Journal of Molecular Catalysis A: Chemical 393 (2014) 191–209

Contents lists available at ScienceDirect

Journal of Molecular Catalysis A: Chemical

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

$NaBH_4$-TMEDA and a palladium catalyst as efficient regio- and chemoselective system for the hydrodehalogenation of halogenated heterocycles

Giorgio Chelucci*, Susanna Figus

Dipartimento di Agraria, Università di Sassari, Viale Italia 39, 07100 Sassari, Italy

ARTICLE INFO

Article history:
Received 5 May 2014
Received in revised form 5 June 2014
Accepted 11 June 2014
Available online 18 June 2014

Keywords:
Hydrodehalogenation
Reduction
Haloheterocycles
Palladium catalysts
Sodium borohydride
N,N,N′,N′-tetramethylethylenediamine

ABSTRACT

The pair $NaBH_4$-TMEDA as hydride source and a palladium catalyst in THF prove to be an efficient system for the hydrodehalogenation of halogenated heterocycles with one or more heteroatoms. In general, $Pd(OAc)_2$-PPh_3 rapidly hydrodehalogenates reactive halo-heterocycles such as bromo-pyridines, -quinolines, -thiophenes, -indoles, -imidazoles, etc., at room temperature in very good yields, whereas in most cases $PdCl_2$(dppf) reduces less reactive halides such as chloro-pyridines, -quinolines, -pyrimidines and bromo-indoles, -benzofurans, etc. Moreover, $PdCl_2$(tbpf) shows to be even more active removing the 2- and 5-chlorine from both thiophene and thiazole rings. The reaction conditions tolerate various functional groups, allowing highly chemoselective reactions in the presence of halide, ester, alkyne, alkene and nitrile substituents. Moreover, with a proper selection of the catalyst it is also possible to obtain a good control in the regioselective hydrodehalogenation of a variety of polyhalogenated substrates.

1. Introduction

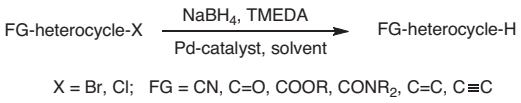
The substitution of halogens from aromatic rings by hydrogen is an important chemical transformation in organic synthesis because this exchange reaction can constitute a key step in the synthesis of heteroaryl-based molecules in a number of cases: (i) a halogen substituent can serve as excellent blocking group for a reactive position of a heterocycle, thus allowing a reaction to be addressed toward a less reactive one; then, after having fulfilled its function the halogen can be removed [1,2]. (ii) In a stereodifferentiating process involving a heteroaromatic compound the presence of a halogen in the heterocyclic ring can help to increase the reaction stereoselectivity, subsequently the removal of the halogen by hydrogen can be pursued [1,3]. (iii) The conversion of a functional group (FG) bonded to a heteroaromatic ring into a halide substituent and its subsequent removal from the heterocycle can constitute a way to convert a C-FG into a C–H bond [4]. (iv) The presence of a halogen on a heterocyclic ring can activate its α-position toward specific reactions, then the halogen can be removed [5]. Finally, (v) it should be noted that often it is not possible to directly introduce a halogen on an unreactive position of a heterocycle as other more reactive free positions are halogenated more quickly; however, a solution to this problem could be the halogenation of both positions, followed by selective removal of the halogen from the more reactive one [6].

A wide variety of hydrodehalogenating systems have been developed over the years for the hydrodehalogenation of halogenated heterocycles [7]. Reduction is usually mediated by a transition-metal catalyst (Ni, Pd, Rh, Pt) and is performed with molecular hydrogen, metal hydrides or hydrogen sources such as formic acid and its salts, hydrazine, alkoxides possessing a β-hydrogen, etc. [7]. A number of hydrogenating systems has been also extended to halogenated heteroaromatics, although the application of several of them to these substrates are rather sporadic. A recent review cover this subject in some extent [6]. Most hydrodehalogenations of halogenated heterocycles are often accomplished by catalytic hydrogenation on metal catalyst, Pd/C or Raney Nickel, and halogen-metal exchange reaction [6]. These processes are often troublesome to execute since the former ignites easily and the latter requires anhydrous conditions and low reaction temperature. For safety and simplicity of operation, a liquid-phase process without using molecular hydrogen is more advantageous.

Interestingly, some alternative methods have been recently described, such as (i) hydrogenolysis of aryl halides with catalytic Pd/C in the presence of hydrazine hydrochloride [8]; (ii) indium-mediated dehalogenation of haloheteroaromatics in water [9]; (iii) reduction of chloroarenes by $Pd(OAc)_2$ in combination with polymethylhydrosiloxane and aqueous KF [10], (iv) dehalogenation of activated and unactivated aryl halides by catalytic Pd-complexes

* Corresponding author. Tel.: +39 0 79 229539; fax: +39 0 79 229559.
E-mail address: chelucci@uniss.it (G. Chelucci).

http://dx.doi.org/10.1016/j.molcata.2014.06.012
1381-1169/



Scheme 1.

under transfer reaction conditions [11,12], (vi) deiodination [13] and dechlorination [14] with sodium formate and catalytic palladium catalysts, (vii) $Fe(acac)_3$ catalyzed hydrodehalogenation of aryl halides with *t*-BuMgCl as reductant [15], and (viii) hydrodehalogenation with sodium borohydride ($NaBH_4$) [16,17].

