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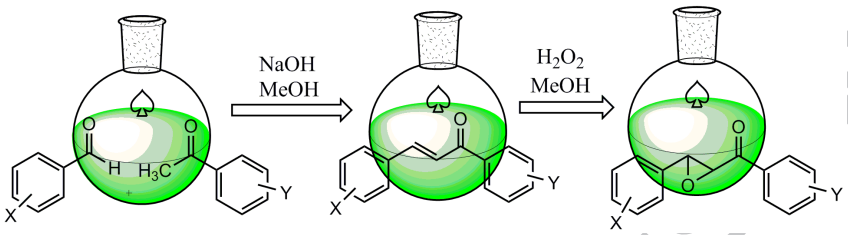

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One-pot synthesis of chalcone epoxides – A green chemistry strategy

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ABSTRACT

Waste minimization is a very important aspect of an environmentally benign protocol. A one-pot consecutive process has been developed for chalcone epoxide synthesis that allows compounds to be prepared without having to isolate and purify the intermediates. The strategy utilizes consecutive Claisen Schmidt condensation and epoxidation reactions to prepare chalcone epoxides from substituted benzaldehydes and acetophenones in good yields.

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At an era of new development and technology, a shift in emphasis towards more environmental friendly chemical approaches has become of great importance. Green chemistry, also widely-known as sustainable chemistry, is the "design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances".[1] This form of environmentally safe chemistry can be applied across the life cycle of different chemical products ranging from research, industry, manufacture, and design.[2] Recent literature shows that green chemistry has the significant potential for not only reducing byproducts, waste pollutants, and energy costs, but also the potential to develop new methodologies towards previously unobtainable chemical products.[3]

One-pot syntheses have been previously introduced as a green chemistry approach.[4] This simple, yet efficient method allows compounds to be prepared without having to isolate and purify the intermediates thereby reducing waste and increasing reaction efficiency. Reacting three or more components in a single operation can avoid the use of large amounts of solvents and expensive purification techniques. There are two forms of one-pot syntheses. In a one-pot multicomponent process, desired reactants are added into one reactor in a single step whereas a one-pot consecutive process occurs when the reactants are added in a series of different stages under different experimental conditions.[5] In this paper, we introduce a simple and efficient one-pot synthesis for chalcone epoxides (Figure 1).

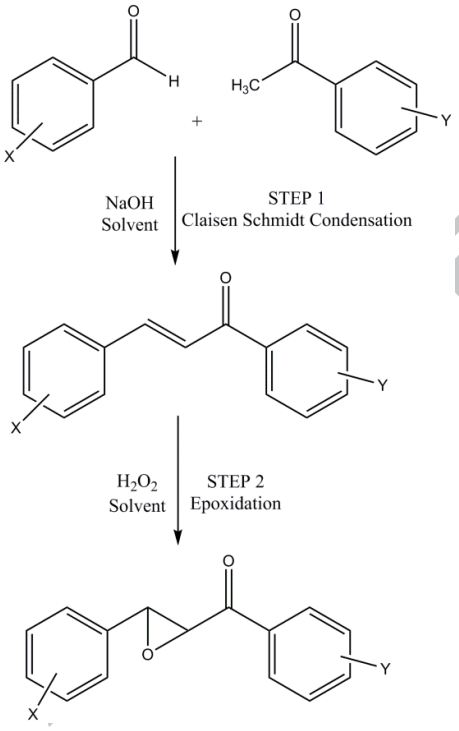


Figure 1: Synthetic design for the one-pot synthesis of chalcone epoxides.

Chalcone epoxides (α,β-epoxyketones) are an important class of organic compounds and used as constituents in perfume formulations, and as intermediates in the production of flavoring substances.[6] They have distinct structural features and high synthetic utility as they not only undergo the usual reactions of epoxides, but are also susceptible to several useful reactions owing to the presence of carbonyl groups.[7] Epoxidation has been widely studied using various reagents, catalysts and reaction conditions.[8] Taking into account green chemistry principles, aqueous hydrogen peroxide is one of the oxidants of choice because of its ease of handling, high active oxygen content and the formation of water as the only byproduct.[9] Armed with this information, we investigated the application of one-pot consecutive reactions of Claisen Schmidt condensation and epoxidation to prepare chalcone epoxides.

