Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 6, No. 12, pp. 1409-1414, 1996

0960-894X/96 $15.00 + 0.00

PII: S0960-894X(96)00241-7

A CONVENIENT PROCEDURE FOR THE SOLUTION PHASE PREPARATION OF 2-AMINOTHIAZOLE COMBINATORIAL LIBRARIES

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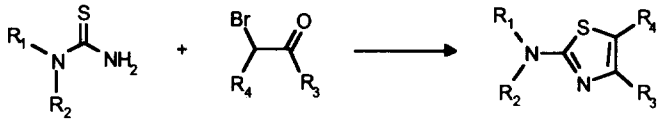
Abstract: A convenient procedure for the solution phase preparation of 2-aminothiazole combinatorial libraries is described. The library preparation is simple, practical, and effective, generating compounds based around a known pharmacophore in high yield and purity. Furthermore, the procedure tolerates a diverse range of functionality in its substrates and is notable in allowing the preparation of compounds containing both free acids and bases without recourse to protection.

The preparation of libraries[1] of compounds for biological screening is currently of enormous interest within both the synthetic and medicinal chemistry communities. Indeed the combinatorial libraries approach has begun to have a significant impact on the drug discovery process and an extensive literature of compound library preparation is beginning to accumulate.[1] Approaches to the construction and testing of compound libraries fall into two broad classes, (i) the preparation and testing of compounds as mixtures or pools, which necessarily involves a decoding[1,2] or tagging[1,3] protocol to determine the structures of active components; or (ii) the preparation and testing of compounds as discrete entities.[4] Similarly the actual chemistries used for library construction fall into two broad classes,[1] (i) solid phase supported methodologies, and (ii) more conventional solution phase chemistries.[5,6] Hitherto, the vast majority of reported library syntheses have employed solid phase methods[1]. In contrast, the use of conventional solution phase chemistry for library preparation has received scant attention. Herein we report the adaptation of the Hantzsch synthesis of 2-aminothiazoles[7] (eq) to allow the ready solution phase preparation of libraries of discrete 2-aminothiazoles. This library preparation is



Equation

simple, rapid, and effective; it generates compounds based around a known pharmacophore in high yield and purity and tolerates a diverse range of functional groups in its substrates. We believe that this library synthesis illustrates the as yet unrealised massive scope of traditional chemistries for library preparation in the solution phase.

2-Aminothiazole is a commonly occurring structural unit in drug molecules. Indeed, 95 papers reporting structures containing 2-aminothiazoles have been published in *Journal of Medicinal Chemistry* in the last ten years,[8] and furthermore, these papers report activity at a diverse range of biological targets. Therefore, there is good precedent to suggest that libraries of 2-aminothiazoles might afford biologically active molecules. The Hantzsch synthesis of 2-aminothiazoles from α-haloketones and thioureas, first reported in 1887,[7] is a robust and well established procedure affording 2-aminothiazoles in high yield from readily accessible substrates. Thus, given their widespread occurrence in biologically active molecules and the robustness of their syntheses, we explored the possibility of solution phase preparation of libraries of 2-aminothiazoles for biological screening.

Modification of the conventional Hantzsch synthesis does indeed allow solution phase preparation of 2-aminothiazole libraries. Use of a dipolar aprotic solvent (DMF) and simple removal of the solvent with a stream of nitrogen readily affords libraries of discrete 2-aminothiazoles. The practical procedure and the versatility and potential of this library preparation are illustrated by way of the 20 component library below (Figure 1).

