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Facile Palladium Catalysed Functionalisation of 1,2-Isothiazoline-3-ones.

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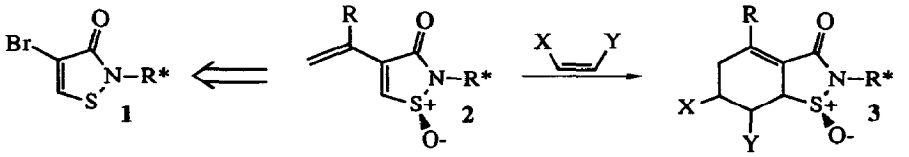
Abstract: A rapid and convenient palladium catalysed method for the regioselective synthesis of a range of usefully functionalised, homochiral 4-substituted 1,2-isothiazoline-3-ones is reported.

The use of heterocyclic systems as masked forms of organic functionality has long been a rich source of novel chemistry. During the course of work directed towards the use of chirality at sulphur to induce facial selectivity, we identified the 1,2-isothiazoline system (**1**) as an interesting and highly functionalised heterocyclic nucleus. Particularly attractive, was the demonstrated ease of oxidation at sulphur to yield 1-S-oxides coupled with the known Diels-Alder reactivity of the 4,5 double bond[1,2]. When homochiral isothiazoline 1-S-oxides were used as dienophiles a high degree of diastereofacial selectivity was observed[2]. Our aim was to develop chemistry leading to homochiral dienes (**2**) which would give possible 1-S-oxide induced diastereofacial selectivity in Diels-Alder reactions. Cleavage of the sulphur nitrogen bond[2] in the predicted Diels-Alder adduct (**3**) would lead to homochiral cyclohexene derivatives.

SCHEME 1

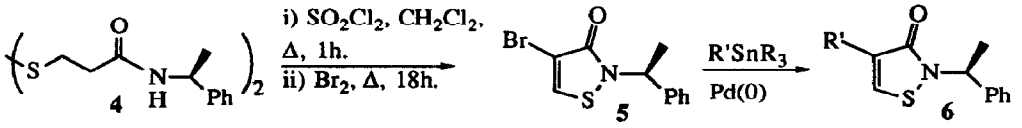


There have been several reports concerning the preparation of simple N-substituted derivatives of the parent heterocycle[3] but few methods have been reported concerning the synthesis of more functionalised systems. Since our eventual requirement was for optically pure 1-S-oxide derivatives of these heterocycles, we chose to develop our chemistry on 2-(S)-α-methyl benzyl derivatives, a readily available source of chirality, as we felt the diastereomeric 1-S-oxides would be readily separable. We further reasoned that a rapid entry to 4-functionalised derivatives would be *via* Stille[4] type coupling onto the corresponding bromo-heterocycle.

In this paper we report a mild and highly efficient route to a range of 4-substituted-1,2-isothiazoline-3-ones utilising palladium catalysed coupling procedures. Diels-Alder chemistry based on these systems is the focus for our current research and will be reported in due course.

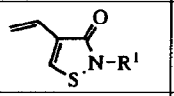
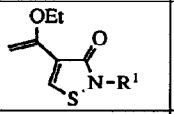
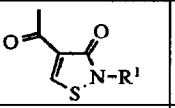
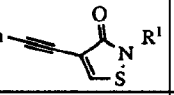
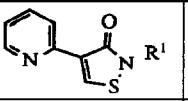
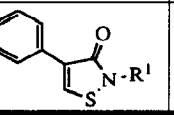
In order to obtain large quantities of 2-(S)-α-methyl benzyl-4-bromo-1,2-isothiazoline-3-one (**5**), we streamlined the previously reported two step synthesis[3] and developed a one pot procedure which gave (**5**) in 73% yield from the amide (**4**) as shown in **SCHEME 2.**

SCHEME 2



The bromide (5) was found to be an excellent substrate for Stille[4] based functionalisation and underwent efficient palladium catalysed coupling to a range of stannanes[5] as summarised in **TABLE 1.**

TABLE 1 Functionalised isothiazolines.

