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Solid-phase synthesis of substituted 1,3,4-thiadiazoles

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Abstract—Two novel and facile syntheses strategies for the synthesis of substituted 1,3,4-thiadiazoles on solid support are described based on a resin-bound thiosemicarbazide: (a) treatment with aldehydes to form immobilised thiosemicarbazones, and oxidative cyclodehydration with iron(III) chloride forms resin-bound 1,3,4-thiadiazoles; and (b) treatment with di-(2-pyridyl)thionocarbonate affords immobilised 1,3,4-thiadiazole-2-thione which is selectively mono-*S*-alkylated to yield resin-bound 2-alkylthio-1,3,4-thiadiazoles. Acidic cleavage with trifluoroacetic acid yields the products from both studies in good yield and excellent purity.

We have recently reported a novel solid-phase synthesis strategy for the formation of substituted 1,3,4-oxadiazoles via a resin-bound isothiocyanate and 1-acylthiosemi-carbazide derivative.[1] As an extension of these studies we investigated the solid-supported synthesis of analogous substituted 1,3,4-thiadiazoles in a new application of immobilised isothiocyanates.[2] Substituted 1,3,4-thiadiazoles have become very useful compounds in medicine, agriculture and in many fields of technology. Some of the technological applications involve dyes,[3] lubricating compositions,[4] optically active liquid crystals,[5] photographic materials[6] and many others. A large number of 1,3,4-thiadiazoles have been patented in the agricultural field as herbicides,[7] fungicides[8] and bacteriocides.[9] In the medical field one of the best known drugs based on a 1,3,4-thiadiazole is acetazolamide (acetazola),[10] a carbonic anhydrase inhibitor launched in 1954. Its indications and usage are many, including the treatment of glaucoma, epilepsy and congestive cardiac failure (Fig. 1).

Solution-phase syntheses of 1,3,4-thiadiazoles have been very closely linked to the syntheses of 1,3,4-oxadiazoles, the oxidation of acylhydrazones being a good example. Thus, the reaction of substituted thiosemicarbazides **1** with aldehydes yields the corresponding substituted thiosemi-carbazones **2**. Oxidative cyclisation of **2** can be achieved with, for example, iron(III) chloride to yield substituted 1,3,4-thiadiazoles **3** in good yield (Scheme 1).[11]

Our thoughts were directed towards the synthesis of a suitable immobilised thiosemicarbazone and the subsequent oxidative cyclodehydration to yield after acid mediated cleavage substituted 1,3,4-thiadiazoles. Another approach involved the cyclisation of the resin-bound thiosemicarbazides **4** with a thiocarbonylating agent, e.g. di-(2-pyridyl)thionocarbonate (DPT), to yield substituted 5-amino-*3H*-1,3,4-thiadiazole-2-thiones **5** which can be mono *S*-alkylated to give after acid mediated cleavage substituted 2-alkylthio-5-amino-

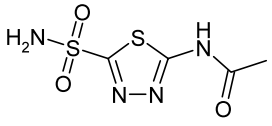
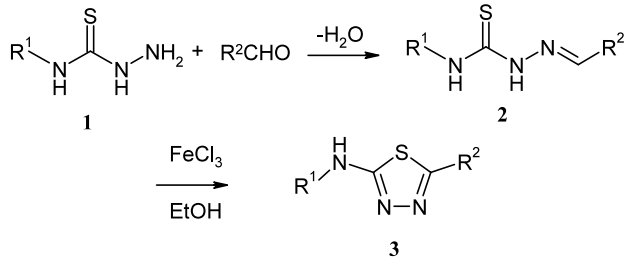


Figure 1.



1 **2** **3**

Scheme 1. Solution-phase synthesis of 1,3,4-thiadiazoles.

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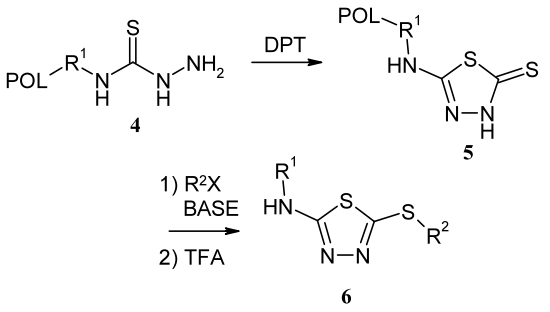


