Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 45 (2004) 1441–1444

Tetrahedron Letters

A robust palladium-catalyzed cyanation procedure: beneficial effect of zinc acetate

Ramakrishnan Chidambaram*

Process Research and Development, Bristol–Myers Squibb, New Brunswick, NJ 08908, USA

Received 1 December 2003; revised 9 December 2003; accepted 9 December 2003

Abstract—Conditions that ensure a more reproducible Pd(0)-mediated procedure to convert aryl bromides to aryl cyanides have been developed that entail the use of zinc dust to keep the Pd in the zero oxidation state and zinc acetate to ensure high catalytic activity. This procedure is applicable to a wide range of substrates and obviates the need for stringent removal of oxygen from the reaction medium.

A very important and useful reaction in organic synthesis is the conversion of an aryl bromide or chloride to an aryl cyanide;[1] several procedures involving the use of transition metals are available.[2] Unfortunately, most of these procedures require high temperatures (~120–140 °C), and more importantly, the reactions tend to be capricious.

Our efforts were directed towards finding a general and scalable procedure to convert substituted bromoacetanilide **I** to the corresponding proprietary cyano compound **II**. The two most recently reported systems for such a conversion are:

(a) $Pd(OAc)_2$ as the catalyst, dppe as a ligand and acetone cyanohydrin as the cyanide source[2] and
(b) $Pd_2(dba)_3$ in combination with dppf [1,1′-bis(diphenylphosphino)ferrocene] as a ligand and $Zn(CN)_2$ as the cyanide source.[3]

Due to safety concerns as well as availability issues associated with acetone cyanohydrin, we decided to focus on the use of the $Pd_2(dba)_3$/dppf system. We found that the cyanation under the reported conditions was not reproducible with conversions varying from 50 to >98 AP (area percent, HPLC) even after careful deoxygenation of the DMF by bubbling in nitrogen at 90 °C. As expected, when the DMF was saturated with oxygen, there was absolutely no conversion of **I** into **II**.

This implicated oxygen as the main source in deactivation of the catalyst, resulting in lower conversion.[4] Since oxygen most likely oxidizes the active palladium(0) species to a palladium(II) species, the in situ use of a reductant might reduce the palladium(II) back to the palladium(0) species and reintroduce it into the catalytic cycle. Since zinc has been used in cyanation reactions to reduce palladium(II) species,[3b,5] we added 3–4 mol % zinc dust to our cyanation reaction and obtained excellent conversion (>99 area percent) of **I** into **II** without the need to deoxygenate the DMF. The cyanation procedure using zinc dust was then successfully scaled up to produce multi-kilogram quantities of **II**. However, attempted cyanation of **I** purchased from a vendor was totally unsuccessful (<5 AP conversion). The difference between the two lots of **I** was that acetic acid was used in our procedure to prepare **I**, whereas the vendor material was prepared in an acetic acid-free environment. Addition of 5 wt % of acetic acid to the cyanation reaction using vendor supplied **I** gave a >99 AP conversion to **II** in ~5 h.

Since acetic acid could potentially generate hydrogen cyanide upon reacting with zinc cyanide, we started looking at safer alternates that would produce the same catalytic effect. Our investigations led to the observation that the use of 3–4 mol % zinc acetate[6] was just as effective as acetic acid in catalyzing the cyanation. In order to ascertain whether the effect of zinc acetate had wide applicability, we examined a wide range of

---

Keywords: Cyanation; Aryl bromides; Palladium; Zinc acetate; Zinc dust.

* Tel.: +1-732-227-6941; fax: +1-732-227-3944; e-mail: ramakrishna.chidambaram@bms.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.040

substrates with varying electronic and steric effects.[7] In all cases reagent grade DMF was used without any additional purification other than performing the reaction under nitrogen.

As seen in Table 1, with the exception of nitro compound **1g** (entry 7) and the free amine **1i** (entry 9), substrates with different electronic and steric effects reacted with excellent conversion and yields. In order to confirm the beneficial effect of zinc acetate, the aryl bromides were dissolved in an appropriate solvent, dried over potassium carbonate to remove any traces of acetic acid that may have been used for their preparation and then cyanated in the presence of zinc dust and in the absence of zinc acetate.[8] The conversion rates were then compared.

The results are summarized in Table 2.

As can be seen in Table 2, with the exception of electron-deficient substrate **1c**, which did not require $Zn(OAc)_2$, the conversions were sharply lower than those in which zinc acetate was used. This pointed to a definite beneficial effect of zinc acetate. In order to understand whether this effect represented a rate enhancement due to the presence of zinc or whether it was an effect of the counterion, the cyanation of **1e** was carried out in the presence of other additives.[9] The results are summarized in Table 3.

Additives such as magnesium acetate and zinc trifluoroacetate also had a beneficial effect, whereas zinc oxide and zinc chloride did not, pointing to a counterion effect rather than a metal effect.