However, most of these methods appear limited to halopyridines, involving other halogenated heterocycles in only some well-defined cases [6]. Therefore, systematic studies addressing the application of a single hydrodehalogenating system to a wide range of halo-heterocycles, also including evidences of chemo- and regioselective reductions, are missing.

In this paper, we report a complete account on the use of the pair sodium borohydride/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine ($NaBH_4$-TMEDA) under palladium catalysts as an efficient system for the hydrodehalogenation a large variety of halogenated heterocycles (Scheme 1) [17]. Moreover, in this circunstance we also show that this system allows both highly chemoselective hydrodehalogenation in the presence of different functional groups and good efficiency in the regioselective reduction of a variety of polyhalogenated substrates.

2. Experimental

2.1. General information

All reactions were carried out under nitrogen in oven-dried glassware with magnetic stirring. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. All solvents were reagent grade. THF was distilled from sodium-benzophenone ketyl and degassed thoroughly with dry nitrogen directly before use. Unless otherwise noted, organic extracts were dried with Na_2SO_4, filtered through a fritted glass funnel, and concentrated with a rotary evaporator (20–30 mmHg). Flash chromatography was performed with silica gel (200–300 mesh) using the mobile phase indicated. Melting points are uncorrected. The NMR spectra were measured on 300 spectrometer at 300 for ^{1}H and 75.4 MHz for ^{13}C in $CDCl_3$ solution with TMS as an internal standard). Chemical shifts (δ) are given in parts per million and coupling constants (J) in hertz.

2.2. Commercial starting materials

2-Bromo-6-phenylpyridine **1a**, (6-Bromo-pyridin-2-yl)-phenyl-methanol **1b**, 5-bromo-2-ethoxypyridine **1e**, 3-bromo-5-phenylpyridine **1f**, 2-chloro-5,6,7,8-tetrahydroquinolin-8-ol **1h**, 5-chloro-2-phenylpyridine **1i**, 2-bromo-6-methylpyridine-3-carbonitrile **1k**, 4-chloropyridine-2-carbonitrile **1l**, 4-chloropyridine-2-carbonitrile **1m**, methyl 6-chloropyridine-3-carboxylate **1n**, (6-bromopyridin-2-yl)(phenyl)methanone **1q**, 1-(6-bromopyridin-2-yl)ethanone **1r**, 2-bromopyridine-3-carbaldehyde **1s**, 2-bromoquinoline **3a**,,3-bromoquinoline **3c**, 2-chloroquinoline **3d**, 2-chloro-4-azaphenanthrene **3e**, (2-chloroquinolin-3-yl)methanol **3f**, 2-chloro-4-azaphenanthrene **3 g**, 1-chloroisoquinoline **3h**, 3-chloroisoquinoline **3i**, 4-bromoisoquinoline **3j**, 4,7-dichloroquinoline **3k**, 2,8-dichloroquinoline **3l**, 1,3-dichloroisoquinoline **3m**, 2-chloroquinoxaline **5a**, 4-chloroquinazoline **5b**, 4-chloro-2,6-dimethoxypyrimidine **5c**, 2,4-dichloro-5-methoxypyrimidine **5d**, 2-bromo-5-phenylthiophene **7a**, 2-(5-bromothiophen-2-yl)-1,3-dioxolane **7b**, (5-bromothiophen-2-yl)methanol **7c**, 4-bromo-2-phenylthiophene **7d**, (4-bromothiophen-2-yl)methanol **7e**, 3-bromo-2,5-diphenylthiophene **7f**, 2-bromo-1-methyl-1*H*-indole **7i**, 2-bromobenzofuran **7j**, 2-(5-bromofuran-2-yl)-1,3-dioxolane **7k**, 3-bromobenzo[*b*]thiophene **7l**, 3-bromo-1-methyl-1*H*-indole **7n**, 3-bromobenzofuran **7o**, 3-chloroobenzo[*b*]thiophene **7q**, 3,5-dibromo-2-phenylthiophene **9a**, 2,3-dibromobenzo[*b*]thiophene **9c**, 2,3-dibromobenzofuran **9f**, 2,3,6-tribromobenzo[*b*]thiophene **9 g**, 4-bromothiophene-3-carbonitrile **9m**, 2-bromo-4-phenylthiazole **11a,** 2-chloro-4-phenylthiazole **11b**, 5-chloro-5-phenylthiazole **11c**, 5-bromo-2-phenylthiazole **11d**, 4-bromo-2-phenylthiazole **11e**, 2-bromobenzo[*d*]thiazole **11f**, 1-benzyl-4-bromo-1*H*-imidazole **11i**, 3-bromoimidazo[1,2-*a*]pyridine **11j**, 2-chloro-1-(4-fluorobenzyl)-1*H*-benzo[*d*]imidazole **11k**, 3-bromo-1-methyl-1*H*-indazole **11l**, 2-chlorobenzo[*d*]oxazole **11m**, 4-bromo-3,5-dimethylisoxazole **11n**, 2-chloro-4-(4-chlorophenyl)thiazole **11o**, 2,5-dichlorobenzo[*d*]thiazole **11p**, 4,5-dibromo-2-phenylthiazole **11q**.