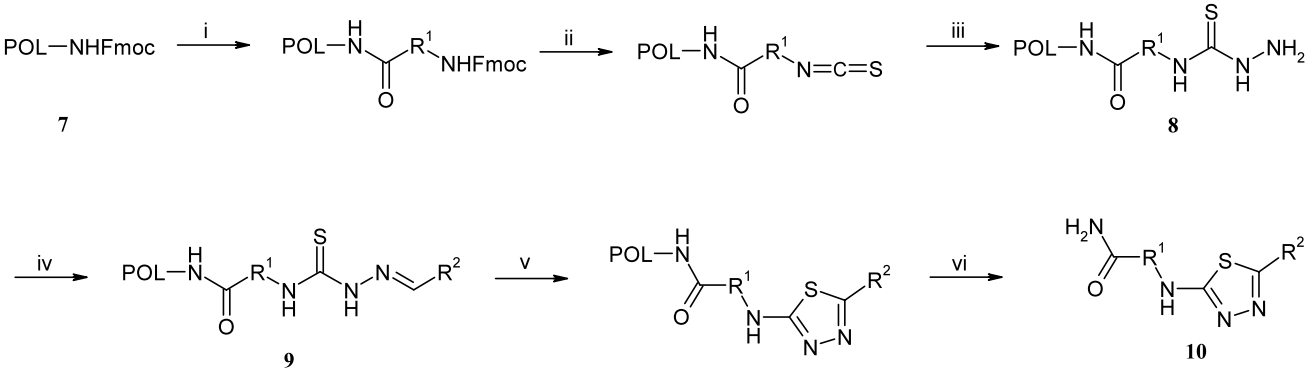
Scheme 2.

1,3,4-thiadiazoles **6** (Scheme 2). In this communication we report the conclusions of both studies and thus two new strategies for the solid-phase synthesis of substituted 1,3,4-thiadiazoles.

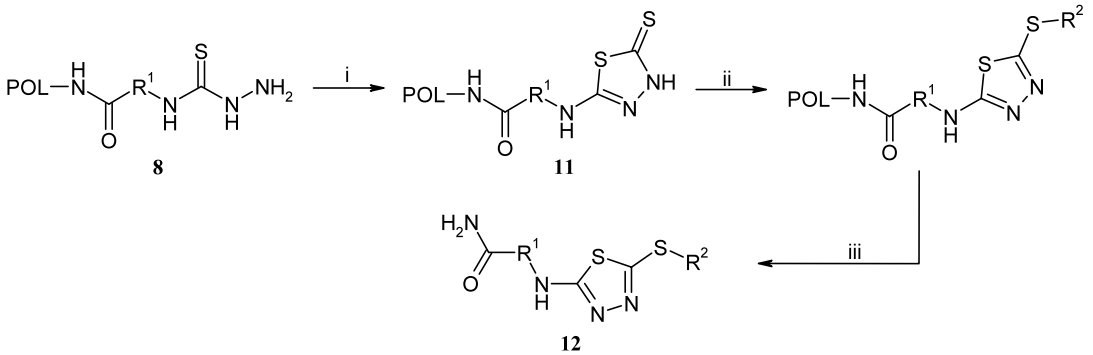
The two procedures outlined in Schemes 3 and 4 were monitored throughout by cleavage of small portions of the resins (5–10 mg) and the resulting intermediates were analysed using HPLC, MS and NMR. Commercial Rink amide resin **7**[12] was first loaded with an Fmoc-protected amino acid via the acid bromide formed in situ (Scheme 3). For these studies R^1 was held constant as 1,4-phenylene-CH_2-(N) derived from 4-(Fmoc-aminomethyl)benzoic acid to exemplify the method. Deprotection and conversion to an immobilised isothiocyanate and thence to the thiosemicarbazide **8** was performed according to the methodology that we have reported,[1] namely thiocarbonylation of the free amino group with DPT and reaction with hydrazine. Reaction of resin **8** with aldehydes in an acidic medium of DMF and trimethyl orthoformate (TMOF) yielded quantitatively the resin-bound thiosemicarbazones **9**. Several Lewis acids and oxidants (Table 1) were selected to investigate the formation of 1,3,4-thiadiazole **10a** from the intermediate resin-bound thiosemicarbazone **9a** prepared by reacting benzaldehyde with immobilised thiosemicarbazide **8**. The substituted 1,3,4-thiadiazole **10a** was released from the resin support after treatment with TFA in DCM (2:1 v/v).