The library was prepared in a 4 × 5 grid of 1 dram glass vials open to the atmosphere using a DPC liquid dispensing robot. Aliquots (0.250 mL) of a 0.10 $molL^{-1}$ solution of thiourea **a** in anhydrous DMF were dispensed into vials 1 through 4, similarly aliquots (0.250 mL) of a 0.10 $molL^{-1}$ solution of thiourea **b** into vials 5–8, **c** into vials 9–12, **d** into vials 13–16 and **e** into vials 17–20. Aliquots (0.250 mL) of 0.10 $molL^{-1}$ solutions of the α-bromoketones **A**–**D** were then dispensed orthogonally into the grid, i.e., α-bromoketone **A** into vials 1, 5, 9, 13, and 17, α-bromoketone B into 2, 6, 10, 14, and 18 etc. The resulting solutions were heated at 70 °C for 5 h, quenched with 10% dimethylamine in ethanol (0.125 mL) and solvent removed by blowing a stream of nitrogen into each vial at ambient temperature for ca. 24 h. This directly afforded the library samples, analyses of which (see below) illustrate the high quality of material afforded by this simple, purification free, library preparation.

HPLC analysis[9] revealed material of high purity and LC coupled mass spectrometery[10] confirmed that in each case the principal component had a molecular ion corresponding to the appropriate thiazole (Table). These components were then unambiguously characterised by high resolution mass spectroscopy[11] (Table). ^{1}H NMR analyses of the materials were all in accord with the desired 2-aminothiazoles in high purity (Figure 2), and in the case of compounds generated from bromoketones **A**, **B**, and **C** the thiazole 5-H signal in the

region δ 6.5–7.0 was diagnostic. ^{1}H NMR analysis (e.g., Figure 2) also revealed traces of residual DMF and dimethylamine hydrobromide resulting from the dimethylamine quench.

