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Solid-phase synthesis of 2-imidazolidinethiones via Mitsunobu reaction of *N*-(2-hydroxyethyl)thioureas

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Abstract—This letter reports the solid-phase synthesis of 2-imidazolidinethiones via the N-cyclization of *N*-(2-hydroxyethyl)thioureas using the Mitsunobu reaction in good yield and purity. This process employed the reductive amination of an ArgoGel-MB-CHO resin to anchor the aminoalcohols, followed by a reaction with isothiocyanates to give the resin-attached *N*-(2-hydroxyethyl)thioureas. Cleavage of the 2-imidazolidinethiones was performed with trifluoroacetic acid.

Substituted thioureas has recently gained much interest as a wide variety of known biological active compounds such as non-nucleoside inhibition of HIV-1 and HIV-2 reverse transcriptases,[1] potent orally active antagonism of the bradykinin B (**2**) receptor,[2] and antioxidant active compounds with potent anti-HIV activity.[3] The solid-phase synthesis of small heterocycles is receiving considerable attention because it can be applied to the rapid generation of diverse libraries of drug-like compounds.[4] Recently, Goff and Houghten reported the synthesis of 2-imidazolidinethiones on solid support by tandem aminoacylation/Michael addition[5] and by reduction of dipeptides/thiocarbonylation with carbonyldiimidazole,[6] respectively. In this letter, we report the solid-phase synthesis of 2-imidazolidinethiones using the intramolecular cyclization of resin bound *N*-(2-hydroxyethyl)thioureas under Mitsunobu conditions, which can be used for the high throughput synthesis of drug libraries for potential drug discovery.

The cyclization of *N*-(2-hydroxyethyl)thioureas can provide different products depending on the reaction conditions and substrates such as S-cyclized,[7] N-cyclized,[8] or O-cyclized[9] products. The cyclization of resin-attached *N*-(2-hydroxyethyl)thioureas has been extended to a solid-phase synthesis protocol for 2-imidazolidinethiones. Resin-bound substrates **6** were designed as precursors to generate 2-imidazolidinethiones, which were conveniently prepared from various commercially available aminoalcohols and isothiocyanates for diversity generation.

Scheme 1 shows the synthetic route of the 2-imidazolidinethione scaffold. The first step in solid-phase reactions was the coupling of various amino alcohols onto an ArgoGel-MB-CHO resin[10] via reductive amination, followed by the protection of the free alcohol **3** with *tert*-butyldimethylsilyl chloride (TBSCl) according to the previous procedures.[11] Treatment of this intermediate with isothiocyanates afforded the thioureas resin **5**, and subsequent deprotection of the silylated hydroxy group with tetrabutyl ammonium fluoride in THF yielded resin **6**. The key reaction step in this scheme, the intramolecular cyclization of resin **6** under Mitsunobu conditions, afforded mainly the required N-cyclized products. The desired 2-imidazolidinethiones were released at 95% TFA (in H_2O) cleavage for 4 h in high yield and purity and characterized by the spectroscopic methods.[12] The results are summarized in Table 1. Resin **6** derived from either aliphatic (entry **8a**) or aryl isothiocyanates (entries **8b–k**) furnished the required N-alkylation products, but aminoalcohol was limited to the primary alcohol.[13]

In summary, a solid-phase synthetic method was developed for the parallel synthesis of a wide range of disubstituted 2-imidazolidinethiones using aminoalcohols and isothiocyanates. The final products were obtained in

