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Microwave-assisted multi-component synthesis of fused 3-aminoimidazoles

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Abstract—A variety of fused 3-aminoimidazoles have been synthesised by a microwave assisted Ugi three-component coupling (3cc) reaction catalysed by scandium triflate in methanol as solvent. Yields of 33–93% have been achieved after just 10 min of microwave irradiation using a simple one-stage procedure. The methodology described is suitable for the rapid and efficient synthesis of a range of fused heterocycles of pharmacological interest. © 2003 Elsevier Science Ltd. All rights reserved.

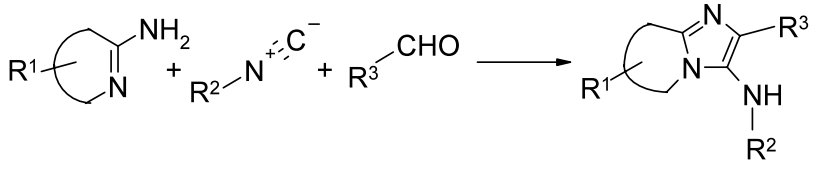
1. Introduction

The advent of single mode microwave reactors, which enable precise control of reaction conditions, has opened the way for the exploration of microwave assisted synthetic methods in combinatorial and parallel synthesis.[1] As part of an ongoing programme of research, we decided to investigate the possibility of using microwaves to accelerate the synthesis of a range of fused 3-aminoimidazoles via a three-component Ugi reaction (Scheme 1).

The reaction of heterocyclic amidines with aldehydes and isocyanides under acid catalysed conditions was first reported in 1998.[2,3] The reaction is considered to proceed via formation of an iminium species followed by a [4+1] cycloaddition with the isocyanide. A variation of this methodology, using scandium triflate as a Lewis acid catalyst, was reported by Blackburn et al.[4] In all cases the yields of the desired fused 3-aminoimidazoles were good, however extended reaction times of up to 72 h were required. The use of microwaves, to accelerate reactions, offers an attractive means of extending the utility of this reaction for use in high throughput library synthesis. An example of a solvent free microwave accelerated version of this Ugi 3cc reaction has been reported by Varma and Kumar.[5] Encouraged by their results we have investigated the potential of microwaves to accelerate the scandium triflate catalysed reaction in solution.[6]

2. Results and discussion

The reaction of 2-amino-5-methylpyridine with 2-naphthaldehyde and benzylisocyanide using scandium triflate as catalyst was carried out in methanol as solvent (Scheme 2). Pre-formation of the imine intermediate was found to be unnecessary and immediate addition of the isocyanide followed by microwave irradiation† in a sealed 10 ml vial (200 W, 160°C, 10 min) gave the best



Scheme 1. Ugi 3cc reaction to form fused 3-aminoimidazoles.

Keywords: Ugi; multi-component reaction; microwave; scandium triflate; heterocycle; imidazole.

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† Microwave reactions carried out using a CEM Discover Synthesis Unit (CEM Corp. Matthews, NC). For further information see: http://www.cem.com

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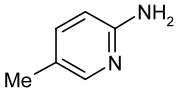
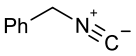
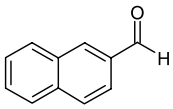
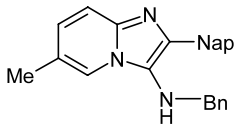
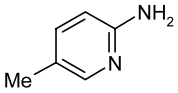
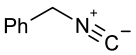
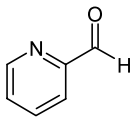
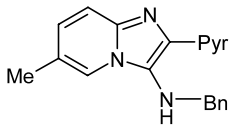
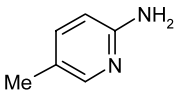
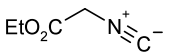
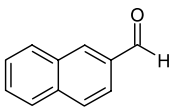
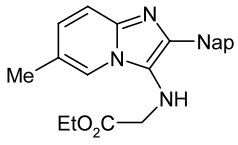
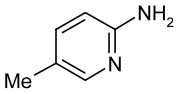
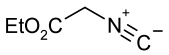
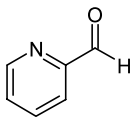
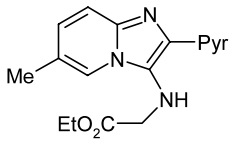
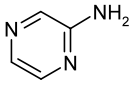
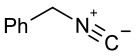
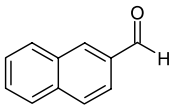
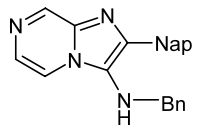
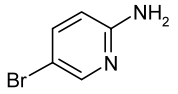
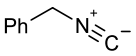
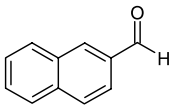
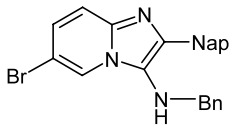
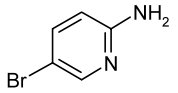
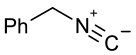
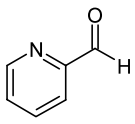
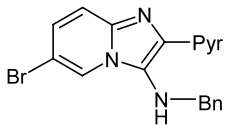
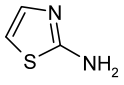
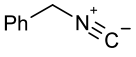
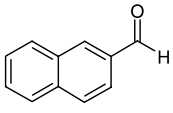
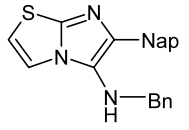
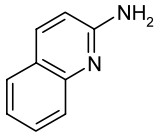
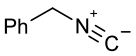
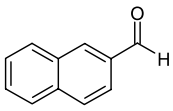
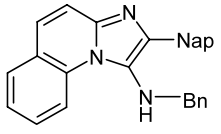
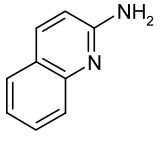
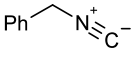
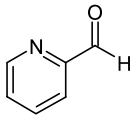
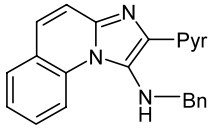
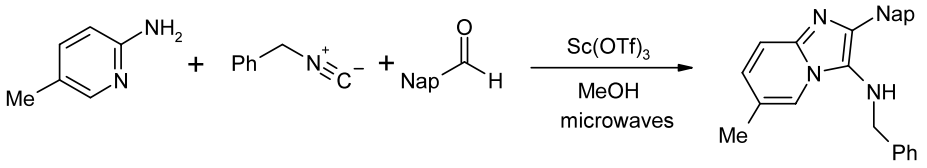
doi:10.1016/S0040-4039(03)00941-9