In an attempt to achieve complete cyclisation, the reaction using iron(III) chloride in DCM:MeOH was performed over 20 h then repeated. The results showed complete conversion of **9a** to **10a** (after cleavage of the resin) in 99% purity by ELS. This optimised procedure was used to prepare other thiadiazoles.

In the second approach, the reaction of resin-bound thiosemicarbazide **8** with 10 molar equivalents of DPT in DCM for 4 h proceeded to yield the resin-bound



Scheme 3. *Reagents and conditions*: POL-NHFmoc = Rink Amide MBHA resin (i) (a) piperidine:NMP (1:4 v/v), 20°C, 20 min; (b) HOOCR^1NHFmoc, PyBrOP, DIPEA, NMP, 20°C, 4 h; (ii) (a) piperidine:NMP (1:4 v/v), 20°C, 20 min; (b) DPT, DCM, 20°C, 2 h; (iii) $H_2NNH_2 \cdot H_2O$, NMP, 20°C, 5 h; (iv) R^2CHO, DMF:TMOF:AcOH (9:9:2 v/v), 20°C, 5 h; (v) $FeCl_3 \cdot 6H_2O$, DCM:MeOH (2:1 v/v), 20°C, 20 h, then washed with DCM:MeOH (2:1 v/v), then step (v) repeated; (vi) TFA:DCM (2:1 v/v), 20°C, 1 h.



Scheme 4. *Reagents and conditions*: (i) DPT, DCM, 20°C, 4 h; (ii) R^2X, 1,4-dioxane, 20°C, 16 h; (iii) TFA:DCM (2:1 v/v), 20°C, 1 h.

Table 1. Selected reagents and solvents used to convert **9a** into **10a**

Reagents[a]	%[b] **9a**	%[b] **10a**
10 equiv. phenyliodine(III) diacetate in DCM	0	0
10 equiv. $FeCl_3$ in THF:MeOH, 1:1 v/v	50	50
10 equiv. $FeCl_3$ in THF:EtOH, 1:1 v/v	67	30
0.2 equiv. $Yb(OTf)_3$ in THF	94	0
10 equiv. BF_3 in dry THF	95	0
10 equiv. $FeCl_3$ in DCM:MeOH, 2:1 v/v	8	92
0.2 equiv. $Sc(OTf)_3$ in THF	76	0

[a] All reactions were run for 16 h at rt, without exclusion of atmospheric oxygen.
[b] Composition percentages given are calculated from ELS peak integration.

