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Microwave-assisted solvent-free parallel synthesis of thioamides

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Abstract

Rapid parallel synthesis of thioamides is described. A library of amides, synthesised by mixing acyl chlorides and diamines, was transformed into the corresponding thioamides utilising Lawesson's reagent as the oxygen/sulphur exchange reagent. Purification by solid-phase extraction afforded the library members in adequate purities and yields.

Keywords: microwave; parallel synthesis; thioamide.

By analysing a large virtual library of a million compounds constructed from frameworks frequently found in drug molecules it was concluded that amides incorporating a basic amine moiety would constitute an interesting family of potentially CNS-active molecules amenable to combinatorial chemistry.[1] However, the therapeutic utility of amides is limited due to considerable degradation in plasma. One approach to increase the half-life of peptides is to substitute one or more amide linkage(s) by thioamide linkage(s), a modification leading to improved resistance to enzyme degradation.[2] Furthermore, the larger and less electronegative sulphur atom, relative to oxygen, might alter the hydrogen-bonding ability and/or induce conformational changes in the modified molecule. As a result, the substitution of thioamides for amides might be productive in the search for novel CNS-active drugs.[3]

Although the synthesis of thioamides has been well documented,[4] to our knowledge, no examples have been reported on the direct conversion of a hydrochloride salt of an amide incorporating a basic amine function into the corresponding thioamide using an oxygen/sulphur exchange reagent. In this communication, our synthetic strategy, an extension of a procedure recently published by Varma and Kumar,[5] is exemplified by the rapid synthesis of a representative 25-membered library of thioamides.

The synthetic route to the thioamide library is illustrated in Scheme 1. Generally, in synthesising a library of compounds for high-throughput biological screening (HTS) it is important not only to generate products with adequate purities, but also to minimise the

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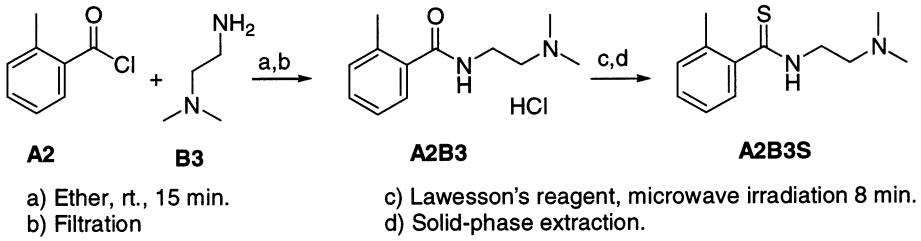
occurrence of assay-interfering byproducts, in our case the amides used as precursors. A multivariate screening analysis of variables influencing the oxygen/sulphur exchange reaction on a model substrate revealed two important variables—the procedure for mixing the solids and the irradiation time. The major obstacle to achieve completion of the reaction was to obtain a homogeneous mixture, at 0.05 mmol scale, of the solid reactants. Several methods were evaluated. The most practical one that gave optimal mixing was to add three small stirring bars and subsequently stir and grind for 10–15 min. Furthermore, an excess of Lawesson's reagent (1.0–1.5 equiv.) was required. Fewer equivalents gave incomplete reactions while larger excess produced thioamides of low purities. Irradiation for 6–7 min at 900 W in a domestic microwave oven led to a 96:4 mixture of the thioamide and the corresponding amide. No byproducts were detected. Shorter irradiation time, 5 min, drastically lowered the thioamide/amide ratio (36:64). Although considerable decomposition of the product occurred at longer irradiation times, e.g. 8 min gave 90% purity of the thioamide in the crude product mixture, 8 min irradiation time was selected for the library synthesis due to a nearly complete consumption of the starting amide; less than 2% remained.



