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**Communication**

# An Efficient Microwave Method for the Synthesis of Imines

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A large variety of aryl and heterocyclic chiral and achiral imines can be generated simply, efficiently, and cleanly through the use of microwave irradiation and the use of a small amount of molecular sieve. Reactions are rapid and complete in a matter of minutes, and can be quantitative, reducing significantly the time and amount of solvents used in compound isolation and purification.

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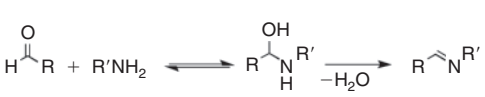
Imines are highly useful precursors for the synthesis of secondary amines, chiral amines, and important biological molecules such as alkaloids.[1] Traditionally imines are synthesised by the condensation of an aldehyde or ketone with a primary amine (Scheme 1), although there are many other variations in the recent literature, including the oxidative coupling of amines with primary alcohols in the presence of various catalysts,[2] the reduction of nitro compounds,[3] and many other alternatives.[4] The more traditional condensation reaction between a primary amine and carbonyl compound generally involves stirring or heating to reflux for extended periods to drive the equilibrium forward, and often requires the use of materials such as molecular sieves (MS), zinc chloride, alumina, $CuSO_4$, titanium chloride and apparatus such as a Dean–Stark apparatus.[5]

The use of microwave (MW) irradiation has improved the efficiency and yields of many reactions since its introduction into organic synthesis, often by reducing reaction times and the need for solvents.[6] There have been a small number of examples of microwave-assisted methods for the synthesis of imines, where the general trend is solvent-free microwave reactions in the presence of a catalyst.[7]

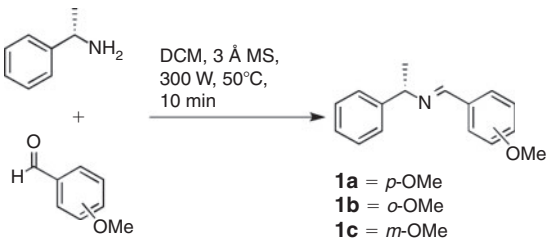
One of the current areas of interest within our group is chiral secondary and tertiary amines derived from (*S*)-*N*-α-methylbenzylamine and their metallation chemistry with alkali metals. In the process, the focus has shifted to a set of imines, (*S*)-*N*-(methoxybenzylidene)-α-methylbenzylamines, due to their similarities with (*S*)-*N*-(methylbenzyl)benzylamine which has been studied in detail within our group.[8] Classical methods for the synthesis of (*S*)-*N*-α-methylbenzylamine derived imines include reaction with an aldehyde by stirring the reaction in dichloromethane (DCM) and 4 Å molecular sieves for 48 h,[9] heating in DCM for 30 min in the presence of $K_2CO_3$,[10] or the use of magnesium perchlorate as a catalyst.[11] Although these methods are successful, reaction times, workup procedures, and the use of expensive or dangerous materials make them less desirable. Herein, we report an efficient and simple microwave synthesis method for the synthesis of a large range of functionalised imines.

By altering the reaction variables of time, temperature, and solvent in a microwave reactor, an efficient synthesis has been developed using commonly found reagents within the laboratory. This convenient method has led to the quantitative synthesis of a large library of chiral and achiral imines in significantly reduced times frames. The amine and aldehyde are reacted in a microwave reactor with 3 Å molecular sieves in DCM at 50°C (maximum of 300 W) for 10 min (Scheme 2). The reaction mixture is filtered and the solvent removed to give, in often quantitative yield, a product in which no further purification is required.

Table 1 compares the synthesis of **1a** with previously reported imine synthesis methods. It is clear that this new method **A** has various synthetic advantages and improvements compared with other pre-existing methods. For example: the use of microwave irradiation significantly reduces reaction times from days to minutes (methods **A** and **B**); no perchlorates, which alone are hazardous due to their explosive nature when heating is involved,[11] need to be used (method **A** versus **D** and **E**); and no workup or purification steps are required unlike methods **B**–**E**, where extraction, recrystallisation,[9] or distillation[10] is necessary.




