Thin layer chromatography as a tool for reaction optimisation in microwave assisted synthesis

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Reaction parameters for the microwave assisted synthesis of N′-substituted arylpiperazines were optimised *via* their rapid synthesis on thin layer chromatography (TLC) plates.

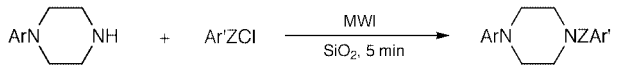
Piperazines form the backbone of many biologically interesting molecules.[1] Their incorporation into biologically active molecules has even been associated with an increase in potency.[2] Recent examples of piperazine-containing molecules include many fluoroquinolone antibiotics, the HIV protease inhibitor Crixivan™ and the PDE-5 inhibitor Viagra™, used for male erectile dysfunction. As part of a program dedicated to the development of new techniques for combinatorial chemistry,[3] we describe herein a simple procedure for reaction optimisation in microwave assisted synthesis.[4] This procedure is exemplified by the rapid derivatisation of a number of monoarylpiperazines.

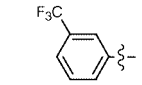
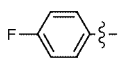
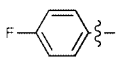
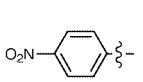
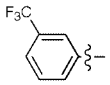
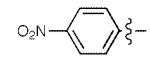
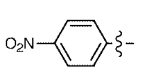
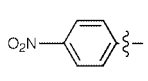
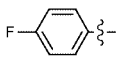
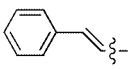
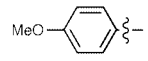
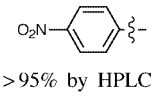
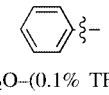
Previously we synthesised several 2-iodobenzylamines as radical precursors for an investigation of the α-alkylation of amines *via* a 1,5-hydrogen shift.[5] During the synthesis of these precursors it was observed that, in some cases, amines would react partially with benzyl halides when co-spotted on a TLC plate.[6] After elution a new spot was sometimes seen that corresponded to that of the expected benzylated amine product. Product conversion was often poor since considerable amounts of unreacted starting materials were usually present. We were able to utilise this information in the design of methodology toward the rapid and efficient synthesis of the arylpiperazine derivatives shown in Table 1.†‡

Initial observations for the co-spotting of an arylpiperazine and an electrophile, either neat or as dilute solutions in CH_2Cl_2, onto a TLC plate confirmed the above in that reactions occurred sporadically if at all, and without complete consumption of the starting material. It was anticipated that the reactions could be accelerated by microwave irradiation of the reagents on a glass-backed TLC plate prior to elution, since the TLC plate would act as a support without the silica gel absorbing or restricting the transmission of microwaves. TLC plates (Merck silica gel 60 F254) with preadsorped reagents were irradiated in a domestic microwave oven with varying power outputs and at various time intervals. Method of application, loading and stoichiometry of the reagents were varied as an array on plates in order to discover the optimum conditions for the reaction. After cooling, the plates were eluted and viewed under UV light (254 nm) and by development with either I_2 or ninhydrin. The most convenient method involved the application of reagents in solution (at a concentration of *ca*. 1 mg in 1 ml CH_2Cl_2) in 5 μl aliquots onto a plate with a 0.2 mm layer of SiO_2. Complete consumption of one or other of the reagents occurred after irradiation for 5 min at an output of 585 watts. Reactions were complete under these conditions, regardless of the stoichiometry of the reagents. Only one product spot was seen, the R_f value of which was consistent with that of the expected product. Confirmation was later afforded through direct synthesis (*vide infra*). A rather serendipitous discovery was made in that excesses of sulfonyl chlorides appeared to degrade under these conditions to a product with a polar baseline spot, presumably the corresponding sulfonic acid. Fortunately the degradation appeared to occur rather more slowly than the desired transformation, and the reactions remained unaffected since the arylpiperazine component was completely consumed to yield the desired product.