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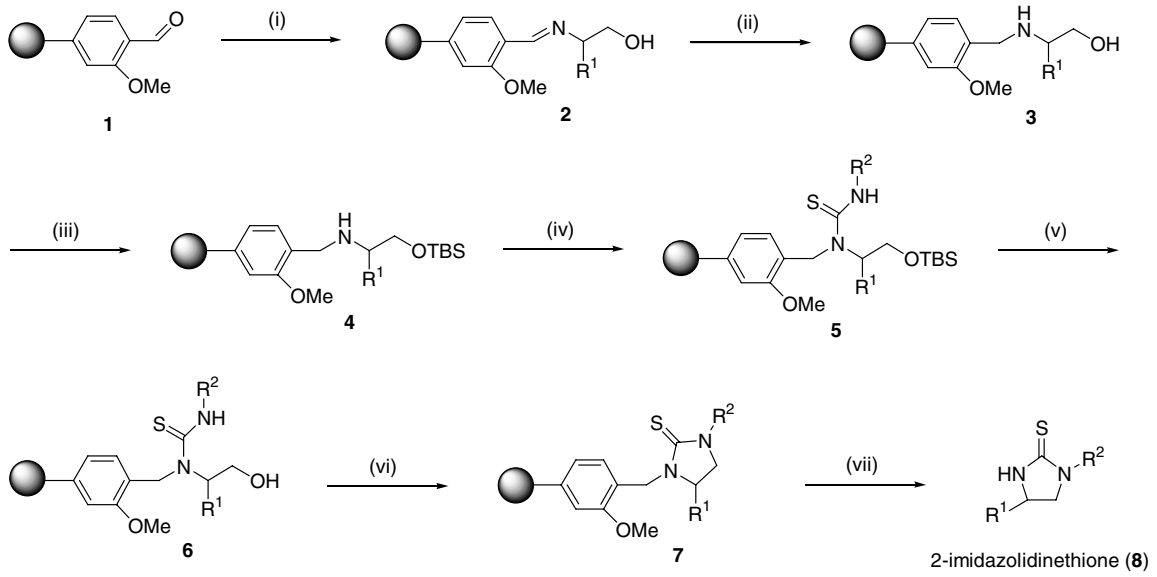

Scheme 1. Solid-phase synthesis approach to 2-imidazolidinethiones. Reagents and conditions: (i) trimethylorthoformate/MeOH = 1/4, $H_2NCH(R^1)CH_2OH$ (2 equiv), 24 h; (ii) boran–pyridine complex (3 equiv), AcOH (3 equiv), 24 h; (iii) TBSCl (3 equiv), DMAP (0.1 equiv), TEA (3 equiv); (iv) R^2NCS (5 equiv), THF; (v) tetrabutyl ammonium fluoride (5 equiv), THF; (vi) DEAD (5 equiv), Ph_3P (5 equiv), CH_2Cl_2, o/n; (vii) 95% TFA/H_2O, 4 h.

Table 1. Synthesis of 2-imidazolidinethione derivatives (**8a**–**k**) from the solid-phase as outlined in Scheme 1

Entry	R^1	R^2	Yield[a] (%)	Purity[b] (%)
8a	H	*i*-Pr	45	72
8b	H	C_6H_5	52	74
8c	H	4-MeC_6H_4	61[c]	81
8d	H	4-$NO_2C_6H_4$	50	99
8e	H	4-ClC_6H_4	66	82
8f	H	3-$CF_3C_6H_4$	40	90
8g	H	4-CNC_6H_4	59	94
8h	H	2-Cl, 4-$NO_2C_6H_3$	71	93
8i	H	2-MeO, 4-$NO_2C_6H_3$	75	95
8j	Me	4-$NO_2C_6H_4$	54	96
8k	(*S*)-*i*-Pr	4-$NO_2C_6H_4$	63	92

[a] Overall yields from the ArgoGel-MB-CHO resin **1** having loading capacity of 0.41 mmol/g.

[b] Purity was determined by HPLC after short-pass silica gel column chromatography.

[c] Mp of free base, 111–112 °C (Ref. 14, mp = 112–113 °C).

seven steps in high purity with moderate to good yield. This synthetic methodology is ideally suited for automated applications, because all the reactions were carried out under ambient conditions.

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(3×5 mL), MeOH (3×5 mL), THF (3×5 mL), and CH_2Cl_2 (3×5 mL) and dried in vacuum to give resin **5**. The deprotection of the silyl group in resin **5** with tetrabutyl ammonium fluoride (5 equiv) was carried out for 15 h, washed with the same solvent system and dried in vacuum for 30 min. Resin **6** in CH_2Cl_2 (5 mL) was incubated in diisopropyl azodicarboxylate (5 equiv) and triphenyl phosphine (5 equiv) for 24 h and washed thoroughly to give resin **7**. Finally, the dried resin was cleaved in a 95% TFA/H_2O solution (5 mL). The cleavage solution was collected by filtration, dried by evaporation and analyzed by HPLC to a purity of 93% after short-pass silica gel column chromatography. 1-(2-Chloro-4-nitrophenyl)imidazolidine-2-thione (**8h**) was characterized as TFA salts: $R_f = 0.6$ (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.4–7.99 (m, 3H), 4.12 (br s, 2H), 3.59 (br s, 2H); ESMS (M^+) 257.

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