purified by recrystallization and were afforded in slightly better yields than those achieved in the authors' procedure discussed in Sect. 7.2.

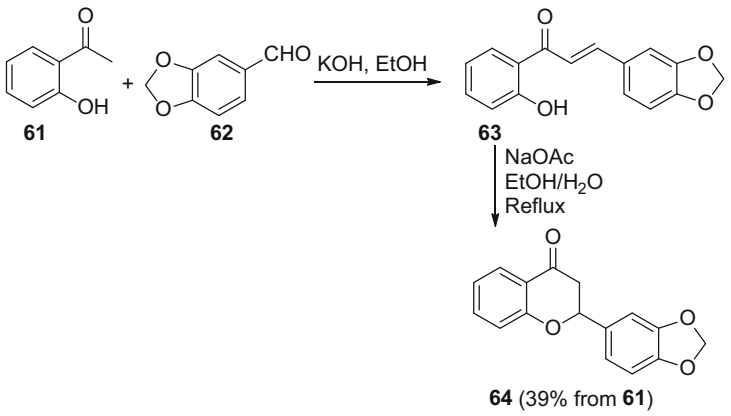
Albogami and co-workers have described the use of microwave irradiation in the one-step synthesis of flavanones. Their procedure involved reactions of acetophenones **52**–**54** with benzaldehyde **33** to give the corresponding flavanones **56**–**58** in 81–88% yield. Further reactions of 4-chlorobenzaldehyde **55** and acetophenones **52** and **53** afforded the corresponding flavanones **59** and **60** in 92 and 88% yield respectively (Scheme 7.8) [10]. This method showed an excellent tolerance of different functional groups on both the acetophenone and benzaldehyde reagents and gave yields of the flavanone that were considerably higher that those achieved by the authors' procedure discussed in Sect. 7.2.

It is important to note that the yields of the majority of the one step-procedures discussed above were not significantly different from those achieved in the authors' three-step procedure discussed in Sect. 7.2. The exceptions that gave significantly higher yields of the flavanones are the reactions catalyzed by an organic base and the one performed under microwave irradiation.

In addition to the one-step procedures discussed above, flavanones have been prepared *via* two-step procedures involving the reaction of 2-hydroxyacetophenones and benzaldehydes to give chalcones followed by cyclisation of the chalcones. The expedient synthesis of flavanone **64** for example



