Tetrahedron Letters 57 (2016) 1066–1070

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Palladium-free Sonogashira-type cross-coupling reaction of bromoisoxazolines or *N*-alkoxyimidoyl bromides and alkynes

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ARTICLE INFO

Article history:
Received 17 December 2015
Revised 12 January 2016
Accepted 19 January 2016
Available online 21 January 2016

Keywords:
Sonogashira-type
Copper catalysis
Catalysis
Isoxazoline

ABSTRACT

A Cu(I)-catalysed Sonogashira-type cross coupling reaction with aliphatic or aromatic bromoisoxazolines or *N*-alkoxyimidoyl bromides and alkynes is reported. The protocol we developed employs catalytic amount of copper(I), non-toxic ligand bathophenanthroline and is tolerant to a wide range of functional groups and is therefore particulary adapted in the context of drug discovery.

Introduction

Palladium and copper co-catalysed Sonogashira-Hagihara cross-coupling reaction is widely used for the formation of sp^2–sp carbon–carbon bonds under mild conditions with aryl or vinyl halides (or triflate) and is frequently employed for the synthesis of biologically active molecules, heterocycles, natural products and in other chemical fields such as electronics or polymers.[1] Typical procedures involve the use of palladium phosphine complexes with CuI as the co-catalyst and large amounts of amines as the solvents or co-solvents.[2] To circumvent the high cost and relative higher toxicity of palladium compared to copper, catalytic systems without palladium have been successfully reported in the literature, combined with ligands such as phosphines,[3] nitrogen[4] and oxygen-containing molecules.[5] Even coupling reactions without the use of any transition metal have been published.[6]

Nevertheless, coupling partners such as acid chlorides and imidoyl halides have received less attention, with only few examples of catalytic coupling reaction between *N*-alkoxybenzimidoyl halides, and alkynes are described in the literature.[7] Those examples were restricted to aromatic groups attached to the sp^2 carbon and with the use of catalytic amount of palladium(II) complex (Scheme 1A).[8]

Here, we describe the first palladium-free cross-coupling reaction between bromoisoxazolines and alkynes in the presence of a catalytic amount of copper bromide and phenanthroline based-ligand (Scheme 1B). An extension to *N*-alkoxylalkylimidoyl bromides is also reported.

Results and discussion

At the outset of our investigations, we carried out the Sonogashira cross-coupling reaction between bromospiroisoxazoline **1a** and phenylacetylene **2a** under standard Sonogashira conditions.[9] Unfortunately, the desired cross-coupling product was not obtained, and a considerable amount of side products was observed.

Solvents were first screened (Table 1) with CuBr as a cheap copper(I) source. For the first time the desired product was observed with the combination of Na_2CO_3 and DMF. (HPLC yield: 4% yield with Bn_2O as the internal standard, Table 1, entry 1), whereas with toluene, THF or 1,4-dioxane as solvents no desired coupled product was detected, suggesting a dissociative pathway.

To reduce the catalytic charge of copper (in our first experiment loaded at 50 mol %) while trying to increase significantly the yield, we investigated different ligands, bases, copper sources (Table 2). At 100 °C, only ligands **L1** and **L8** containing aromatic nitrogen as donor groups (Table 2, entries 1 and 5) yielded the desired compound **3aa** with more than 10% HPLC yield, compared to those bearing secondary and tertiary amines (Table 2, entries 2–4).

