Readily Prepared Resin-Bound Thioimidates as Reagents for the Synthesis of Amidines

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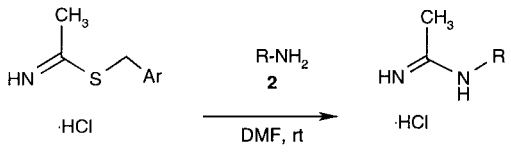
Abstract: The use of commercially available resins to prepare novel and stable polymer supported thioimidates was investigated. Polymer supported thioimidates were found to enable acetamidine formation in a convenient manner, with a significantly easier work-up than solution-phase reactions.

Key words: amine, acetamidine, scale-up, solid-phase synthesis, polymers

A variety of procedures for the synthesis of amidines have previously been reported.[1,2] Among them, the use of thioimidates such as S-benzylthioacetimidate hydrochloride[3] or hydrobromide or S-(2-naphtylmethyl) thioacetimidate is well established.[4] The exploitation of thioimidates as general reagents for the synthesis of substituted acetamidines capitalises on their ability to react with poor nucleophilic amines. The reaction of thioimidate hydrochlorides with amines occurs smoothly in methanol or ethanol at room temperature in an inert atmosphere. However, the method has significant drawbacks when applied to large-scale synthesis.

During the course of our investigations in process research directed towards the scale up of the synthesis of selective NOS inhibitors[5], we sought alternative amidination procedures.

The key transformation in the above process involved the use of thioimidates to convert amines to acetamidines. Thus, the thioimidates **1a,b** can be prepared from the corresponding benzyl or naphtyl chlorides and treated with amine **2a** to give the amidine **3a**[5] using standard procedures (Scheme 1). [6,7]



1 a **Ar**=Ph
b **Ar**=Naphth

3

2a, 3a **R**=$(CH_2)SO_2CH_2CH(NHBoc)COOH$

Scheme 1

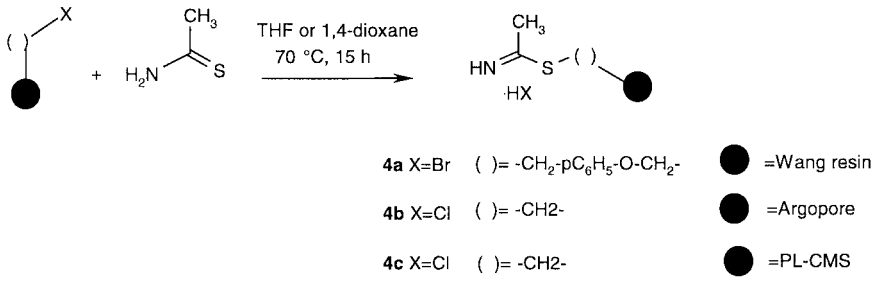
Unfortunately, S-benzyl thioimidate results in the generation of benzyl mercaptan as an unwanted reaction by-product. The use of S-(2-naphtylmethyl)thioacetimidate bromide represents a great improvement since it affords acetamidines and non odorous thiol byproducts. Nevertheless, in our hands some reagent-related impurities were detected in the final drug substance and proved to be difficult to be completely removed without any chromatographic procedure during the scale-up phase.

New procedures or alternative work-ups were therefore needed.

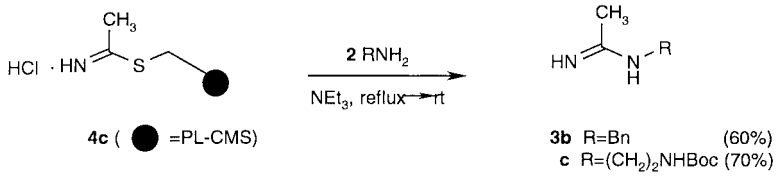
The current interest in solid-phase organic synthesis has led to a renewed interest in a complementary technique in which solid supported reagents are used in solution phase chemistry. In an effort to make the above reaction more convenient, we linked the methyl thioacetamide moiety to polymer supports (Scheme 2) and here report on initial studies for the preparation of such reagents and their reactivity. The new polymer-supported reagent results from reaction of methyl thioacetamide with different polymer types.[8] Wang Bromo resin, Argopore and chloromethyl-polystyrene (PL-CMS) were selected for a preliminary screening and gave respectively the new polymer supported thioimidates **4a-c** (Scheme 2).[9]

PL-CMS afforded from 70% to 90% substitution of the benzylic chlorine atoms by the thio function, whereas 50% was obtained with the Wang Bromo resin. Data obtained from running MAS^{1}H NMR spectra with Argopore resin are not predictable due to the resin properties. Nevertheless, subsequent reaction with amine **2a** (entry 5, Table) indirectly confirms the expected functionalisation.

Reaction of the polymer-bound thioimidate was initially carried out by adding suspension of the amine to the resin and leaving the mixture stirring overnight at room temperature. A variety of experiments were then tried using **2a** as substrate and are reported in the Table (entries 1-6). Although a good conversion was observed (entry 6, Method A) isolation of **3a** by simple filtration was not feasible since the reaction never went to completion.[10] An additional problem in our hands was the very poor solubility of amine **2a** in the most suitable solvents used with the selected resins. The use of dioxane/water gave the best result in terms of conversion.