Table 1. One-stage Ugi 3cc reaction of an aldehyde, amidine and isocyanide

Exp. No.	Amidine	Isocyanide	Aldehyde	Product	Yield (%)[a]
1					93
2					78
3					50[b]
4					62[b]
5					65
6					81
7					72
8					33
9					79
10					65

a. Isolated yields
b. EtOH used as solvent to avoid transesterification



Scheme 2. Microwave assisted Ugi 3cc reaction of 2-amino-5-methylpyridine with benzylisocyanide and 2-naphthaldehyde.

results. It is noteworthy that in the absence of scandium triflate only a 25% conversion was achieved after 2 h in the microwave at 160°C.

This optimised method[7] was then applied to a number of reactions where the heterocyclic amidine, aldehyde and isocyanide were varied (Table 1). The more reactive, electron rich, amidines in combination with benzylisocyanide gave high yields (65–93%) in all cases. Less reactive amidines such as aminopyrazine and aminothiazole gave reduced conversion to product and some side product formation was observed particularly in the case of aminothiazole. Bienayme et al. have postulated that unreactive amidines of this type suffer from a competing reaction of MeOH with the imine intermediate leading to poorer conversion to the Ugi product.[2] They have reported that the use of a less nucleophilic reaction solvent such as trifluoroethanol helps to prevent this side reaction leading to improved yields in the Ugi reaction. An investigation into similar solvent effects in our reaction is currently underway and the results will be presented in due course. Use of ethyl isocyanoacetate as the isocyanide gave slightly reduced yields compared to benzylisocyanide and in these cases it was necessary to use ethanol as solvent to avoid problems with partial transesterification.

3. Conclusion

We have developed a rapid and efficient microwave assisted method for the synthesis of a range of fused 3-aminoimidazoles in moderate to good yields via an Ugi 3cc reaction. This methodology should prove useful for the synthesis of libraries of such derivatives with improved efficiency using high throughput synthesis methods.

References

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7. *Typical procedure*: 2-Amino-5-methylpyridine (0.23 mmol) was dissolved in methanol (1 ml) and scandium triflate (0.01 mmol) added with stirring at room temperature. 2-Naphthaldehyde (0.23 mmol) was added followed by benzylisocyanide (0.23 mmol) and the vessel sealed with a pressure cap and irradiated with microwaves (200 W) maintaining a temperature of 160°C for 10 min. The mixture was allowed to cool, then diluted with DCM (2 ml) and water (1 ml). The organic phase was separated and the aqueous phase extracted with DCM (2×5 ml). The combined organics were dried over sodium sulfate, filtered and the solvent evaporated. Purification by column chromatography on silica gel eluted with 2% MeOH–DCM gave the product isolated as a white solid (78 mg, 93%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.26 (3H, s), 3.55 (1H, bt, J 6 Hz), 4.20 (2H, d, J 6.2 Hz), 6.95 (1H, dd, J 9.2, 1.7 Hz), 7.25–7.38 (5H, m), 7.43–7.50 (3H, m), 7.68 (1H, s), 7.79–7.89 (3H, m), 8.14 (1H, dd, J 8.6, 1.7 Hz), 8.40 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.38, 52.49, 116.56, 120.07, 121.50, 124.99, 125.56, 125.75, 125.86, 126.12, 127.56, 127.63, 127.67, 128.15, 128.30, 128.71, 131.51, 132.68, 133.63, 135.52, 139.1, 140.61; MS (ES^+) 364 (MH^+, 100%).