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Substituted 2-amino-1,3,4-thiadiazines: a novel solid-phase approach

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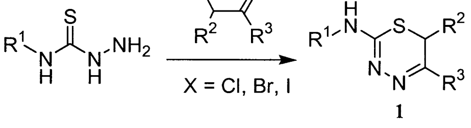
Abstract—A novel and facile strategy for synthesis of substituted 2-amino-1,3,4-thiadiazines on solid support is described. Resin bound isothiocyanate prepared from an immobilised primary amine and di-(2-pyridyl)thionocarbonate was reacted with hydrazine hydrate to form the intermediate thiosemicarbazide. Further reaction with a range of α-bromoketones followed by mild acidic cleavage from the solid support released the substituted 2-amino-1,3,4-thiadiazines in respectable yields and excellent purity. © 2002 Elsevier Science Ltd. All rights reserved.

Chemists working in the area of solid-phase synthesis have over the last decade generated an impressive collection of solid supported strategies.[1] The application of traditional solution-phase reactions on solid support has by no means been unchallenging; however the demanding procedure of optimisation has rewarded the medicinal chemist. The time required to conduct a thorough structure–activity relationship can be drastically shortened with the application of a robust solid-phase synthesis strategy. Parallel syntheses combined with high throughput screening have proven to be two very important tools in accelerating the lead discovery process.[2] With the constant need and challenge for new structurally diverse leads we decided to investigate a new solid supported strategy for the synthesis of substituted 2-amino-1,3,4-thiadiazines; 5-aryl-2-dialkylamino-6*H*-1,3,4-thiadiazines have been reported to possess analgesic and 5-lipoxygenase inhibitory activity.[3] To our knowledge, no previous attempts have been made to synthesise 1,3,4-thiadiazines on solid support.

The major route to substituted 2-amino-6*H*-1,3,4-thiadiazines **1** via traditional solution-phase synthesis is the condensation of α-haloketones with thiosemicarbazides (Scheme 1).[4] In a previous study we have described the formation of an intermediate resin-bound isothiocyanate in the preparation of substituted 1,3,4-oxadiazoles[5] and *N*,*N*′,*N*″-substituted guanidines.[6] Reaction of the immobilised isothiocyanate with hydrazine followed by *S*-alkylation with a range of α-bromoketones and cyclodehydration was the basis of the present study. In our attempts to find the optimal synthesis protocol, we selected a range of solvents and reaction conditions to investigate the formation of substituted 2-amino-1,3,4-thiadiazines on solid support. In this communication we report the conclusions of this study and hence a novel solid-phase strategy for the synthesis of substituted 1,3,4-thiadiazines.

The route developed is outlined in Scheme 2, and the various stages are discussed below. Optimisation of the procedure was monitored throughout by cleavage of small portions (5–10 mg) of the intermediate resin followed by HPLC, MS and NMR analysis.

Commercial Wang resin[7] was first loaded with Fmoc-β-Ala-OH employing *N*,*N*′-diisopropylcarbodiimide (DIC) in the presence of a catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP). The reaction of Wang resin and Fmoc protected amino acids when employing the symmetric anhydride strategy does not always yield quantitative esterification,[8] therefore, as a general procedure, the resin was 'capped' with acetic anhydride. Deprotection of the resin-bound amino acid



Scheme 1.

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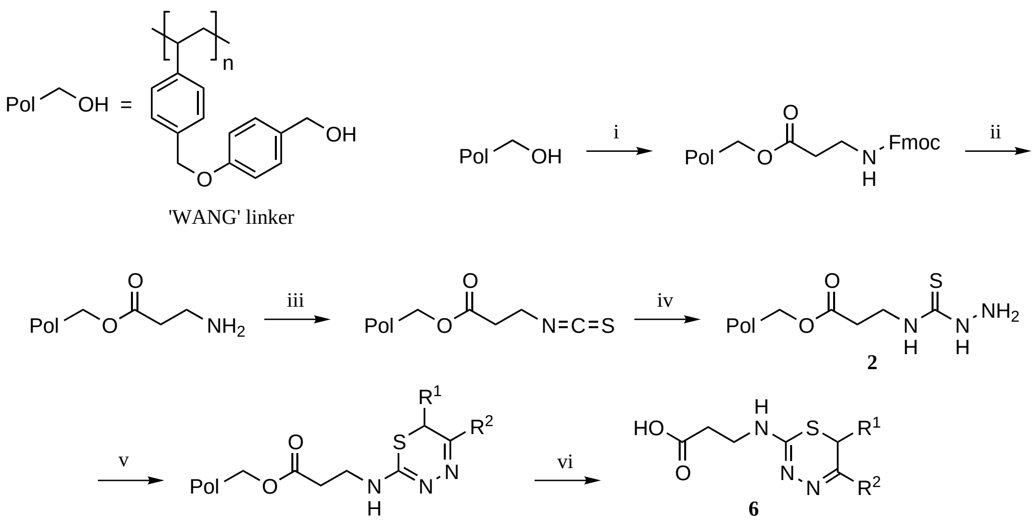