Table 3. Purities, yields and MS data of 1,3,4-thiadiazoles **10** and **12**

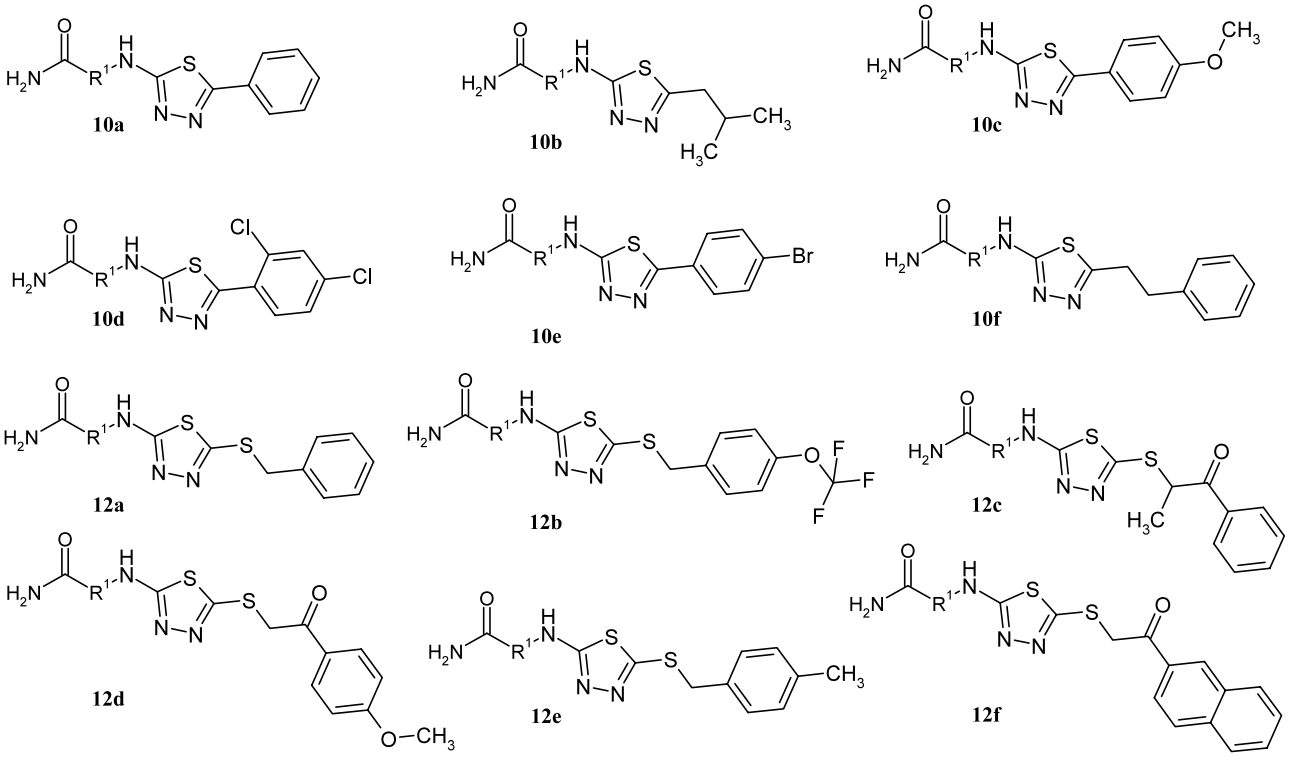
Compound	% Purity[a]	% Yield[b]	M_w	m/z $[M+H]^+$
10a	98	70	310	311.2
10b*	98	63	290	291.4
10c	95	45	340	341.2
10d*	82	12	378	379.2
10e	98	74	390	391.2
10f	99	74	338	339.2
12a*	99	49	356	357.2
12b	99	68	440	441.2
12c*	99	51	398	399.4
12d	85	72	414	415.2
12e	99	75	370	371.2
12f	80	59	434	435.2

[a] Purities given are calculated from ELS peak integration.
[b] Yields given are calculated from NMR concentration studies.
* NMR data given.[14]

thione **11** in quantitative yield as demonstrated after cleavage (Scheme 4). Mono-alkylation of thione **11** was found to proceed best when employing activated alkylating agents (e.g. α-haloketones) in 1,4-dioxane without the presence of base.[13] Release of the final substituted 1,3,4-thiadiazoles **12** was again achieved by treatment with TFA in DCM. A small library of substituted 1,3,4-thiadiazoles **10** and **12** was synthesised using the strategies outlined in Scheme 3 and Scheme 4, with R^1 held constant as 1,4-phenylene-CH_2-(N) to exemplify the method. The results are presented in Tables 2 and 3.

In summary, we have investigated and developed two novel facile solid-phase synthesis strategies for the formation of substituted 1,3,4-thiadiazoles. Immobilised thiosemicarbazones formed by the reaction of aldehydes with a resin-bound thiosemicarbazide were treated with a solution of iron(III) chloride to induce an oxidative cyclisation. TFA-mediated cleavage yielded the substituted 2-amino-1,3,4-thiadiazoles in good yield and excellent purity. In another investiga-

Table 2. Structures of representative 1,3,4-thiadiazoles synthesized



tion resin-bound thiosemicarbazide was treated with DPT to form quantitatively, the corresponding immobilised 5-amino-3*H*-1,3,4-thiadiazole-2-thione. Further reaction with activated alkylating agents followed by TFA mediated resin cleavage yielded substituted 2-alkylthio-5-amino-1,3,4-thiadiazoles in good yield and high purity.

