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# Microwave synthesis of α-cyano chalcones

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ABSTRACT

A novel methodology for facile production of α-cyano chalcones under microwave irradiation is described. Utilizing a Knoevenagel condensation between benzoylacetonitriles and aromatic aldehydes, substituted chalcones are generated via a 15-min, one-pot synthesis. Diversification of aromatic groups, including electron-withdrawing, electron-donating, and heterocyclic substitutions, has led to the isolation of over twenty colored, solid chalcone products. Furthermore the methodology can be extended to the synthesis of benzylidenemalononitriles as well as methyl and ethyl α-cyano cinnamates.

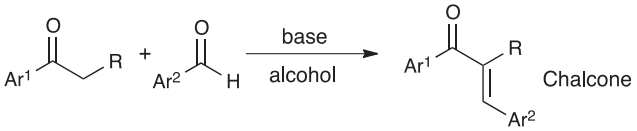


Chalcones, or 1,3-diarylpropenones, are common moieties in biologically active molecules, with considerable agricultural, pharmaceutical, and synthetic applications, as they compose essential building blocks of agrochemicals,[1] anticancer agents,[2] scavenging, and chelating agents,[3] and various medicinal agents, including antiinflammatories,[4] and PET scan imaging probes.[5] A common synthetic approach toward the synthesis of chalcones is via the Knoevenagel condensation[6] many of which utilize microwave techniques[7] (Scheme 1).

We were particularly interested in the synthesis of α-substituted cyano chalcones due to their ability to be further functionalized. Cyano-substituted chalcones have been utilized for nitrocyclopropanation reactions,[8] and for the synthesis of Krohnke pyridines,[9] quinolones, chromenes,[10] functionalized 2,3-dihidroixazoles,[11] and pyrazolo pyridines.[12] Upon surveying the literature a number of methodologies exist for the generation of phenyl-substituted chalcones, but few report the synthesis of α-substituted cyano chalcones. The examples that are reported have limited generality, and report low yields and/or require long reaction times. For example, Inokuma,[8] Lawrence,[2g] and Ryabukhim[13] report the synthesis of α-substituted cyano chalcones in high yield (75–96%) but reaction times of 24–48 h with conventional heating methods are needed to achieve these yields. Blum,[14] Gazit,[15] Kolosov,[12] report generating α-substituted cyano chalcones in shorter reaction times (15 min to 3 h) but with lower conversions (15–45%). Reports of protocols utilizing microwave techniques are limited in overall generality and scope.[7b,7c] We were most intrigued by Kolosov et al. conditions, which produced α-cyano chalcones in 15 min, albeit in a low yield (30–46%).

Herein we report a useful method for the synthesis of an array of α-substituted cyano chalcones utilizing a microwave reactor. The reaction is versatile on a range of substrates and requires minimal post-reaction purification. Furthermore we have confirmed the stereochemistry of the alkene in our chalcones and have extended our methodology to generate benzylidenemalononitriles as well as methyl and ethyl α-cyano cinnamates.

We began our study by examining the condensation of benzoyl acetonitrile (**1**) with *N*,*N*-dimethyl benzaldehyde (**2**) to form the desired amino α-substituted cyano chalcone (**3**) (Scheme 2). We started by modifying the protocol reported by Kolosov et al. that produced desired α-substituted chalcone **3** in a 30% yield, by utilizing a microwave reactor in place of the previously reported conventional heating method. Originally we began by treating benzoyl acetonitrile with 1.2 equiv of the aromatic aldehyde in 2-pentanol (1.66 M to the ketone), in the presence of 8 mol % of piperidine base catalyst. Initially we allowed the reaction to run for 15 min at 120 °C at which time an orange solid was observed. The product was washed with a mixture of hexanes and 2-pentanol and allowed to air dry producing chalcone **3** in an 88% yield as an orange crystal.