Table 1: Reaction conditions and results for one-pot syntheses of chalcone epoxides

Entry	Solvent	NaOH/ molar eq.	H_2O_2/ molar eq.	Time/ h	Yield[b] %
1	Ethanol	1.5	1.5	3	19
2	Ethanol	1.5	2.5	3	43
3	Ethanol	1.5	3.0	3	43
4	Ethanol	1.5	2.5	5	45
5	Methanol	1.5	1.5	3	72
6	Methanol	1.5	2.5	3	86
7	Methanol	1.5	3.0	3	86
8	Methanol	1.5	2.5	5	87

[a] 4-chlorobenzaldehyde (5 mmol), acetophenone (5 mmol) and 30% aq. NaOH (7.5 mmol) at r.t. followed by 30% H_2O_2 at 0 °C. [b] Isolated yields.

The reaction conditions for one-pot synthesis was developed using 4-chlorobenzaldehyde and acetophenone (Figure 2). First 4-chlorobenzaldehyde and acetophenone were stirred at room tempearature in the presence of 1.5 molar equivelant of 30% aqueous NaOH in ethanol for 1.5 h to complete the step 1; Claisen Schmidt condensation. The formation of a solid product of chalcone was observed. To the reaction mixture, a solution of 30% H_2O_2 was then dropwise added at 0 °C and stirred another 1.5 h to complete the epoxidation step. After vacuume filtration, the solid product was recovered and analyzed using spectroscopic methods. The highest yield of 43% was obtained in ethanol when 2.5 molar equivelant of H_2O_2 was used (Table 1, entry 2). In addition, the synthesis was performed by increasing the molar equivelant of H_2O_2 and extending the overall reaction time from 3 to 5 hours by increasing the reaction time of each step in an hour (Table 1, entries 3 and 4). However, the reaction yield was not significantly changed with the change of these parameters. When the same reaction conditions were used to carry out the reaction in methanol, the percent yield of chalcone epoxide was increased up to 86% (Table 1, entry 6). It is possible that the greater solubility of intermediate chalcone in methanol over ethanol improves the overall reaction yield.[10] Again, increasing the molar equivalency of H_2O_2 or extending the overall reaction time in methanol did not significantly improve the yields (Table 1, entris 7 and 8). Having established the optimum conditions for the reaction (Table 1, entry 6), we then proceeded to investigate its generality and scope. A series of one-pot syntheses of various substituted benzaldehydes and substituted acetophenones were performed in methanol and these results are provided in Tables 2 and 3.

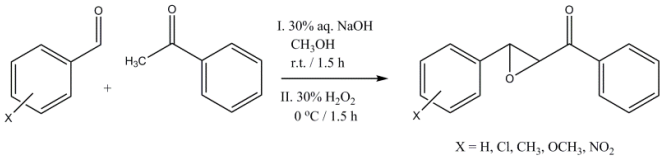
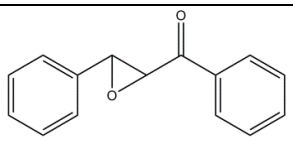
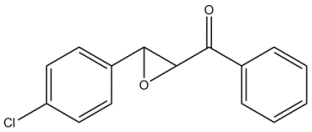
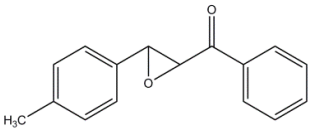
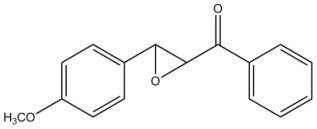
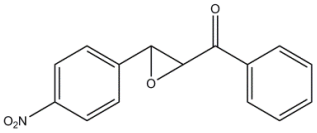
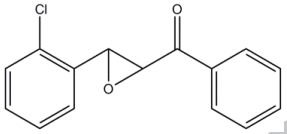
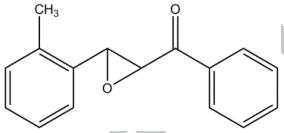
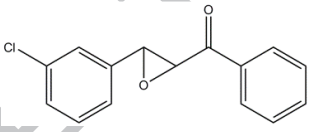
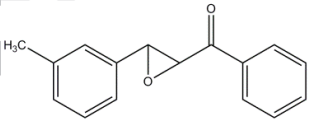