Scheme 7.8 Microwave mediated one-step synthesis of flavanones **56–60**

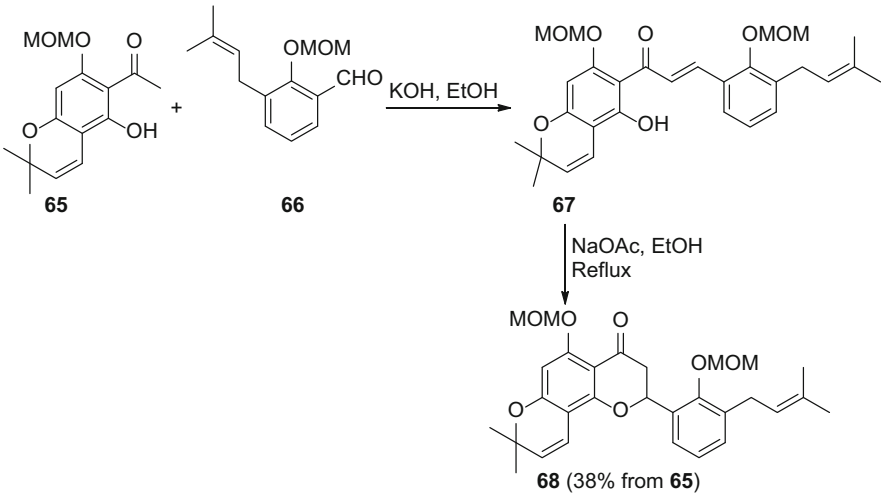


Scheme 7.9 Synthesis of flavanone **64** in two steps

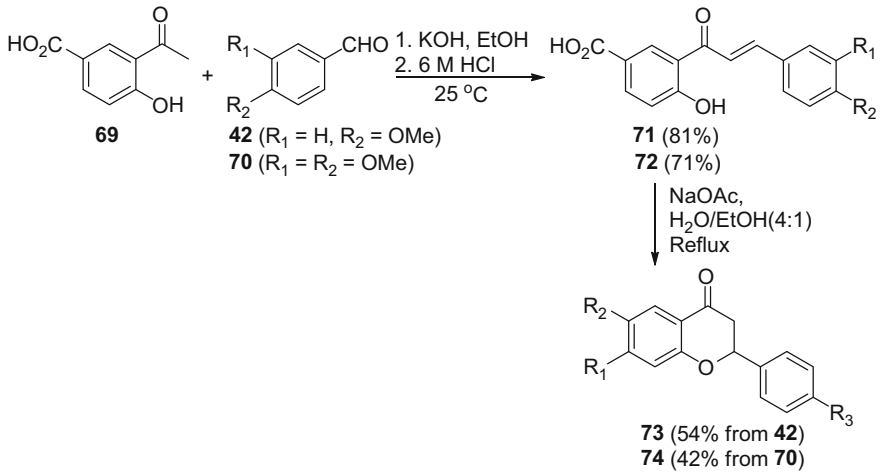
was achieved by the condensation of 2-hydroxyacetophenone **61** and benzaldehyde **62** in the presence of KOH in ethanol to give chalcone **63** that was subsequently cyclized in the presence of sodium acetate (NaOAc) under reflux, Scheme 7.9 [11]. The overall percentage yield of this reaction was 39% and was significantly lower than that of the authors' three-step procedure discussed in Sect. 7.2.

A similar two-step procedure was used by Rao and co-workers in the preparation of the protected derivative of a prenylated flavanone isolated from *Dalea boliviana*. Condensation of 2-hydroxyacetophenone **65** and benzaldehyde **66** in the presence of KOH gave chalcone **67** that was cyclized in the presence of NaOAc under reflux to give flavanone **68** in overall yield of 38% (Scheme 7.10) [12]. The prenyl units did not significantly affect the yield of the reaction when compared to the reaction summarized in Scheme 7.9.

A third approach to flavanones in two steps by Mardjan and co-workers involved condensation of 2-hydroxyacetophenone **69** with benzaldehydes **42** and **70** to give the corresponding chalcones **71** and **72** in 81 and 71% yield respectively. Cyclisation of chalcones **71** and **72** in the presence of NaOAc gave the corresponding flavanones **73** and **74** in overall yields of 54 and 42% respectively (Scheme 7.11) [13]. The presence of the acid group in the 2-acetophenone reagent



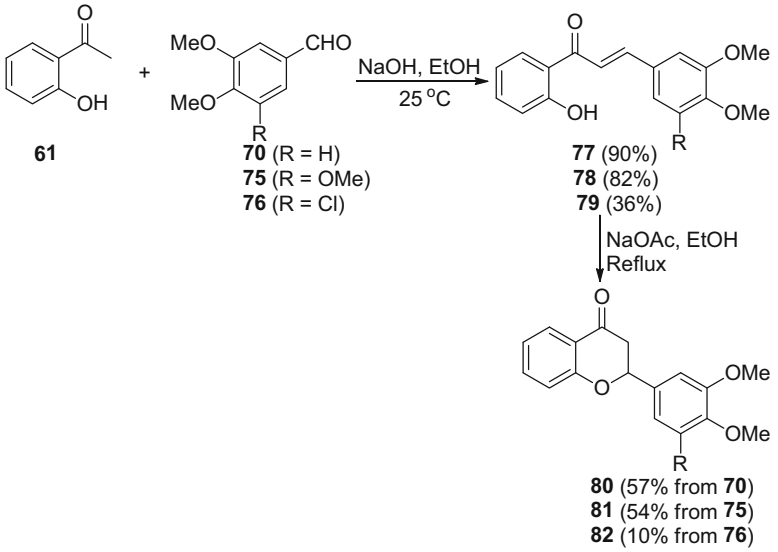
Scheme 7.10 Synthesis of flavanone **68** in two steps



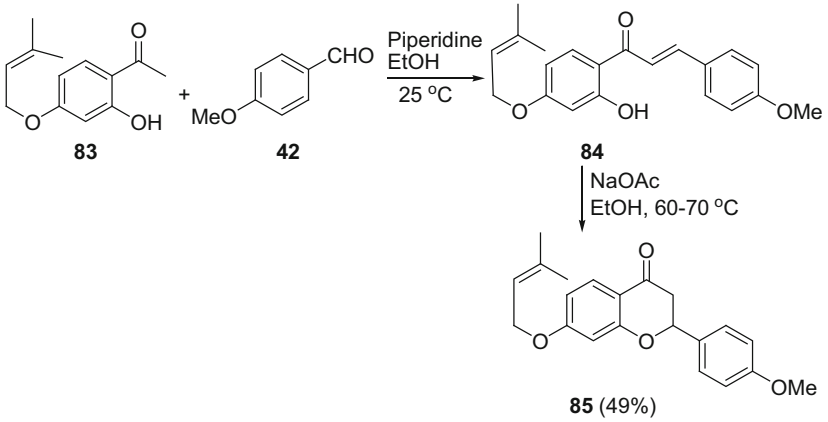
Scheme 7.11 Synthesis of flavanones **73** and **74** in two steps

is suspected to be responsible for the increase in the overall yield of this procedure. The overall yields are comparable to those achieved by the authors' procedure discussed in Sect. 7.2.

