

# Clean six-step synthesis of a piperidino-thiomorpholine library using polymer-supported reagents

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**Polymer-supported reagents and other solid sequestering agents may be used to generate a library of piperidino-thiomorpholine derivatives without any chromatographic purification steps.**

The growing speed of biological evaluation of potential drug substances during the past years has imposed the need to develop new methods for the fast and efficient generation of new chemical entities. In general, chemical libraries containing large numbers of compounds may be prepared either on polymer supports or in solution.<sup>1a</sup> The use of supported reagents combines the advantages of polymer supported reactions (*e.g.* allowing the application of a large excess of the reagent without the need for additional purification steps) with the benefits of solution phase chemistry (*e.g.* the ease of monitoring the progress of the reaction by simply applying LC-MS or TLC techniques). While, many solid-supported reagents have been described,<sup>1a-d</sup> only a few have been used in combinatorial chemistry.<sup>2a-e</sup> Furthermore, multi-step reaction sequences using polymer supported reagents are rare,<sup>3</sup> although there is a growing interest in sequestering agents on solid supports.<sup>2e,4</sup> Recent work in our group has focussed on the development of orchestrated multi-step methods using polymer supported reagents for the preparation of chemical compound libraries.<sup>5</sup> In this communication we wish to report a further example using various supported reagents for the efficient construction of heterocyclic derivatives.

Thiomorpholine analogues have found applications in medicine and agriculture.<sup>6</sup> Therefore, development of a simple, fast and flexible method to generate libraries of such compounds was desirable. Consequently we have designed a route to piperidino-thiomorpholines as potentially interesting chemical scaffolds using a series of polymer-supported reagents.

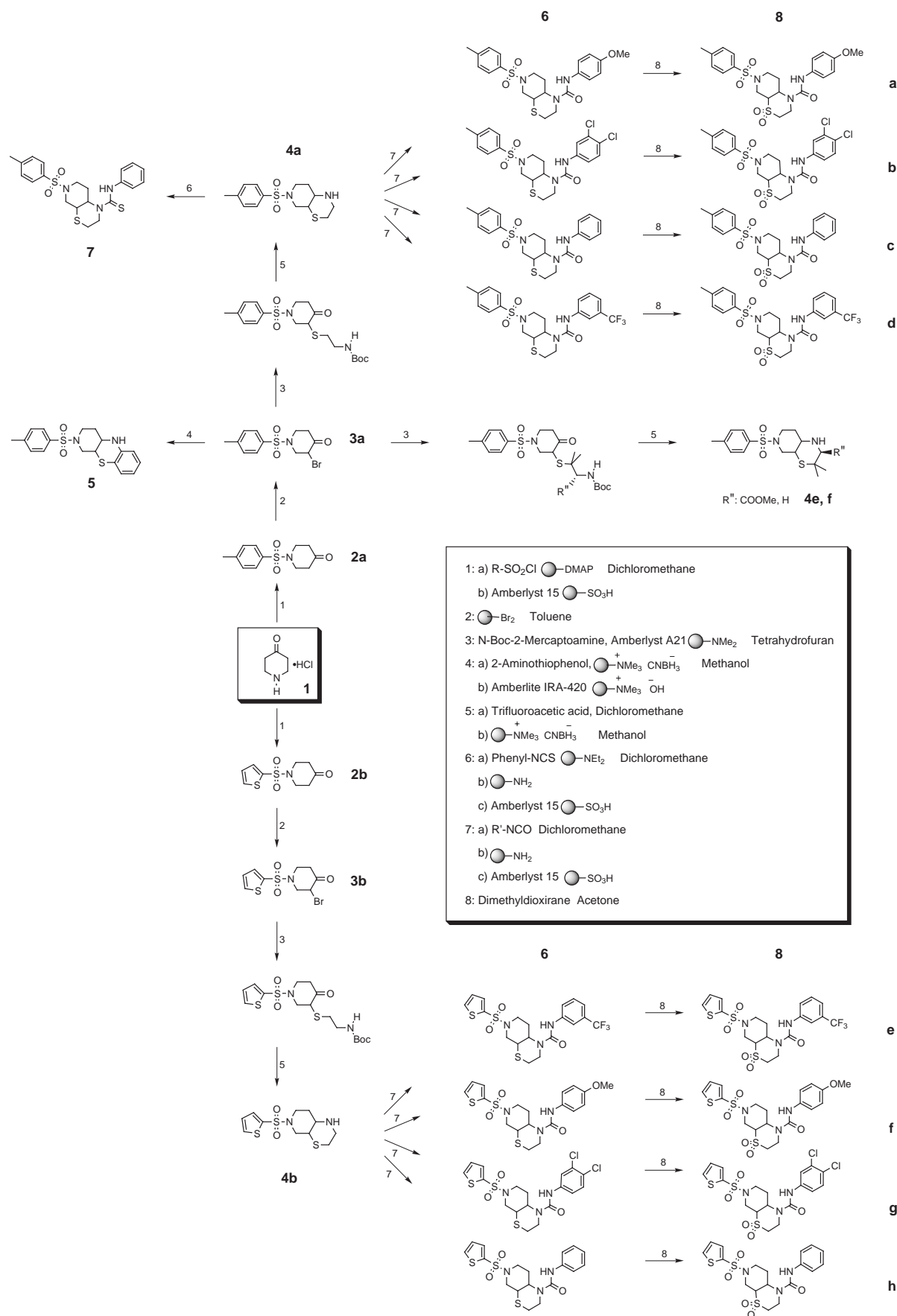
Starting from commercially available 4-piperidone hydrochloride hydrate **1** (Schemes 1 and 2) the nitrogen was derivatised with a range of commercially available sulfonyl chlorides to give the corresponding sulfonamides **2a–2d** in high yields and purities (reaction 1). This reaction was carried out using carefully dried polymer supported (dimethylamino)pyridine in dichloromethane<sup>5c</sup> with excess of amine being removed by addition of acidic Amberlyst 15 as a sequestering agent.

