Pergamon

SCIENCE @ DIRECT®

Tetrahedron Letters 44 (2003) 8601–8603

TETRAHEDRON LETTERS

Polymer-supported organotin reagents in the catalytic Stille reaction

Alejandro G. Hernán, Vincent Guillot, Alexander Kuvshinov and Jeremy D. Kilburn*

Combinatorial Centre of Excellence, Department of Chemistry, University of Southampton, Southampton SO17 1BJ, UK

Received 24 July 2003; revised 5 September 2003; accepted 12 September 2003

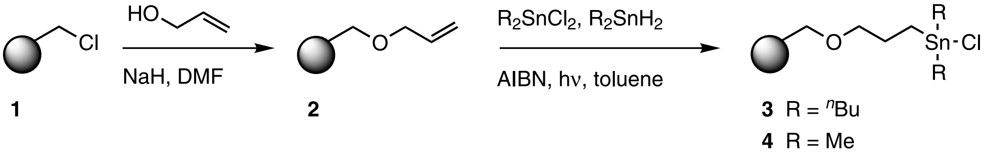
Abstract—Polymer-supported dibutyltin chloride and dimethyltin chloride resins were synthesised and used in Maleczka's catalytic Stille reaction.

The palladium-catalysed Stille coupling of a vinyl stannane to an organic halide is a widely used carbon–carbon bond forming reaction, but suffers from the formation of stoichiometric tin by-products.[1] Recent work by Maleczka has demonstrated that formation of a vinyl stannane coupling partner, by in situ hydrostannylation of an alkyne, allows the reaction to be carried out with as little as 5 mol% of trimethyltin chloride (which gave significantly better yields than tributyltin chloride) as the precursor tin reagent.[2] The catalytic cycle developed by Maleczka raises the possibility of using a solid supported tin reagent, which can be removed by filtration at the end of the reaction and potentially giving coupled products completely free of residual tin impurities. In this communication we describe the synthesis of a polymer-supported dimethyltin chloride reagent, which has been successfully used in the Maleczka catalytic Stille coupling.

Several examples of resin-bound dibutyltin chloride and hydride reagents have been previously described[3] and have been investigated extensively in tin hydride mediated radical reactions[3a,d] and stoichiometric Stille couplings,[3b,e] but to our knowledge the analogous resin bound dimethyltin chloride and hydride reagents have not been reported. In order to investigate the potential of resin bound tin reagents in Maleczka's catalytic Stille protocol we prepared both dibutyltin chloride and dimethyltin chloride resins **3** and **4**.

The resins **3** and **4** were prepared by hydrostannylation of resin-bound allyl ether **2**, prepared from Merrifield resin **1** (1.6 mmol/g, 1% DVB).[3f,g,i] Hydrostannylation of the alkene was accomplished using Neumann's procedure[3a] with Bu_2SnHCl, prepared in situ from a 1:1 mixture of Bu_2SnH_2[4] and Bu_2SnCl_2, and gave dibutyltin chloride resin **3** as a white solid (Scheme 1).

Dimethyltin chloride resin **4** was prepared by an analogous procedure. Me_2SnH_2 was most conveniently prepared on a small scale by reduction of Me_2SnCl_2 using Bu_3SnH, followed by distillation, according to Kuivila's method.[5] The Me_2SnH_2, which decomposed rapidly,[6] was mixed immediately with Me_2SnCl_2 to produce Me_2SnHCl and used for the hydrostannylation of resin **2**. The excess of Me_2SnHCl used in the synthesis of **4** decomposed during the reaction forming a grey precipitate (presumably metallic tin). An acidic wash (1:1 1N HCl/MeOH) removed the impurities to give **4** as a white solid. Both polymers **3** and **4** were character-



Scheme 1.

Keywords: Stille reaction; polymer-supported; tin chloride.

* Corresponding author. Tel.: +44-23 80593596; fax: +44-23 80596805; e-mail: jdk1@soton.ac.uk

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.09.143

ised by tin and chlorine microanalysis and by gel-phase ^{13}C and ^{119}Sn NMR.[7] The NMR data was consistent with the literature.[3c,8] Confident in the structure of both polymers we tested them in the catalytic Stille protocol described by Maleczka.