Figure 2: One-pot synthesis of substituted benzaldehydes with acetophenone.

Table 2: Results of the one-pot syntheses of chalcone epoxides from substituted benzaldehydes and acetophenone[a]

Entry	Substituted benzaldehyde	Chalcone epoxide	Yield[b] %
1	Benzaldehyde		84
2	4-chloro benzaldehyde		86
3	4-methyl benzaldehyde		61
4	4-methoxy benzaldehyde		43
5	4-nitro benzaldehyde		72
6	2-chloro benzaldehyde		85
7	2-methyl benzaldehyde		60
8	3-chloro benzaldehyde		64
9	3-methyl benzaldehyde		48

[a] Substituted benzaldehyde (5 mmol), acetophenone (5 mmol) and 30% aq. NaOH (7.5 mmol) at r.t. followed by 30% H_2O_2 (12.5 mmol) at 0 °C. [b] Isolated yields.

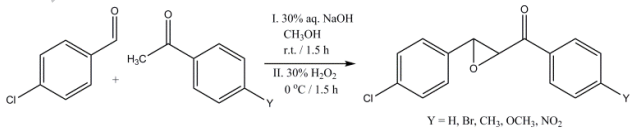
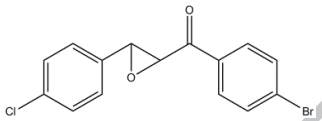
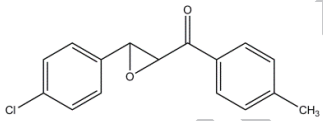
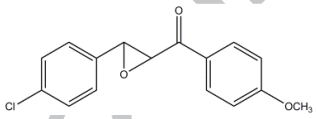
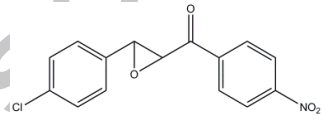


Figure 3: One-pot synthesis of substituted acetophenones with 4-chlorobenzaldehyde.

Table 3: Results of one-pot syntheses of chalcone epoxides from substituted acetophenones and 4-chlorobenzaldehyde[a]

Entry	Substituted acetophenone	Chalcone epoxide	Yield[b] %
1	4-bromo acetophenone		84
2	4-methyl acetophenone		74
3	4-methoxy acetophenone		68
4	4-nitro acetophenone		62

[a] 4-chlorobenzaldehyde (5 mmol), substituted acetophenone (5 mmol) and 30% aq. NaOH (7.5 mmol) at r.t. followed by 30% H_2O_2 (12.5 mmol) at 0 °C. [b] Isolated yields.

The one-pot syntheses of substituted benzaldehydes with acetophenone resulted the corresponding chalcone epoxides in moderate to good yields under these conditions (Table 2).[11,12] The electronic effect of the substituents on benzaldehyde showed slight influence on the reactions. The benzaldehyde derivatives with electron withdrawing groups gave higher yields when comparing to those with electron donating groups. While the yields of 4- and 2-substituted benzaldehydes were comparable, 3-substituted benzaldehydes showed somewhat lower yields (Table 2, entries 8 and 9). One-pot syntheses performed using substituted acetophenone with 4-chlorobenzaldehyde also afforded corresponding chalcone epoxides in good yields (Figure 3, Table 3).[11.13] 4-chlorobenzaldehyde was used in these reactions as it afforded the best yield with acetophenone (Table 2, entry 2). The electronic effect of the substituents on acetophenone showed no significant influence on these syntheses.