At higher temperature (120 °C), phenanthroline **L1** and 2,2′-bipyridyl **L8** (Table 2, entries 6 and 7) associated with CuBr were

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http://dx.doi.org/10.1016/j.tetlet.2016.01.070
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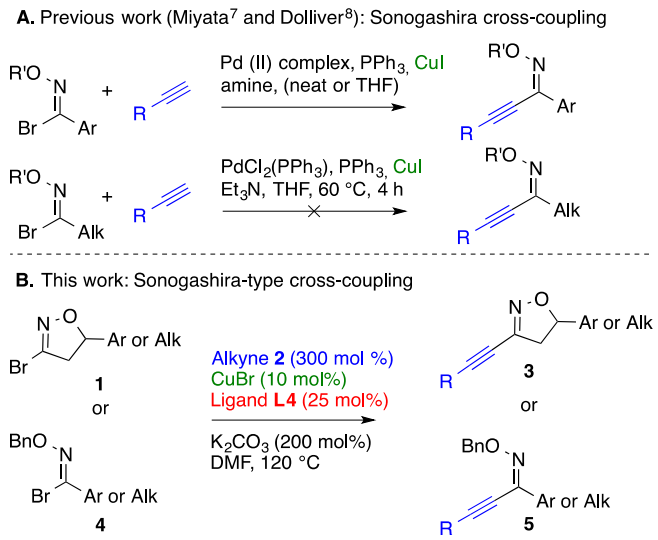


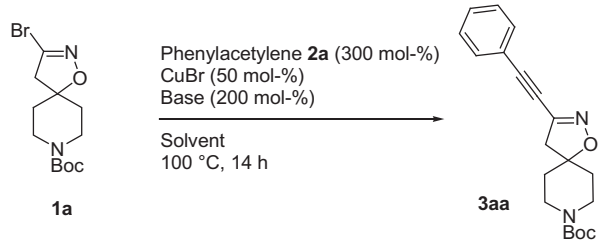
Scheme 1.

able to catalyse the reaction, affording respectively 61% and 40% HPLC yield. At 140 °C (Table 2, entry 8) the formation of the desired compound was not improved. The use of K_2CO_3 afforded a significant better yield (Table 2, entry 9). When phenanthroline based-ligands (**L1** to **L4**) were used, we were allowed to halve the catalytic loadings of CuBr and ligands respectively to 10 and 25 mol %. 4,7-dihydroxy-1,10-phenanthroline **L2** (Table 2, entry 10) failed to catalyse the reaction while neocuproin **L3** (Table 2, entry 11) was less effective than phenanthroline **L1** (Table 2, entry 12). Interestingly, the reaction was as efficient with CuI (Table 2, entry 13) and CuBr (Table 2, entry 12) as copper sources, whereas CuCl (Table 2, entry 14) was less efficient for this transformation. When the reaction was carried out at 120 °C using 25 mol % of bathophenanthroline **L4** (Table 2, entry 15), 200 mol % of K_2CO_3 and 10 mol % of CuBr, a quantitative HPLC yield was obtained and the desired compound was isolated with a 84% yield after flash chromatography. The copper free reaction (entry 16) did not lead to any formation of the cross-coupling product, excluding a competitive addition-elimination reaction pathway catalysed by the phenanthroline alone.

Next, we explored the scope of this reaction starting with substituted terminal alkynes. Electron rich (4-methoxyphenylacetylene **2c**) and electron poor aromatic alkynes (4-fluorophenylacetylene **2b** and 2-ethynylpyridine **2e**) afforded the coupling products in excellent yields but no conversion was observed with 1-ethynyl-4-nitrobenzene (**2d**). Interestingly 2-ethynylpyridine **2e** showed a remarkable reactivity, affording complete consumption of the starting bromoisoxazoline **1a** within 3 h.

The phenylacetylene derivatives (**2a** to **2e**) afforded in general better yields compared to aliphatic or functionalized alkynes **2f** to **2i**. Aliphatic alkynes **2g** and **2h** also afforded the targeted compounds in good yields however to overcome the Castro-Stephens homocoupling reaction, ten equivalents of cyclohexylacetylene **2f** and cyclopropylacetylene **2i** were used for the synthesis of the corresponding isoxazolines **3af** and **3ai**. To broaden the scope of the reaction, we performed the reaction with bromoisoxazolines bearing an ester (**1b** and **1c**), a free alcohol (**1e**) or a *tert*-butylcarbamate group (**1f**) and we also succeeded in isolating the desired compounds in good yields. The *cis*-fused ring isoxazoline **3da** was also easily obtained following the same protocol (Table 3).