**Scheme 1.** Knoevenagel condensation towards chalcones.

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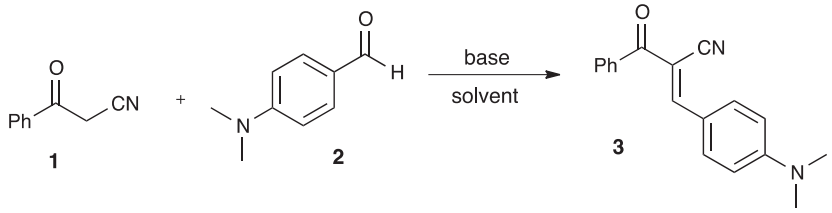
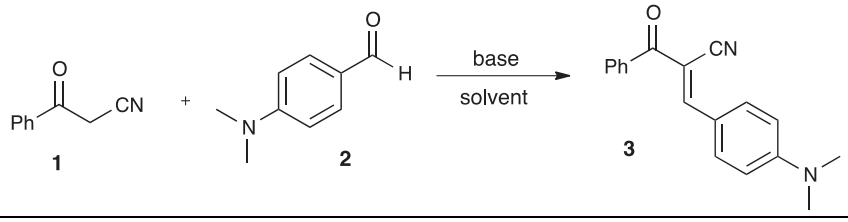


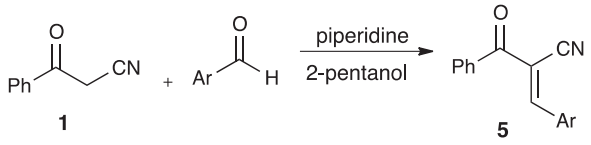

**Scheme 2.** Initial synthesis of α-cyano chalcone via Knoevenagel condensation.

**Table 1**
Optimization of reaction conditions




| Entry | Equiv of CHO | Base | Solvent | Time (m) | Wash solvent | Yield |
|---|---|---|---|---|---|---|
| 1 | 1.2 | Piperldine | 2-Pentanol | 1 | Hex/pentane | 73 |
| 2 | 1.2 | Piperidine | 2-Pentanol | 5 | Hex/pentane | 95 |
| 3 | 1.2 | Piperldine | 2-Pentanol | 10 | Hex/pentane | 95 |
| 4 | 1.2 | Piperldine | 2-Pentanol | 15 | Hex/pentane | 95 |
| 5 | 1.2 | NaOH | EtOH | 10 | Hex/pentane | 89 |
| 6 | 1.2 | NaOH | 2-Pentanol | 10 | Hex/pentane | 78 |
| 7 | 1.2 | Piperldine | EtOH | 10 | Hex/pentane | 93 |
| 8 | 1.1 | Piperldine | 2-Pentanol | 10 | Hexane | 97 |

**Table 2**
Diversification of chalcones via substituted aldehydes

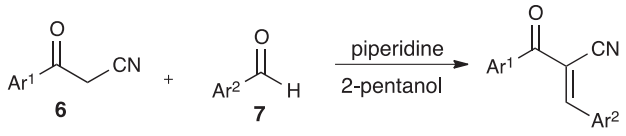


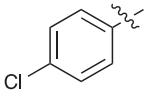
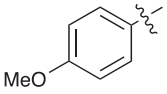
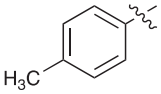
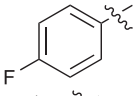
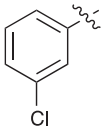

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **5a** | | 85% | **5b** | S | 90% | **5c** | Et | 91% |
| **5d** | N | 97% | **5e** | OMe | 95% | **5f** | OH | 86% |
| **5g** | Cl | 83% | **5h** | Br | 93% | **5i** | $NO_2$ | 85% |

Excited by the initial success of this reaction we began exploring an array of reaction conditions to further optimize this particular system. We examined a number of variables including reaction time (entries 1–4), reaction solvent, and bases (Table 1). Originally, we allowed the reaction to proceed for 15 min but later found the reaction to be complete after 10 min of microwave heating. Next, the solvent system for the reaction was examined (entries 5 and 7). Both EtOH and pentanol were examined with no significant observed differences when using either solvent in the actual reaction.[7] Both piperidine and NaOH were utilized as bases, with the piperidine being the preferred base.