The synthesis was also completed via conventional two-step method using 4-chlorobenzaldehyde and acetophenone (5 molar equiv. of each). After completing the step 1 using 30% NaOH (3 molar equiv.) in methanol, intermediate chalcone was isolated in 92% yield. Epoxidation of chalcone in the second step using 30% NaOH (3 molar equiv.) and 30% H_2O_2 (5 molar equiv.) afforded the final epoxide in 90% yield. The overall yield of chalcone epoxide obtained from the two-step method was calculated to be 83%. When comparing with the conventional method, the developed one-pot synthesis eliminates the isolation time for the intermediate and reaction-set up time for the second step. In addition, one-pot synthesis uses less solvents and reagents which minimizes the waste formation. Methanol was used only once in this method and NaOH added in step 1 to initiate the Claisen Schmidt condensation, also activates the H_2O_2 used in step 2 for the epoxidation of intermediate chalcone (Figure 4).[14]

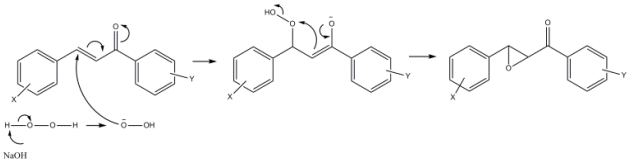


Figure 4: Mechanism for the epoxidation step

In conclusion, we have developed a one-pot greener synthesis for chalcone epoxides using consecutive reactions of Claisen Schmidt condensation and epoxidation with low concentration of hydrogen peroxide. The epoxides were synthesized from substituted benzaldehydes and acetophenones and obtained in good yields. The developed strategy allows chalcone epoxides to be prepared without having to isolate and purify chalcone intermediates. Selective ring opening of these chalcone epoxides in ionic liquids are currently being investigated in this laboratory.

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11. Representative procedure: A 30 wt% aq. NaOH solution (1 mL) was added to a mixture of substituted benzaldehyde (5 mmol), substituted acetophenone (5mmol) and methanol (10 mL), and stirred at room temperature for 1.5 h. The reaction mixture was heated to dissolve the solid and a 30% hydrogen peroxide solution (1 mL) was added. Then, the reaction was stirred between 0-2 ^{o}C for 1.5 h. The final chalcone epoxides were recovered by vacuum filtration.

12. All products exhibited spectral properties consistent with the assigned structures. ^{1}H, ^{13}C and IR data are as follows. Table 2, entry 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 6.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 2H), 7.38 (m, 5H), 4.27 (d, J = 2 Hz, 1H), 4.08 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 135.6, 134.1, 129.2, 129.0, 128.9, 128.5, 125.9, 61.1, 59.5; IR (ν/cm^{-1}) 3074, 1687, 1450, 1280. Entry 2: 7.98 (d, J = 7.6 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.24 (d, J = 2 Hz, 1H), 4.05 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 135.5, 135.0, 134.2, 134.1, 129.1, 129.0, 128.5, 127.2 , 61.0, 58.8; IR (ν/cm^{-1}) 3008, 1680, 1350, 1200. Entry 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 6.8 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.29 (d, J = 2 Hz, 1H), 4.05 (d, J = 2 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 139.2, 135.6, 134.1, 132.6, 129.6, 128.9, 128.4, 125.9, 61.2, 59.6, 21.4; IR (ν/cm^{-1}) 3050, 1655, 1400, 1350. Entry 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 4.29 (d, J = 2 Hz, 1H), 4.01 (d, J = 2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 160.4, 135.6, 134.0, 130.3, 128.9, 128.5, 127.3, 114.3, 61.2, 59.5, 55.5; IR (ν/cm^{-1}) 3065, 1690, 1420, 1280. Entry 5: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 7.6 Hz, 2H), 7.61 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.24 (d, J = 2 Hz, 1H), 4.04 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 148.4, 142.9, 135.3, 134.4, 129.1, 128.5, 126.7, 124.2, 60.9, 58.1; IR (ν/cm^{-1}) 3025, 1695, 1420, 695. Entry 6: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.3 Hz, 2H), 7.15-7.61 (m, 9H), 4.34 (d, J = 2 Hz, 1H), 4.11 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 134.9, 134.1, 133.9, 133.7, 129.8, 129.5, 128.9, 128.5, 126.2, 124.8, 60.1, 57.2; IR (ν/cm^{-1}) 3020, 1688, 1600, 1350. Entry 7: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 7.4 Hz, 2H), 7.74 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.3 Hz, 2H), 7.25-7.15 (m, 4H), 4.21 (d, J = 2 Hz, 1H), 4.02 (d, J = 2 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 139.5, 135.9, 135.7, 134.6, 129.9, 129.1, 128.9, 128.2 , 126.8, 123.5, 61.5, 59.2, 21.4; IR (ν/cm^{-1}) 3021, 1675, 1580,

