ChemComm
www.rsc.org/chemcomm

Pd-catalysed cross coupling of terminal alkynes to diynes in the absence of a stoichiometric additive

Ian J. S. Fairlamb,[a] **Patrick S. Bäuerlein,**[a] **Lester R. Marrison**[b] **and Julia M. Dickinson**[b]
[a] *Department of Chemistry, University of York, Heslington, York, UK YO10 5DD. E-mail: ijsf1@york.ac.uk; Fax: 44 1904 432515; Tel: 44 1904 434091*
[b] *Department of Chemistry and Materials, Manchester Metropolitan University, Faculty of Science and Engineering, Chester Street, Manchester, UK M1 5GD*

Received (in Cambridge, UK) 18th December 2002, Accepted 24th January 2003
First published as an Advance Article on the web 7th February 2003

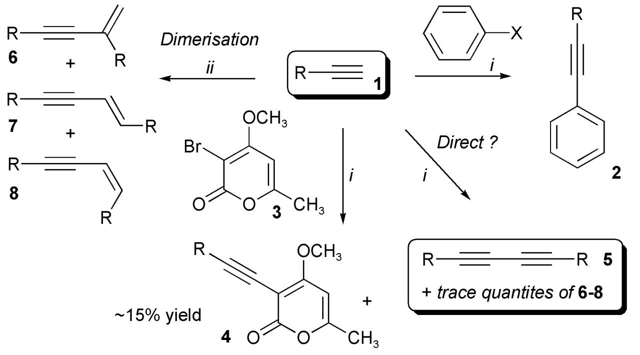
An efficient, room temperature procedure for the cross-coupling of a range of terminal alkynes, using standard Sonogashira cross-coupling conditions (Pd/Cu) is presented. At higher reaction temperatures, head-to-tail or head-to-head dimerisation affords 1,3- and 1,4-disubstituted enynes, respectively as minor products.

The Sonogashira Pd-catalysed cross-coupling reaction[1] has proven to be a powerful method for the formation of arylalkynyl derivatives (**1**→**2**, Scheme 1). However, peculiarities in this cross-coupling reaction have been noted by us[2] and other workers in this field.[3] Indeed, Pd-catalysed cross coupling of **3** to give **4** in the presence of CuI in a CH_3CN/Et_3N solvent mixture at 80 °C is low yielding. It is complicated by dehalogenation of **3**, accompanied by the formation of diynes **5** and trace quantities of enynes **6–8**. Given this result, in the absence of **3**, we envisaged access to an extremely efficient method for the synthesis of diynes. However, such a proposal assumes that the presence of **3** is not a prerequisite for diyne formation.

Diynes may be synthesised in a number of ways.[4] The Glaser coupling (oxidative dimerisation) of terminal alkynes in the presence of $CuCl_2$ and O_2 is without question the best-known reaction, although difficulties are sometimes encountered.[5] There are several Pd(0)-Cu(I) catalysed cross coupling reactions: (1) dimerisation of terminal alkynyl halides with terminal alkynes;[6] (2) dimerisation of terminal alkynes using chloroacetone in benzene;[7] (3) ethyl bromoacetate in THF;[8] (4) allyl bromide under phase transfer conditions;[9] (5) and reactions employing stoichiometric I_2 (using a Pd(II) pre-catalyst). These synthetic methods are in the main good, however with the exception of (1), all require the addition of a stoichiometric reagent to reoxidise Pd(0) to Pd(II).

Herein we report a new method for the formation of diynes, in the absence of an obvious oxidant, which can be performed under anhydrous conditions. The latter point is important as the procedure avoids side reactions associated with the Glaser reactions, where O_2 is used as the oxidant. Furthermore, it avoids the formation of alkynyl halides, as in the Sonogashira–Hagihara coupling reaction, and does not require the addition of stoichiometric reagents (*e.g.* $BrCH_2CO_2Et$, $ClCH_2COCH_3$, I_2 *etc.*).

