Reactions of salicylaldehyde and enolates or their equivalents: versatile synthetic routes to chromane derivatives

Ishmael B. Masesane* and Zelalem Yibralign Desta

Abstract

The reported methodologies for the synthesis of chromane derivatives through the reaction of salicylaldehyde and enolates are discussed. The enolates and their equivalents involved in the reactions discussed in this article were derived from ketones, nitroalkanes, malononitrile and α,β-unsaturated compounds.

Introduction

The chromane skeleton is found in a myriad of medicinally important compounds that have a broad range of biological activities [1-7]. Consequently, the synthesis of chromane derivatives has attracted the attention of synthetic chemists over the years [1-17]. Among the reported methodologies for the synthesis of chromane derivatives, the reaction of salicylaldehyde and enolates or their equivalents has gained a prominent position. The key features of the synthesis of chromane derivatives by the reaction of salicylaldehyde and enolates are summarized retrosynthetically in Scheme 1.

This review will summarize the reported methods for the syntheses of chromane derivatives from the reaction of salicylaldehyde and enolates or their equivalents. For the purposes of this review, chromane derivatives will include flavans, flavones, chromenes and chromones. The synthetic methods in the literature will be compared and contrasted in terms of their generality, selectivity and percentage yields.

Review

Chromane derivatives from the reaction of salicylaldehyde with enolates derived from ketones

The reaction of salicylaldehyde (5) and enolates derived from acetophenone (7) has been employed by a number of chemists in the synthesis of flavans and flavones. Flavans are chromane derivatives with a C-2 phenyl substituent while flavones are chromane derivatives with a carbonyl functional group at C-4, a carbon–carbon double bond between C-2 and C-3, and a C-2

Keywords:
acetophenone; chromane; enolates; malononitrile; Michael addition; salicylaldehyde
Scheme 1: Retrosynthetic analysis of chromane 1.

Scheme 2: General reaction of salicylaldehyde (5) and acetophenone (7) in the synthesis of flavan 10 and flavone 11. Xue and co-workers have utilized the reaction of salicylaldehyde 12 and acetophenone 13 in the racemic synthesis of the naturally occurring flavan 16 (Scheme 3) [18]. To begin, a solution of 12 and 13 in CH$_3$OH was stirred in the presence of KOH at room temperature to give chalcone 14. To set the stage for the cyclisation reaction, the trans carbon–carbon double bond

Scheme 3: Synthesis of flavan 16 by Xue and co-workers.
must either be isomerized to the *cis* form or completely reduced. In this case, chalcone 14 was treated with H₂ in the presence of a catalytic amount of Pd to give intermediate 15 in 99% yield. It is instructive to draw attention to the fact that both the carbon–carbon and carbon–oxygen double bonds of 14 were reduced by H₂/Pd, a reagent usually used for the reduction of carbon–carbon double bonds. To complete the synthesis, Lewis acid mediated cyclization of intermediate 15 and acidic cleavage of the MOM protected hydroxy group delivered the desired flavan 16 in good yield.

On the basis of the above precedent by Xue and co-workers, our group accomplished the synthesis of an array of flavans of type 10 [19]. The synthesis begins with a Knoevenagel reaction of salicylaldehyde (5) and acetophenone derivatives 7 to give the corresponding chalcones of type 9 in 66–85% yields. Contrary to Xue’s reduction method where H₂/Pd was used, we used NaBH₄ in the reduction of both the carbon–carbon and carbon–oxygen double bonds of chalcone derivatives 9 to give the corresponding alcohols 17. It is noteworthy that the carbon–carbon double bond was also reduced by NaBH₄, a reagent usually used for the reduction of carbonyl groups. Cyclization was achieved by heating intermediates 17 under reflux in acetic acid to give the corresponding flavans of type 10 in 62–87% yields (Scheme 4).