950. Entry 8: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.1 Hz, 2H), 7.60 (t, J = 7.0 Hz, 1H), 7.47 (t, J = 7.4 Hz, 2H), 7.23-7.31 (m, 4H), 4.22 (d, J = 2 Hz, 1H), 4.02 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 137.9, 134.8, 134.6, 134.2, 130.5, 129.3, 129.0, 128.5, 125.8, 60.9, 58.6; IR (ν/cm^{-1}) 3010, 1669, 1200, 750. Entry 9: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.4 Hz, 2H), 7.77 (t, J = 7.2 Hz, 1H), 7.60 (t, J = 7.3 Hz, 2H), 7.27-7.16 (m, 4H), 4.28 (d, J = 2 Hz, 1H), 4.02 (d, J = 2 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 139.1, 135.9, 135.8, 134.1, 130.0, 129.0, 128.8, 128.4 , 126.4, 123.1, 61.1, 59.6, 21.5; IR (ν/cm^{-1}) 3009, 1688, 1230, 980.

13. All products exhibited spectral properties consistent with the assigned structures. ^{1}H, ^{13}C and IR data are as follows. Table 3, entry 1: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.8 Hz, 2H), 7.61 (d, J = 7.2 Hz, 2H), 7.54 (d, J = 7.2 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.16 (d, J = 1.6 Hz, 1H), 4.03 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 144.0, 136.8, 132.2, 129.9, 129.8, 129.6, 128.1, 127.1, 61.0, 58.9; IR (ν/cm^{-1}) 3024, 1690, 1420, 690. Entry 2: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 2H), 7.35 (d, J = 7.2 Hz, 2H), 7.30-7.25 (m, 4H), 4.22 (d, J = 2 Hz, 1H), 4.04 (d, J = 2 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 145.3, 134.2, 134.0, 133.1, 129.7, 129.5, 128.6, 127.2 , 60.9, 58.7, 21.9; IR (ν/cm^{-1}) 3015, 1685, 1215, 750. Entry 3: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.8 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 7.36 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 4.19 (d, J = 2 Hz, 1H), 4.04 (d, J = 2 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 164.4, 142.5, 136.2, 134.5, 130.9, 129.6, 129.2, 113.9 , 60.9, 58.5, 55.6; IR (ν/cm^{-1}) 3000, 1655, 1100, 695. Entry 4: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 7.2 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.34 (d, J = 7.2 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.23 (d, J = 2.0 Hz, 1H), 4.03 (d, J = 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8, 135.4, 135.1, 134.2, 134.1, 129.1, 129.0, 128.4, 127.2, 61.0, 58.8; IR (ν/cm^{-1}) 3024, 1690, 1420, 690.

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