This was followed by a bromination  $\alpha$  to the keto-function using polymer supported pyridinium bromide perbromide<sup>7</sup> in toluene at 10 °C (reaction 2). This process needed careful control of the reaction temperature, as higher temperatures resulted in the formation of a substantial amount of the undesired dibromination product. Similar bromination using amberlyst resins has also been described.<sup>8</sup>

The  $\alpha$ -bromo ketones **3a–3d** were then reacted with *N*-Boc-protected aliphatic 1-amino-2-thiols in tetrahydrofuran using Amberlyst A21 as base to effect the coupling (reaction 3). Cleavage of the Boc-group using trifluoroacetic acid in dichloromethane yielded the corresponding imine directly which could

**Table 1** Summary of polymer supported reactions

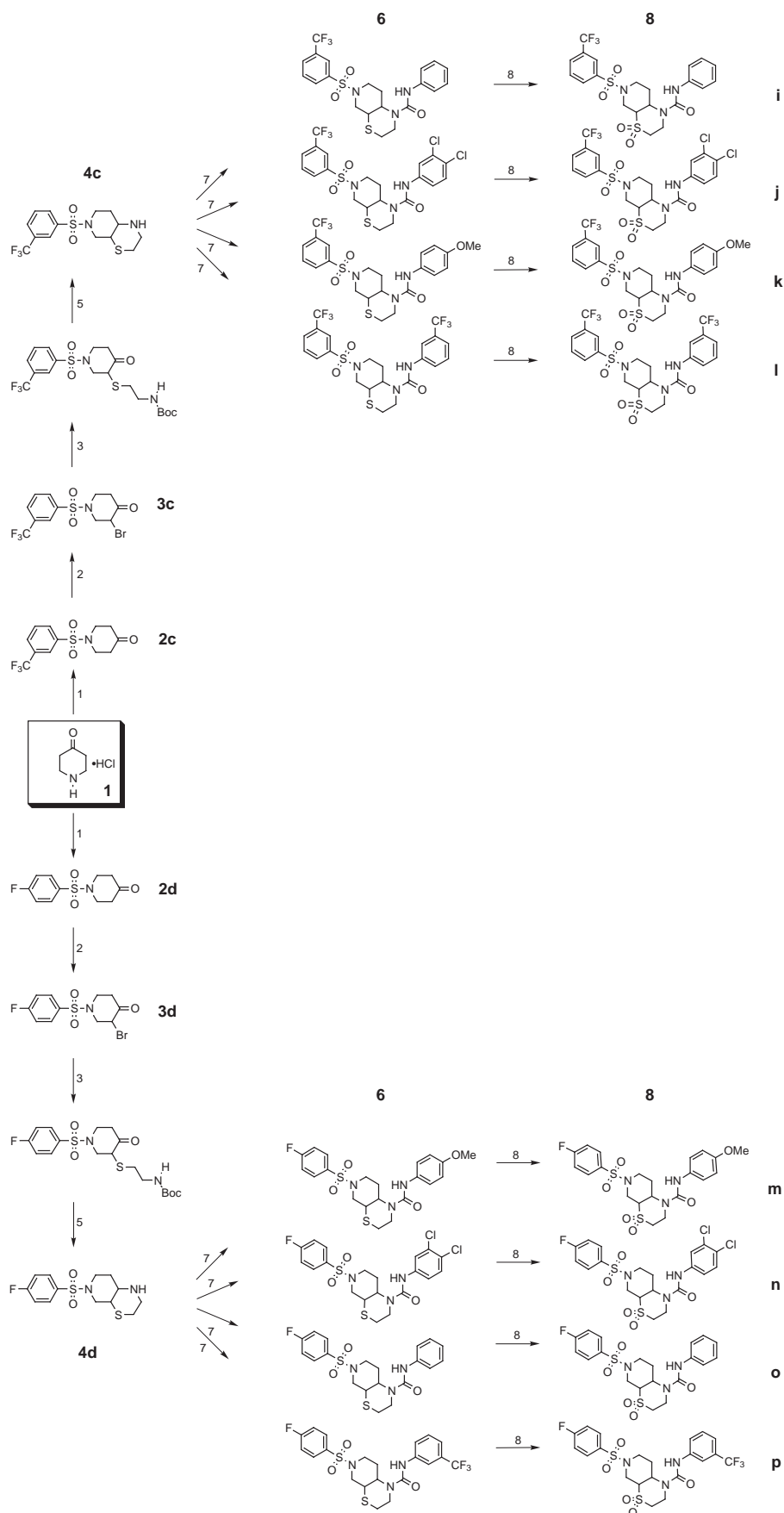
	Yield (%) <sup>13</sup>	LC-Purity (%)	ES-MS <sup>14</sup>		Yield (%) <sup>13</sup>	LC-Purity (%)	ES-MS <sup>14</sup>
<b>2a</b>	94	90	268.12	<b>6l</b>	80	>90	552.66
<b>2b</b>	32	>95	—	<b>6m</b>	Quant.	>97	466.25
<b>2c</b>	87	>95	306.13	<b>6n</b>	Quant.	>98	504.26
<b>2d</b>	66	90	—	<b>6o</b>	Quant.	>98	436.30
