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A Sequential Metal-Catalyzed C-N Bond Formation in the Synthesis of 2-Amido-Indoles

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Abstract

A sequential metal-catalyzed C-N bond formation employing *ortho*-haloaryl acetylenic bromides is described. The initial amidation is highly selective for C^{sp}-N bond formation, leading to *o*-haloaryl-substituted ynamides that can be useful building blocks, while the overall sequence provides a facile construction of 2-amido-indoles.

Given the importance of heterocyclic manifolds,¹ we have been developing synthetic methods that feature ynamides²⁻³ en route to various heterocycles.⁴ These efforts led us to examine a possible entry for constructing amide substituted indoles.⁵⁻⁷ Specifically, as shown in Scheme 1, this pathway would commence with *ortho*-haloaryl acetylenic bromides **1** and adopt a consecutive metal-catalyzed C-N bond formation⁸ with the first involving the sp-hybridized carbon⁹⁻¹³ in an *N*-alkynylation manner, and the second one pertaining to an sp²-hybridized carbon in a *N*-arylation manner.^{8,14} The second C-N bond formation can also occur in a tandem manner with the ensuing indole formation promoted by the metal^{15,16} in a 5-*endo*-dig cyclization mode via **3**. While copper can be employed to catalyze the C^{sp}-N formation,⁹⁻¹³ we intend to utilize palladium for the C^{sp2}-N formation.¹⁵ If this sequential C-N bond formation is selective, it would constitute a facile entry to *de novo* 2-amido-indoles^{17,18} **5** from *ortho*-haloaryl acetylenes **1**, which can be readily derived from aromatic aldehydes in two steps.¹⁹ We report here synthesis of 2-amido-indoles via a sequential metal-catalyzed C-N bond formation.

A selective amidative cross-coupling of *ortho*-haloaryl acetylenic bromides **1**²⁰ could be readily established as shown in Scheme 2. By employing 10 mol% CuSO₄·5H₂O and 20 mol % of 1,10-phenanthroline,¹³ ynamide **6-Cl** was attained in 87% yield from **1-Cl**. The amidation remained selective when using **1-Br** and even **1-I**, leading to **6-Br** and **6-I** in 84% and 86% yield, respectively. Under the same conditions, ynamides **7-Cl** and **7-Br** were obtained also via a highly selective C^{sp}-N formation.

A diverse array of *ortho*-haloaryl acetylenic bromides could be subjected to this selective amidation to give ynamides **8-16** [Figure 1]. Moreover, a range of cyclic and acyclic amides including sulfonamides could be employed for the *N*-alkynylation to afford ynamides **17-23** in good yields.

Having established this selective amidation, we recognized that we have an excellent protocol to access *o*-haloaryl-substituted ynamides **6-23**, which represent a new class of functionally rich building blocks that could be utilized in a number of transformations involving either the *o*-haloaryl or ynamido motif [Figure 2], leading to rapid assembly of structural complexity.

To illustrate such synthetic potential, we chose to pursue aminative cross-coupling of aryl halides^{8,14} to access 2-acetylenic anilines en route to 2-amido-indoles via metal-promoted 5-*endo*-dig cyclization.^{15-19,21} As shown in Scheme 3, when ynamide **7-Br** was subjected to amination conditions employing 2.5 mol% Pd₂(dba)₃ and *p*-Tol-NH₂, 2-amido-indole **24** was obtained in good yields when using either 5.0 mol% of van Leeuwen's xantphos²² or Buchwald's X-phos as ligands.²³ Intriguingly, the use of X-phos appears to shorten the reaction time relative to xantphos while BINAP was not useful. On the other hand, amination of **7-Cl** led to **24** in 78% yield only when using X-phos. It is noteworthy that amination of **6-I** gave only 26% yield of corresponding indole [not shown], thereby suggesting that aryl chlorides and bromides are better suited in this operation than aryl iodides.

The generality of this tandem amination-5-*endo*-dig cyclization is shown in Table 1, featuring a range of different amines and *o*-chloroaryl- or *o*-bromoaryl-substituted ynamides in excellent yields for their respective reactions. X-ray crystallographic analysis of 2-amido-indole **28** reveals unique orthogonality of three planes: 2-Oxazolidone, the indole ring, and the *para*-tolyl ring [Figure 3]. Structures with related orthogonality have been shown²⁴ to possess inhibitory activities against human peptidyl prolyl *cis/trans* isomerase [PPI] Pin-1,²⁵ which catalyzes the isomerization of prolyl peptides from *cis* to *trans*^{26,27} and accommodates such orthogonality at its active site. We are currently investigating such potential biological activity.

We have described here a sequential metal-catalyzed C-N bond formation employing *ortho*-haloaryl acetylenic bromides. The initial amidation is highly selective for C^{sp}-N bond, leading to *o*-haloaryl-substituted ynamides that can be useful building blocks. The overall sequence provides a facile construction of 2-amido-indoles possessing a unique structural manifold.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. N-Alkynylation Products.^a

a. Reaction conditions are the same as those in Scheme 2. All are isolated yields.

Figure 2. Synthetic Potential of o-Haloaryl Ynamides

Figure 3. X-Ray Structure of 2-Amido-Indole 28

Scheme 1.

Scheme 2.

Scheme 3.

2-amido-indoles			yield [%] ^c
6-Br		25; R = <i>p</i> -Tol	91
6-Br		26; R = <i>o</i> -Tol	82

yield [%]^c

2-amido-indoles

28

65

2-amido-indoles		yield [%] ^c
29	60
	12	

yield [%]^c

2-amido-indoles

72

30

64

31

14

15

yield [%]^c

2-amido-indoles

80

32

yield [%]^c

2-amido-indoles

18-Br

33

71

yield [%]^c

34: R¹
= H

35: R¹
= CO₂Me

19

20

yield [%]^c

2-amido-indoles

21

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