Scheme 2. *Reagents and conditions*: (i) (a) $HOOC(CH_2)_2NHFmoc$, DIC, DMAP, DMF:DCM (1:1 v/v), 20°C, 16 h; (b) 5% Ac_2O, NMP:DIPEA (5:1 v/v), 20°C, 20 min; (ii) piperidine:NMP (1:4 v/v), 20°C, 20 min; (iii) DPT, DCM, 20°C, 3 h; (iv) $NH_2NH_2{\cdot}H_2O$, NMP, 20°C, 5 h; (v) $R^1CHBrCOR^2$, DMF, 20°C, 16 h; (vi) TFA:DCM (1:1 v/v), 20°C, 2 h.

with piperidine followed by reaction with di-(2-pyridyl)thionocarbonate (DPT) yielded the immobilised isothiocyanate intermediate. Further reaction with hydrazine monohydrate (7 molar equivalents) in 1-methyl-2-pyrrolidone (NMP) at 20°C for 5 h yielded the corresponding resin-bound thiosemicarbazide **2** without cleavage from the resin. Even when 5 molar equivalents of hydrazine hydrate were reacted over the extended time of 16 h, only a trace of hydrazinolysis was observed, despite reports that cleavage can be achieved by the reaction of large excesses of hydrazine (50 molar equivalents in DMF, 66 h) with acids anchored to benzyl alcohol resins.[8] Initial attempts to synthesise 1,3,4-thiadiazines from resin **2** using DMSO as the solvent showed that activated α-bromoketones e.g. 4-cyanophenacyl bromide yielded a significant amount of the doubly alkylated by-product **5**, whereas reaction with de-activated α-bromoketones e.g. 2-bromo-2′,4′-dimethoxy-acetophenone yielded the uncyclised intermediate **3** (Scheme 3).

We found that mono-alkylation followed by complete cyclodehydration was solvent dependent, and the results of the study (Table 1) showed that DMF yielded products of superior purity.

Release of the final substituted 2-amino-1,3,4-thiadiazines **6** was achieved by treatment with 50% trifluoroacetic acid (TFA) in dichloromethane (DCM). A small library of 1,3,4-thiadiazines was synthesised using this strategy. The results are given in Table 2.[9]

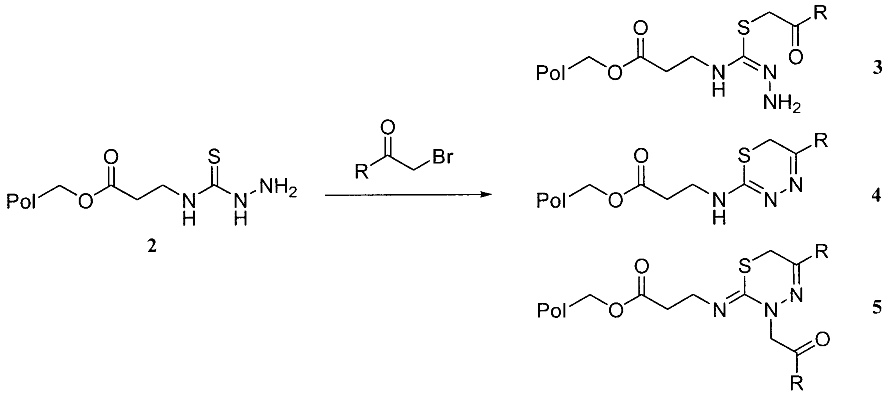
In summary, we have studied and developed a new solid supported strategy for the synthesis of substituted

