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1,3,4-Oxadiazole formation; a novel solid support strategy

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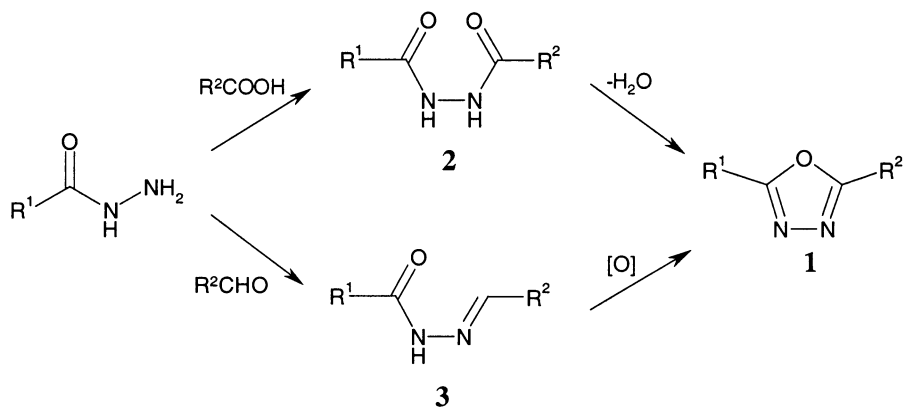
Abstract—A new approach to the synthesis of 1,3,4-oxadiazoles on solid support is described. Resin bound 1-acyl thiosemicarbazides were treated with a variety of dehydrating agents at different temperatures, which revealed that thiosemicarbazides were effectively cyclised by 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl); mild acidic cleavage from the solid support released the substituted 1,3,4-oxadiazoles in excellent purity.

Over the past decade solid supported chemistry in drug discovery has been accepted to a level whereby today there are very few pharmaceutical and academic institutions that are not actively involved. The concept 'rapid parallel synthesis' which has been one of the lures to the medicinal chemist facilitates the preparation of large structurally related compound libraries; in conjunction with high throughput screening this has saved the medicinal chemist considerable man-hours in repetitive synthesis. A spin-off associated with 'rapid parallel synthesis' has been the construction of an impressive database of solid supported organic reactions, with recent emphasis on the formation of small heterocyclic drug-like molecules on solid supports.[1]

Examples of such a pharmacophore are substituted 1,3,4-oxadiazoles. These have been of interest to the medicinal chemist for many years, they have been shown to exert anti-inflammatory,[2] antibacterial,[3] anticonvulsant,[4] and hypoglycaemic[5] properties. Substituted 1,3,4-oxadiazoles **1** have been synthesised by traditional synthesis via several approaches, two of the more popular being the cyclisation of diacylhydrazides **2**, and the oxidation of acylhydrazones **3** (Scheme 1). A solid phase approach has been reported only twice to our knowledge,[6] both of which achieved the 1,3,4-oxadiazole synthesis via cyclodehydration of a diacylhydrazide intermediate. Our thoughts were directed towards cyclodesulphurisation of the acyl thiosemicar-



Scheme 1.

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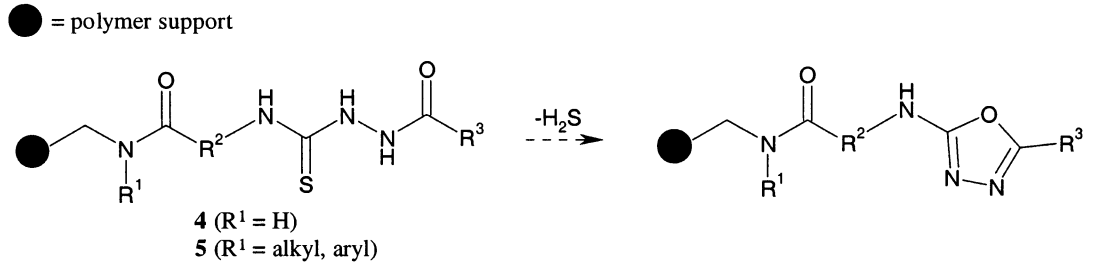


Scheme 2.