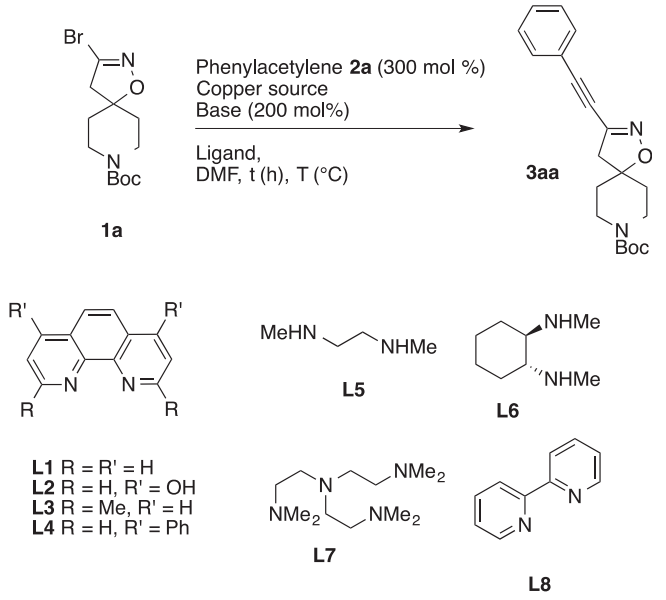
Table 1
Solvent optimization of the Sonogashira-type cross-coupling reaction with bromoisoxazoline **1a** and phenylacetylene **2a**[a]



Entry	Base	Solvent	Yield[b] (%)
1	Na_2CO_3	DMF	4
2	Na_2CO_3	THF	nr[c]
3	Na_2CO_3	Toluene	nr[c]
4	Na_2CO_3	1,4-Dioxane	nr[c]

[a] Conditions: bromoisoxazoline **1a** (0.157 mmol, 100 mol %), phenylacetylene **2a** (300 mol %), base (200 mol %), CuBr (50 mol %) in DMF (1.5 mL) at 100 °C for 14 h.
[b] HPLC yield of **3aa** relative to Bn_2O as the internal standard.
[c] No reaction.