**Scheme 1.** Imine equilibrium.




**Scheme 2.** The microwave synthesis of **1a**, **1b**, and **1c**.

**Table 1. Comparison of the new method (A) with previous methods (B–E) for the synthesis of 1a**

| Method | Catalyst | Solvent | Temp [°C] | Time | Yield [%] |
|---|---|---|---|---|---|
| **A** | 3 Å MS, MW[A] | DCM | 50 | 10 min | 98 |
| **B** | 4 Å MS | DCM | 20–25 | 48 h | 86–96[9] |
| **C** | $K_2CO_3$ | DCM | 40[B] | 30 min | –[C] [10] |
| **D** | $Mg(ClO_4)_2$ | DCE[D] | 20–25 | 8 h | 100[11] |
| **E** | $Mg(ClO_4)_2$ | DCE[D] | 84 | 1 h | 90[11] |

[A]Microwave irradiation.
[B]Heated on a steam bath.
[C]Yields not reported.
[D]DCE = dichloroethane.

To determine the versatility of this method, a range of functionalised and unfunctionalised amines and aldehydes were reacted as summarised in Table 2. In 26 of the 32 entries, essentially quantitative conversion to the imine product was achieved.

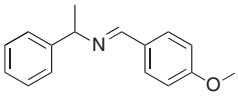
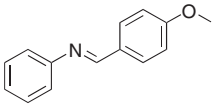
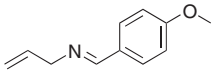
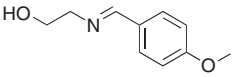
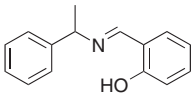
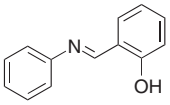
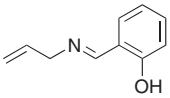
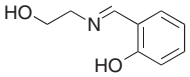
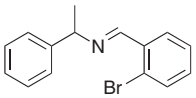
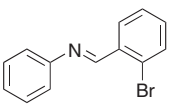
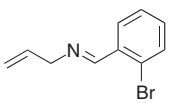
The general trend appears to be that the aldehydes that possess a phenyl functionality work better than those without. However, when the aldehyde was substituted with a strong electron withdrawing group on the phenyl ring (entries **13**–**16** and **25**–**28**) the reaction required longer reaction times.

Similarly, the presence of a heteroatomic group on the aldehyde (entries **17**–**20** and **25**–**28**), also requires longer reaction times for higher conversion rates to be achieved. Interestingly, with pyridine substituted aldehydes, particularly low product conversions are seen, even after extended reaction times and with higher temperatures, with the recovery of unreacted starting products primarily isolated.

Looking into the literature, the most similar microwave methods reported would be that of Varma et al.[7b] or Bekdemir and Efil.[12] Both reactions are solvent-free, with either K-10 clay or catalytic amounts of β-ethoxyethanol (β-EE) used, respectively (Scheme 3). While solvent-free reactions are desirable, most still require extraction and separation from the catalyst, which ironically involve solvent. In the case of our method (**A**), using a solvent is beneficial as it permits the easy workup of the reaction mixture, simply via filtration and the removal of the solvent. However it is also beneficial that uniform heating throughout the reaction mixture is able to occur giving a greater energy transfer,[13] a likely contribution to why these imines can be synthesised in a quick manner in the presence of a common dehydrating agent. Overall our method demonstrates short reaction times, with minimal workup procedures. The versatility of this simple method as a highly useful tool for the synthesis of aryl-based imines is highlighted by the variety of successful imines synthesised.

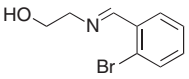
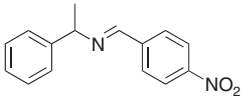
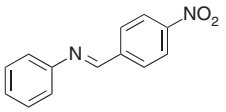
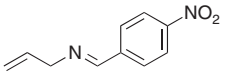
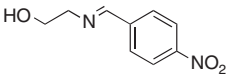
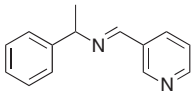
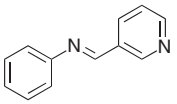
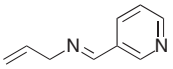
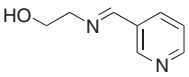
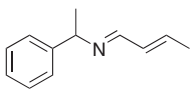
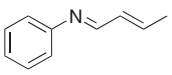
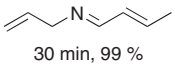
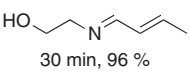
Following on from the success of the aldehydes, the reaction was next extended to ketones, notoriously less reactive and harder to convert to imines compared with aldehydes.[14] A series of reaction conditions were trialled using cyclohexanone and (*S*)-*N*-α-methylbenzylamine as the two starting materials, as summarised in Table 3. Of all the conditions tested the most suitable reaction conditions were found to be 3 Å molecular sieves, 80°C, in EtOH for 10 min. An array of reactions was conducted using these conditions; however, no other ketone reaction proceeded to give any conversion to the final imine product. Full details of all tested reactions are provided in the Supplementary Material.