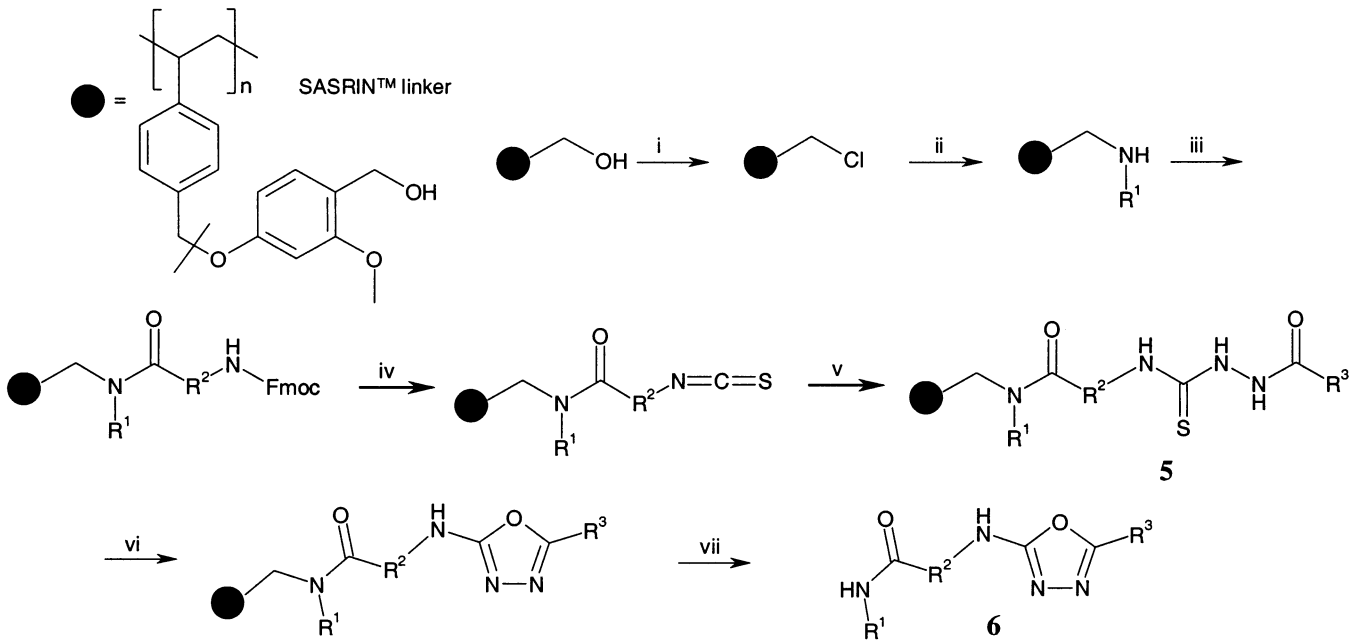
bazide intermediate **4** reported by Wilson et al.[7] (Scheme 2).

It has been described in the literature that dicyclohexylcarbodiimide can be used as a reagent for the formation of 1,3,4-oxadiazoles from acyl thiosemicarbazides in solution.[8] In our attempts to find the best method for ring closure of substituted acyl thiosemicabazides **5**, we selected a range of conditions and reagents to investigate 1,3,4-oxadiazole formation. In this communication we report the conclusions of this study and thus a new strategy for the solid phase synthesis of 1,3,4-oxadiazoles.

The procedure outlined in Scheme 3 was monitored throughout by cleavage of small portions of the resins (5–10 mg) and the resulting intermediates were analysed using MS and NMR.

SASRIN™ resin[9] was first converted to the chloromethyl analogue using the mild chlorination agent triphenylphosphonium dichloride made in situ by combining triphenylphosphine and hexachloroethane in THF.[10] The resin bound benzylic chloride could then be substituted by amines[11] and subsequently converted to the acyl thiosemicarbazide **5** as previously reported,[7] using the sequence illustrated in Scheme 3. Release of the final 1,3,4-oxadiazoles **6** after ring closure was afforded by treatment with 50% TFA in DCM.

The results of the study (Table 1) showed that cyclisation with EDC·HCl generally yielded products of superior purity. NMP was the solvent of choice for cyclisation throughout our studies; however, the solubility of EDC·HCl in NMP was so low that the carbodiimide had to be dispensed as a slurry. Employing DCC at 80°C in DMSO yielded products free from the starting acyl thiosemicarbazide **5**, but the products were contaminated with an unacceptable quantity of 1,3-dicyclohexylurea. Because our goal was a procedure suitable for automation, an alternative to the use of DCC or slurries of EDC·HCl in NMP had to be found. EDC·HCl proved to be sufficiently soluble in DMSO (0.08 mmol/ml), and treatment of resin **5** with this solution at 80°C for 16 hours led to complete cyclisation to 1,3,4-oxadiazole **6**. A small library of 1,3,4-oxadiazoles was synthesised using this strategy, all having R^2 as $(CH_2)_2$, to exemplify the method. The results are given in Table 2.



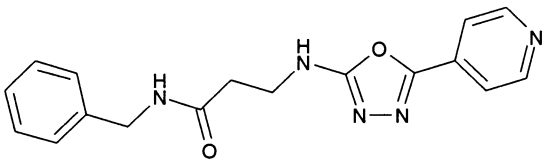
Scheme 3. (i) Ph_3P, C_2Cl_6, THF (dry), 20°C, 6 h; (ii) R^1NH_2, NMP, 20°C, 16 h; (iii) $HOOCR^2NHFmoc$, PyBrOP, DIPEA, NMP, 20°C, 4 h; (iv) (a) piperidine:NMP (1:4 v/v), 20°C, 20 min; (b) di-(2-pyridyl)thiocarbonate, DCM, 20°C, 2 h; (v) $R^3CONHNH_2$, NMP, 20°C, 16 h; (vi) EDC·HCl, DMSO, 80°C, 16 h; (vii) TFA:DCM (1:1 v/v), 20°C, 1 h.