Table 1. Selected conditions and reagents for conversion of resin **2** to **4d**[a]

Solvent[b]	% **4d** (% **3d**, **5d**)	Solvent[b]	% **4d** (% **3d**, **5d**)
1,4-Dioxane	74 (10, 7)	NMP	84 (6, 4)
DMF	98 (1, 0)	DMSO	51 (17, 15)
1,2-Dichloropropane	10 (80, 0)	DCM	74 (5, 7)

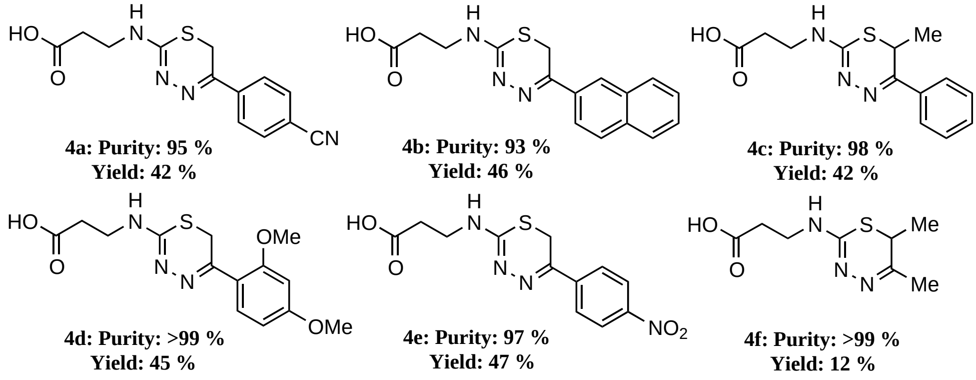
[a] Results are given as purity of **4d** (ELS peak integration).

[b] All reactions were run over 16 h at room temperature.



Scheme 3.

Table 2. Library of 1,3,4-thiadiazines prepared[a]



4a: Purity: 95 %
Yield: 42 %

4b: Purity: 93 %
Yield: 46 %

4c: Purity: 98 %
Yield: 42 %

4d: Purity: >99 %
Yield: 45 %

4e: Purity: 97 %
Yield: 47 %

4f: Purity: >99 %
Yield: 12 %

[a] Purity is calculated from ELS peak integration. Percentage yield is calculated from NMR concentration studies and the original loading of the Wang resin.

2-amino-1,3,4-thiadiazines. The synthetic strategy yielded the substituted 2-amino-1,3,4-thiadiazines in respectable yields and high purities.

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9. Data for **4a**: δ_H [300 MHz; $(CD_3)_2SO$] 8.08–7.93 (4H, m, Ar-H), 4.18 (2H, s, SCH_2), 3.67 and 2.65 (each 2H, t, $J=6.6$ Hz, $COCH_2CH_2N$). Calcd for $C_{13}H_{12}N_4O_2S{\cdot}C_2F_3O_2{\cdot}0.8H_2O$: C, 43.23; H, 3.53; N, 13.44. Found: C, 43.22; H, 3.35; N, 13.08. LC-MS (ESI): *m/z*: 289.4 $[M+H]^+$. Data for **4d**: δ_H [300 MHz; $(CD_3)_2SO$] 7.47 (1H, d, $J=8.7$ Hz, Ar-H), 6.73 (1H, d, $J=2.3$ Hz, Ar-H), 6.65 (1H, dd, $J=8.7$, 2.3 Hz, Ar-H), 4.09 (2H, s, SCH_2), 3.87 and 3.84 (each 3H, s, OCH_3), 3.65 and 2.65 (each 2H, t, $J=6.4$ Hz, $COCH_2CH_2N$). Calcd for $C_{14}H_{17}N_3O_4S{\cdot}C_2F_3O_2{\cdot}0.8H_2O$: C, 42.54; H, 4.37; N, 9.30. Found: C, 42.59; H, 4.03; N, 9.17. LC-MS (ESI): *m/z*: 324.4 $[M+H]^+$.