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12. Rink Amide MBHA resin (100–200 mesh, 1% DVB, 0.64 mmol/g) was purchased from Novabiochem, Laufelfingen, Switzerland.
13. Double alkylation was observed when incorporating DIPEA into the alkylation procedure. Although the double alkylated product was not fully characterised (MS only) it was assumed that over-alkylation had taken place on the acyclic N-5 nitrogen.
14. **4-[(5-Isobutyl-1,3,4-thiadiazol-2-ylamino)methyl]-benzamide (10b)**: ^{1}H NMR (DMSO-d_6): $\delta=8.16$ (t, $J=5.6$ Hz, 1H, CH_2NH), 7.93 (bs, 1H, $CONH_2$), 7.83 (d, $J=8.3$ Hz, 2H, Ar-H), 7.41 (d, $J=8.3$ Hz, 2H, Ar-H), 7.32 (bs, 1H, $CONH_2$), 4.50 (d, $J=5.6$ Hz, 2H, CH_2NH), 2.67 (d, $J=6.8$ Hz, 2H, $CH_2CH(CH_3)$), 1.95–1.82 (m, 1H, $CH_2CH(CH_3)$), 0.90 (d, $J=6.4$ Hz, 6H, $CH_2CH(CH_3)$); ^{13}C NMR (DMSO-d_6): $\delta=168.5$, 167.9, 157.6, 142.4, 133.4, 127.9, 127.4, 47.9, 38.5, 29.0, 22.2; HRMS (Q-TOF-ES) calcd for $C_{14}H_{18}N_4OS$ (MH^+): 291.128, found 291.129.

4-{[5-(2,4-Dichlorophenyl-1,3,4-thiadiazol-2-yl-amino]-methyl}benzamide (10d): ^{1}H NMR (DMSO-d_6): $\delta=8.60$ (t, $J=6.0$ Hz, 1H, CH_2NH), 8.03 (d, $J=8.6$ Hz, 1H, Ar-H), 7.94 (bs, 1H, $CONH_2$), 7.83 (d, $J=8.3$ Hz, 2H, Ar-H), 7.80 (d, $J=1.9$ Hz, 1H, Ar-H), 7.56 (dd, $J=1.9$, 8.6 Hz, 1H, Ar-H), 7.44 (d, $J=8.3$ Hz, 2H, Ar-H), 7.34 (bs, 1H, $CONH_2$), 4.62 (d, $J=6.0$ Hz, 2H, CH_2NH); ^{13}C NMR (DMSO-d_6): $\delta=170.3$, 167.9, 151.0, 142.1, 135.0, 133.5, 131.7, 131.5, 130.2, 128.7, 128.3, 127.9, 127.5, 47.9; HRMS (Q-TOF-ES) calcd for $C_{16}H_{12}N_4OSCl_2$ (MH^+): 379.019, found 379.021.

4-[(5-Benzylsulfanyl134thiadiazol2ylamino-methyl]benzamide (12a): ^{1}H NMR (DMSO-d_6): $\delta=8.34$ (t, $J=5.6$ Hz, 1H, CH_2NH), 7.94 (bs, 1H, $CONH_2$), 7.84 (d, $J=8.3$ Hz, 2H, Ar-H), 7.39–7.23 (m, 8H, Ar-H and $CONH_2$), 4.50 (d, $J=5.6$ Hz, 2H, CH_2NH), 4.30 (s, 2H, SCH_2); ^{13}C NMR (DMSO-d_6): $\delta=169.8$, 167.9, 150.1, 142.1, 137.3, 133.4, 129.3, 128.8, 127.9, 127.8, 127.5, 47.7, 38.7; HRMS (Q-TOF-ES) calcd for $C_{17}H_{16}N_4OS_2$ (MH^+): 357.084, found 357.086.

4-{[5-(1-Methyl2oxo2phenylethylsulfanyl-1,3,4-thiadiazol-2-ylamino]methyl}benzamide (12c): ^{1}H NMR (DMSO-d_6): $\delta=8.48$ (t, $J=5.6$ Hz, 1H, CH_2NH), 8.00 (d, $J=7.1$ Hz, 2H, Ar-H), 7.94 (bs, 1H, $CONH_2$), 7.85 (d, $J=8.3$ Hz, 2H, Ar-H), 7.68–7.64 (m, 1H, Ar-H), 7.56–7.51 (m, 2H, Ar-H), 7.39 (d, $J=8.3$ Hz, 2H, Ar-H), 7.34 (bs, 1H, $CONH_2$), 5.25 (q, $J=6.8$ Hz, 1H, $CHCH_3$), 4.52 (d, $J=5.6$ Hz, 2H, CH_2NH), 1.49 (d, $J=6.8$ Hz, 3H, $CHCH_3$); ^{13}C NMR (DMSO-d_6): $\delta=196.1$, 171.2, 167.9, 145.9, 141.9, 135.1, 133.8, 133.5, 129.0, 129.0, 127.9, 127.5, 47.7, 46.5, 17.4; HRMS (Q-TOF-ES) calcd for $C_{19}H_{18}N_4O_2S_2$ (MH^+): 399.095, found 399.096.