Efforts were then directed towards understanding the role of $Zn(OAc)_2$ in the catalytic cycle. Cyanation of **I** (Fig. 1) was carried out in the absence of $Zn(OAc)_2$ for about 3.5 h at which point there was <5 area percent conversion as expected, 4 mol% of $Zn(OAc)_2$ and 3 mol% of zinc dust were then added to the reaction mixture. The conversion increased to 50 area percent after 4 h and then stalled. However, in a separate experiment, when 3 mol% of zinc dust and 4 mol% of $Zn(OAc)_2$ were introduced 24 h after the cyanation was carried out in the absence of $Zn(OAc)_2$, there was no additional conversion beyond that observed early in the experiment.[10]

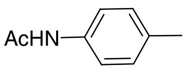
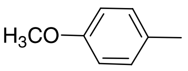
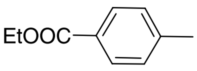
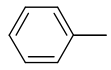
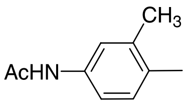
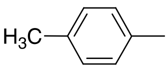
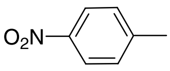
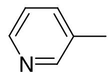
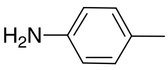
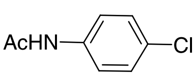
The fact that the cyanation reaction slowed down significantly and finally stalled suggests an irreversible competitive deactivation of the catalyst and that $Zn(OAc)_2$ presumably keeps the catalyst 'alive' in the catalytic cycle long enough to complete the cyanation.

In the presence of cyanide ions, palladium is known to generate species such as $[Pd^0(CN)_n]^{n-}$, which can no longer participate in the catalytic cycle.[2] These compounds have strongly bound cyanide groups on the palladium[11] that interfere with the necessary oxidative addition and thus slow down the conversion.

Additionally, when cyanation of **1e** was carried out with 0.1 mol% of $K_2Pd(CN)_4$ or $Pd(CN)_2$ along with 3–4 mol% Zn dust and 3–4 mol% $Zn(OAc)_2$, there was only about a 50% conversion after 9 h (compared to >99% conversion using normal conditions). Using 0.1 mol% of a less tightly bound, easily reducible palladium compound like $Pd(OAc)_2$[11,12] to cyanate **1e**, the conversion was >95 AP after 9 h.

Table 1. Cyanation of aryl bromides in the presence of zinc acetate[1]

$$\underset{\mathbf{1}}{\text{Ar-Br}} \longrightarrow \underset{\mathbf{2}}{\text{Ar-CN}}$$

Ar	Time (h)	Conversion (HPLC area percent)	Isolated yield[a]
 1a	12	>98	91
 1b	14	>99	94
 1c	2	>99	92
 1d	6	>99	89
 1e	9	>99	90
 1f	7	>99	87
 1g	3	<1	—
 1h	3	>99	80
 1i	24	~20	Not isolated[b]
 1j	5	Not detected	—

[a] Unless otherwise stated, all reactions were carried out on a 5-g scale. Isolated yields have not been optimized. The materials isolated were compared with authentic samples (^1H and ^{13}C NMR). The reactions were run with 0.1 mol% $Pd_2(dba)_3$, 0.25 mol% dppf, 3–4 mol% Zn dust and 3–4 mol% $Zn(OAc)_2$ in DMF containing 1% by volume water.

[b] The formation of product was checked by comparing the retention time on the HPLC with an authentic sample.

Table 2. HPLC area percent conversion of substrates in the absence of zinc acetate but in the presence of zinc dust

$$\underset{\mathbf{1}}{\text{Ar-Br}} \longrightarrow \underset{\mathbf{2}}{\text{Ar-CN}}$$

Substrate[a]	AP Conversion [without $Zn(OAc)_2$][b]; (time, h)	AP Conversion with $Zn(OAc)_2$ (from Table 1); (time, h)
1a	75 (12)	>98 (12)
1b	11 (24)	>99 (14)
1c	>99 (2)	>99 (2)
1d	14 (9)	>99 (6)
1e[c]	60 (12)	>99 (9)
1f	49 (6)	>99 (6)
1h	80 (3)	>99 (3)

[a] The substrates were dissolved in MTBE or ethyl acetate, dried over potassium carbonate, filtered and then the solvents removed under reduced pressure.

[b] The reactions were run with 0.1 mol% $Pd_2(dba)_3$, 0.25 mol% dppf and 3–4 mol% Zn dust in DMF containing 1% by volume water.

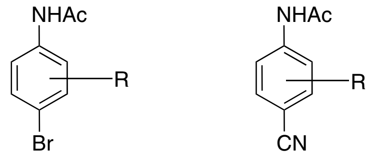
[c] This potassium carbonate washed substrate was also cyanated in the presence of $Zn(OAc)_2$. The conversion was >99 area percent (~90–92% isolated yields).