Recently, Sashidhara and co-workers achieved the synthesis of flavone 11 relying on the reaction of salicylaldehyde (5) and an enolate derived from acetophenone (7, Scheme 5) [20]. To begin, chalcone 9 was prepared in 85% yield by the Knoevenagel reaction of salicylaldehyde (5) and acetophenone (7) in the presence of KOH (aq) in ethanol as reported by Mazimba and co-workers. Chalcone 9 was then oxidatively cyclized in the presence of iodine and in a solvent-free environment to give flavone (11) in 72% yield. Methyl-, methoxy- and chloro-substituted acetophenones were also well tolerated in the reaction to give the corresponding flavones in comparable yields.

It is conceivable that enolates derived from other ketones instead of acetophenone could be reacted with salicylaldehyde to give chromane derivatives. To this end, Yu Ling and co-workers reported the efficient synthesis of chromane deriva-

---

**Scheme 4:** Synthesis of flavans of type 10 by Mazimba and co-workers.

**Scheme 5:** Sashidhara and co-workers synthesis of flavone (11).
tive 19 through the reaction of salicylaldehyde (5) with dimes-done (18) in the presence of a catalytic amount of KF/Al₂O₃ (Scheme 6) [21]. The reaction is thought to proceed through a Knoevenagel condensation, a Michael addition and an intramolecular cyclization. The reaction was repeated with chloro-, bromo-, dichloro-, dibromo-, methyl- and nitro-substituted salicylaldehydes. The nitro- and 3,5-dibromo-substituted salicylaldehydes reacted with 18 to give the lowest yields of 60–70% while the other substituted salicylaldehydes reacted to give corresponding chromane derivatives in yields comparable to those achieved when 5 was used.

Further studies by Costa and co-workers revealed that the reaction of salicylaldehyde (5) with 2 equivalents of malonitrile (20) in the presence of NaHCO₃ afforded 2-aminochromone 22 in 91% yield (Scheme 8) [22]. This product is thought to be the result of a Michael addition of the extra malononitrile to product 21.

In addition to inorganic bases such as Na₂CO₃ and NaHCO₃, the use of amines in catalytic and quantitative amounts in the synthesis of chromane derivatives by the reaction of salicylaldehyde (5) and malononitrile (20) has been reported. Costa and co-workers used Et₃N in the reaction of salicylaldehyde and 2 equivalents of malononitrile (20) in CH₃OH to afford 2-aminochromone 24 in 94% yield (Scheme 9) [22].
In 2009, Shanthi and co-workers reported the use of the amino acid L-proline as a catalyst in a three component reaction of salicylaldehyde, malononitrile and indole for the synthesis of 2-aminochromene 27 in 90% yield (Scheme 10) [23]. The synthesis proceeds through a cascade reaction of salicylaldehyde (5) and malononitrile (20) involving an aldol reaction followed by intramolecular cyclization and finally a dehydration to give intermediate 21. A subsequent Michael addition of the indole (25) to intermediate 21 gives cation 26, which loses a proton to give the product 27. Although Shanti and co-workers used a chiral catalyst, no data was provided on the stereoselectivity of this reaction.

In a study related to that of Shanti and co-workers, Yang and co-workers used chiral amine-thiourea catalyst 31 in a three-component enantioselective reaction of salicylaldehyde (5), acetonitrile (28) and nitromethane (30) to give 2-aminochromene 32 in 88% yield and 84% enantiomeric excess (Scheme 11) [24]. The reaction was found to be equally efficient when malononitrile (20) and cyanoacetate 29 were used instead of 28. The reaction is thought to proceed through a cascade reaction between salicylaldehyde (5) and acetonitrile (28) involving an aldol reaction, cyclization and dehydration. A subsequent Michael addition of nitromethane (30) to the product of the cascade reaction gave the desired product 32.

Kovalenko and co-workers used a quantitative amount of piperidine in the reaction of malononitrile derivative 35 as an enolate equivalent and salicylaldehydes 5 to give 2-iminochromenes 36 in good yields [25]. No Michael addition
product was observed. 2-hydroxy-5-methoxybenzaldehyde (5a) gave product 36a in a higher yield of 81% compared to salicylaldehyde (5), which gave the corresponding product 36 in 71% yield (Scheme 12).

