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Traceless solid phase synthesis of 2-substituted pyrimidines using an 'off-the-shelf' chlorogermane-functionalised resin †

Alan C. Spivey,*[a,b] Ratnasothy Srikaran,[a] Christopher M. Diaper[a] and David J. Turner[a]

[a] *Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, Yorkshire, UK S3 7HF*

[b] *Department of Chemistry, Imperial College London, South Kensington campus, London, UK SW7 2AZ. E-mail: a.c.spivey@imperial.ac.uk; Fax: +44 (0)20 75945833; Tel: +44 (0)20 75945841*

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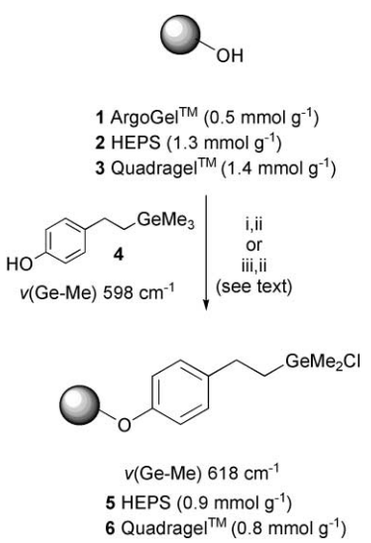
The parallel solid phase synthesis of an 18-member library of 2-substituted pyrimidines is described using a chlorogermane-functionalised resin. The success of the key Pinner-type condensations between a resin-bound enaminone and an array of amidine hydrochlorides highlights the stability of arylgermane linkers (*cf.* arylsilanes) towards strongly basic/nucleophilic conditions.

In the last few years, solid phase synthesis (SPS) and parallel techniques have been employed extensively to accelerate the preparation of new chemical entities (NCEs) for property screening.[1] Prominent applications include the synthesis of libraries of functionalised heterocycles in drug discovery[2] and crop protection programs,[3] and of conjugated polyheterocycles as new electronic materials.[4] Linker selection plays a vital role in the design of such libraries[5] and 'traceless' linkers are often preferred since they leave no 'belly-button' functional group on the released library members.[6]

We have previously described a germanium-based traceless linker for the SPS of substituted pyrazoles[7] and oligothiophenes[8] and highlighted aspects of the reactivity of arylgermanes that may make them superior to arylsilanes for such applications. For example, as a consequence of the greater β-effect of Ge *cf.* Si, arylgermanes undergo more facile S_EAr cleavage than arylsilanes.[9] This allows for cleavage with concomitant functionalisation using a wide range of electrophiles [*e.g.* $E^+ = I^+$ (ICl), Br^+ (Br_2), Cl^+ (NCS)][10] and for traceless cleavage using mild acid (*e.g.* TFA). This is particularly significant for π-deficient heterocycles for which arylsilane-based linkers are unsuitable due to the harsh conditions (*e.g.* HF) required for traceless cleavage.[11] Moreover, arylgermanes are stable towards strongly basic/nucleophilic conditions whereas arylsilanes are not.[8,12]

Here we highlight the utility of an arylgermane linker for the traceless synthesis of a library of 2-substituted-4-phenylpyrimidines by condensation of an immobilised acetophenone-derived enaminone with a series of amidines under strongly basic/nucleophilic conditions. The synthesis employs a readily prepared chlorogermane-functionalised resin which is stable and can be stored for 'off-the-shelf' use. This strategy obviates the need to pre-assemble a linker–scaffold conjugate prior to immobilisation as required previously.[7,10]

Our initial attempts to prepare a chlorogermane-functionalised resin involved the attachment of trimethylgermylethylphenol **4**[7] to ArgoGel™-OH‡ (**1**) *via* Mitsunobu-type coupling using TMAD–PBu_3 in toluene[13] followed by 'on-resin' mono-chlorodemethylation. However, the ArgoGel™ proved to be incompatible with the strongly Lewis acidic conditions required for mono-chlorodemethylation [$SnCl_4$–$MeNO_2$ (1 : 1) at 50 °C].§ Reasoning that this failure was likely due to complexation of the $SnCl_4$ with the Lewis basic PEG side chains of ArgoGel™, we investigated this transformation on hydroxyethylpolystyrene (HEPS™, **2**)‡ and on Quadragel™-OH‡ (**3**). For these resins we coupled the phenol **4** *via* chlorodehydration of the resins with $SOCl_2$ in DMF–CCl_4 then Williamson etherification with Cs_2CO_3–*n*-Bu_4NI in DMF. Compared to the Mitsunobu protocol, this was more economical and gave improved loading levels. Mono-chlorodemethylation proceeded smoothly on both of these resins as judged by IR and microanalysis, giving chlorogermane-functionalised resins **5** and **6** respectively (Scheme 1).



