Tetrahedron 74 (2018) 606–617

Contents lists available at ScienceDirect

Tetrahedron

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

Chan-Lam cross-coupling reaction based on the Cu_2S/TMEDA system

Kateřina Janíková [a], Lukáš Jedinák [a], Tereza Volná [b], Petr Cankař [a, *]

[a] Department of Organic Chemistry, Palacký University, 17. Listopadu 1192/12, 77146, Olomouc, Czech Republic
[b] Institute of Molecular and Translation Medicine, Faculty of Medicine, Palacký University, Hněvotínská 5, 77900, Olomouc, Czech Republic

ARTICLE INFO

Article history:
Received 12 November 2017
Received in revised form
18 December 2017
Accepted 20 December 2017
Available online 22 December 2017

Keywords:
Chan-Lam coupling
Copper(I) sulfide
Arylation
Imidazole
Benzimidazole

ABSTRACT

A catalyst based on the readily available Cu_2S/TMEDA system using a stable copper(I) source was developed for the Chan-Lam cross-coupling reaction. The capability of the catalyst was demonstrated with 1*H*-benzo[*d*]imidazol-2(3*H*)-one, 1*H*-benzo[*d*]imidazole, and 1*H*-imidazole together with electron-deficient, electron-rich, and sterically demanding boronic acids at room temperature in the presence of atmospheric oxygen to give the cross-coupling products in moderate to excellent yields. In addition, the coupling reaction of 1*H*-benzo[*d*]imidazole with several pinacol or neopentylglycol boronates indicated further potential of the catalyst. The reaction conditions tolerate the hydroxyl and bromo functional groups. The catalytic system also enables to synthesize the mono-N-substituted anilines from primary aliphatic amines. However, the two model compounds for the secondary and aromatic amines, piperidine and aniline, do not react. Two sterically demanding products with the restricted C–N bond rotation, synthesized by the *N*-arylation of 1*H*-benzo[*d*]imidazol-2(3*H*)-one with *o*-tolylboronic acid, enabled to confirm the atropisomers prepared by the Chan-Lam cross-coupling reaction. Furthermore, an example of one-pot Chan-Lam and Suzuki-Miyaura reaction has been reported.

1. Introduction

The *N*-arylazole structural motif is common in numerous biologically active compounds.[1] Therefore, procedures allowing simple and efficient construction of such patterns would represent a significant contribution to the field of medicinal chemistry.[2] Apart from less universal and time consuming *de novo* synthetic methods,[3] there are several reactions enabling direct arylation of heterocycles. Presumably, the oldest method is classical nucleophilic aromatic substitution utilizing aryl halides,[4] which, however, suffers from the poor substrate scope, as only electron deficient aryl halides offer reasonable reactivity.[5] The activation of C-halogen bonds via oxidative addition by transitional metals significantly improved the reactivity, and also extended the substrate scope. Nevertheless, the requirement of high reaction temperature and/or strong base limits such C–N couplings, typically referred as Ullman-Goldberg[6] or Buchwald-Hartwig reactions.[7]

Copper mediated coupling of arylboronic acids with various types of nucleophiles, known as the Chan-Lam reaction, represents an experimentally simple procedure that forms C(sp^2)-heteroatom bond under mild reaction conditions, thus allowing incorporation of otherwise sensitive substrates.[8] Moreover, the reaction tolerates various functionalities including halogens; therefore it offers compatibility with subsequent transformations of C-halogen bonds, such as Suzuki-Miyaura reaction.[9]

Synthetically relevant *N*-arylations (or alkenylations) of heterocycles via Chan-Lam reaction have been reported with various copper salts or complexes, ligands or bases, and solvents.[10] Despite significant progress being made with copper catalysts since seminal reports by Chan, Lam, and Evans (1999), there still remains space for the development. The goal would be stable, inexpensive, and easily available copper catalyst, which enables arylation of *N*-heterocycles at room temperature, especially with electron-poor or sterically demanding boronic acids. Ideally, the reaction should be performed under ambient atmosphere without a need for additional oxidant or oxygen atmosphere.[11]