After completion of the reaction the solid is isolated via vacuum filtration, washed with a minimal amount of a solvent and allowed to dry. Initially a mixture of hexanes and 2-pentanol or ethanol was utilized for washes.[16] In many of our original trials we noticed small amounts of residual aldehyde present in our purified product even after washing, so to alleviate this problem we decreased the amount of aldehyde we utilized in the reaction to 1.1 equiv (entry 8). After decreasing the amount of aldehyde, only a minimal amount of cold hexane was required to isolate the desired solid product in a 97% yield for reactions run with 2-pentanol. For this particular system the reaction gave the best

**Table 3**
Diversification of chalcones via substituted ketones and aldehydes




| Entry | $Ar_1$ | $Ar_2$ | Yield | |
|---|---|---|---|---|
| 1 |  | $-C_6H_4NMe_2$ | 93 | **8a** |
| 2 | | $-C_4H_3S$ | 87 | **8b** |
| 3 | | 4-$MeC_6H_4$ | 87 | **8c** |
| 4 | | 4-$ClC_6H_4$ | 88 | **8d** |
| 5 | | 4-$NO_2C_6H_4$ | 95 | **8e** |
| 6 |  | $-C_6H_4NMe_2$ | 95 | **8f** |
| 7 | | $-C_4H_3S$ | 80 | **8g** |
| 8 | | 4-$MeC_6H_4$ | 92 | **8h** |
| 9 | | 4-$ClC_6H_4$ | 86 | **8i** |
| 10 | | 4-$NO_2C_6H_4$ | 98 | **8j** |
| 11 |  | $-C_6H_4NMe_2$ | 92 | **8k** |
| 12 | | $-C_4H_3S$ | 81 | **8l** |
| 13 | | 4-$MeC_6H_4$ | 86 | **8m** |
| 14 | | 4-$ClC_6H_4$ | 82 | **8n** |
| 15 | | 4-$NO_2C_6H_4$ | 98 | **8o** |
| 16 |  | $-C_6H_4NMe_2$ | 98 | **8p** |
| 17 |  | $-C_6H_4NMe_2$ | 98 | **8q** |

results with piperidine and 2-pentanol for 10 min. Furthermore, we found the reaction scalable giving the product in the same high yield on a multitude of scales (mg to multi-gram).

After optimizing the initial reaction in detail we explored utilizing these conditions to form other α-cyano substituted chalcones by looking at the reaction of benzoyl acetonitrile with an array of substituted aldehydes (Table 2). All reactions in Table 2 were run on 1 mmol scale at 120 °C for 15 min in 2-pentanol. An extra 5 min of reaction time were added for some substrates, particularly with benzaldehyde and 4-hydroxy benzaldehyde, due to the presence of small amounts of unreacted ketone after 10 min of reaction time. A variety of substituted products generated a variety of colored chalcones in high yield with minimal purification.

We next looked to further expand the reaction to even more substituted chalcones by introducing substitution at the benzophenones and aldehydes (Table 3). We were pleased that the additional diversity could be expanded using our methodology with all products being isolated with the same simple purification method previously described. All chalcones generated were isolated as varying colored solids in high yield.

The Knovenagel reaction is known to primarily give the acyl and aryl group *trans* to one another but we wanted to confirm this under the current conditions. We were able to confirm the configuration of the double bond of the α-substituted cyano chalcones by conducting a number of HMBC experiments measuring carbon–proton couplings of the olefin to confirm its geometry. Figure 1 shows the result of one of these experiments. The $^1H$ δ/$^{13}C$ δ crosspeak at 8.03/116.7 (ppm) corresponds to H,CN coupling ($J$ = 14.0 Hz).This is consistent with the trans $^3J_{CH}$ couplings reported in the literature.[17] The $^3J_{CH}$ for a *cis* relationship is approximately 8.5. Furthermore the H,CO coupling at $^1H$ δ/$^{13}C$ δ crosspeak 8.03/187.1 (ppm) is $J$ = 6.3 Hz, which is consistent with the literature values predicted for this particular alkene geometry.[17] If this relationship was *trans* rather than *cis* we would expect $J$ values greater than 20. All these values are consistent with the coupling constants indicative of a *trans*-H,CN relationship, and *cis*-H,CO relationship. We conducted a HMBC experiment for each compound and all the coupling constants are included in the Supplementary data.