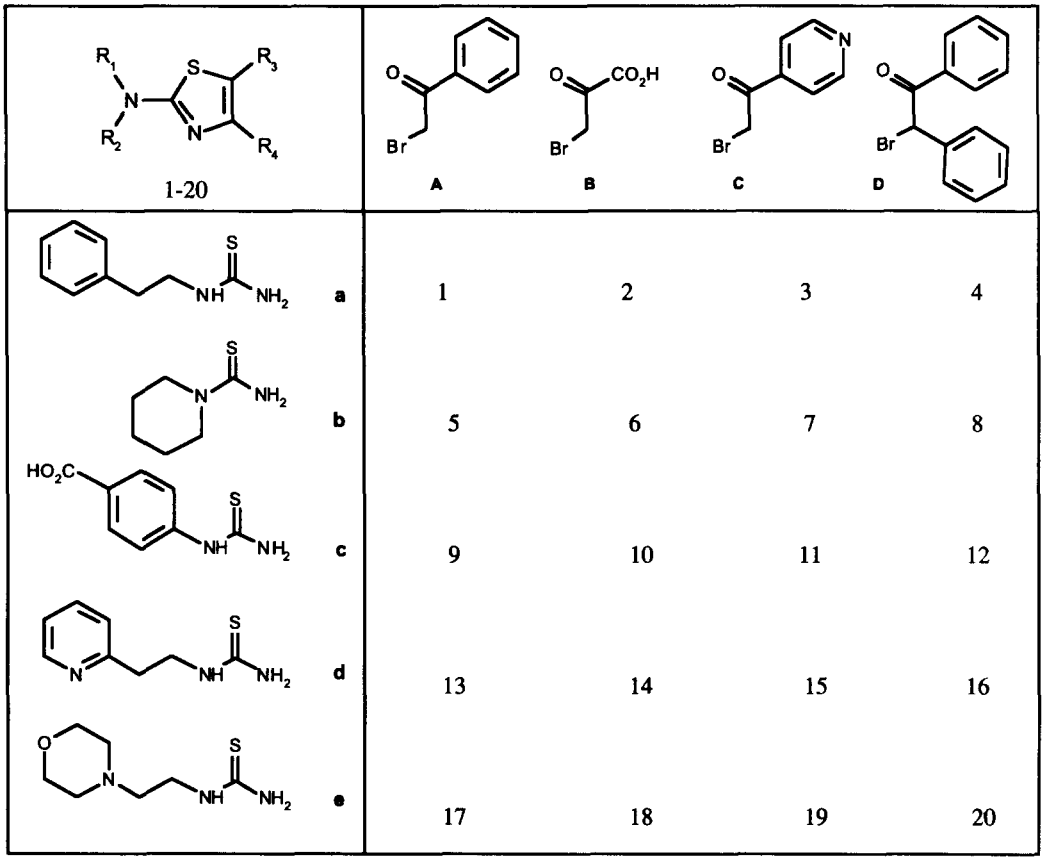


Figure 1. Illustrative 2-aminothiazole library

Whilst the library described above (Figure 1) is only of modest size its purpose is purely illustrative. The range of functional groups included in the α-bromoketone and thiourea substrates for this library demonstrate the versatility and scope of this procedure. Given the range of functionality tolerated, one can readily visualise a diverse range of potential library substrates and products. Indeed, we have successfully prepared a library of 2,500 compounds by this procedure simply using commercially available substrates.

Table. HPLC purity[9] and high-resolution mass spectral data[11] for the illustrative library

Sample	Purity[a] (%)	Molecular Formula	Theoretical Mass[b]	Measured Mass[b]	Sample	Purity[a] (%)	Molecular Formula	Theoretical Mass[b]	Measured Mass[b]
1	84	$C_{17}H_{16}N_2S$	281.111245	281.11119	11	44	$C_{15}H_{11}N_3O_2S$	298.06502	298.064797
2	94	$C_{12}H_{12}N_2O_2S$	249.069775	249.06941	12	82	$C_{22}H_{16}N_2O_2S$	373.10108	373.101018
3	79	$C_{16}H_{15}N_3S$	282.106494	282.10628	13	86	$C_{16}H_{15}N_3S$	282.10649	282.106565
4	83	$C_{23}H_{20}N_2S$	357.142546	357.14233	14	>98	$C_{11}H_{11}N_3O_2S$	250.06502	250.064839
5	90	$C_{14}H_{16}N_2S$	245.111245	245.11124	15	96	$C_{15}H_{14}N_4S$	283.10174	283.101918
6	>98	$C_9H_{12}N_2O_2S$	213.069775	213.06956	16	90	$C_{22}H_{19}N_3S$	358.13780	358.137545
7	84	$C_{13}H_{15}N_3S$	246.106494	246.10644	17	>98	$C_{15}H_{19}N_3OS$	290.13271	290.132976
8	>98	$C_{20}H_{20}N_2S$	321.142546	321.14267	18	85	$C_{10}H_{15}N_3O_3S$	258.09123	258.091401
9	76	$C_{16}H_{12}N_2O_2S$	297.069775	297.06969	19	96	$C_{14}H_{18}N_4OS$	291.12796	291.127788
10	85	$C_{11}H_8N_2O_4S$	264.184200	264[c]	20	>98	$C_{21}H_{23}N_3OS$	366.16401	366.163813

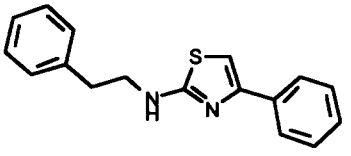
[a]Excludes Dimethylformamide and Dimethylamine Hydrobromide (see text).
[b]Molecular ions correspond to MH^+.
[c]Ion too weak for high resolution characterisation.

The range of thioureas **a**–**e** clearly illustrate that *N*-alkyl, *N*-aryl, *N*-monosubstituted, and *N,N*-disubstituted thioureas are all suitable substrates for this procedure. The successful use of α-bromoketone **B** and thiourea **c** indicates that this procedure is unaffected by the presence of acidic groups, similarly the successful use of α-bromoketone **C** and thioureas **d** and **e** indicates that basic groups are also tolerated. Furthermore the successful pairings of α-bromoketone **B** and thioureas **d** and **e** indicate that this procedure will tolerate acidic and basic substrates simultaneously.

In preparing prospective compound libraries for random screening it is desirable that the library includes a wide range of biologically recognised functional groups. Acidic and basic functional groups often play a key role in the binding of a ligand to a biological target, hence the ability to generate libaries containg compounds displaying both free acids or bases without recourse to protection is a notable feature of this 2-aminothiazole library synthesis. Indeed this feature stands in contrast to almost all combinatorial library syntheses reported to date, where if acidic or basic groups can be revealed at all, deprotection steps are required.