Upon identification of the optimum reaction parameters, the reactions were scaled up to several hundred milligrams in size. Reagents were dissolved in a minimum amount of CH_2Cl_2 and adsorbed onto silica gel (230–400 mesh). After removal of solvent the mixture was irradiated for 5 min. The silica gel was allowed to cool and was then washed with CH_2Cl_2 and the washings filtered through a Celite pad. Evaporation of the solvent *in vacuo* yielded the desired product in high yield and purity. Although unnecessary, it was often advantageous to use a slight excess of the amine component to drive the reaction to completion and facilitate isolation of the final product in pure form, without the need to resort to chromatography. Reactions involving equimolar amounts of reagents worked equally as

Table 1 Arylpiperazine derivatives formed *via* microwave assisted synthesis



Entry	Ar	Ar′	Z	Isolated yield[a] (%)
1			SO_2	91
2			SO_2	77
3			SO_2	96
4			CH_2	99
5			CH_2	99
6			CH_2	75
7			CO	93
8			CO	97
9			CO	72

[a] Purity >95% by HPLC [10% H_2O–(0.1% TFA)MeCN on a Hypersil column].

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well, though occasionally the purity of the final product was compromised due to the presence of small amounts of unreacted halides. Fortuitously, reactions involving an equimolar amount or excess of sulfonyl halides were unaffected since the unreacted material degraded under the reaction conditions (*vide supra*). Interestingly, all reactions were high yielding and afforded *N′*-substituted products in high purity. The presence of electron-withdrawing groups on the arylpiperazine, *e.g.* 1-(4-nitrophenyl)piperazine in entries 3, 5, and 9, didn't appear to impede reaction. It has been reported previously that the presence of electron-withdrawing groups in the aryl ring of arylpiperazines diminishes the nucleophilicity of the secondary amine.[7]

Reactions on silica gel were performed without incident and somewhat surprisingly without salt formation. It is thought that silica gel scavenges any HCl formed in the reaction, thereby negating salt formation. When reactions were performed in the absence of silica gel or by using finely ground glass as the support none of the desired products were isolated. TLC analysis of these reactions indicated the absence of product. However, the presence of a new and more polar baseline spot was seen, presumably the corresponding amine salt formed in the presence of HCl generated *in situ*.

In summary, reactions performed on a TLC plate are a powerful tool for rapid reaction optimisation. The method is suitable in particular for microwave assisted reactions since the plate can be used as an inert support. The technique is applicable to combinatorial chemistry where reactions often have to be optimised prior to library synthesis. Moreover it is possible to combine this technique with bioautographical screening and analytical methods.[8] Use of this technology for the synthesis and screening of combinatorial libraries will be described in due course.

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Notes and references

† All compounds gave satisfactory spectral data.

‡ *Typical procedure*: 1-(α,α,α-trifluoro-*m*-tolyl)piperazine (0.25 g, 1.1 mmol) in CH_2Cl_2 (1 ml) and 2-nitrobenzenesulfonyl chloride (0.24 g, 1.1 mmol) in CH_2Cl_2 (1 ml) were mixed thoroughly with silica gel (Merck 230–400 mesh, 1 g) in a glass vial and the solvent removed under reduced pressure. The mixture was then irradiated in a domestic microwave oven (Electrolux NF4884) at an output of 585 watts for 5 min. Water (50 ml) was placed in another vessel and irradiated simultaneously. After cooling to room temperature the product was dissolved in CH_2Cl_2 (*ca.* 5 ml) and filtered through a Celite pad. The solvent was removed under reduced pressure to afford the corresponding sulfonamide as a yellow solid (0.41 g, 91%, > 98% pure by HPLC); R_f 0.55 (MeOH–CH_2Cl_2, 5%); δ_H($CHCl_3$, 300 MHz) 8.01 (1H, d, *J* 9.3), 7.72 (2H, m), 7.63 (1H, m), 7.37 (1H, t, *J* 7.7), 7.14 (3H, m), 3.51 (4H, m), 3.31 (4H, m).

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6 L. Williams, unpublished results.
7 M. Hepperle, J. Eckert and D. Gala, *Tetrahedron Lett.*, 1999, **40**, 5655.
8 Patent pending.

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