Finally, we explored the possibility of utilizing these reaction conditions to react cyanoacetates and malonitrile with various substituted aldehydes. We are happy to report that we can also utilize these species for the microwave assisted Knoevenagel condensation to produce an array of cyano-substituted alkenes, typically in a high yield (Table 4). This is a useful extension of this particular methodology to form an array of CN substituted alkenes beyond substituted chalcones.

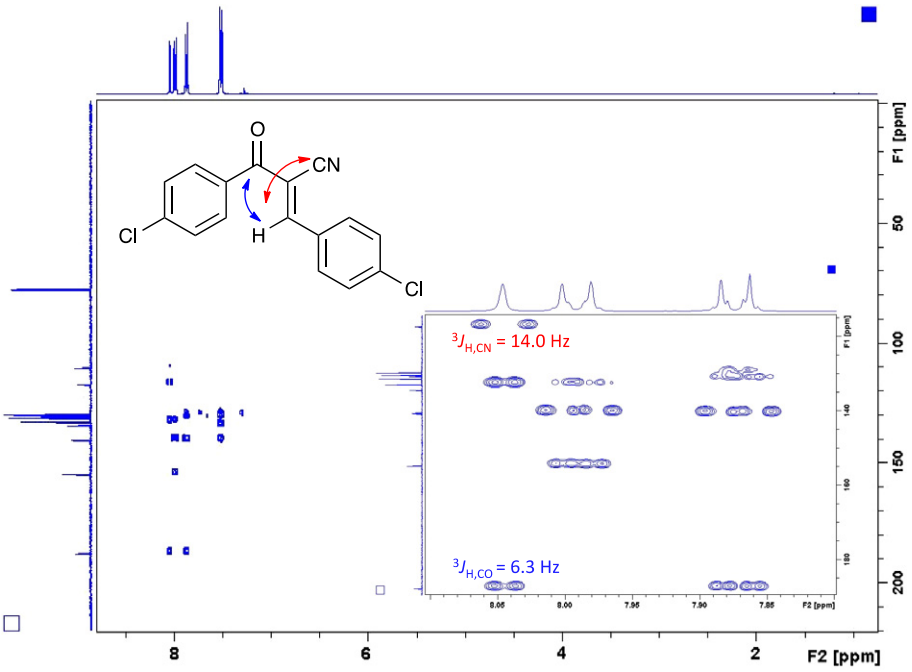
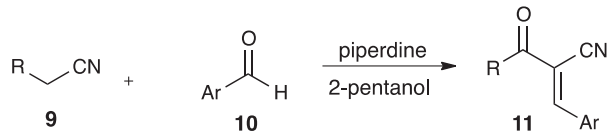



**Figure 1.** HMBC determination of stereochemistry: (E)-chalcone (**8d**).

**Table 4**
Application of cyanoacetates and malonitriles




| R | Ar | 75 | Yeild |
|---|---|---|---|
| $EtO_2C$ | $-C_6H_4NMe_2$ | 75 | **11a** |
| $EtO_2C$ | $-C_6H_4Cl$ | 82 | **11b** |
| $EtO_2C$ | $-C_4H_3S$ | 80 | **11c** |
| $MeO_2C$ | $-C_6H_4NMe_2$ | 84 | **11d** |
| $MeO_2C$ | $-C_6H_4Cl$ | 73 | **11e** |
| CN | $-C_6H_4NMe_2$ | 98 | **11f** |
| CN | $-C_6H_4Cl$ | 82 | **11g** |

## Conclusion

In conclusion we report a new method for the synthesis of substituted α-cyano chalcones and α-substituted acrylates. This method produces these products efficiently in short reaction times with high yields and needs minimal purification. We continue to study the utilization of these reaction conditions to explore other types of substituted chalcones.

## Acknowledgments

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## Supplementary data

Supplementary data (all experimentals, $^1H$, and $^{13}C$ NMR spectra of various compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.109.

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