



Facile and convenient synthesis of aryl hydrazines via copper-catalyzed C–N cross-coupling of aryl halides and hydrazine hydrate

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ARTICLE INFO

Article history:

Received 22 January 2014

Received in revised form 31 March 2014

Accepted 14 April 2014

Available online 19 April 2014

Keywords:

C–N Cross-coupling reaction

Copper catalysis

Hydrazine hydrate

Aryl bromides

Preparation of aryl hydrazines

ABSTRACT

An efficient and convenient method for the synthesis of aryl hydrazines has been developed via copper-catalyzed cross-coupling of aryl bromides and hydrazine with a readily accessible ligand and water as a solvent. The multigram scale procedure is applicable to aryl bromides bearing both moderately electron-donating and electron-withdrawing substituents in the aromatic nucleus. No column chromatography is required to obtain aryl hydrazine hydrochlorides in good yields.

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1. Introduction

Aryl hydrazines are widely used as intermediates in the synthesis of various nitrogen-containing heterocyclic systems such as indoles,¹ indazoles,² arylpyrazoles,³ and aryltriazoles.⁴ These heterocyclic compounds are of biological and medicinal interest.⁵ Preparation of aryl hydrazines is typically carried out via the reduction of the corresponding diazonium salts with tin(II) compounds⁶ or alkali metal bisulfites,⁷ but these methods have substantial drawbacks. Firstly, they involve the generation of unstable diazonium intermediates, which makes this method dangerous at multigram use. Secondly, they produce large volumes of toxic aqueous wastes. Furthermore, yields of aryl hydrazines can be decreased because their deamination is often facile under the reaction conditions, especially for aryl hydrazines with donor substituents.⁸ The alternative classical method for the synthesis of aryl hydrazines is based on nucleophilic aromatic substitution of aryl halides with hydrazine. However, such uncatalyzed processes can be applied only for strongly electron-deficient substrates.⁹

Over the last years palladium- and copper-catalyzed cross-coupling reactions of aryl halides and amines—Buchwald–Hartwig reactions¹⁰ and modified Ullmann reactions,¹¹ respectively—have

represented the most effective instruments for the construction of new C–N bonds in aromatic systems. Perhaps, because hydrazine is a strong reducing agent capable of destroying a metal-containing system, its derivatives such as benzophenone hydrazone¹² and BOC-hydrazines¹³ have been used in palladium-catalyzed cross-coupling in several studies. Stradiotto et al. have recently reported the first palladium-catalyzed method for synthesis of aryl hydrazines from hydrazine.¹⁴ While this protocol has obvious advantages, as compared to the classical methods for the synthesis of aryl hydrazines, a number of drawbacks restrict its applicability. To illustrate, the reactions were conducted in a nitrogen-filled glovebox with the high loading of an expensive catalyst (1.5–10 mol % of $[\text{Pd}(\text{cinnamyl})\text{Cl}]_2$) and 4.5–6 mol % of the ligand Mor-DalPhos).

Copper-catalyzed C–N couplings of aryl halides with amines (Ullmann reaction), which can be performed with cheap catalysts and often do not require inert atmosphere, have recently become as popular as Buchwald–Hartwig reactions.¹⁵ Although tremendous progress has been achieved in the field of Ullmann reactions over the past decades, only one paper describing the cross-coupling of unprotected hydrazine with aryl halides catalyzed by copper has been published.¹⁶ The authors performed the coupling reactions of hydrazine and aryl iodides with 10 mol % CuI as a catalyst, PEG-400 as a solvent, and 200 mol % K_3PO_4 as a base in a sealed tube at 120 °C for 6 h. The apparent disadvantages of this method are a large amount of PEG-400 (2 mL/1 mmol ArI) and excess hydrazine (1 mL of 85% aqueous hydrazine/1 mmol ArI) obstructing the

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isolation of product from the reaction mixtures. Furthermore, all of aryl hydrazines (except for phenylhydrazine) had to be transformed into their *N*-tosyl derivatives in order to be isolated. All of these factors appear to restrict the synthetic utility of the method described.