Scheme 1. Representative reaction for the synthesis of thioamides, illustrating the model substrate used to optimise the oxygen/sulphur exchange reaction

The intermediate amide library was synthesised by assembling the building blocks depicted in Fig. 1. Amide synthesis and subsequent oxygen/sulphur exchange reaction produced the thioamides according to the following protocol: the diamine was added to an ethereal solution of an acyl chloride in a Teflon-capped vial.[6] Salt precipitation was instant.[†] The solvent was

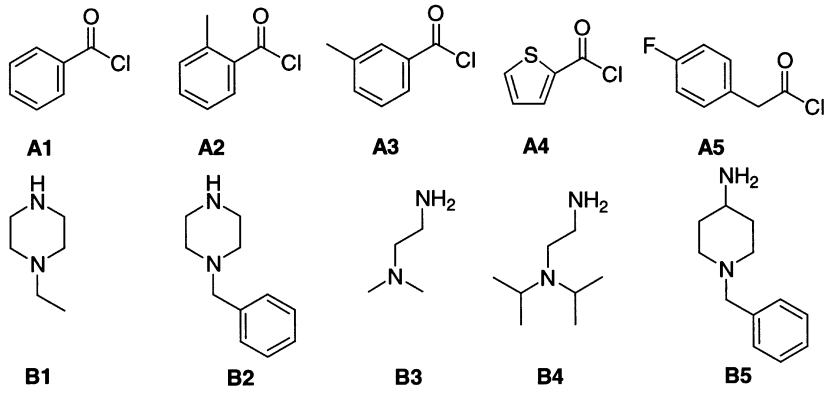


Figure 1. Building blocks for the amide library synthesis

[†] CH_2Cl_2 was used as solvent in cases where the acyl chlorides had low solubility in ether. After completion of the reaction the salt was precipitated by addition of ether.

removed by filtration, where the Teflon cap served as the filter. Lawesson's reagent (1.0–1.5 equiv.) was added to the salt and the resulting mixture of solids was mixed thoroughly and thereafter irradiated for 8 min in a domestic microwave oven (900 W, Whirlpool M401). Solid-phase extraction (SPE) afforded the thioamides in adequate purities and yields (Table 1).

Table 1
Purities[a] and yields[b] for the amide and thioamide libraries

Comp.	Purity% (yield%)	Comp.	Purity% (yield%)	Comp.	Purity% (yield%)	Comp.	Purity% (yield%)	Comp.	Purity% (yield%)
A1B1	100	**A2B1**	100	**A3B1**	100	**A4B1**	100	**A5B1**	75
A1B1S	100 (89)	**A2B1S**	96 (81)	**A3B1S**	98 (91)	**A4B1S**	100 (47)	**A5B1S**	85 (61)
A1B2	99	**A2B2**	93	**A3B2**	81	**A4B2**	90	**A5B2**	89
A1B2S	92 (71)	**A2B2S**	93 (79)	**A3B2S**	97 (87)	**A4B2S**	95 (43)	**A5B2S**	81 (65)
A1B3	76	**A2B3**	70	**A3B3**	68	**A4B3**	97	**A5B3**	82
A1B3S	85 (63)	**A2B3S**	38 (61)[c]	**A3B3S**	44 (69)[c]	**A4B3S**	91 (39)	**A5B3S**	80 (71)
A1B4	100	**A2B4**	68	**A3B4**	96	**A4B4**	79	**A5B4**	95
A1B4S	35 (71)[c]	**A2B4S**	62 (56)[c]	**A3B4S**	77 (56)	**A4B4S**	90 (56)	**A5B4S**	51 (60)[c]
A1B5	98	**A2B5**	64	**A3B5**	99	**A4B5**	99	**A5B5**	58
A1B5S	96 (67)	**A2B5S**	85 (73)	**A3B5S**	80 (73)	**A4B5S**	96 (38)	**A5B5S**	81 (65)

[a] Purities were measured on a HP1100 LC–MS using DAD. Eluent: 8 mM ammonium acetate in CH_3CN/water. UV-data were measured at UV_{max}. Matrix characterisation by NMR, performed on one fifth of the products, confirmed LC.

[b] Yields of the crude product mixture after SPE purification using ISOLUTE SCX ion-exchange cartridges.

[c] Discarded compounds.

A correlation can be seen between the purities in the intermediate amide library and the thioamide library. In the amide library, 68% of the members had +80% purity and the average purity was 87%. Corresponding values for the thioamide library were that 76% of the library members had a purity +80% and the average was 81%. All thioamides with a purity below 80±3% and/or with an amide impurity above 3% were discarded. The remaining 80% of the library was considered to be of adequate quality for HTS utilising the R-SAT™ technology.[7]

In conclusion, we have developed a rapid and practical method for parallel synthesis of thioamides incorporating a basic amine moiety, delivering products of adequate quality for high-throughput biological screening.

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