<b>3a</b>	84	85	331.99	<b>6p</b>	Quant. <sup>15</sup>	>98	504.44
<b>3b</b>	85	90	339.90	<b>7</b>	76	>98	448.17
<b>3c</b>	42	85	401.94	<b>8a</b>	Quant.	>96	494.43
<b>3d</b>	78	90	352.09	<b>8b</b>	Quant.	>98	534.08
<b>4a</b>	Quant. <sup>16</sup>	>98	313.07	<b>8c</b>	Quant.	>97	464.23
<b>4b</b>	Quant.	>90	305.05	<b>8d</b>	Quant.	>98	533.09
<b>4c</b>	Quant.	>92	367.15	<b>8e</b>	Quant.	>98	523.99
<b>4d</b>	Quant.	>97	317.05	<b>8f</b>	Quant.	>97	486.90
<b>4e</b>	90	>95	399.17	<b>8g</b>	Quant.	>98	523.76
<b>4f</b>	Quant.	>85	341.19	<b>8h</b>	Quant.	>98	455.94
<b>5</b>	80	>97	361.12	<b>8i</b>	Quant.	>95	518.33
<b>6a</b>	Quant.	>95	462.45	<b>8j</b>	Quant.	>95	586.24
<b>6b</b>	Quant.	>97	502.35	<b>8k</b>	Quant.	>95	548.34
<b>6c</b>	Quant.	>98	432.28	<b>8l</b>	Quant.	>95	586.16
<b>6d</b>	92	>95	501.30	<b>8m</b>	Quant.	>98	498.24
<b>6e</b>	50	>98	492.36	<b>8n</b>	Quant.	>98	538.34
<b>6f</b>	62	>95	454.15	<b>8o</b>	Quant.	>98	467.09
<b>6g</b>	Quant.	>98	492.32	<b>8p</b>	Quant.	>98	523.99
<b>6h</b>	Quant.	>96	424.21	<b>9a</b>	~60 <sup>17</sup>	—	403.18
<b>6i</b>	39	>85	486.15	<b>9b</b>	~60 <sup>17</sup>	—	421.12
<b>6j</b>	51	>92	554.49	<b>9c</b>	~60 <sup>17</sup>	—	433.19
<b>6k</b>	49	>50	516.63				