The objective of our work was to design a new and more efficient method of aryl hydrazines synthesis using copper-catalyzed C–N cross-coupling reaction of hydrazine with aryl halides. It has been recently found that copper catalysts containing oxalyl dihydrazide derivatives (CONHNH'R'')₂ as ligands allow C–N cross-coupling processes in water in the presence of phase transfer catalysts (PTCs).^{17–20} For example, the catalytic systems of Cu(0,I,II)/(CONHNH₂)₂(**L1**)/hexane-2,5-dione(**A1**)¹⁷ and Cu(0,II)/PhNHNHCOCONHNH₂(**L2**)/hexane-2,5-dione(**A1**)¹⁹ were successfully applied for arylation of anilines. Inspired by these results, we used the ligand systems based on the derivatives of oxalyl dihydrazide for copper-catalyzed arylation of hydrazine. As an extension of their applicability for catalysis in water, we are the first to report a new method for the synthesis of aryl hydrazines hydrochlorides via copper-catalyzed cross-coupling of aryl bromides with hydrazine in an aqueous solution.

2. Results and discussion

The reaction of bromobenzene with hydrazine hydrate was chosen as a model process for the study. We carried out the CuBr/**L1**/**A1**-catalyzed reaction of bromobenzene with hydrazine hydrate for 1 h and detected that the conversion of bromobenzene was 96% and the yield of phenylhydrazine was 73%.²¹ In addition, aniline (3%), which was the by-product formed by deamination of phenylhydrazine, was found in the reaction mixture (Table 1, entry 1). As we suppose based on the data of Pd-catalyzed C–N cross-

coupling of aryl halides with hydrazine,¹⁴ the rest of the starting material was turned into benzene, whose yield we did not determine in the optimization experiments.

We optimized the reaction conditions by screening the ligand systems of RNHNHCOCONHNH₂ (ligand **L**)/ketone (additive **A**) (Table 1). Initially, it is worth to note that the reaction did not proceed without addition of the ligand system (Table 1, entry 2). At the same time, the ligand system did not catalyze this process without a copper source (Table 1, entry 3). The ligand **L1** and the additive **A1** did not work properly without each other (Table 1, entries 4, 5). The ligand system of **L1**/**A1** proved to be slightly more active than the ligand system of **L2**/**A1** (Table 1, entries 1, 6). However, the drawback of the ligand system of **L2**/**A1** was that **L2** reacted with hydrazine to give an additional amount of phenylhydrazine. This was proven by the reaction of 1-bromo-4-methoxybenzene with hydrazine hydrate where phenylhydrazine was found in the reaction mixture. Therefore, our further investigation was concentrated on the ligand systems composed of **L1** and different mono- and dicarbonyl compounds as additives. The additives such as cyclohexanone (**A2**) (entry 7), pentane-2,4-dione (**A3**) (entry 8), and 1,4-diphenylbutane-1,4-dione (**A4**) (entry 9) proved to be less efficient than hexane-2,5-dione (**A1**).

To optimize the reaction conditions we varied the hydrazine hydrate amount, base, and PTC (Table 2). The optimal amount of hydrazine hydrate was found to be 200 mol % (Table 2, entries 1–3). The bases, which were used (Table 2, entries 2, 4–8) led to high conversions of bromobenzene, but the yield of the target product was maximal with K₃PO₄ and decreased markedly when KOH, K₂CO₃, K₂HPO₄ or Na₃PO₄ were applied. This decrease was probably a result of hydrolysis of bromobenzene²² (in addition to the previously mentioned reduction). Selectivity was maximal in the case of K₃PO₄ possibly due to its strong basicity (pK_a=12.3 for the conjugate acid) and low nucleophilicity.²³ Cetyltrimethylammonium bromide (CTAB) or tetrabutylammonium bromide (TBAB) was applied as a PTC with near equal efficiency for the model reaction (Table 2, entries 2, 9). The reaction proceeded without a PTC (Table 2, entry 10), however, the conversion of the substrate and selectivity of the process were less than in the presence of a PTC. Further, the reaction showed similar level of efficiency at the lower PTC loadings (5 mol % and 2 mol %) (Table 2, entries 11, 12).