To investigate the dimerisation of terminal alkynes, we initially focused on the standard conditions taken from the Sonogashira coupling of **3** with phenyl acetylene **1a** ($[PdCl_2(PPh_3)_2]$ (3 mol%), CuI (3 mol%), triethylamine/CH_3CN solvent mixture (1.6 : 1 v/v)) at reflux under an argon



Scheme 1 *Reagents and conditions*: *i*, [Pd] (Cat.), ligand, CuI (Cat.), Et_3N, solvent, 80 °C; *ii*, $Pd(OAc)_2$, ligand, benzene, 80 °C.

Table 1 Effect of Pd-catalyst on the dimerization of 1-heptyne **1b**[a]

$H_3C(H_2C)_4{-}{\equiv}$ **1b** $\xrightarrow{\text{conditions}}$ $H_3C(H_2C)_4{-}{\equiv}{-}{\equiv}{-}(CH_2)_4CH_3$ **5b**

Entry	Temp. (°C)	Catalyst[b]	Diyne/enyne[c]	Yield (%)[d]
1	80	$Pd(OAc)_2/PPh_3$ (2 h)	4.37 : 1	>97
2	80	$Pd(PPh_3)_4$ (2 h)	2.52 : 1	>97
3	80	$Pd(dba)_2/PPh_3$ (2 h)	3.81 : 1	92
4	80	$PdCl_2(PPh_3)_2$ (2 h)	2.80 : 1	>97
5	25	$PdCl_2(PPh_3)_2$ (24 h)	11.34 : 1	>97
6	25	$PdCl_2(PPh_3)_2/PPh_3$ (24 h)	Diyne only[e]	97

[a] Reaction conditions: 2.0 mmol of 1-heptyne, Et_3N (2.5 mL), CH_3CN (1.5 mL), CuI (3 mol%) at appropriate temp. [Pd] = 3 mol%. Additional ligand (9 mol%). [b] Numbers in parenthesis are reaction times. [c] The enyne fraction accounts for the total amount of enynes **6–8** formed. [d] Isolated yields of tetradeca-6,8-diyne **5b**. [e] Enynes **6–8** not detected by ^1H NMR spectroscopy (270 MHz).

Table 2 Effect of reaction temperature and additional ligand on $PdCl_2(PPh_3)_2$ catalyzed dimerization of 1-heptyne **1b**[a]

$H_3C(H_2C)_4{-}{\equiv}$ **1b** $\xrightarrow{\text{conditions}}$ $H_3C(H_2C)_4{-}{\equiv}{-}{\equiv}{-}(CH_2)_4CH_3$ **5b**

Entry	Temp. (°C)[b]	Ligand[c]	Product purity (%)[d]	Conv. (%)[e]
1	80 (2)	Ph_3P	90	>95
2	80 (2)	dppp	92	>90
3	80 (2)	dppf	82	>90
4	80 (2)	(*o*-tol)$_3$P	95	>90
5	60 (3.5)	Ph_3P	>99	>90
6	60 (3.5)	dppp	92	>90
7	60 (3.5)	dppf	95	>90
8	60 (3.5)	(*o*-tol)$_3$P	98	>90
9	40 (5)	Ph_3P	>99	>97
10	40 (5)	dppp	95	>90
11	40 (5)	dppf	94	>90
12	40 (5)	(*o*-tol)$_3$P	>99	>90
13	25 (24)	Ph_3P	>99	>99
14	25 (24)	dppp	94	>90
15	25 (24)	dppf	>99	>90
16	25 (24)	(*o*-tol)$_3$P	>99	>90

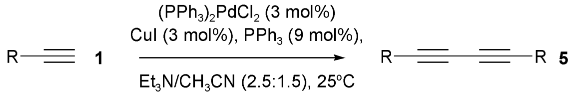
[a] Reaction conditions: 2.0 mmol of 1-heptyne, Et_3N (2.5 mL), CH_3CN (1.5 mL), CuI (3 mol%), $(PPh_3)_2PdCl_2$ (3 mol%) at appropriate temperature. [b] Number in parenthesis is the reaction time in hours. [c] Additional ligand: For Ph_3P and (*o*-tol)$_3$P (9 mol %). For [1,3]-bis(diphenylphosphino)propane (dppp) and [1,1′]-bis(diphenylphosphino)ferrocene (dppf) (4.5 mol%). [d] % Purity determined by ^1H NMR data of the crude reaction mixture. [e] Based on conversion and loss of 1-heptyne **1b** by ^1H NMR data of the crude reaction mixture.