Scheme 1 Preparation of chlorogermane-functionalised resins. *Reagents and conditions*: i, **4** (3 equiv.), TMAD (4.2 equiv.), PBu_3 (5 equiv.), PhH, rt, 16 h; ii, $SnCl_4$ (5 equiv.), $MeNO_2$, 50 °C, 20 h; iii, a) $SOCl_2$ (1.5 equiv.), DMF–CCl_4 (1 : 10), rt, 16 h then b) **4** (2 equiv.), Cs_2CO_3 (2.2 equiv.), $^nBu_4NI$ (10 mol%), MeCN, 90 °C, 20 h.

We opted to employ Quadragel™-based resin **6** for our library synthesis because of its favourable swelling properties in alcohol solvents (*vide infra*) and superior NMR characteristics. Batches of chlorogermane-functionalised Quadragel™ **6** can be stored in the dark under nitrogen for more than 3 months without detectable decomposition.

Pyrimidines are common components of drug substances and a number of methods for their preparation by SPS have been reported.[14] Most of these are Pinner-type syntheses [NCN + C_3] in which either the '1,1-diamine' (NCN) or the '1,3-dicarbonyl' (C_3) components are resin-bound. We envisaged employing a new variant of the latter strategy involving condensation of a *p*-acetophenone-derived enaminone, anchored

† Electronic supplementary information (ESI) available: experimental procedures and key data for all the reactions described. See http://www.rsc.org/suppdata/ob/b3/b303064d/

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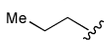
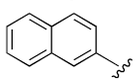
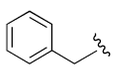
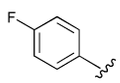
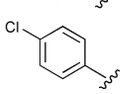
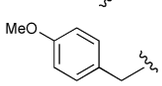
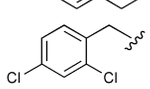
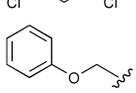
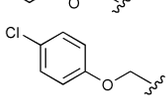
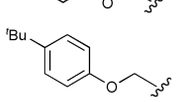
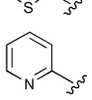
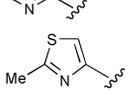
Table 1 GC-MS data for library. *Reagents and conditions:* see Scheme 3

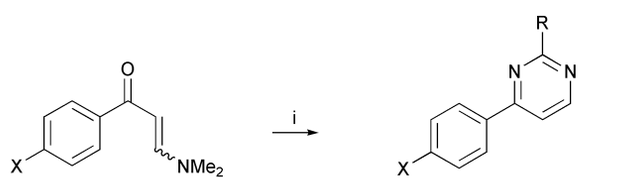
Compound	R	MW	Crude GC-MS purity (%)	Isolated yield[a] (%)
13		184	96	70
14		198	89	65
15		196	37	20
16		232	98	80
17		282	68	45
18		246	32	15
19		250	79	60
20		266	95	75
21		276	96	85
22		315	82	70
23		262	58	40
24		296	69	45
25		318	87	50
26		238	74	60
27		233	75	65
28		253	27	10

[a] After PLC purification.

to the resin *via* germanium, with a series of amidines.¶ In solution, enaminones have been reported to condense with thiourea,[15] amidines,[16] and guanidines[17] to give 2-mercapto-, 2-alkyl/aryl-, and 2-aminoalkyl/arylpyrimidines, respectively, in moderate to good yields.

Before proceeding with the SPS we examined the condensation of acetamidine and benzamidine hydrochlorides with trimethylgermyl enaminone **7**‖ in solution to give pyrimidines **9** and **10**. Optimal conditions for both involved using excess NaOMe in EtOH at reflux (Scheme 2).[16] Interestingly, trimethylsilyl (TMS) enaminone **8** affords an intractable mixture of products under these conditions comprising few signals in the crude ^{1}H-NMR attributable to either the pyrimidine or TMS groups. This contrasting behaviour probably reflects differences in pπ–dπ conjugation between Ge/Si and the aryl ring[18] and the greater stability of arylgermanes *cf.* arylsilanes towards nucleophile-induced *ipso*-demetalation. It certainly underscores the advantages of arylgermane immobilisation for SPS under strongly basic/nucleophilic conditions.