2.3. Starting materials prepared according to reported procedures

2-Bromo-3-(1,3-dioxolan-2-yl)pyridine **1c** [18], 2-bromo-6,8-methano-7,7-dimethyl-5,6,7,8-tetrahydroquinoline **1d** [17*b*], 2-chloro-6,8-methano-7,7-dimethyl-5,6,7,8-tetrahydroquinoline **1g** [19], 2-bromo-3-(phenylethynyl)pyridine **1o** [20], 2-bromobenzo[*h*]quinoline **3b** [21], 2-bromobenzo[*b*]thiophene **7h** [22], 3-bromo-2-phenylbenzo[*b*]thiophene **7m** [23], 3-bromo-1-methyl-1*H*-indole **7n** [24], 3-bromobenzofuran **7o** [25], 2-chloro-5-phenylthiophene **7p** [26], 3,5-dibromo-2-phenylthiophene **9b** [27], 2,3-dibromo-1-methyl-1*H*-indole **9d** [28], methyl 2,3-dibromo-1*H*-indole-1-carboxylate **9e** [29], 2,3,5-tribromobenzofuran **9h** [30], methyl 5-bromothiophene-2-carboxylate **9i** [31], 3-bromo-2-(phenylethynyl)benzo[*b*]thiophene **9j** [32], 3-Bromo -2-(4-vinylphenyl)benzo[*b*]thiophene **9k** [33], 3-bromo-2-(3-cyanophenyl)benzo[*b*]thiophene **9l** [33], 2-chlorobenzo[*d*]thiazole **11g** [34], 1-benzyl-2-bromo-1*H*-imidazole **11h** [35], 2,5-dibromo-4-phenylthiazole **11q** [36], 1-benzyl-4,5-dibromo-1*H*-imidazole **11r** [33], 1-benzyl-4,5-dibromo-1*H*-imidazole **11s** [37], 1-benzyl-2,4,5-tribromo-1*H*-imidazole **11t** [38], 2-bromo-5-chloro-4-phenylthiazole **13a** [33], 4-bromo-5-chloro-2-phenylthiazole **13b** [39].

2.4. Commercial products

2-Phenylpyridine **2a**, phenyl(pyridin-2-yl)methanol **2b**, 3-(1,3-dioxolan-2-yl)pyridine **2c**, 2-ethoxypyridine **2e**, 3-phenylpyridine **2f**, 5,6,7,8-tetrahydroquinolin-8-ol **2 g**, 3-bromo-5-methylpyridine **2h**, 6-methylpyridine-3-carbonitrile **2i**, pyridine-2-carbonitrile **2j**, *N*-(pyridin-2-yl)ethanamide **2k**, methyl pyridine-3-carboxylate **2l**, 3-(phenylethynyl)pyridine **2m**, (*Z*)-3-styrylpyridine **2n[1]**, (*E*)-3-styrylpyridine **2n[2]**, phenyl(pyridin-2-yl)methanone **2o**, 1-(pyridin-2-yl)ethanone **2p**, pyridine-3-carbaldehyde **2q**, quinoline **4a**, 7,8-benzoquinoline **4b**, quinolin-3-ylmethanol **4c**, isoquinoline **4d**, 7-chloroquinoline **4e**, 8-chloroquinoline **4f**, quinoxaline **6a**, quinazoline **6b**, 2,4-dimethoxypyrimidine **6c**, 4-chloro-5-methoxypyrimidine **6d**, 2-phenylthiophene **8a**, 2-(thiophen-2-yl)-1,3-dioxolane **8b**, thiophen-2-ylmethanol **8c**, 2,5-diphenylthiophene **8d**, 1-(thiophen-2-yl)ethanol **8e**, benzo[*b*]thiophene **8f**, 1-methyl-1*H*-indole **8g**, benzofuran **8h**, 2-(furan-2-yl)-1,3-dioxolane **8i**, benzo[*b*]thiophene **8j**, 2-phenylbenzo[*b*]thiophene **8k**, 3-bromo-2-phenylthiophene **10a**, 4-bromo-2-phenylthiophene **10b**, 3-bromobenzo[*b*]thiophene **10c**, 2,3-dibromo-1-methyl-1*H*-indole **10d**, 3-dibromobenzofuran **10f**, 3,6-dibromobenzo[*b*]thiophene **10g**, 3,5-dibromobenzofuran **10h**,