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Letters

Important consequences for gas chromatographic analysis of the Sonogashira cross-coupling reaction ☆

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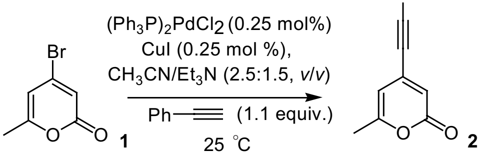
Abstract—On following the kinetics of the Sonogashira alkynylation reaction of halogenated 2-pyrone **1** with phenylacetylene we have found that turnover continues to occur in sample vials even after quenching by commonly employed silica adsorption methods and product elution with small quantities of CH_2Cl_2. Trace quantities of Pd are carried through the silica plug. Addition of a CH_2Cl_2 solution of 1,2-bis(diphenylphosphino)ethane (dppe) to the quenched sample inhibits the reaction and represents a more reliable method for determining yields and reaction kinetics.

Pd-Catalysed carbon–carbon and carbon–heteroatom bond-forming processes represent some of the most important and widely applied reactions in synthetic chemistry.[1] Classic examples include Heck, Negishi, Sonogashira, Stille, Suzuki and the recently developed Hartwig–Buchwald cross-coupling reactions. Some of these reactions have been used extensively in benchmarking new Pd catalysts, where high catalyst activity, prolonged catalyst lifetime and selectivity are important. One of the principal techniques employed to monitor Pd-catalysed cross-coupling reactions is gas chromatography (GC). This technique is considered a reliable means of determining the extent of reaction, as well as for mapping important reaction kinetics. Indeed, GC analysis of these reactions is routine in many laboratories. Despite this, there are no scientifically proven literature protocols for quenching aliquots withdrawn during reactions. Rather, one of the most commonly adopted methods is via their passage through a small silica plug, followed by elution with a relatively nonpolar solvent such as chloroform or dichloromethane. We believed that this was an effective means of stopping the reaction. However, recent work in our laboratories has shown that further reaction does occur after passing the sample through a silica plug. This observation came about through a need to obtain accurate kinetic data for the Sonogashira reaction,[2] where analysis was performed in triplicate at specific times during the reactions. We set about systematically correlating GC sampling time against product conversion and our results unequivocally revealed that reaction continues even using a vast excess of silica.

Herein we report our observations on the Sonogashira reaction of 4-bromo-6-methyl-2-pyrone **1** (1 mmol) with phenylacetylene (1.1 mmol) to give the cross-coupled product **2** catalysed by a common palladium(II) precatalyst, $(Ph_3P)_2PdCl_2$ (0.25 mol%), in the presence of co-catalytic CuI (0.25 mol%) in an acetonitrile/triethylamine mixture at room temperature (Scheme 1).[3]

For this cross-coupling reaction, we have found that the presence of the palladium catalyst is essential, although a requirement for CuI is not.[4] It is also of interest to note that catalyst loadings of ~5 mol% result in lower yields of **2** at room temperature. Previously, we had



Scheme 1. Sonogashira alkynylation of **1**.

Keywords: Palladium; Sonogashira; Cross-coupling reactions; 2-Pyrones.

☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.03.060

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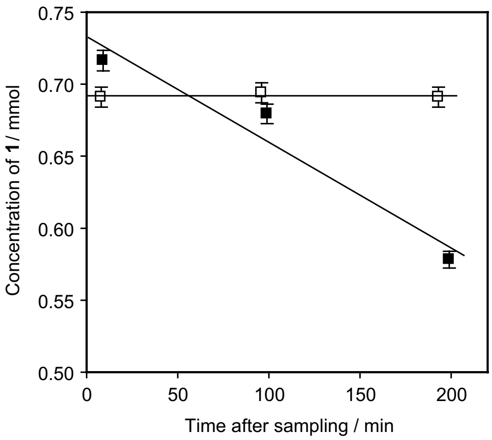