Herein, we present a novel Cu_2S/TMEDA system as a readily available catalyst for the Chan-Lam reaction using just 5 mol% of Cu_2S (10 mol% of [Cu]) at room temperature and under ambient atmosphere. The Cu_2S/TMEDA system originally came out from the optimization of *N*-arylation involving benzimidazolone **1** as a model substrate. The fact that benzimidazolone **1** possess two reactive sites brought a question, if this compound can be substituted selectively to form monoaryl derivatives, or diarylated

* Corresponding author.
E-mail address: petr.cankar@upol.cz (P. Cankař).

https://doi.org/10.1016/j.tet.2017.12.042
0040-4020/

compounds will be unavoidable (side)products of the reaction. Furthermore, this method was extended to the *N*-arylation of 1*H*-benzo[*d*]imidazole, 1*H*-imidazole, and primary aliphatic amines.

2. Results and discussion

Our experiments started with a mixture of benzimidazolone **1**, *p*-tolylboronic acid **2a** (2 equiv.), copper acetate (0.5 equiv.), and TMEDA (1 equiv.) in CH_2Cl_2 under ambient atmosphere (Table 1, entry 1). The reaction produced only 13% of mono-arylated compound **3a** together with 6% of di-arylated compound **4a** after 24 h, while 77% of starting material **1** remained unchanged. From CH_2Cl_2, MeOH, MeCN, and DMF tested in the combination with $Cu(OAc)_2$/TMEDA (entries 1–4), DMF performed best, yet it led to compound **3a** in only 27% after 24 h.

Substitution of $Cu(OAc)_2$ with CuCl significantly improved the rate of the Chan-Lam reaction (entry 5), thus 45% of mono-arylated product **3a** was formed after 3 h, together with 5% of di-arylated derivative **4a**. Prolonging the reaction time to 24 h revealed 47% of **3a**, 15% of **4a**, and 36% of starting material **1**. Slightly lower reactivity was observed with CuI and Cu_2O (entries 6 and 7), while 25 mol% of Cu_2S (entry 8) displayed the most promising catalytic activity from all tested copper compounds, giving 50% of mono-arylated derivative **3a**, 8% of di-arylated derivative **4a**, and 39% of starting material **1** after 3 h. Increasing TMEDA to two equivalents did not have any significant effect on the reaction (entry 9). Examination of pyridine and Et_3N as plausible ligands for Cu_2S brought inferior yields in comparison to the Cu_2S/TMEDA system (entries 10 and 11). The Chan-Lam coupling reaction using Cu_2S without any ligand was very sluggish (entry 12).

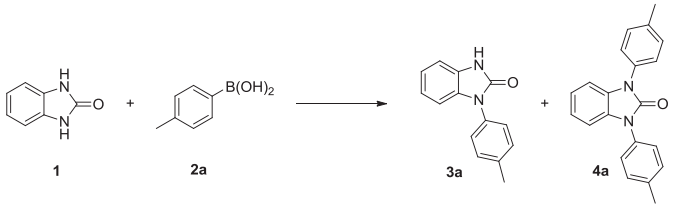
HPLC analyses after 3 and 24 h demonstrated that mono-aryl derivative **3a** was a major product after 3 h and its concentration decreased after 24 h as a consequence of formation of di-arylated derivative **4a** (Table 1, entry 8). This observation prompted us to explore the reaction progress with the Cu_2S/TMEDA using various amounts (25%, 10%, 5% and 2.5%) of Cu_2S, one equivalent of TMEDA, and two equivalents of boronic acid **2a** in DMF (Fig. 1A–D). Use of Cu_2S at 25% molar ratio (50% of [Cu]) showed that the amount of product **3a** was increasing up to 3 h, when it reached its maximum at 49% (Fig. 1A). Then it began to decrease, while the percentage of **4a** was constantly increasing. After approximately 5 h, the amount of both arylated products **3a** and **4a** was equal. Around 6 h **4a** became the major compound in the reaction mixture and after 24 h it reached 60%, while **3a** was formed in 29% and 4% of staring material **1** remained.