The reactivity of chlorobenzene and iodobenzene was compared with that of bromobenzene (Table 3, entries 2, 13, 14). The reaction of iodobenzene produced approximately the same yield of the product and the conversion of the substrate as the reaction of bromobenzene. In contrast, chlorobenzene was inert in this process even under more drastic reaction conditions (8 h, 120 °C).

It is known that hexane-2,5-dione can react with oxalyl dihydrazide to give *N,N'*-bis(2,5-dimethylpyrrol-1-yl)oxalamide (**L3**) via a Paal–Knorr reaction.²⁴ We synthesized **L3** from **L1** and **A1** and compared the catalytic activity of CuBr/**L3** with that of CuBr/**L1**/**A1** in the reaction of hydrazine hydrate with bromobenzene. The yield of phenylhydrazine increased from 73% up to 86% in the reaction when CuBr/**L3** was used (Table 3, entry 1). The optimization experiments with this catalytic system (Table 3) showed its enhanced activity as compared with CuBr/**L1**/**A1**. The amount of CuBr and **L3** could be diminished down to 2.5 and 4 mol %, respectively, without a loss of phenylhydrazine yield (Table 3, entry 2). A moderate yield of the target product (66%) was obtained in the reaction with 0.6 mol % of CuBr and 1.2 mol % of **L3** (Table 3, entry 4). In addition, arylation of hydrazine could proceed at room temperature but with a relatively low yield of the target phenylhydrazine (21%) at a moderate conversion of bromobenzene (59%) (Table 3, entry 6). Presumably, reductive hydrodehalogenation of bromobenzene is the main process at room temperature. The same problem occurred for the reaction of chlorobenzene with hydrazine hydrate where

Table 1
Cross-coupling of bromobenzene and hydrazine hydrate using different ketones as components of the ligand system^a

<chem>c1ccccc1Br</chem> + N ₂ H ₄ ·H ₂ O $\xrightarrow[100\text{ mol}\% \text{ K}_3\text{PO}_4, \text{ H}_2\text{O}, 110^\circ\text{C}, 1\text{ h}]{5\text{ mol}\% \text{ CuBr}, 10\text{ mol}\% \text{ L}, 10\text{ mol}\% \text{ ketone (A)}, 10\text{ mol}\% \text{ CTAB}}$ <chem>c1ccccc1NNH2</chem>				
L1: <chem>N#NCC(=O)N#N</chem> L2: <chem>N#NCC(=O)N#N</chem> A1: <chem>CC(=O)CCC(=O)C</chem> A2: <chem>C1CCCCC1=O</chem> A3: <chem>CC(=O)CCC(=O)C</chem> A4: <chem>CC(=O)C(c1ccccc1)CC(=O)c2ccccc2</chem>				
Entry	L+A	Conversion, ^b %	Yield of PhNHNH ₂ , ^b %	Yield of PhNH ₂ , ^b %
1	L1 + A1	96	73	3
2	—	3	0	0
3 ^c	L1 + A1	0	0	0
4	L1	38	9	0
5	A1	6	0	0
6	L2 + A1	90	69	4
7	L1 + A2	13	9	0
8	L1 + A3	24	9	0
9	L1 + A4	4	3	0

^a Reaction conditions: bromobenzene (1 mmol), N₂H₄·H₂O (2 mmol), CuBr (0.05 mmol), **L** (0.1 mmol), **A** (0.1 mmol), CTAB (0.1 mmol), K₃PO₄ (1 mmol), H₂O (50 mg), 110 °C, 1 h.

^b Determined by GC analysis (internal standard—4-chloro-1-methoxybenzene that is stable under the reaction condition). Conversion is based on consumption of bromobenzene.

^c Without any copper source.

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