We were now in a position to proceed with SPS using the chlorogermane-functionalised Quadragel™ resin. Immobilisation of the required dioxolane-protected 4-lithioacetophenone,



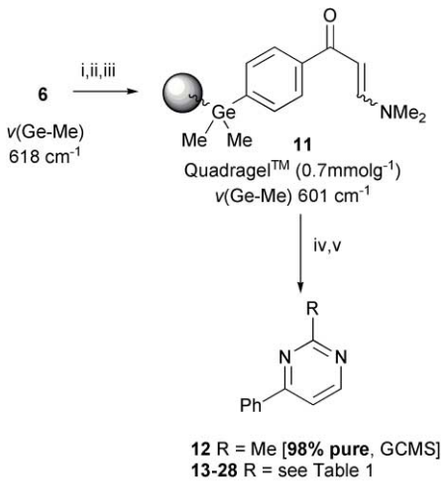
7 X = $GeMe_3$ [**8** X = $SiMe_3$]

9 X = $GeMe_3$, R = Me [**85%**]
10 X = $GeMe_3$, R = Ph [**70%**]

Scheme 2 Condensation of enaminone **7** with amidines. *Reagents and conditions*: i, RC(=NH)NH_2·HCl (3 equiv.), NaOMe (3.7 equiv.), EtOH, 85 °C, 12 h.

deprotection with PPTS, and condensation with Bredereck's reagent gave resin-bound enaminone **11**. The suitability of resin **11** for library synthesis was verified by a trial condensation with acetamidine hydrochloride followed by electrophilic *ipso*-degermylative cleavage using TFA. This gave 2-methylpyrimidine **12** in > 98% crude purity (GC-MS; 85% isolated yield).

All the resin functionalisation steps were conveniently monitored by IR because the position of the linker's sharp *ν*(Ge-Me)



Scheme 3 Library synthesis. *Reagents and conditions*: i, *p*-$BrC_6H_4C(OCH_2CH_2O)Me$ (2 equiv.), BuLi (2 equiv.), THF, −78 °C, 3 h then rt, 8 h; ii, PPTS, THF–H_2O (~10 : 1), 70 °C, 15 h; iii, Bredereck's reagent (10 equiv.), THF, 70 °C, 16 h; iv, $RC(=NH)NH_2 \cdot HCl$ (excess), NaOMe (excess), EtOH, 85 °C, 12 h; v, TFA, rt, 12 h.

absorption at *ca.* 600 cm^{-1} is very sensitive to the electronic characteristics of the attached aryl group (Scheme 3).

An array of 16 alkyl, aryl and heteroaryl substituted amidine hydrochlorides was then employed for the parallel SPS of a library of 2-substituted-4-phenylpyrimidines on a ~0.02 mmol scale. The resulting pyrimidines were released from the resin in a traceless fashion using TFA and the crude washings analysed directly by GC-MS (see Table 1). All the amidines formed the expected products although crude purities ranged from 27–98%. Generally, alkyl derived substituted pyrimidines were obtained in very high purity, otherwise there was no obvious correlation between the crude purity and the nature of the substituent.

To conclude, we have developed an efficient 'off-the-shelf' chlorogermane-functionalised Quadragel™ resin for SPS and demonstrated its utility for the traceless synthesis of a library of 2-substituted-4-phenylpyrimidines. The success of the strategy highlights the stability of the arylgermane linkage towards the strongly basic/nucleophilic conditions employed for the key condensation step.

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Notes and references

‡ ArgoGel™-OH (Argonaught Technologies) is a DVB crosslinked PS-based resin with bifurcated, hydroxyl-terminated PEG grafts containing ~60 oxyethyl repeat units. HEPS (Rapp Polymere) is a DVB crosslinked PS resin containing no PEG. Quadragel™ (Avecia Ltd.) is a DVB crosslinked PS-based resin with hydroxyl-terminated PEG grafts containing 4 oxyethyl repeat units.

§ Using a soluble model system we investigated a large number of alternative conditions for mono-demethylation but failed to establish less harsh conditions for this type of transformation.

¶ We have previously used enaminone-functionalised ArgoGel™ for pyrazole synthesis by condensation with a series of hydrazines. See ref 7.

‖ Enaminones **7** and **8** were prepared by treating Me_3GeBr/Me_3SiCl with dioxolane-protected 4-lithioacetophenone, deprotection with PPTS, and condensation with Bredereck's reagent.[7]

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