Almost identical results were obtained with 10% of Cu_2S (Fig. 1B). The same trend, but lower reaction rate was observed with molar ratio at 5% and 2.5% of Cu_2S (Fig. 1C and D). It seems that the reaction has an induction period at the 2.5% catalyst loading (Fig. 1D), which was not observed at the higher loadings. Then, it was obvious from all diagrams that both benzimidazolones **1a** and **3a** underwent *N*-arylation at similar rate. While the amount of **3a** increased in time, it became more available for subsequent *N*-arylation to yield **4a**. Therefore no more than approximately 50% of **3a** can be obtained from this reaction. However, the limit 50% can be potentially exceeded in case of a significantly slower rate of second *N*-arylation caused by stereo-electronic effects (*vide infra*). Reducing the ratio of benzimidazolone **1**/boronic acid **2a** to 1:1 did not avoid the formation of **4a**, only led to a higher content of unreacted starting material **1**.

Despite 10% of Cu_2S was optimal for the model Chan-Lam reaction in study, molar ratio at 5% also offered acceptable reaction rate and product conversion; therefore 5% of Cu_2S (10% of [Cu]), 1 equivalent of TMEDA, and two equivalents of boronic acid **2a-n** were used in subsequent experiments. Boronic acids **2a-n** with various stereo-electronic substitution patterns were employed in the Chan-Lam reaction using benzimidazolone **1** as a substrate (Table 2).

When the Chan-Lam reaction between benzimidazolone **1** and *p*-tolylboronic acid **2a** was quenched after 8 h, mono-arylated product **3a** was isolated in 40% yield and di-arylated product **4a** in 17% yield. In general, the separation of **1**, **3**, and **4** by column chromatography was facile due to distinct polarity of most compounds. Using unsubstituted phenylboronic acid **2b**, phenyl

Table 1
Optimization of the Chan-Lam reaction.



Entry	[Cu]	Ligand	Solvent	Time [h]	**1** (%)[a]	**3a** (%)[a]	**4a** (%)[a]
1	$Cu(OAc)_2$	TMEDA	CH_2Cl_2	24	77	13	6
2	$Cu(OAc)_2$	TMEDA	MeOH	24	73	19	3
3	$Cu(OAc)_2$	TMEDA	MeCN	24	78	17	3
4	$Cu(OAc)_2$	TMEDA	DMF	24	60	27	5
5	CuCl	TMEDA	DMF	3 (24)	46 (36)	45 (47)	5 (15)
6	CuI	TMEDA	DMF	3 (24)	58 (44)	32 (43)	3 (9)
7	Cu_2O	TMEDA	DMF	3 (24)	53 (5)	34 (26)	3 (49)
8	Cu_2S	TMEDA	DMF	3 (24)	39 (7)	50 (33)	8 (55)
9	Cu_2S	TMEDA[b]	DMF	3 (24)	35 (4)	49 (31)	11 (56)
10	Cu_2S	Pyridine	DMF	3 (24)	44 (25)	37 (43)	4 (16)
11	Cu_2S	Et_3N	DMF	3 (24)	58 (42)	30 (40)	2 (9)
12	Cu_2S	none	DMF	3 (24)	95 (94)	2 (2)	<1 (<1)

General conditions: Benzimidazolone **1** (0.5 mmol), boronic acid **2a** (1.0 mmol), ligand (0.5 mmol), copper salt (0.25 mmol for $Cu(OAc)_2$, CuCl and CuI; or 0.125 mmol for Cu_2O and Cu_2S), solvent (2 mL), rt, air.

[a] HPLC yield determined from LCMS after 3 or 24 h using *N*-Fmoc-L-alanine as an internal standard.

[b] 1.0 mmol (2 equiv.) of TMEDA were used.