In another approach, Ghorbani-Vaghei and co-workers used a \(N,N,N',N'\)-tetrabromobenzene-1,3-disulfonamide (TBBDA) mediated Knoevenagel reaction of salicylaldehyde (5) and two equivalents of malononitrile (20) or its derivative 29 to give the corresponding 2-aminochromene derivatives 22 and 37 in 92 and 82% yields respectively (Scheme 13) [26]. It is instructive to note that TBBDA is a versatile reagent in organic synthesis and has been reported to be efficient in oxidation of primary and secondary alcohols [27], in bromination of aromatic compounds [28], as catalytic reagents for silylation of alcohols, phenols, and thiols using hexamethyldisilazane [29], in conversion of urazoles to triazolinediones [30], and in oxidation of 1,3,5-trisubstituted pyrazolines [31].

Molecular sieves have been used as solid-phase catalysts in the preparation of 2-aminochromenes from salicylaldehyde derivatives and cyanoorganic compounds. Yu and co-workers reported the one-pot synthesis of 2-aminochromene 39 in 86% yield from the reaction of bromosalicylaldehyde 38 and cyanoacetate 29 in the presence of 3 Å molecular sieves (Scheme 14) [32]. Various derivatives of 39 were prepared in good yields by employing nitro-, methoxy-, and chloro-substituted salicylaldehydes instead of 38. Other solid catalysts such as 4 Å molecular sieves, 5 Å molecular sieves and \(\text{Al}_2\text{O}_3\) were found to be effective in catalyzing the reaction but resulted in lower yields (50–63%) of product 39 [32].

Heravi and co-workers, on the other hand, used a mesoporous molecular sieves (MCM-41)-catalyzed Knoevenagel reaction of salicylaldehyde (5) and malononitrile (20) to give 2-iminochromene 21 in 94% yield (Scheme 15) [33]. The generality of Haravi’s method was demonstrated by the reactions of 3-hydroxy-, 4-hydroxy-, 5-hydroxy-, 4-methoxy- and 5-bromosalicylaldehyde with malononitrile (20) to give the
corresponding 2-iminochromene derivatives in yields of at least 90%. MCM-41 can be reused for up to five cycles with an insignificant drop in percentage yields (80%).

At this juncture, it is instructive to draw attention to the fact that the yields of the molecular-sieve-catalyzed reactions of salicylaldehydes and enolate equivalents derived from malononitrile and its derivatives are comparable to those of reactions mediated by inorganic bases such as Na₂CO₃ (Scheme 7) and NaHCO₃ (Scheme 8). However molecular sieves have the advantage that they are recyclable.

**Chromane derivatives from the reaction of salicylaldehyde and enolates derived from α,β-unsaturated compounds**

The tandem reaction of salicylaldehyde and α,β-unsaturated compounds has proved to be a reliable route to chromane derivatives. In general, this reaction involves an oxo-Michael addition of salicylaldehyde (5) to α,β-unsaturated compounds of type 40 to give enolate intermediates of type 41. Enolate intermediates 41 then undergo an intramolecular Knoevenagel condensation to give chromane derivatives 42 (Scheme 16).

Kawase and co-workers reported the K₂CO₃-mediated tandem reaction of salicylaldehyde derivatives of type 43 and α,β-unsaturated ester 44 in the synthesis of 2,2-dimethylchromene 45 in moderate yields (Scheme 17) [34]. The dehydration reaction in this case was accompanied by decarboxylation. The best yields were achieved when methoxy-, methyl-, chloro-, bromo- and phenyl-substituted salicylaldehydes were used as reagents. The nitro-, hydroxy-, ethoxy- and acetyl-substituted salicylaldehydes on the other hand gave poor yields or no products at all. Related reactions involving a K₂CO₃-mediated tandem reaction of salicylaldehyde with acrolein and alkenes with two electron withdrawing groups to give the corresponding chromane derivatives have been reported [35-37]. The percentage yields of the chromane derivatives in these reports were comparable to those reported by Kawase and co-workers.