Entry	Product	Catalytic system	mol eq. of catalyst	mol eq. of stannane	Temp[a] (°C)	reaction time (h.)	Yield (%)
1		$[Pd(PPh_3)_4]$	0.05	1.5	110	4	80
2		$[Pd(PPh_3)_4]$	0.1	1.1	110	4[b]	69[c]
3		$[Pd(PPh_3)_4]$	0.1	1.2	110	4[b]	69[d]
4		$Pd(OAc)_2$ + 2 PPh_3	0.1	1.2	90	4	75
5		$Pd(OAc)_2$ + 2 PPh_3	0.1	1.2	110	24	69
6		$Pd(OAc)_2$ + 2 PPh_3	0.1	1.2[e]	90	4	63[f]

R^1= (S)-α-methyl benzyl, [a] solvent = toluene, [b] reagent added over 1h., [c] purified using alumina chromatography, [d] purified using silica gel chromatography, [e] tributyl stannanes used except for phenyltrimethyltin, [f] 70% conversion, 90%yield.

We found the choice of catalyst was fundamental to the success of the Stille reaction[4]. There have been many publications on various Stille[4] catalytic systems including the use of copper iodide both with[6] and without[7] palladium as a co-catalyst. Farina and Krishnan[8] have reported the increase in rate and yield using soft palladium ligands e.g. $AsPh_3$. Tributyl phosphine has also been used as a ligand in a highly reactive palladium (0) catalyst[9]. For the coupling of vinyltributyltin to the bromide (5), **SCHEME 3**, our initial attempts utilised $Pd(PPh_3)_4$ as a catalyst, but due to the rapid decrease in reactivity of the catalyst over a few days, we investigated the *in situ* generation of the catalytic complex. The results of *in situ* catalytic coupling reactions using vinyltributyltin are summarised in **TABLE 2.**[10]

SCHEME 3

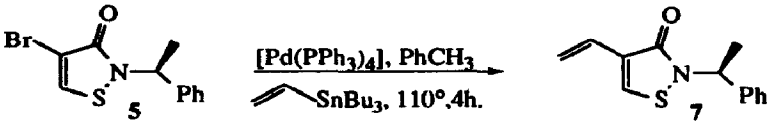


TABLE 2 *In situ* Catalytic Conditions for Production of (**7**)

Catalytic system	mol eq. of Catalyst	Solvent	Temp. (°C)	Reaction time (h.)	Yield (%)
$Pd(OAc)_2$ + 2 PPh_3	0.1	THF	60	16	12
$PdCl_2$ + 2 PPh_3	0.1	THF	60	18	12
$PdCl_2$ + 2 PPh_3	0.1	toluene	100	4	18
$Pd(OAc)_2$ + 1 PBu_3	0.1	THF	R.T.	60	20.5
$PdCl_2$ + 2 PPh_3	0.1	toluene	110	4	36-40
Pd_2dba_3 + 4 PPh_3	0.1	toluene	110	4	52
$[Pd(PPh_3)_4]$	0.05	toluene	110	4	80

The coupling of 1-ethoxyvinyltributyltin proved to be problematic (**SCHEME 4**). Rapid catalyst decomposition occurred, i.e. in 15min, on addition of a 1.5molar excess of the stannane. However, extending the period of addition increased the yield. A reduction in the mole equivalents of tin reagent present lengthened the life of the catalyst and increased the yield further. When the amount of catalyst used was doubled to 0.1mol equivalents and 1-ethoxyvinyltributyltin was added over 1 hour the yield increased to 69% as seen in **TABLE 3**. The 2-(S)-α-methyl benzyl-4-(1-ethoxyvinyl)-1,2-isothiazoline-3-one (**8**) can be purified using chromatography on alumina but is very unstable and readily hydrolyses, either on standing or on contact with silica gel, to the ketone (**9**).