**Table 2. The library of imines synthesised, their reaction times, and conversions**

| | Amine | Aldehyde | Product, time, conversion[A] |
|---|---|---|---|
| **1** | $PhCH(CH_3)NH_2$ | 4-(MeO)-PhCH=O |  10 min, 100 % |
| **2** | $PhNH_2$ | 4-(MeO)-PhCH=O |  10 min, 100 % |
| **3** | $CH_2{=}CHCH_2NH_2$ | 4-(MeO)-PhCH=O |  10 min, 100 % |
| **4** | $HO(CH_2)_2NH_2$ | 4-(MeO)-PhCH=O |  10 min, 100 % |
| **5** | $PhCH(CH_3)NH_2$ | 2-(OH)-PhCH=O |  10 min, 100 % |
| **6** | $PhNH_2$ | 2-(OH)-PhCH=O |  10 min, 100 % |
| **7** | $CH_2{=}CHCH_2NH_2$ | 2-(OH)-PhCH=O |  10 min, 100 % |
| **8** | $HO(CH_2)_2NH_2$ | 2-(OH)-PhCH=O |  10 min, 100 % |
| **9** | $PhCH(CH_3)NH_2$ | 2-(Br)-PhCH=O |  10 min, 100 % |
| **10** | $PhNH_2$ | 2-(Br)-PhCH=O |  10 min, 100 % |
| **11** | $CH_2{=}CHCH_2NH_2$ | 2-(Br)-PhCH=O |  10 min, 100 % |

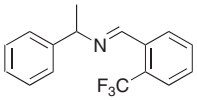
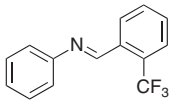
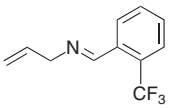
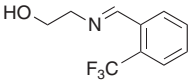
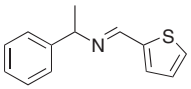
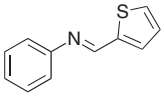
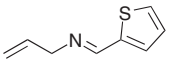
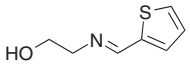
(*Continued*)

**Table 2. (Continued)**

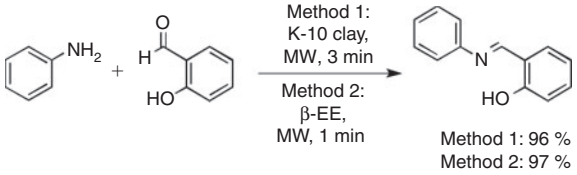
| | Amine | Aldehyde | Product, time, conversion[A] |
|---|---|---|---|
| **12** | $HO(CH_2)_2NH_2$ | 2-(Br)-PhCH=O |  10 min, 100 % |
| **13** | $PhCH(CH_3)NH_2$ | 4-($NO_2$)-PhCH=O |  30 min, 100 % |
| **14** | $PhNH_2$ | 4-($NO_2$)-PhCH=O |  30 min, 97 % |
| **15** | $CH_2=CHCH_2NH_2$ | 4-($NO_2$)-PhCH=O |  30 min, 100 % |
| **16** | $HO(CH_2)_2NH_2$ | 4-($NO_2$)-PhCH=O |  30 min, 100 % |
| **17** | $PhCH(CH_3)NH_2$ | $C_5H_5N$-2-CH=O |  30 min, 11 % |
| **18** | $PhNH_2$ | $C_5H_5N$-2-CH=O |  30 min, 7 % |
| **19** | $CH_2=CHCH_2NH_2$ | $C_5H_5N$-2-CH=O |  30 min, 43 % |
| **20** | $HO(CH_2)_2NH_2$ | $C_5H_5N$-2-CH=O |  30 min, 12 % |
| **21** | $PhCH(CH_3)NH_2$ | $CH_3CH=CHCH=O$ |  30 min, 89 % |
| **22** | $PhNH_2$ | $CH_3CH=CHCH=O$ |  30 min, 61 % |
| **23** | $CH_2=CHCH_2NH_2$ | $CH_3CH=CHCH=O$ |  30 min, 99 % |
| **24** | $HO(CH_2)_2NH_2$ | $CH_3CH=CHCH=O$ |  30 min, 96 % |

(*Continued*)