In addition to K₂CO₃, tertiary-amine-mediated tandem reactions of salicylaldehyde and α,β-unsaturated compounds to give chromane derivatives have been reported. Stukan and co-workers, for example, used an Et₃N-mediated reaction of salicylaldehyde (5) and nitropropene 46 in the synthesis of 2,3-disubstituted chromene 47 in a low yield of 28% (Scheme 18) [38]. Slightly better yields (33–40%) were achieved when 5-bromo-, 5-chloro- and 3,5-dichloro-substituted salicylaldehydes were employed in the reaction.

Ravichandran utilized a classical 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed Baylis–Hillman reaction of salicylaldehyde (5) and α,β-unsaturated compounds 48–51 in the syn-
thesis of the corresponding chromenes 52–55 (Scheme 19) [39]. These reactions were performed in water as the solvent and the chromenes were isolated in yields of 71–79%. It is instructive to note that the Baylis–Hillman products were not detected or isolated in this work.

Scheme 19: Ravichandran’s synthesis of 3-substituted chromenes 52–55.

The mechanism of the DABCO-catalyzed reaction of salicylaldehyde and α,β-unsaturated compounds in the synthesis 3-substituted chromenes was proved to proceed through the Baylis–Hillman reaction by Kaye and co-workers [40,41]. Their work involved the reaction of salicylaldehyde (5) with tert-butyl acrylate (56) to give the Baylis–Hillman product 57, which was subsequently cyclized in the presence of acetic acid to give chromene 58 in a low yield of 24%, together with coumarin 59 in 40% yield (Scheme 20).

An asymmetric amine-catalyzed reaction of salicylaldehyde (5) and α,β-unsaturated aldehyde 60 in the synthesis of 2-phenylchromene (62) was reported by Govender and co-workers [42]. The asymmetric union of salicylaldehyde (5) and aldehyde 60 was brought about by dissolving these two substances in CH₂Cl₂ in the presence of catalytic amounts of TMS-protected prolinol derivative 61 (Scheme 21). Methoxysalicylaldehyde 5a reacted much faster than salicylaldehyde (5) with higher isolated yield of 2-phenylchromene 63 but at the expense of enantioselectivity. The best enantioselectivity (90% ee) was achieved when the aliphatic aldehyde 2-hexenal was used in the reaction instead of 60. However, the reaction suffered from very poor yields (15–21%). The reaction is thought to proceed through the condensation of aldehyde 60 and prolinol 61 to give a chiral iminium-ion intermediate. This intermediate then undergoes a domino reaction involving a Michael reaction with salicylaldehyde (5), followed by an intramolecular aldol reaction and final dehydration to give the desired chromene derivative.

Related work involving asymmetric reaction of salicylaldehyde derivatives and α,β-unsaturated carbonyl compounds in the syn-
thesis of 2-phenylchromenes was reported by Li and co-workers (Scheme 22) [43]. Their strategy involved the reaction of salicylaldehyde (5) and unsaturated aldehyde 60 in the presence of catalytic amounts of TES-protected prolinol 64 and benzoic acid. High yields (87%) and excellent enantioselectivity (88%) of 2-phenylchromene 62 were achieved when the reaction was performed in 1,2-dichloroethane as the solvent. The presence of the benzoic acid additive is thought to be responsible for the increase in the enantioselectivity and higher yields of this reaction when compared to that of Govender and co-workers. It is also instructive to note that the catalyst loading for Li and co-workers was three times higher than that for Govender and co-workers.

Conclusion
This paper has demonstrated the versatility of the reactions of salicylaldehyde with enolates or their equivalents in the synthesis of chromane derivatives. These reactions can be run under quite mild conditions and are ideal for the synthesis of chromane derivatives due to their operational simplicity. The development of enantioselective reactions of salicylaldehyde and enolates to give nearly optically pure chromane derivatives is a memorable highlight of this review. Future work will undoubtedly focus on transformation of the products of the discussed reactions of salicylaldehyde with enolates to biologically active compounds and natural products.

Acknowledgements
We thank DAAD-NAPRECA for the scholarship (ZYD), the University of Botswana and the Royal Society of Chemistry for financial support.