Scheme 2



Scheme 3

Table Reaction of resin bound thioimidates with amines to give amidines

Entry	Amine	Solvent	Resin [a] (eq)	Results (**3/2** ratio, **3** yield)	React. Cond. (°C, h)
1	**2a**	DMF/Ethanol 2/1	**4b** (2)	**3a+2a** [b]	(20, 15)
2	**2a**	DMF/Ethanol 2/1	**4c** (2)	**3a+2a** [b]	(20, 15)
3	**2a**	DMF	**4b**(2)	**3a+2a** [b]	(20, 15)
4	**2a**	DMF	**4c**(2)	**3a+2a** [b]	(20, 15)
5	**2a**	Dioxane/water 7/3	**4a** (2)	**3a+2a** [b]	(20, 15)
6	**2a**	Dioxane/water 7/3	**4c**(2)	**3a / 2a** (84/16) [c]	Method A
7	**2b**	THF, NEt_3	**4c** (7)	**3b** (60%)	Method B
8	**2c**	THF, NEt_3	**4c** (7)	**3c** (70%)	Method B

[a]stoichiometry calculated on the basis of the typical loading of starting commercially available resins, assuming 100% functionalisation with thiourea.
[b]**3a**/**2a** ratio ca. 1/1 calculated by HPLC; [c]isolation of **3a** not carried out in these cases.

In order to overcome the solubility issue and with the aim of getting a complete reaction, amines **2b** and **2c** were selected as simpler models to optimise the reaction (entries 7-8, Scheme 3, Method B). By using a larger excess of resin **4c** (from PL-CMS) a complete conversion of the starting amine **2** into the acetamidine was thus observed by HPLC. After aqueous work-up to remove traces of triethylamine, **3b**[4] and **3c** were isolated in 60% and 70% yield, respectively, as pure compounds. [11]

In summary, polymer-bound thioacetamidine reagents were prepared and their potential use as reagent for acetimidation reaction was demonstrated. The polymer-supported approach affords easy isolation of the products from thioamidation, provided that the reaction goes to completion. Even though further studies remain to be done to establish the scope and limitations of this procedure, this paper marks the first efforts in adapting the reaction to polymer-supported reagents.

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References and Notes

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(8) Argopore-Cl (loading 1.06 mmol/g) was purchased from ARGONAUT Technologies; PL-CMS (loading 1.98 mmol/g) from Polymer Laboratories and Bromo-Wang (loading 1.19 mmol/g) from NOVA BIOCHEM.

(9) **General procedure to synthesise Polymer-Bound thioimidate.** The reaction mixtures resulting from the addition of 0.5 g of each resin to 3 mL of 1M solution of thioacetamide in the selected solvent (THF for Argopore and Chloromethylpolystyrene and 1,4-dioxane for Bromo-Wang), were left at 70 °C for 15 h. After filtration, washing with the selected solvent and drying, the degree of substitution was determined quantitatively by NMR analysis. The new resins were fully characterised by MAS ^{1}H NMR Spectroscopy. (400 MHz CD_2Cl_2): δ 4.5 (m, 2H, -CH_2Cl of the commercial available PL-CMS resin), 2.5 (m, 3H, -CH_3-)

(10) **Reaction of polymer-bound thioimidate (Method A).** A suspension of amine **2a** (0.0296 g; 0.1 mmol) in 3 mL of solvent (dioxane/water 7/3) was added to resin **4c** (0.1 g; 2 eq calculated assuming loading 1.98 mmol/g) and left at room temperature overnight. The resulting suspensions were stirred overnight at room temperature, then filtered and the solution concentrated under vacuum to give almost quantitatively a crude material containing **3a** and unreacted **2a** in 84/16 ratio. HPLC analysis (Hypersil BDS, 25 × 4.6 cm, water/acetonitrile 85/15+0.1% $HClO_4$, 1 mL/min; r.t. (min) of comp. **3a**: 8.28; r.t. (min) of unreacted compound **2a**: 7.18. Spectroscopic and analytical data for compound **3a**[5] are in agreement with those obtained by solution phase experiments.

(11) **Reaction of polymer-bound thioimidate (Method B).** A typical experiment was carried out as follow: (3.5 g; 7 eq calculated assuming loading = 1.98 mmol/g) of **4c** were added to amine **2b** (0.107 g; 1 mmol) or **2c** (0.160 g; 1 mmol) in 40 mL of THF in the presence of triethylamine (0.97 mL; 7 eq). The suspension was left at reflux for 3 h and at r.t. for 20 h. The reaction was monitored by HPLC until disappearance of the starting amine. (Luna C18(2), 50 × 2.0 mm, Mobil Phase A1 = water with 0.05%TFA, Mobil Phase B1 = Acetonitrile with 0.05%TFA, from 100% A1 t = 0 to 95/5 B1/A1 t = 8. r.t. (min) of compound **2b**: 0.898; r.t. (min) of compound **3b**: 1.894. r.t. (min) of compound **2c**: 3.549; r.t. (min) of compound **3c:** 2.246.
The resin was filtered off, washed with methanol and the resulting solution concentrated under vacuum. After aqueous work-up to remove traces of triethylamine, **3b** was isolated in 60% yield and **3c** in 70% yield, respectively. The latter was converted into the corresponding hydrochloride and characterised as salt.
Compound 3b[4]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (bs, 2H); 7.2-7.35 (m, 5H); 4.26 (s, 2H); 1.97 (s, 3H). **Compound 3c** (as hydrochloride): calc. $C_9H_{19}N_3O_2$ HCl: C: 45.47 H8.45 N17.68 found C: 45.73 H8.44 N17.23; MS (FAB) *m/e* 202 (MH^+); IR ν_{max} 3264 and 3112 (NH and NH_2), and 1694, 1677, 1645 (C=O and C=N) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (bs, 2H); 7.2-7.35 (m, 5H); 4.26 (s, 2H); 1.97 (s, 3H).

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