**Table 2. (Continued)**

| | Amine | Aldehyde | Product, time, conversion[A] |
|---|---|---|---|
| **25** | $PhCH(CH_3)NH_2$ | 2-($CF_3$)-PhCH=O |  30 min, 100 % |
| **26** | $PhNH_2$ | 2-($CF_3$)-PhCH=O |  30 min, 100 % |
| **27** | $CH_2=CHCH_2NH_2$ | 2-($CF_3$)-PhCH=O |  30 min, 100 % |
| **28** | $HO(CH_2)_2NH_2$ | 2-($CF_3$)-PhCH=O |  30 min, 100 % |
| **29** | $PhCH(CH_3)NH_2$ | $C_4H_4S$-2-CH=O |  30 min, 100 % |
| **30** | $PhNH_2$ | $C_4H_4S$-2-CH=O |  30 min, 100 % |
| **31** | $CH_2=CHCH_2NH_2$ | $C_4H_4S$-2-CH=O |  30 min, 100 % |
| **32** | $HO(CH_2)_2NH_2$ | $C_4H_4S$-2-CH=O |  30 min, 100 % |

[A]Determined by $^1H$ NMR spectroscopy.




**Scheme 3.** Microwave synthesis of imines in the literature: via K-10 clay[7b] or catalytic β-ethoxyethanol.[12]

In general, the synthesis of imines from ketones is much more difficult than from aldehydes. This is due to ketones having a lower reactivity and thus requiring higher temperatures, longer reaction times, and often the use of catalysts.[14] Even though this microwave method doesn't give a full conversion, the reaction can be done in 10 minutes, followed by a distillation to obtain the pure compound.

**Table 3. Systematic approach to improving the reaction of a ketone with an amine, with the most successful highlighted**

| Temp [°C] | Solvent | Time [min] | Conversion[A] [prod : sm[B]] |
|---|---|---|---|
| 50 | DCM | 10 | 28 : 72 |
| 50 | DCM | 20 | 62 : 38 |
| 50 | DCM | 30 | 66 : 34 |
| 70 | MeOH | 10 | 49 : 51 |
| 70 | MeOH | 20 | 64 : 36 |
| 70 | MeOH | 30 | 41 : 59 |
| 80 | EtOH | 10 | 78 : 22 |
| 80 | EtOH | 20 | 63 : 37 |
| 80 | EtOH | 30 | 58 : 42 |

[A]Determined by $^{1}$H NMR spectroscopy.
[B]Ratio of product (prod) to starting material (sm).

## Conclusion

We have shown microwave irradiation methods to be a practical and simple method for the synthesis of a range of functionalised and unfunctionalised imines. Unlike traditional methodologies requiring catalysts, long reaction times, or multiple purification steps, our method allows fast conversion times, no workup or purification steps, and quantitative conversions in most cases tested. Extending this method to ketones proved largely unsuccessful; however, further work on the addition of catalysts and a wider range of starting materials and amines is being investigated.

## Experimental

### *Apparatus, Materials, and Measurements*

All chemicals used were obtained from commercial suppliers and used as received with the exception of aniline, which was purified by distillation. Dichloromethane was taken from an MBRAUN SPS-800 solvent purification system and stored over 4 Å molecular sieves before use. $^{1}$H and $^{13}$C NMR spectra were recorded on a Bruker Avance DRX 400 spectrometer at 400 ($^{1}$H) and 100 MHz ($^{13}$C), or a Bruker Avance DPX 300 spectrometer at 300 ($^{1}$H) and 75 MHz ($^{13}$C). Mass spectrometric data were determined on an Agilent 6540 UHD Accurate Mass Q-TOF liquid chromatography mass spectrometer or with an Agilent 1200 Series HPLC, with the mass spectrometer fitted with an Agilent Jet Stream source. A CEM Discover Labmate microwave reactor operating at a maximum of 300 W was used.

### *General Procedure for Compounds (**1**–**32**)*

A microwave vial containing 3 Å molecular sieves (160–220 mg) and dry DCM (3 mL) was stirred. The selected amine (2 mmol) and the chosen aldehyde (2 mmol) were added consecutively and the microwave vial was capped. The resulting mixture was reacted in a microwave reactor at 50°C (maximum of 300 W) for 10 min, unless otherwise stated. The reaction mixture was filtered and the solvent removed under vacuum to yield the desired product.

## Supplementary Material

Full experimental details and the $^{1}$H and $^{13}$C NMR spectra of compounds **1**–**13**, **15**–**16**, and **25**–**32** can be found on the Journal's website.

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