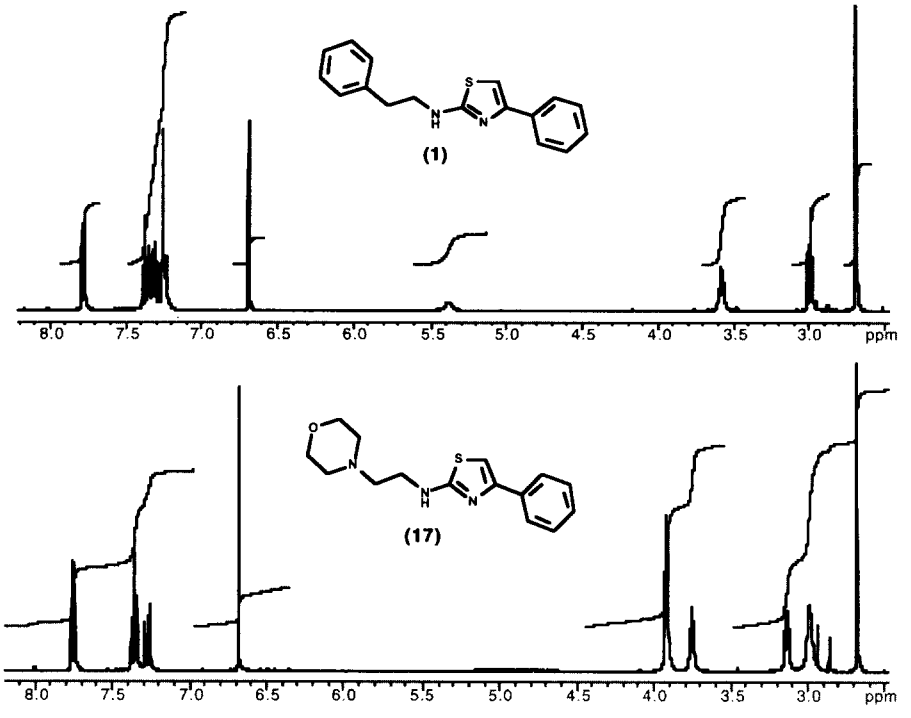
The product of α-bromoketone **A** and thiourea **a**, 2-aminothiazole (**1**), is a known pharmacological agent. This compound (Fanetizole) is an anti-inflammatory agent[12,13] that was reported[14] to have reached phase II clinical trails for the treatment of rheumatoid arthritis. That the procedure described herein can so readily

generate a known pharmacological agent such as Fanetizole (1) serves to illustrate the potential of this methodology to generate libraries which do contain biologically active molecules.



Fanetizole (1)

Figure 2 400MHz 1H NMR (CDCl3) Spectra of Library Samples 1 and 17



a. Signal at ca. δ 2.7 arises from dimethylamine hydrobromide (see text).

The relative practical ease with which 2-aminothiazole libraries can be prepared according to the procedure described here is worth stressing. The vast majority of combinatorial library syntheses reported thus far involve solid supported methodologies[1] that by their very nature require specialised techniques and

equipment with which the practising medicinal chemist may be unfamiliar. In contrast, the use of the solution phase library synthesis described herein would require little specialized knowledge.

In summary, we have developed a straightforward and effective procedure for generating libraries of discrete 2-aminothiazoles in a single solution phase step. This purification free procedure affords libraries based around a known pharmacophore, generates samples of high purity with minimal by-products and will tolerate substrates bearing both acidic and basic functionality without recourse to protection. We have successfully used this procedure to prepare libraries of several thousand compounds. The scope of this procedure to generate 2-aminothiazole libraries is limited only by the availability of substrates.

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(*Received in USA* 3 *January* 1996; *accepted* 22 *May* 1996)