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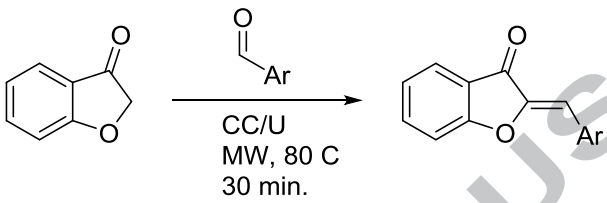

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# Rapid synthesis of aurones under mild conditions using a combination of microwaves and deep eutectic solvents

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ABSTRACT

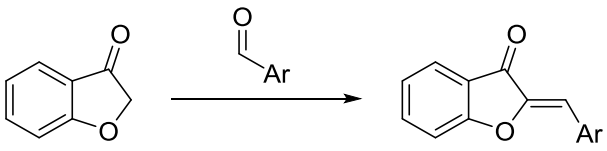
The combination of microwave heating and the deep eutectic solvent formed from choline chloride and urea has resulted in a new, essentially neutral, yet rapid method for the synthesis of a wide range of aurone derivatives. While isolated yields remain somewhat variable, in virtually every case, a significant increase in yield has been observed on going from conventional thermal heating to microwave heating. In addition, some compound inaccessible using prior methods have become reproducibly available using this modification. Further application of the combination of DES and microwave heating is expected to be highly promising and of general utility.



## 1. Introduction

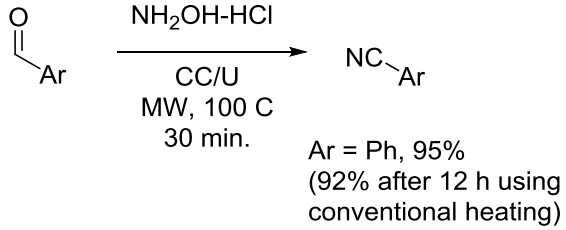
Aurones are an interesting sub-family of the flavonoids primarily found in plants that produce yellow flowers.[1] As might be expected, they exhibit a wide range of biological activities, including anti-cancer, anti-fungal, anti-microbial, and anti-inflammatory.[2] This range of activity has further resulted in the development of a number of routes that can be used for their synthesis. By far the most common and simple of these approaches is the condensation of an aldehyde with a benzofuranone (coumaranone). (Scheme 1) This can be accomplished using a wide range of conditions, including the nearly neutral conditions reported earlier by this group.[3] While exceedingly mild and thus compatible with a wide range of aldehyde substrates, including very sensitive ones such as 2-furaldehyde, these reactions tended to require extended reaction times, often requiring >12 hours for completion. As efforts to further probe biological applications have moved forward, these long reaction times have proven to be a significant obstacle to timely progress. Further the long reaction times can, in certain cases, result in partial decomposition and/or the formation of E/Z isomeric mixtures. As a result, a mild, yet quicker set of reaction conditions are required.

Scheme 1. Condensation Approach to Aurones.




One option that seemed possible was the use of microwave heating. Microwave heating has been used over the last several years to dramatically increase the rate and often yield of reactions.[4] In general, this impact is greater in more polar solvents due to their greater ability to absorb microwave radiation from a typical microwave reactor. Deep Eutectic solvents (DES) are certainly polar solvents, and thus would be expected to be readily applicable to microwave accelerated reaction conditions. Despite this obvious potential, only a single report exists in which deep eutectic solvents and microwave heating have been combined. Nagarkar and co-workers reported the synthesis of nitriles from aldehydes by reaction with hydroxylamine hydrochloride in the choline chloride/urea (CC/U) deep eutectic solvent.[5] (Scheme 2) By application of microwave heating, reaction times were reduced from hours to minutes and yields were similar to slightly improved. Based upon this previous study, the combined application of microwave heating and DES to the synthesis of aurones was undertaken.

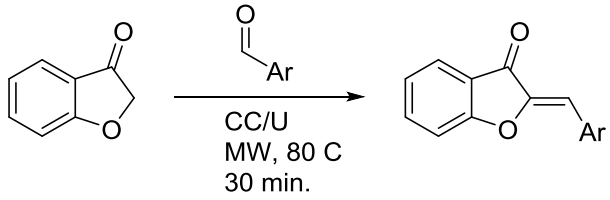
Scheme 2. Nagarkar Nitrile Synthesis.




Using a CEM Discover microwave reactor, we combined an aldehyde with benzofuran-3(2H)-one in a 1:2 molar ratio of choline chloride/urea as solvent.[6] (Scheme 3) The reaction was heated to 90 C for 30 minutes. After completion, the reaction mixture was partitioned between water and methylene chloride. Following concentration of the organic layer, the crude product was purified by simple trituration with ether in a simplification that we had earlier noted. As can be seen, the results were quite significant. The first test case afforded complete conversion of

the benzofuran-3(2H)-one in the 30 minute reaction time and resulted in an improved yield of 20% compared to 3% using our previously reported conditions.

Scheme 3. Aurone Synthesis in Deep Eutectic Solvent using Microwave Heating.




Armed with this promising result, a number of examples were studied to determine the scope of this improvement. (Table 1) In most cases, the yield was increased dramatically and in every case there was at least some improvement. Due to the much more rapid rate at which these reactions could be performed, we have been able to prepare an increasing number of new aurone derivatives, including several that are completely new.[7] Some, such as terphthalaldehyde had failed during prior attempts to synthesize these unusual compounds. (Table 1, entry 8) The one clear limitation that has been identified so far is with nitro-containing compounds. (Table 1, entry 13) In this case, a decreased yield was observed. Nevertheless, this new combination of generally increased reaction scope and improved speed has served to expand the range of new aurones available for study.

Table 1. Comparative Results for Aurone Synthesis – Conventional versus Microwave Heating.

| Entry | Aldehyde | Yield Conventional Heating (2-13 hours) | Yield Microwave Heating (30 minutes) |
|---|---|---|---|
| 1[3] | 4-cyanobenzaldehyde | 67% | 70% |
| 2[8] | 3-chlorobenzaldehyde | 15% | 45% |
| 3[9] | o-tolualdehyde | <5% | 26% |
| 4[10] | p-tolualdehyde | 63% | 80% |
| 5[11] | 4-trifluoromethylbenzaldehyde | <5% | 96% |
| 6 | 3-trifluoromethylbenzaldehyde | <5% | 81% |
| 7 | 2-trifluoromethylbenzaldehyde | <5% | 33% |
| 8 | Terphthalaldehyde | 0% | 33% |
| 9 | 4-iodobenzaldehyde | 13% | 56% |
| 10 | 5-hydroxymethyl-2-furfural | 3% | 20% |
| 11 | 3-fluorobenzaldehyde | 36% | 39% |
| 12* | Thiophene-2-carboxaldehyde | 34% | 36% |
| 13[3] | 4-nitrobenzaldehyde | 59% | 17% |

* = 6-hydroxybenzofuranone used in this reaction.

In conclusion, the combination of a deep eutectic solvent and microwave heating appears to have great potential for the efficient and rapid synthesis of many interesting compounds. The potential for further application is under investigation and these results will be reported in due course.

## Acknowledgments

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## Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

- The use of microwaves to accelerate the rate of reactions in deep eutectic solvents is reported.
- In addition to rate enhancement, yields are generally improved.
- The potential for this to be broadly applicable to synthesis in deep eutectic solvents is proposed.