Tetrahedron Letters 54 (2013) 4518–4521

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Expanding the scope of silane-mediated hydrodehalogenation reactions

Gary M. Noonan *, Barry R. Hayter, Andrew D. Campbell, Timothy W. Gorman, Benjamin E. Partridge, Gill M. Lamont

AstraZeneca Mereside, Alderley Park, Cheshire SK10 4TG, United Kingdom

ARTICLE INFO

Article history:
Received 12 February 2013
Revised 31 May 2013
Accepted 14 June 2013
Available online 24 June 2013

Keywords:
Hydrodehalogenation
Palladium catalysed
Silane

ABSTRACT

A palladium-catalysed, silane-mediated hydrodehalogenation (HDH) reaction with increased substrate scope has been developed. Whereas previous attempts to reduce carboxylic acid or phenol-containing aryl halides using silane-based HDH conditions failed, the current protocol allows efficient access to the reduced products. Chemoselective HDH in the presence of sensitive functional groups is also presented.

Halogenated arenes and heteroarenes are widely utilised building blocks in organic chemistry. The carbon–halogen bond usually serves as a functional handle in carbon–carbon or carbon–heteroatom bond forming reactions, however, the removal of 'redundant halides' from reaction products is sometimes necessary. These 'redundant halides' derive from the use of halides as activating/blocking groups[1,2] for other transformations, or due to the fact that it is sometimes easier to access, via chemical synthesis or commercial sources, a more extensively halogenated compound.

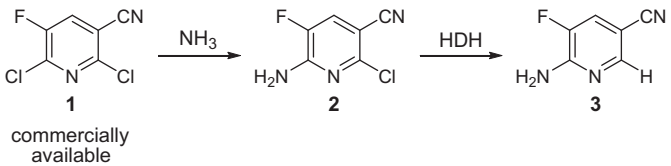
Many methodologies have been developed for the selective removal of halogens from arenes and heteroarenes.[2–10] While the methodologies cited above have proven effective in many situations, they all suffer limitations. HDH reactions employing harsh reagents such as Grignard reagents or other strong bases[3–7] provide limited functional group tolerance, while other methodologies are of limited substrate scope,[7,10] or employ undesirably high reaction temperatures.[9]

Of the hydrodehalogenation (HDH) methods that have been developed to-date, those which utilise silanes as cheap and readily available reducing agents are particularly attractive. Silane-based HDH methodologies avoid the use of hydrogen gas (which is an explosion risk and is not always accessible), and provide chemoselective conditions for HDH in the presence of sensitive functionalities. Although a number of reports of silane-mediated palladium-catalysed HDH exist,[11–13] these published methodologies are of limited substrate scope. Conditions employing polymethylhydrosilane with potassium fluoride as the base were completely ineffective for phenolic and carboxylic acid containing substrates, while protocols employing triethylsilane as a reducing agent have only demonstrated the reduction of a single aryl chloride (chlorobenzene).[11–13] Herein we report a chemoselective silane-mediated HDH protocol which addresses these limitations.

To facilitate a drug discovery campaign we wished to access the polyfunctional pyridine **3** (Scheme 1).

Compound **3** was not commercially available so we utilised 2,6-dichloropyridine **1** as the starting material. Access to the desired compound would then be achieved via selective displacement of the 6-chloro substituent with ammonia, followed by reduction (HDH) of the unwanted carbon–chlorine bond.

We initially attempted the HDH of **2** under catalytic hydrogenation conditions [H_2 (1 atm), Pd/C], but this led to the simultaneous reduction of the nitrile functionality, as well as the formation of secondary amine side-products. Dissolving metal type reductions (using Zn/AcOH or Zn/TFA) were then trialed, however, despite being relatively successful in providing the desired product, issues during the reaction work-up, that is, nitrile hydrolysis, led us to

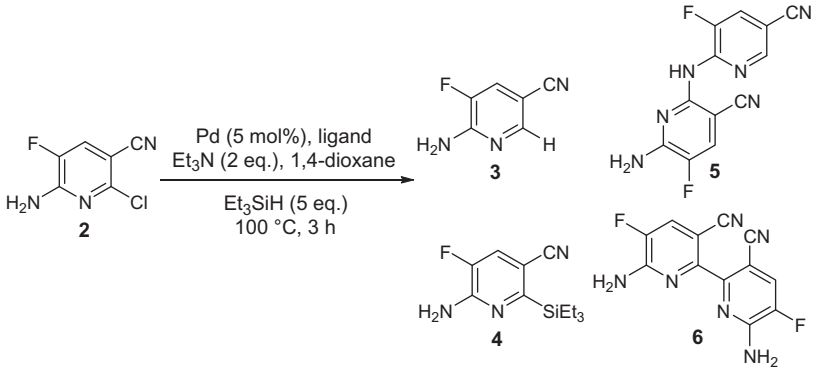


Scheme 1. Synthetic route to polyfunctional pyridine **3**.