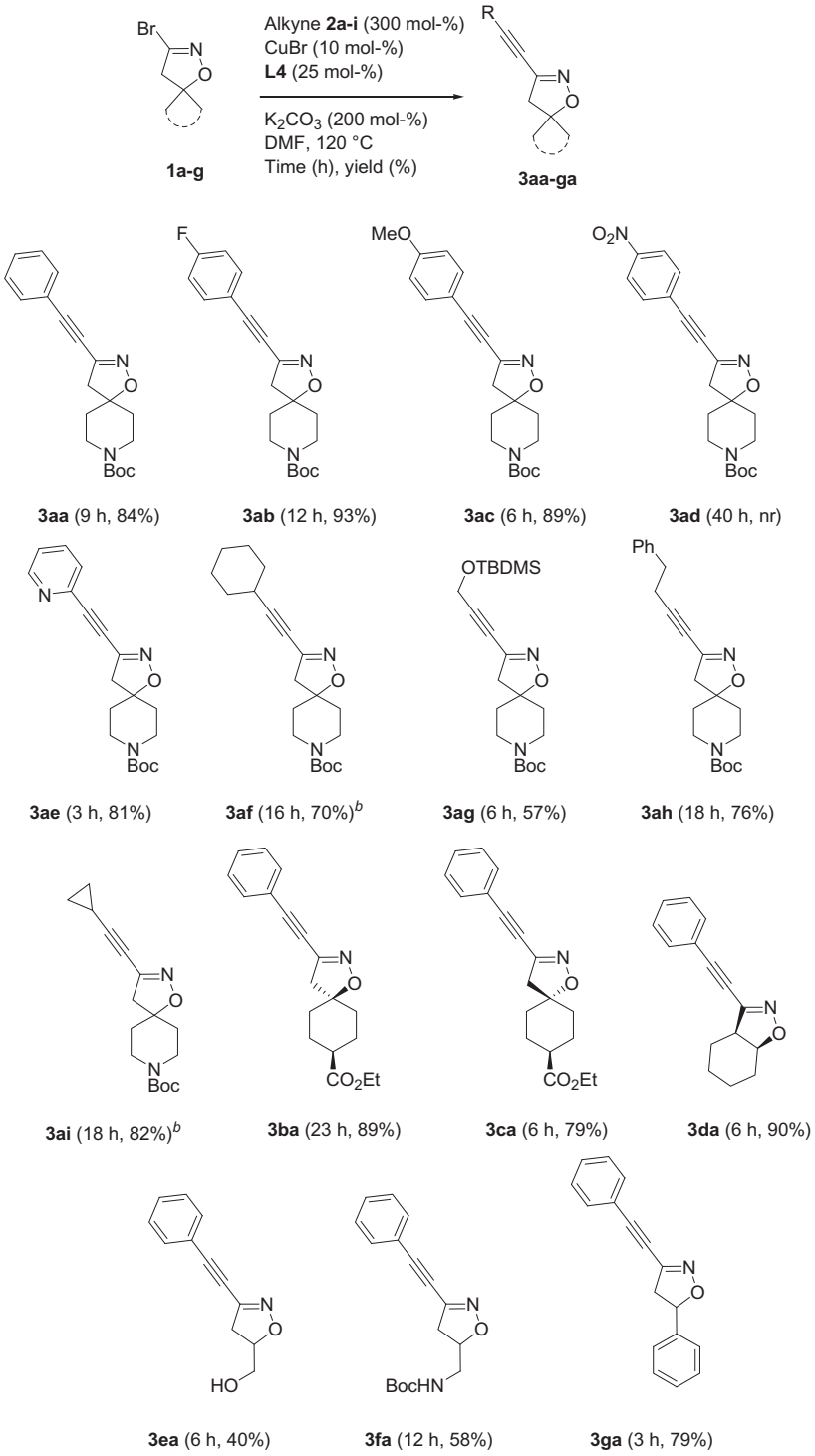
Table 2
Ligand optimization of the Sonogashira-type cross-coupling reaction with bromoisoxazoline **1a** and phenylacetylene **2a**[a]



Entry	Base	Cu source (mol %)	Ligand (mol %)	Time (h)	Temp. (°C)	Yield [b]
1	Na_2CO_3	CuBr (20)	**L1** (50)	14	100	16
2	Na_2CO_3	CuBr (20)	**L5** (50)	14	100	8
3	Na_2CO_3	CuBr (20)	**L6** (50)	14	100	9
4	Na_2CO_3	CuBr (20)	**L7** (50)	14	100	5
5	Na_2CO_3	CuBr (20)	**L8** (50)	14	100	15
6	Na_2CO_3	CuBr (20)	**L1** (50)	20	120	61
7	Na_2CO_3	CuBr (20)	**L8** (50)	20	120	40
8	Na_2CO_3	CuBr (20)	**L1** (50)	20	140	65
9	K_2CO_3	CuBr (20)	**L1** (50)	3	120	84
10	K_2CO_3	CuBr (10)	**L2** (25)	9	120	nr[c]
11	K_2CO_3	CuBr (10)	**L3** (25)	9	120	20
12	K_2CO_3	CuBr (10)	**L1** (25)	9	120	73
13	K_2CO_3	CuI (10)	**L1** (25)	9	120	72
14	K_2CO_3	CuCl (10)	**L1** (25)	9	120	57
15	K_2CO_3	CuBr (10)	**L4** (25)	9	120	91 (84[d])
16	K_2CO_3	—	**L1** (50)	20	120	nr[c]

[a] Conditions: bromoisoxazoline **1a** (0.157 mmol, 100 mol %), phenylacetylene **2a** (300 mol %), base (200 mol %), copper source, ligand, DMF (1.5 mL).
[b] HPLC yield of **3aa** relative to Bn_2O as the internal standard.
[c] No reaction.
[d] Isolated yield after flash chromatography.