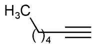
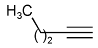
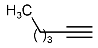
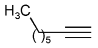
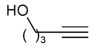
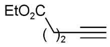
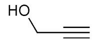
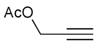
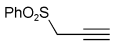
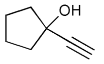
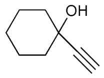
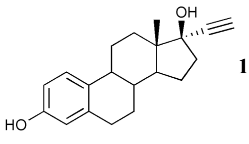
DOI: 10.1039/b212430k

atmosphere, 3 h). Thus, in the absence of **3**, phenyl acetylene **1a** was dimerised to give the diyne **5a** in 75% yield. Further addition of PPh_3 (9 mol%) enhances the yield of the diyne to 98%. We turned our attention to the alkyl substituted acetylenes and found that the enyne side products **6–8** were much more prominent. Four general Pd-catalysts were screened, employing 1-heptyne **1b** as our benchmark substrate (Table 1). The production of enyne side products varies according to choice of catalyst. Decreasing the reaction temperature to room temperature substantially reduces the formation of enynes **6–8** (compare entries 4 & 5, Table 1). To our delight carrying out the reaction at 25 °C with additional PPh_3 resulted in suppression of the enynes (entry 6, Table 1). It should be noted that these reactions do not proceed in the absence of triethylamine.

We were intrigued by the effect of additional ligand and thus carried out investigations with other chelating phosphines, in the presence of $[PdCl_2(PPh_3)_2]$ as the catalyst, at a variety of different temperatures (Table 2). On close inspection of Table 2 one can see quite clearly that the presence of either unidentate (Ph_3P and $(o\text{-tol})_3P$) or bidentate ligands (dppp and dppf) serves to reduce the formation of the enyne side products. The employment of unidentate ligands results in generally higher selectivity for the diyne product, a trend which is observed at each temperature. Overall, it was found that additional Ph_3P provided reproducibly higher yields of the diyne products.

Table 3 Dimerization of various terminal alkynes using optimised conditions[a]



Entry	Alkyne		Diyne (%)[b]
1	$\mathrm{Ph}{-}{\equiv}$	**1a**	>97 (98) **5a**
2		**1b**	>99 (96) **5b**
3		**1c**	>99 (96) **5c**
4		**1d**	>99 (94) **5d**
5		**1e**	>97 (98) **5e**
6	$\mathrm{Me_3Si}{-}{\equiv}$	**1f**	(80) **5f**
7		**1g**	(80) **5g**
8		**1h**	(80) **5h**
9		**1i**	>97 (98) **5i**
10		**1j**	0 **5j**
11		**1k**	0 **5k**
12		**1l**	(95) **5l**
13		**1m**	(95) **5m**
14		**1n**	(82) **5n**

[a] Reaction conditions: 2.0 mmol of alkyne, Et_3N (2.5 mL), CH_3CN (1.5 mL), CuI (3 mol%), $(PPh_3)_2PdCl_2$ (3 mol%), PPh_3 (9 mol%), at 25 °C for 24 h. [b] Determined by GC analysis (hexadecane standard) (values in parenthesis are isolated yields after flash chromatography).