In a typical procedure the tin chloride resin (6–100 mol%) was suspended in an aqueous Na_2CO_3/THF mixture (1:20), with an alkyne **6**, palladium catalyst system (1 mol% Pd_2dba_3, 1 mol% $PdCl_2(PPh_3)_2$ and 4 mol% tri-2-furylphosphine) and polymethylhydrosiloxane (PMHS) (1.5 equiv.). Aryl iodide or bromide **5** (1.5 equiv.) was added over 15 h by syringe pump. Using these optimised conditions, as reported by Maleczka with trimethyltin chloride, the coupling of β-bromostyrene and *o*-iodoanisole with various alkynols[9] proceeded in good yield (Table 1) despite the multiple phases in which the catalytic cycle has to take place (aqueous, organic and polymeric). Substoichiometric (30 mol%) amounts of the dimethyltin chloride resin **4** could be used satisfactorily, but lower amounts of resin (6 mol%) did give significantly reduced yields. Clearly the reducing agent PHMS is able to regenerate the polystyrene bound $R(Me)_2SnH$ in contrast to its reported ineffectiveness for the regeneration of $R(Bu)_2SnH$ in the polymer supported catalytic Barton–McCombie deoxygenation of secondary alcohols.[3h]

After chromatographic purification the reaction products were obtained microanalytically pure and tin analysis showed low or insignificant tin content (<5–60 ppm).[10] In comparison, using the same chromatographic purification of reactions conducted using soluble trimethyltin chloride, gave products with tin impurities >500 ppm.

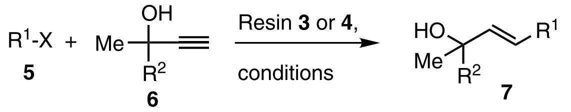
The dimethyltin chloride resin **4** also gave much better results than the dibutyltin chloride resin **3** which is in good agreement with the superiority of Me_3SnCl in comparison with Bu_3SnCl in Maleczka's cycle. Maleczka reported that the catalytic cycle suffers from deactivation of the organotin hydride intermediates by oxidative coupling to give distannane species. We had thought that the catalytic cycle might be more tolerant to various reaction conditions using polymer-supported organotin reagents since the effective isolation of the reactive sites might result in the suppression of the oxidative coupling.[11] However, a dramatic decrease in yield was observed when changing to other solvents (DMF) or catalytic systems ($Pd(PhCN)_2Cl_2/Ph_3As$) routinely used in Stille couplings. Reaction optimisation using the less reactive Stille coupling partner bromobenzene was also unsuccessful.

In summary, we report the use of catalytic amounts of polymer-supported organotin reagents in a Stille reaction. The polystyrene-based reagents present similar chemical limitations to the soluble tin chloride reagents in the same catalytic cycle. Work is currently underway to improve the performance of the reagent and to exploit the potential technical advantages of this method.

Acknowledgements

The authors acknowledge the supporting partners of the Southampton Combinatorial Centre of Excellence for financial support. The funding partners are Amersham Health and Amersham Biosciences, AstraZeneca,

Table 1.



R^1-X	Alkyne	Resin	Resin (equiv.)	Conditions	Yield of **7** (%)
4-Iodoanisole	$R^2=Ph$	**4**	1.0	a	63
4-Iodoanisole	$R^2=Ph$	**4**	0.3	a	60
4-Iodoanisole	$R^2=Ph$	**4**	0.06	a	21
4-Iodoanisole	$R^2=Ph$	**3**	1.0	a	20
4-Iodoanisole	$R^2=Ph$	**4**	1.0	b	5
4-Iodoanisole	$R^2=Ph$	**4**	1.0	c	0
4-Iodoanisole	$R^2=Me$	**4**	0.3	a	57
4-Iodoanisole	$R^2=Me$	**4**	0.3	c	10
4-Iodoanisole	$R^2=C_6H_{11}$	**4**	0.3	a	55
β-Bromostyrene	$R^2=Ph$	**4**	0.3	a	50
β-Bromostyrene	$R^2=Ph$	**3**	1.0	a	15
β-Bromostyrene	$R^2=Me$	**4**	0.3	a	67
β-Bromostyrene	$R^2=Me$	**4**	0.3	c	7
β-Bromostyrene	$R^2=Ph$	**4**	0.3	a	60
Bromobenzene	$R^2=Ph$	**4**	0.3	a	9
Bromobenzene	$R^2=Ph$	**4**	1.0	b	0

Conditions: (a) 1 mol% $Pd_2Cl_2(PPh_3)_2$, 1 mol% Pd_2dba_3, 4 mol% $(2\text{-furyl})_3P$, 1.5 equiv. PMHS, Na_2CO_3, H_2O/THF, reflux; (b) 1 mol% $Pd(PhCN)_2$, Ph_3As, 1.5 equiv. PMHS, Na_2CO_3, H_2O/THF, reflux; (c) 1 mol% $Pd_2Cl_2(PPh_3)_2$, 1 mol% Pd_2dba_3, 4 mol% $(2\text{-furyl})_3P$, 1.5 equiv. PMHS, Na_2CO_3,H_2O/DMF, reflux.