References
1. Chang, S.; Grubbs, R. H. J. Org. Chem. 1998, 63, 864–866. doi:10.1021/jo9712198
2. Gowrisankar, S.; Lee, K.-Y.; Kim, J.-N. Bull. Korean Chem. Soc. 2007, 28, 624–628. doi:10.5012/bkcs.2007.28.4.624
3. Ibrahim, M. A.; Ali, T. E.; Alnemer, Y. A.; Gabr, Y. A. ARKIVOC 2010, (9), 98–135.
4. Khadem, S.; Marles, R. J. Molecules 2012, 17, 191–206. doi:10.3390/molecules17010191
5. Patil, R. B.; Sawant, S. D.; Thombare, P. A. Int. J. Pharm. Tech. Res. 2012, 4, 375–381.
6. Corradini, E.; Foglia, P.; Giancanti, P.; Gubbiotti, R.; Samperi, R.; Laganà, A. Nat. Prod. Res. 2011, 25, 489–495. doi:10.1080/14786419.2010.482054
7. Verma, A. K.; Pratap, R. Tetrahedron 2012, 68, 8523–8538. doi:10.1016/j.tet.2012.06.097
8. Cha, J.-H.; Cho, Y.-S.; Koh, H.-Y.; Lee, E.; Kim, Y.-T.; Yang, H.-H.; Kang, H.-Y. Bull. Korean Chem. Soc. 2004, 25, 1123–1124. doi:10.5012/bkcs.2004.25.8.1123
9. Lee, J.-I.; Son, H.-S.; Jung, M.-G. Bull. Korean Chem. Soc. 2005, 26, 1461–1463. doi:10.5012/bkcs.2005.26.9.1461
10. Miyazaki, H.; Honda, Y.; Honda, K.; Inoue, S. Tetrahedron Lett. 2000, 41, 2643–2647. doi:10.1016/S0040-4039(00)00236-7
11. Petasis, N. A.; Butkevich, A. J. Organomol. Chem. 2009, 694, 1747–1753. doi:10.1016/j.orgchem.2008.11.050
12. Rodriguez, I.; Iborra, S.; Rey, F.; Corma, A. Appl. Catal. A: Gen. 2000, 194–195, 241–252. doi:10.1016/S0926-860X(99)00371-3
13. Shi, Y.; Shi, M. Org. Biomol. Chem. 2007, 5, 1499–1504. doi:10.1039/b618984a
14. Wang, Q.; Finn, M. G. Org. Lett. 2000, 2, 4063–4065. doi:10.1021/ol006710r
15. Yadav, J. S.; Reddy, B. V. S.; Chandraiah, L.; Jagannadh, B.; Kumar, S. K.; Kunwar, A. C. Tetrahedron Lett. 2002, 43, 4527–4530. doi:10.1016/S0040-4039(02)00816-X
16. Yadav, J. S.; Reddy, B. V. S.; Parisse, C.; Carvalho, P.; Rao, T. P. Tetrahedron Lett. 2002, 43, 2999–3002. doi:10.1016/S0040-4039(02)00440-9
17. Yadav, J. S.; Reddy, B. V. S.; Aruna, M.; Venugopal, C.; Ramalingam, T.; Kumar, S. K.; Kunwar, A. C. J. Chem. Soc., Perkin Trans. 1 2002, 165–171. doi:10.1039/B109538M
18. Xue, J. J.; Zhang, X. S.; Liang, X. Z.; Li, Y. Chin. Chem. Lett. 2003, 14, 443–444.
19. Mazinova, O.; Masesane, I. B.; Majinda, R. R. Tetrahedron Lett. 2011, 52, 6716–6718. doi:10.1016/j.tetlet.2011.09.147
20. Sashidhara, K. V.; Kumar, M.; Kumar, A. Tetrahedron Lett. 2012, 53, 2355–2359. doi:10.1016/j.tetlet.2012.02.108
21. Li, Y.; Chen, H.; Zeng, Z.; Wang, X.; Shi, D.; Tu, S. Chin. J. Org. Chem. 2005, 25, 846–849.
22. Costa, M.; Areias, F.; Abrunhosa, L.; Venancio, A.; Proenca, F. J. Org. Chem. 2008, 73, 1954–1962. doi:10.1021/jo702552f