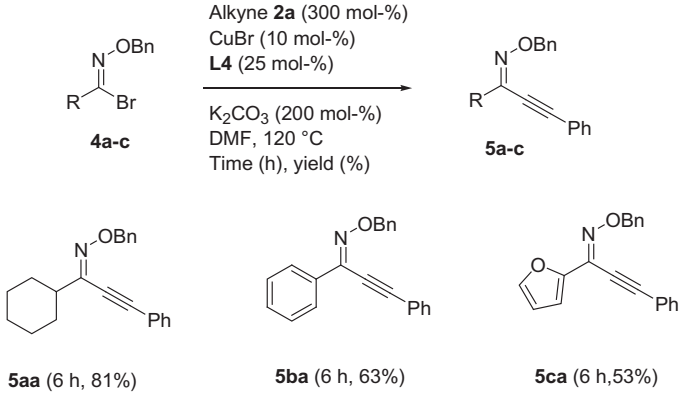
Table 3
Scope of the Cu(I)-catalysed Sonogashira-type cross-coupling reactions between bromoisoxazolines **1a–g** and alkynes **2a–i**[a]



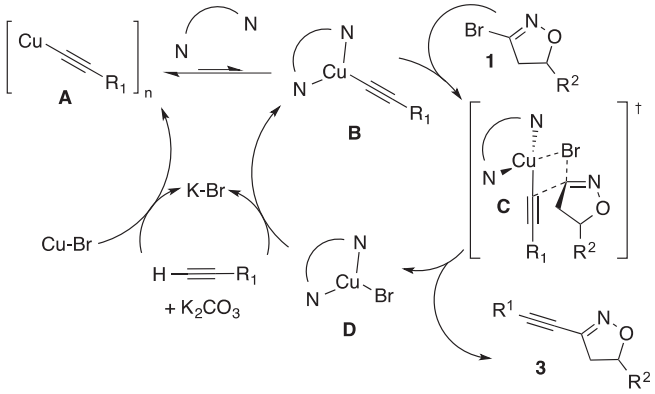
[b] 1000 mol % of alkyne was used.
nr = no reaction, Boc = *tert*-butylcarbamate, Ph = Phenyl, TBDMS = *tert*-butyldimethylsilyl.
[a] Conditions: bromoisoxazoline **1a–g** (100 mol %), alkyne **2a–i** (300 mol %), K_2CO_3 (200 mol %), CuBr (10 mol %), bathophenanthroline **L4** (25 mol %), in DMF (0.1 M) at 120 °C. Reaction time and isolated yields after flash chromatography are in brackets.

Once bromoisoxazolines **1a–g** were shown to be excellent reagents under our conditions, we turned our attention to the Sonogashira-type coupling with *N*-benzyloxyimidoyl bromides **4a–c** (Table 4). Interestingly, Miyata and co-workers pointed out one example containing the cyclohexyl group attached to the C=N double bond but the product was not isolated due to blank;the decomposition of the substrate. The optimal conditions were applied to cyclohexyl *N*-benzyloxyimidoyl bromides **4a** to

Table 4
Scope of the Cu(I)-catalysed Sonogashira-type cross-coupling reactions between *N*-alkoxyimidoyl bromides **4a–c** and phenylacetylidene **2a**[a]



[a] Conditions: Reaction carried out with *N*-benzyloxyimidoyl bromides **4a–c** (0.2 mmol, 100 mol %), alkyne **2a** (300 mol %), K_2CO_3 (200 mol %), CuBr (10 mol %), bathophenanthroline **L4** (25 mol %), in DMF (1.5 mL) at 120 °C. Isolated yields after flash chromatography.