GlaxoSmithKline, Eli Lilly, CN Biosciences, Organon, Pfizer and Roche.

References

1. (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771–1780; (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React. (New York)* **1997**, *50*, 1–652.
2. (a) Maleczka, R. E., Jr.; Terstiege, I. *J. Org. Chem.* **1998**, *63*, 9622–9623; (b) Maleczka, R. E., Jr.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384–385; (c) Maleczka, R. E., Jr.; Lavis, J. M.; Clark, D. H.; Gallagher, W. P. *Org. Lett.* **2000**, *2*, 3655–3658; (d) Gallagher, W. P.; Terstiege, I.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 3194–3204; (e) Maleczka, R. E., Jr.; Gallagher, W. P. *Org. Lett.* **2001**, *3*, 4173–4176.
3. See for example: (a) Gerigk, U.; Gerlach, M.; Neumann, W. P.; Vieler, R.; Weintritt, V. *Synthesis* **1990**, 448–452; (b) Kuhn, H.; Neumann, W. P. *Synlett* **1994**, 123; (c) Dumartin, G.; Kharboutli, J.; Delmond, B.; Pereyre, M.; Biesemans, M.; Gielen, M.; Willem, R. *Organometallics* **1996**, *15*, 19–23; (d) Chemin, A.; Deleuze, H.; Maillard, B. *Eur. Polym. J.* **1998**, *34*, 1395–1404; (e) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2534–2537; (f) Enholm, E. J.; Schulte, J. P., II *Org. Lett.* **1999**, *1*, 1275–1277; (g) Enholm, E. J.; Gallagher, M. E.; Moran, K. M.; Lombardi, J. S.; Schulte, J. P., II *Org. Lett.* **1999**, *1*, 689–691; (h) Boussaguet, P.; Delmond, B.; Dumartin, G.; Pereyre, M. *Tetrahedron Lett.* **2000**, *41*, 3377–3380; (i) Zhu, X.; Blough, B. E.; Carroll, F. I. *Tetrahedron Lett.* **2000**, *41*, 9219–9222.
4. Bu_2SnH_2 was prepared by $NaBH_4$ reduction of Bu_2SnCl_2 in monoglyme: Birnbaum, E. R.; Javora, P. H. *J. Organomet. Chem.* **1967**, *9*, 379–382.
5. Kuivila, H. G.; Kennedy, J. D.; Tien, R. Y.; Tyminski, I. J.; Pelczar, F. L.; Khan, O. R. *J. Org. Chem.* **1971**, *36*, 2083–2088.
6. Clark, H. C.; Furnival, S. G.; Kwon, J. T. *Can. J. Chem.* **1963**, *41*, 2889–2897.
7. Resin **1**: Sn: 13% = 1.04 mmol/g; Cl: 3.86% = 1.1 mmol/g; ^{13}C NMR: (C_6D_6, 300 MHz): δ 13.7, 15, 18.4, 26.0, 26.7, 27.8, 40.3 (br), 71 (br), 73.1; ^{119}Sn NMR (C_6D_6; 112 MHz): δ 63.8 relative to $(CH_3)_4Sn$.
   Resin **2**: Sn: 14.9% = 1.3 mmol/g; Cl: 4.81% = 1.4 mmol/g; ^{13}C NMR (C_6D_6, 300 MHz): δ −0.1, 16.3, 25.9, 71.1, 73.2; ^{119}Sn NMR (C_6D_6; 112 MHz): δ 59 relative to $(CH_3)_4Sn$.
8. Mitchell, T. N. *J. Organomet. Chem.* **1973**, *59*, 189–197.
9. Alkynols were used as the alcohol functionality assisted in the purification of the products, but unfunctionalised alkynes can also be used: see Ref. 2.
10. Tin analysis was carried out by digesting the sample in sulphuric acid followed by ICP (Inductively Coupled Plasma) analysis, and was performed by Medac Ltd.
11. In practice the coupling and oxidative reactions of polymer-supported organotin reagents has been noted in several instances using resins with low crosslinking. For a discussion see Ref. 3d.