Table 3. Effect of other additives on the cyanation reaction with **1e**

$$\underset{\mathbf{1}}{\text{R-Br}} \longrightarrow \underset{\mathbf{2}}{\text{R-CN}}$$

Additive	Conversion (AP)[a]
NaOAc (9)	85 (stalled)
$Mg(OAc)_2$ (9)	>99
$ZnCl_2$ (9)	55
$Zn(OCOCF_3)_2$ (9)	>99
ZnO (9)	40
No additive	60

[a] The reactions were run for 9 h with 0.1 mol% $Pd_2(dba)_3$, 0.25 mol% dppf, 3–4 mol% Zn dust and 4 mol% additive in DMF containing 1% by volume water.



I II

Figure 1.

These data are again consistent with a scenario in which $Zn(OAc)_2$ keeps the catalyst active in the catalytic cycle. In the absence of $Zn(OAc)_2$, a palladium species that can no longer be activated by the $Zn/Zn(OAc)_2$ combination appears to form irreversibly. At this juncture it is not clear as to whether the role of $Zn(OAc)_2$ is to just activate the palladium catalyst.

In summary, a much more robust and reliable cyanation of aromatic bromo compounds has been developed in which the introduction of zinc acetate in combination with a reducing agent such as zinc dust keeps the palladium from being deactivated even when reagent grade DMF is used without stringent deoxygenation controls. Mechanistic implications of this observation as well as other applications of this system are currently being investigated.

Acknowledgements

The author thanks Drs. Percy Manchand, William Nugent, Edward Delaney, Richard Mueller, David Kronenthal and Wendel Doubleday for fruitful discussions. The author also thanks Profs. Barry Trost and Donna Blackmond for their valuable insights.

References and notes

1. (a) Ellis, G. P.; Ronmey-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779; (b) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1074; (c) House, H. O.; Fisher, W. F. *J. Org. Chem.* **1969**, *34*, 3626; (d) Kleeman, A.; Engel, J.; Kutscher, B.; Reichart, D. *Pharmaceutical Substances: Syntheses, Patents, Applications*. Fourth ed.; Georg Thieme: Stuttgart, 2001.
2. Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664, and references cited therein.
3. (a) Maligres, P. E.; Waters, M. S.; Fleitz, F.; Askin, D. *Tetrahedron Lett.* **1999**, *40*, 8193–8195; (b) Jin, F.; Confalone, P. N. *Tetrahedron Lett.* **2000**, *40*, 3271–3273.
4. Attempts to quantitate the dissolved oxygen in DMF were unsuccessful since DMF dissolved the available probe sensors.
5. Okano, T.; Iwahara, M.; Kiji, J. *Synlett* **1998**, 243.
6. When the cyanation of **1e** was run with 50 mol% of $Zn(OAc)_2$, the reaction was very sluggish (only 50 HPLC area percent completion after 9 h).
7. Representative procedure for cyanation. To a 100-mL, 3-necked flask connected to a nitrogen-inlet adapter and reflux condenser was charged the substrate **1e** (5 g; 21.9 mmol), DMF (10 mL), water (100 μL), dppf (0.03 g; 0.06 mmol), $Pd_2(dba)_3$ (0.1 mol%; 0.02 g; 0.02 mmol), $Zn(CN)_2$ (1.39 g; 11.8 mmol), zinc dust (4 mol%; 0.06 g; 0.88 mmol) and $Zn(OAc)_2$ (4 mol%; 0.16 g; 0.88 mmol). The mixture was heated and the temperature maintained between 90 and 100 °C. The reaction was monitored by HPLC and was worked up after the reaction was deemed complete (<2 AP of starting material). Workup of liquid products were done according to the procedure described in Ref. 4. Workup of solid products were done according to the procedure described in Ref. 3. Commercially available starting materials were used for the cyanations and the isolated products were compared with authentic samples that were purchased from various vendors.
8. The substrates were dissolved in either methyl *t*-butyl ether or ethyl acetate, dried over K_2CO_3 for 30 min, filtered and the solvent removed under reduced pressure. Cyanations were then carried out as described above without the $Zn(OAc)_2$. The reaction rates were compared by HPLC area percent.
9. The substrates were cyanated as described in Ref. 7 with the appropriate additive being added instead of $Zn(OAc)_2$.
10. No additional conversion was observed with **1a**, **1b** and **1e** when $Zn(OAc)_2$ and additional Zn dust were added 24 h after cyanation was carried out without $Zn(OAc)_2$.

11. Nakamura, M.; Fujiwara, S. *J. Coord. Chem.* **1972**, *1*, 221–227.
12. When $Pd(OAc)_2$ or $K_2Pd(CN)_4$, which are palladium(II) species, were used in the absence of zinc dust, the conversion was <5 HPLC area percent. The cyanation of **1e** using 5 mol% of $Pd(OAc)_2$, Zn dust and dppf without any $Zn(OAc)_2$ resulted in a reaction that was 80 HPLC area percent complete after 9 h. However, the reaction profile indicated the formation of several unidentified impurities (totaling ~15 HPLC area percent) that were not seen during the course of a normal cyanation reaction.