Table 1. Selected reagents and conditions used to convert **5b** into **6b**. Results are given as percentage purity of **6b** (ELS peak integration). The number in parentheses is the percentage of unreacted **5b**

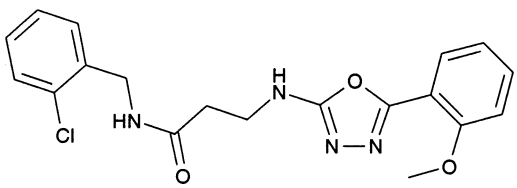
Reagents and conditions[a]	20°C	50°C	80°C
10 equiv. DIIC[b] in dry DMSO	4 (95)	20 (78)	71 (28)
10 equiv. EDC·HCl[c] in dry DMSO	50 (49)	74 (26)	95 (4)
10 equiv. DCC[d] in dry DMSO	21 (75)	4 (3)	96 (0)
50% DMF/TMOF[e]	0 (99)	4 (91)	5 (71)
10 equiv. EDC·HCl in dry NMP	93 (4)	98 (0)	98 (0)
10 equiv. Ph_3P and 10 equiv. C_2Cl_6 in dry THF	90 (7)	93 (0)	86 (0)

[a] All reactions were run over 10 hours.
[b] DIIC (1,3-diisopropylcarbodiimide).
[c] EDC·HCl (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride).
[d] DCC (1,3-dicyclohexylcarbodiimide).
[e] TMOF (trimethyl orthoformate).

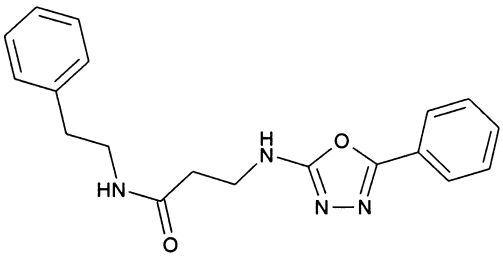
Table 2. A selection of 1,3,4-oxadiazoles prepared. Purity given is calculated from ELS peak integration. The number in parentheses is percentage yield calculated from the crude weight obtained and the original loading of the SASRIN™ resin[12]



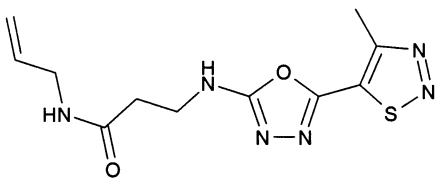
6a: 92 (67)



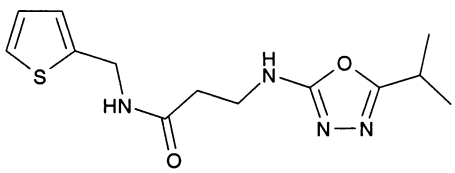
6d: 95 (70)



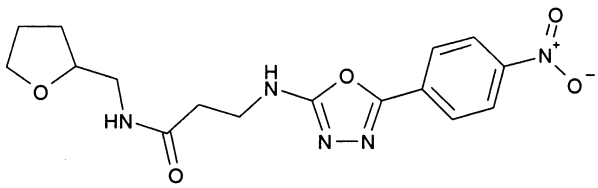
6b: 90 (46)



6e: 97 (92)



6c: 100 (44)



6f: 96 (83)

In conclusion, we have studied and developed a new strategy for the preparation of 1,3,4-oxadiazoles on solid support. The 2,5-disubstitued 1,3,4-oxadiazoles were synthesised in seven steps providing 44–92% overall yields and excellent purity.

Acknowledgements

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9. SASRIN™ resin (2-methoxy-4-alkoxybenzyl alcohol resin) was purchased from Bachem, Bubendorf, Switzerland.
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12. NMR data for compound **6a**: δ_H [400 MHz; CD_3OD] 8.74 (2H, bs, pyridyl-$CH_{2,6}$), 7.97 (2H, d, $J=5.6$ Hz, pyridyl-$CH_{3,5}$), 7.27 (5H, m, Ar-H), 4.37 (2H, s, Ar-CH_2), 3.69 (2H, t, $J=6.6$ Hz, NCH_2), 2.63 (2H, t, $J=6.8$ Hz, COCH_2).
    NMR data for compound **6c**: δ_H [400 MHz; CD_3OD] 7.27 (1H, dd, $J=1.5$, 5.1 Hz, thienyl-C2-H), 6.97 (1H, dd, $J=1.0$, 3.4 Hz, thienyl-C4-H), 6.92 (1H, dd, $J=3.4$, 4.9 Hz, thienyl-C3-H), 4.53 (2H, s, thienyl-CH_2), 3.55 (2H, t, $J=6.6$ Hz, NCH_2), 3.02 (1H, h, $J=6.9$ Hz, $(CH_3)_2CH$), 2.54 (2H, t, $J=6.6$ Hz, COCH_2), 1.30 (6H, d, $J=6.8$ Hz, $2CH_3$).