Figure 1. A graph showing the consumption of **1** at specified times: (■) reaction sample quenched with a silica plug and elution with CH_2Cl_2; (□) reaction sample quenched with a silica plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial.

determined that reflux conditions were required for efficient cross-coupling of **1** with phenylacetylene at this catalyst loading. Thus a room temperature protocol was made possible by lowering the catalyst loading for this particular substrate.[3a]

Figure 1 shows the results of repeated GC analysis of a 'quenched' sample, withdrawn from the reaction mixture after 1 h and stored at room temperature. A strong and reproducible time dependence was apparent, with an additional ~15% substrate conversion noted after only 3 h storage prior to analysis. In order to confirm that this striking effect arose from residual Pd, a solution of dppe in CH_2Cl_2 was added to samples immediately after their elution through the silica adsorbent.[5]

It is clear that dppe addition completely eliminated continued reaction within stored samples, presumably by irreversibly binding the palladium(0) species, are unable to effect the catalytic reaction. The importance of quenching for GC analysis is evident from examining reaction profiles obtained during the alkynylation of **1** (Fig. 2). The dppe protocol reveals conventional silica treatments introduce a systematic error of ~10% in calculated GC conversions. This finding also has implications for initial rates and associated turnover frequencies from studies wherein adsorption over silica gel represents the sole quenching step.

It is important to note that the adsorption capacity of Kieselgel silicas (typically >0.1 mmol Pd g^{-1}) vastly exceeds the Pd content of each reaction sample (0.08 μmol); our observations do not reflect overloading of the silica plugs.[6]

In summary, we have found that typical quenching procedures for GC analysis of the Sonogashira reaction are inadequate for substrate **1**. The direct addition of dppe to the analysis sample inhibits any further reaction and represents a more reliable procedure for quantitative analysis of these reactions. The protocol highlights that methods used to improve the accuracy of GC

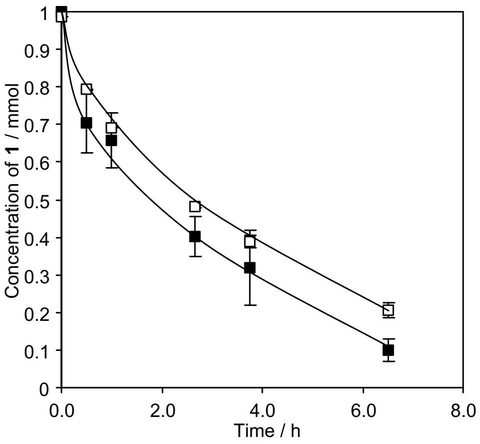

Figure 2. Reaction profiles showing the consumption of **1** at specified times (triplicate samples for each sample time were run by GC): (■) reaction sample quenched with a silica plug and elution with CH_2Cl_2; (□) reaction sample quenched with a silica plug, elution with CH_2Cl_2, followed by addition of a dppe solution to the GC sample vial.

analysis (i.e., multiple injections) actually introduce a systematic error in overall reaction conversion. Potentially, our results have implications for other homogeneous Pd-catalysed processes. Our ongoing research is examining whether this is a generic effect for organohalide substrates.[7]

Supporting information: The complete GC-analysis data and calculated response factors for **1** and **2** are available.

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4. It should be noted that there is no reaction between **1** and phenylacetylene in the absence of the palladium catalyst. In the absence of CuI, the reaction does occur, albeit at a slower rate. See supporting information for exact procedure used and complete details of the GC analysis.
5. Reaction mixture (250 μL) was passed through a silica plug (1.21 g) and eluted with CH_2Cl_2 (Kieselgel 60; particle size 0.035–0.070 mm, 220–440 mesh, purchased from Fluka). The resultant fraction was then treated with 100 μL of a 3.3 mmol dppe solution in CH_2Cl_2 (~4 equiv of dppe per the maximum theoretical Pd concentration).
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7. We have established that similar results are obtained when 4-nitrobromobenzene is employed as the electrophilic substrate instead of **1**.