On mechanistic grounds an oxidant should not be required. To address whether O_2 acts as an oxidant, the reaction was conducted under strictly anhydrous conditions (solvents were degassed using freeze–pump–thaw cycles) under an argon atmosphere using our standard conditions at 25 °C $[PdCl_2(PPh_3)_2]$ (3 mol%), CuI (3 mol%), PPh_3 (9 mol%) in dry Et_3N/CH_3CN (2.5 : 1.5, v/v)). The reaction gave the diyne **5b** in >92% yield. Thus the reaction does *not* require the presence of O_2. Using these standard conditions, a range of terminal alkynes were evaluated for homocoupling (Table 3). The yields for the other alkyl acetylenes **1c–1e** were essentially quantitiative (entries 2–5, Table 3). Dimerisation of trimethylsilyl acetylene **1f**, pent-5-yn-1-ol **1g**, ethyl but-4-yne carboxylate **1h** and propargyl alcohol **1i** all resulted in homocoupling to give the diynes **5f–i** in good yields (entries 6–9, Table 3). Enynes **6–8** were not observed in these reactions. Switching to propargyl acetate **1j** and propargyl phenylsulfone **1k** resulted in no reaction (entries 10,11, Table 3). It is plausible that **1j** and **1k** oxidatively adds to palladium, possibly resulting in allene formation/decomposition. The cyclic alkynols **1l**, **1m** and **1n** couple efficiently using our reaction conditions (entries 12–14, Table 3). The latter example demonstrates that structurally complex terminal alkynes can be dimerised in good yield.

In summary, our method for the dimerisation of alkynes is efficient for the synthesis of a variety of diynes at room temperature. The method is tolerant to a range of functional groups and does not require the addition of stoichiometric reagents, such as I_2, chloroacetone, allyl bromide or ethyl bromoacetate. Our reactions show that terminal alkynes readily dimerise under seemingly standard conditions (Et_3N, CH_3CN, cat. CuI and cat. $[PdCl_2(PPh_3)_2]$ at reflux) for the Sonogashira cross-coupling reaction. Detailed mechanistic studies are currently being pursued to understand this process more fully. Future studies will address cross-dimerisation possibilities.[10]

We are indebted to Dr G. C. Lloyd-Jones (University of Bristol) and Professor R. J. K. Taylor (York) for valuable comments and mechanistic insights. Johnson Matthey PLC provided a generous loan of Pd salts. IJSF acknowledges the University of York for financial support in the form of an IRPF grant.

Notes and references

1 K. Sonogashira, in *Comprehensive Organic Synthesis*, Vol. 3, Pergamon Press, 1990, p. 521.
2 L. R. Marrison, *PhD Thesis*, Manchester Metropolitan University, UK, 1998; L. R. Marrison, J. M. Dickinson and I. J. S. Fairlamb, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3509; L. R. Marrison, J. M. Dickinson, R. Ahmed and I. J. S. Fairlamb, *Tetrahedron Lett.*, 2002, **43**, 8853.
3 E. V. Tretyakov, D. W. Knight and S. F. Vasilevsky, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3713.
4 (*a*) R. J. K. Taylor, in *Organocopper Reagents: A Practical Approach*, Oxford University Press, 1994; (*b*) P. Siemsen, R. C. Livingston and F. Diederich, *Angew. Chem., Int. Ed.*, 2000, **39**, 2632.
5 A. S. Hay, *J. Org. Chem.*, 1962, **27**, 3320; E. Valenti, M. A. Pericas and F. Serratosa, *J. Am. Chem. Soc.*, 1990, **112**, 7405.
6 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467.
7 R. Rossi, A. Carpita and C. Bigelli, *Tetrahedron Lett.*, 1985, **26**.
8 A. Lei, M. Srivastava and X. Zhang, *J. Org. Chem.*, 2002, **67**, 1969.
9 M. Vlasa, I. Ciocan-Tarta, F. Margineanu and I. Oprean, *Tetrahedron*, 1996, **52**, 1337.
10 B. M. Trost, M. T. Sorum, C. Chan, A. E. Harms and G. Rühter, *J. Am. Chem. Soc.*, 1997, **119**, 698.