23. Shanthi, G.; Perumal, P. T.; Rao, U.; Sehgal, P. K. Indian J. Chem. 2009, 48B, 1319–1323.
24. Yang, G.; Luo, C.; Mu, X.; Wang, T.; Liu, X.-Y. Chem. Commun. 2012, 48, 5880–5882. doi:10.1039/c2cc30731f
25. Kovalenko, S. M.; Bylov, I. E.; Sychik, K. M.; Chernykh, V. P.; Bliskin, Y. V. Molecules 2005, 11, 1146–1165. doi:10.3390/51001146
26. Ghorbani-Vaghei, R.; Toghraili-Semironi, Z.; Karimi-Nami, R. J. Braz. Chem. Soc. 2011, 22, 905–909.
27. Ghorbani-Vaghei, R.; Veisi, H.; Amiri, M. J. Chin. Chem. Soc. 2007, 54, 1257–1260.
28. Ghorbani-Vaghei, R.; Jalili, H. Synthesis 2005, 1099–1102. doi:10.1055/s-2005-861851
29. Ghorbani-Vaghei, R.; Zolfegi, M.; Chegeny, M.; Veisi, H. Tetrahedron Lett. 2006, 47, 4505–4508. doi:10.1016/j.tetlet.2006.03.157
30. Zolfegi, M. A.; Ghorbani-Vaghei, R.; Mallakpour, S.; Chehardoli, G.; Choghamarani, A. G.; Yazdi, A. H. Synthesis 2006, 1631–1634. doi:10.1055/s-2006-926446
31. Ghorbani-Vaghei, R.; Azanifar, D.; Maleki, B. Bull. Korean Chem. Soc. 2004, 25, 953–954. doi:10.5012/bkcs.2004.25.7.953
32. Yu, N.; Aramini, J. M.; Germann, M. W.; Huang, Z. Tetrahedron Lett. 2000, 41, 6993–6996. doi:10.1016/S0040-4039(00)01195-3
33. Heravi, M. M.; Poormohammad, N.; Yahia, Sh.; Beheshtiba, Y. S.; Baghemejad, B.; Malakooti, R. Bull. Chem. Soc. Ethiop. 2010, 24, 273–276.
34. Kawase, Y.; Yamaguchi, S.; Horita, H.; Taneko, J.; Kameyama, H. Bull. Chem. Soc. Jpn. 1982, 55, 1153–1155. doi:10.1246/bcsj.55.1153
35. Conli, C.; Desideri, N. Bioorg. Med. Chem. 2010, 18, 6480–6488. doi:10.1016/j.bmc.2010.06.103
36. Yamaguchi, S.; Saltoh, T.; Kamiyama, M.; Enomoto, H.; Kawase, Y. J. Heterocycl. Chem. 1992, 29, 755–758. doi:10.1002/jhet.570290412
37. Sharma, K. K.; Krupadanam, G. L. D. Synth. Commun. 2002, 32, 1557–1562. doi:10.1081/SCC-120004416
38. Stukan, E. V.; Makarenko, S. V.; Berestovitskaya, V. M. Russ. J. Gen. Chem. 2011, 81, 155–157. doi:10.1134/S1070363211010294
39. Ravichandran, S. Synth. Commun. 2001, 31, 1233–1235. doi:10.1081/SCC-100104009
40. Kaye, P. T.; Musa, M. A.; Xolani, W.; Nocanda, X. N.; Robinson, R. S. Org. Biomol. Chem. 2003, 1, 1133–1138. doi:10.1039/b300360d
41. Musa, M. A. Applications of the Baylis-Hillman reaction in the synthesis of coumarin derivatives. Ph.D. Thesis, Rhodes University, 2002. http://eprints.ru.ac.za/2319/
42. Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. Tetrahedron: Asymmetry 2006, 17, 1763–1767. doi:10.1016/j.tetasy.2006.06.028
43. Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. Chem. Commun. 2007, 507–509. doi:10.1039/b611502k