* Corresponding author. Tel.: +44 1625 233264.
E-mail address: gary.noonan@astrazeneca.com (G.M. Noonan).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.06.063

Table 1
Screening of the hydrodehalogenation conditions



Entry[a]	Catalyst	**2**[b]	**3**[b]	**4**[b]	**5**/**6**[b,c]
1	$Pd_2(dba)_3$/*t*-Bu-X-Phos[d]	62	24	—	14
2	$Pd(PPh_3)_2Cl_2$	96	4	—	—
3	$Pd(dppf)_2Cl_2$	85	15	—	—
4	$Pd_2(dba)_3$/X-Phos[d]	—	88	—	12
5	$Pd(A\text{-}Phos)_2Cl_2$	—	85	15	—
6	$Pd(dtbpf)Cl_2$	—	91	9	—

[a] Reactions carried out using 0.6 mmol substrate in 3 mL of 1,4-dioxane.
[b] Percentage product is based on LC–MS (uncalibrated) of the crude reaction mixtures.
[c] Structures **5** and **6** are both possible based on $[M+H]^+$ observed in crude LC–MS data.
[d] 10 mol % ligand.

seek an alternative approach. Thus we explored palladium-silane based hydrodehalogenation conditions and Table 1 outlines the results of our initial catalyst screen.

Analysis of the crude reaction mixtures (Table 1) was carried out by LC–MS and the percentage value shown for each compound **2**–**6** was that observed in the uncalibrated chromatogram (UV detection). The identities of the side-products **4**–**6** are proposed based on mass ions observed in the crude LC–MS data.[14]

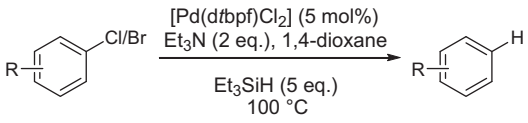
The most successful catalysts were those derived from bulky, electron-rich phosphines, with both monodentate (entry 5) and bidentate ligands (entry 6) proving successful. The reaction using $[Pd(dtbpf)Cl_2]$ (entry 6) was particularly effective, producing mainly the desired product, together with a small amount of the silylated side-product **4**.

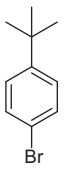
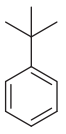
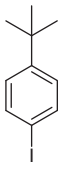
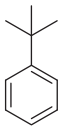
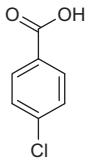
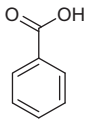
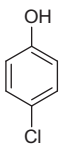
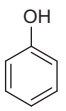
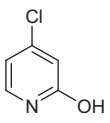
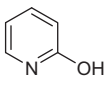
This reaction (entry 6) was then repeated using a ^1H NMR internal standard. After 1 h clean conversion to the required product was observed, with an internal standard based yield of 68% (see Supplementary data for details). The reaction mixture was allowed to stir for a further 30 min, after which a small impurity started to become apparent in the ^1H NMR spectrum. The reaction was stopped after 2 h and following work-up and purification, the required product was isolated in a 56% yield (average of two runs).[15] Although the isolated yields were moderate, this methodology provided the required synthetic intermediate in a quick and efficient manner.

As hydrodehalogenation is a reaction we utilise on a regular basis, we decided to explore the scope of the current HDH conditions. We were particularly interested in testing these reaction conditions in the hydrodehalogenation of substrates which have previously failed to produce the desired product using related protocols. The results of this study are presented in Table 2.

We carried out initial test reactions on 4-bromo/iodo *tert*-butylbenzene. The reaction of 4-bromo-*tert*-butylbenzene produced the desired product in a moderate yield (entry 1), whereas reduction of the iodo analogue was less efficient (entry 2). Significant unknown impurities were observed in both reactions, with 33% of an unknown side-product observed for the 4-iodo substrate. These

Table 2
Substrate scope of the hydrodehalogenation conditions[17,18]



Entry	Substrate	Time (h)	Product	Yield[a]
1		16		75[b]
2		16		47[c]
3		16		98 (65)
4		20		87[d]
5		16		(70)[d]

(*continued on next page*)