SCHEME 4

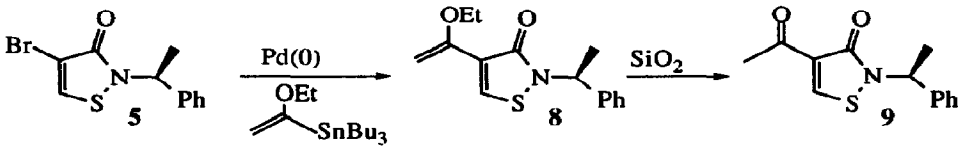


TABLE 3 Coupling Conditions for Production of (**8**)

mol.eq.of tin reagent	mol eq. of $[Pd(PPh_3)_4]$	Temp.[a] (°C)	Reaction time	(5)	(8)	(9)
1.5	0.03	110	15min	83%	—	—
1.5	0.05	110	1h.	32%	—	31%
1.5	0.05	65	24h.	62%	26%	—
1.1[b]	0.05	110	2.5h.	44%	40%	—
1.1[c]	0.05	110	4h.	39%	46%	—
1.1[c]	0.1	110	4h.	—	69%	—

[a] solvent = toluene, [b] stannane added over 0.5h., [c] stannane added over 1h.

Other couplings were attempted with allyltributyltin and ethynyltributyltin. There was evidence by NMR that some coupling had occurred with the latter substrate, to form a small amount of 4-ethynyl isothiazoline-3-one, but the product decomposed on silica to give a mixture of unidentifiable products.

In conclusion we have successfully functionalised the 1,2-isothiazoline nucleus at the 4-position with a variety of substrates in high yields. The Diels-Alder reactivity of these products and the corresponding 1-S-oxides will be described in due course.

Acknowledgements.

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10. Typical preparation of 2-(S)-α-methyl benzyl-4-vinyl-1,2-isothiazoline-3-one (3): 2-(S)-α-methyl benzyl-4-bromo-1,2-isothiazoline-3-one (0.2g, 7.2 mmol) and $Pd(PPh_3)_4$ (0.05 mol eq.) were dissolved in toluene ($5cm^3$). Vinyltributyltin (0.3 cm^3, 1.0 mmol) was added and the reaction mixture stirred at 110°C for 4hrs. under argon and then left to reach room temperature. The solvent was removed *in vacuo* and the residue purified by column chromatography, (silica gel C60 ethyl acetate : petrol 1:1). 2-(S)-α-methyl benzyl-4-vinyl-1,2-thiazoline-3-one was recrystallised from hexane to give opaque needle crystals. Yield = 0.13g, 80% , m.p. 53.0 - 54.8°C.
^1H NMR (300MHz $CDCl_3$) 1.75 [3H, d, 7Hz, ($C(Ph)HC\underline{H}_3$)], 5.35 [1H, dd, 12Hz (cis), 1Hz (gem)], 5.88 [1H, q, 7Hz ($CH_3C\underline{H}Ph$)], 6.22 [1H, dd, 18Hz (trans) 1Hz (gem)], 6.55 [1H, dd, 18Hz (trans) 12Hz (cis)], 7.33 [5H, m, (Ph)], 7.85 [1H, s, (H-5)] ^{13}C NMR (400MHz $CDCl_3$) 166.42 [C-3], 140.21 [C-8], 132.99 [C-5], 128.69 [(meta) Ph], 128.16 [(para) Ph], 127.37 [$\underline{C}H=CH_2$], 127.16 [(ortho) Ph], 123.64 [C-4], 116.62 [$CH=\underline{C}H_2$], 52.52 [$\underline{C}H(CH_3)$], 19.80 [$CH(\underline{C}H_3)$].
M.S.(EI) m/e (%) 231 (M+) (15), 127 (30), 105 ($PhCHCH_3$+) (100), 77 (23), 55 (10). Calculated for $C_{13}H_{13}NOS$: C 67.52% H 5.67% N 6.05% S 13.84.%. Found C 67.7% H 5.65% N 5.95% S 14.0.%. IR(cm^{-1})1670 -1620(C=O). $[\alpha]_D^{25}$ -302.2° (c= 0.10 %, methanol)

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