Scheme 1

be reduced with polymer supported cyano borohydride in methanol<sup>5c,9</sup> to give the corresponding thiomorpholine derivatives **4a–4f** (reaction 5). Alternatively, the Boc-group could be cleaved by shaking a solution of the compound with Amberlyst

15 in dichloromethane.<sup>10</sup> The reduction of the imines resulted in the formation of two diastereomers (*cis* and *trans* about the ring junction, where the *trans*-product predominates in  $\approx 2:1$  ratio). It was also demonstrated that aromatic 2-aminothiophenols



Scheme 2 (For reagents see Scheme 1).

were compatible with the reductive amination conditions to give the thiomorpholine derivatives (e.g. **5**). In the example attempted (reaction 4), the excess of the 2-aminothiophenol was removed by treatment of the reaction mixture with Amber-

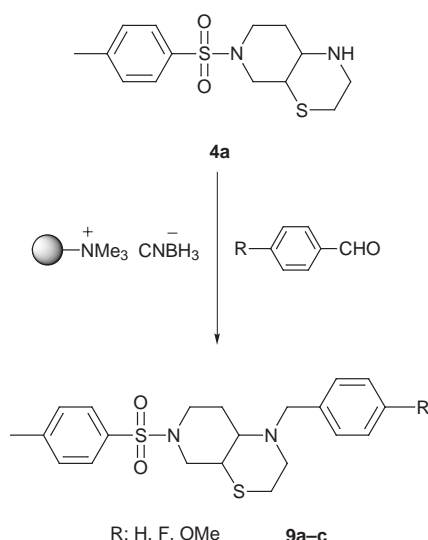
lite IRA-420 to act as a sequestering agent which could be removed by filtration.

The amino function of the thiomorpholine unit could be further elaborated with a range of commercially available

isocyanates (reaction 7) and isothiocyanates (reaction 6) to furnish ureas **6a–6p** and thioureas (e.g. **7**), respectively. The reaction of the isothiocyanate required the presence of diethylaminomethyl polystyrene<sup>11</sup> as basic catalyst. The excess quantities of the isocyanates and isothiocyanates were scavenged with aminomethyl polystyrene. This was followed by a brief treatment of the reaction solution with Amberlyst 15 and resulted in pure products being isolated. If desired, the diastereomeric mixture could be separated by classical methods to aid <sup>1</sup>H NMR spectroscopic determination of the products.

The resultant thiomorpholine derivatives could be treated with a solution of dimethyldioxirane in acetone to give the corresponding sulfones **8a–8p** also in a clean reaction process (reaction 8).<sup>12</sup> After complete conversion the dimethyldioxirane was evaporated together with the solvent to afford the pure products.

An attempt to alkylate the amino function in **4a** reductively with a range of aromatic aldehydes using the cyano borohydride methodology showed gradual, clean conversion to the products **9a–9c**, but was not synthetically useful because the reaction could not be driven to completion in these cases without requiring excessive reagent sequestration (Scheme 3).



Scheme 3

In conclusion we have developed a new clean *multi-step* preparation of piperidino-thiomorpholines **6** and their corresponding sulfones **8** starting from 4-piperidone **1** by a process which is suitable for automated synthesis. Although we have only generated a library of 32 ureas (**6a–p**, **8a–p**) to demonstrate the versatility of sequentially applying polymer supported reagents and sequestering agents in synthetic sequences, many further analogues could, in principle, be prepared by this route. Due to the high yielding nature of all reactions this could be carried out without the need for any chromatographic purification. All intermediates were essentially pure according to LC-MS and could be isolated by intercepting part of the reaction streams. Yields and purities of the various products are given in Table 1.

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- Yield for reaction from precursor compound.
- Masses given are obtained in positive mode and are *M* + *H* or in some cases *M* + *NH*<sub>4</sub>. No mass ions were observed for compounds **2b** and **2d** under ES-MS conditions.
- cis*:*trans* ratio by separation was determined to be ~1:2.
- Quantitative on 40 mg scale, 74% on 200 mg scale.
- About 60% conversion after 2 days, but reaction does not go to completion on extended reaction time.

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