Scheme 2. Proposed reaction mechanism for the Sonogashira-type cross coupling.

afford the coupling product **5aa** in a good yield (81%). *N*-Alkoxyimidoyl bromides bearing a phenyl (**4b**) or a furyl (**4c**) group afforded respectively **5ba** and **5ca** in moderate yields from 53% to 63%.

Mechanism

A putative mechanism was proposed as outlined in Scheme 2 on the basis of Bolm and co-workers work. They suggested that a resting state (form **A**) was a polymeric complex which was in equilibrium with an active monomeric complex (form **B**) which was activated by the phenanthroline-based ligand by forming a soluble [Cu(phenanthroline)(phenylacetylene)] complex.

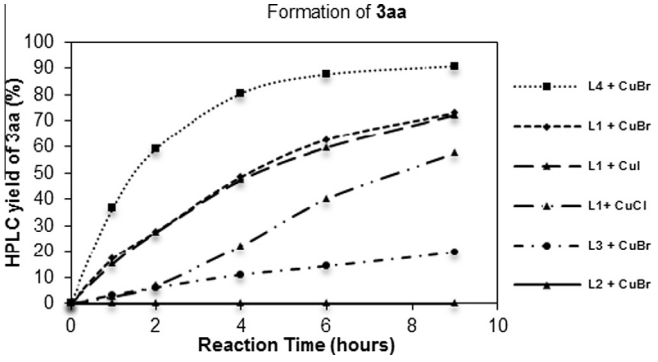


Figure 1. Benchmark of **L1–4** and copper source by ex situ monitoring of formation of **3aa** by HPLC. (Sorted in order of reactivity.)

Reactivity of the associated ligands

Previous reports suggested that a stable chelate and strongly donating ligands were required to actively catalyse the reaction.[10] We observed that the substituents on the phenanthroline ring have a strong impact on the reaction rate as depicted in Figure 1 while copper source can be indifferently CuI or CuBr. 4,7-Dihydroxy-1,10-phenanthroline **L2** inhibits the coupling reaction and neocuproin **L3** slows the reaction compared to phenanthroline **L1**.

Moderate donating group such as phenyl rings on the 4 and 7 positions of the phenanthroline ring (bathophenanthroline **L4**) seems to ideally balance the formation of the active monomeric catalyst **B** and the C–C bond formation leading to **D** via the supposed intermediate **C**. Detailed study of the actual mechanism is in progress.

Conclusions

We report the palladium-free Sonogashira-type cross-coupling reaction between a large set of bromoisoxazolines and alkynes. The protocol we developed allowed us to broaden this reaction to alkyl and aromatic *N*-benzyloxyimidoyl bromide derivatives. The protocol described herein demonstrates that copper can replace the conventional, expensive and toxic Pd-catalysed for the catalysis of Sonogashira cross-coupling reactions. Bathophenanthroline was used as a non-toxic ligand. The mild conditions used allow the cross coupling to be carried out in the presence of functional groups. More importantly the catalytic system tolerates a range of electron-poor and electron-rich phenylacetylene derivatives and aliphatic alkynes.

Acknowledgments

We are grateful to the institutions that support our laboratory: Inserm, Université Lille Nord de France, Institut Pasteur de Lille, EU, Région Nord-Pas de Calais, and PRIM, Pôle de Recherche Interdisciplinaire du Médicament. This project is funded by ANR (ANR-14-CE14-0027).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.070.

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9. Sonogashira conditions used: bromoisoxazoline **1a**, $PdCl_2(PPh_3)_2$ (10 mol %), phenylacetylene **2a** (200 mol %), TEA (200 mol %), CuI (10 mol %), PPh_3 (10 mol %), THF.
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