In another approach to the chalcone intermediate, Ketabforoosh and co-workers used NaOH instead of KOH as the base in the condensation of 2-hydroxyacetophenone and aldehydes as illustrated in Scheme 7.12. Reactions of 2-hydroxyacetophenone **61** and benzaldehydes **70**, **75** and **76** gave chalcone intermediates **77**, **78** and **79** respectively [14]. It is worth noting that the reaction



Scheme 7.12 Synthesis of flavanones **80**–**82** in two steps



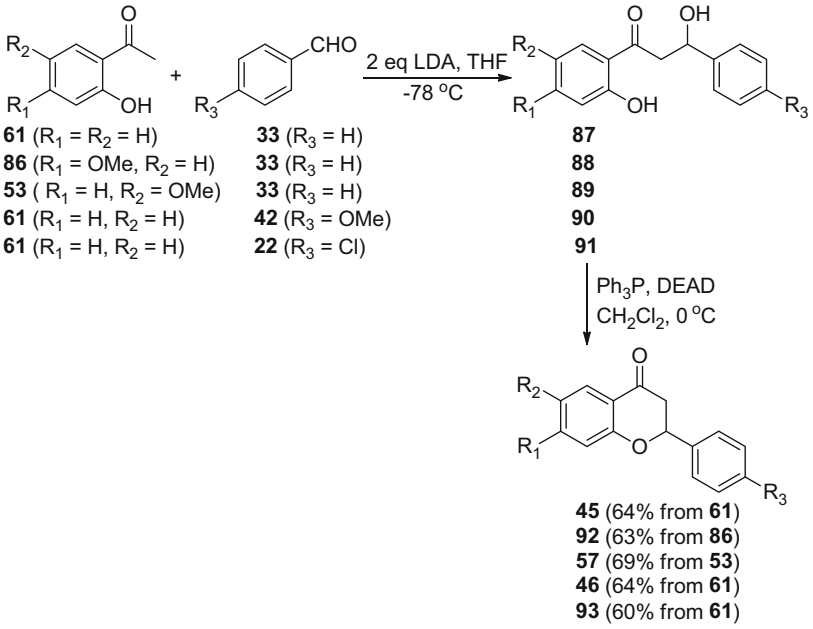
Scheme 7.13 Synthesis of flavanone **85** in two steps

that involved the chloro-substituted benzaldehyde **76** gave the corresponding intermediate **79** in a very poor yield of 36%. Subsequent cyclisation of the chalcone intermediates **77**–**79** afforded the corresponding flavanones **80**–**82** in overall yields of 57, 54 and 10% respectively.

Bhasker and co-workers have reported the piperidine-mediated condensation of 2-hydroxyacetophenone **83** and benzaldehyde **42** in the synthesis of chalcone intermediate **84** that was subsequently cyclized in the presence of NaOAc to give flavanone **85** in overall yield of 49% (Scheme 7.13) [15].

An interesting two-step procedure was reported by Lee and co-workers and it involved the lithium diisopropylamide (LDA)-mediated condensation of 2-hydroxyacetophenones **53**, **61** and **86** and benzaldehydes **22**, **33** and **42** in THF to give an array of 3-hydroxyketone intermediates that were subsequently cyclized to give flavanones [16]. The condensation of benzaldehyde **33** and 2-hydroxyacetophenones **53**, **61** and **86** under these conditions afforded the corresponding 3-hydroxyketone intermediates **89**, **87** and **88** respectively. Cyclisation of intermediates **87**, **88** and **89** by treating them with triphenylphosphine/diethyl azodicarboxylate (Ph_3P/DEAD) in CH_2Cl_2 at 0 °C afforded the corresponding flavanones **45**, **92** and **57** in overall yields of 63–69%, as shown in Scheme 7.14. In a parallel sequence of reactions, 2-hydroxyacetophenone **61** underwent condensation reactions with benzaldehydes **22** and **42** to give the corresponding hydroxyketone intermediates that were cyclised to afford flavanones **93** and **46** respectively.

In general, the two-step procedures involving the reaction of 2-hydroxyacetophenones or its derivatives and benzaldehydes afforded the flavanones in comparable yields to those achieved in the authors' three-step procedure for the synthesis of flavanones from cinnamic acids described in Sect. 7.2.



Scheme 7.14 Synthesis of flavanones **45**, **46**, **57**, **92** and **93**

7.4 Conclusion

A comparative review of the synthesis of flavanones via the reaction of cinnamic acids and phenols and via the reaction of 2-hydroxyacetophenones and benzaldehydes was achieved. Both methods afforded the flavanones in yields that were not in general significantly different. The two methods are highly complementary. Flavanones that are not accessed through one method are easily prepared using the other procedure.

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