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Copper-catalyzed oxidative ring closure of ortho-cyanoanilides with hypervalent iodonium salts: arylation – ring closure approach to imino-benzoxazines

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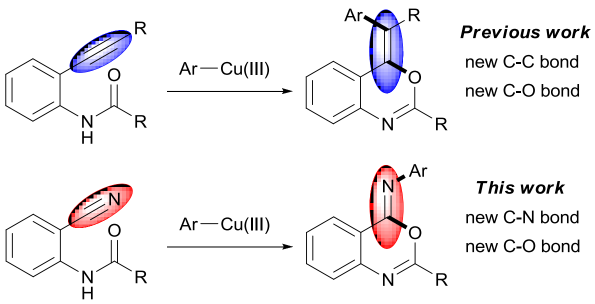
Abstract. A novel, highly modular synthetic methodology based on an oxidative arylation-cyclization strategy was developed for the construction of iminobenzoxazine derivatives in the copper-catalyzed reaction of ortho-cyanoanilides and diaryliodonium salts.

Keywords: C-N bond formation, C-O bond formation, copper; heterocycles, hypervalent compounds,

Copper-catalyzed syntheses of aromatic and heteroaromatic systems are intensively studied areas of current organic syntheses.[1] Recently, our research group developed a novel copper-catalyzed reaction[2] for the synthesis of benzoxazines from ortho-ethynylacetanilides and diaryliodonium salts[3] using the concept of aromatic electrophile generation via the intermediacy of Cu(III) species[4] described previously by Gaunt et al.[4a-h] Similarly to acetylene function, activation of a nitrile group with a copper catalyst and iodonium salts for the construction of heterocyclic skeletons such as quinolines, quinazolines and tetrahydroacridines in the presence of carbon-carbon triple bond via carbocation generation has recently been described by Chen et al.[5]

Considering the activation ability of Cu(III)aryl species toward acetylenes and nitriles, we aimed to extend the applicability of our ring closure concept to ortho-acetaminobenzonitriles. The replacement of the C-C triple bond with a nitrile group ortho position to the amide moiety would provide iminobenzoxazines[6] through similar cyclization path (Scheme 1).

Beyond the importance of the conceptual aspects of the transformation, the realization of this chemical approach would provide a new synthetic route to iminobenzoxazines, a synthetically useful compound class.[7] Moreover, benzoxazines are important due to their biological activity and their application in medicinal chemistry. For example, 1,3-benzoxazines act as potassium channel openers,[8] 1, 4-benzoxazines and benzothiazines were designed and synthesized for evaluation as new aldose reductase inhibitors,[9] and 1,3-benzoxazine-2,4-(3H)-dione derivatives showed antimycobacterial and antituberculotic activity.[10] Additionally, iminobenzoxazines, imino-benzothiazines and iminoquinazolines can be used for controlling invertebrate pests.[11]

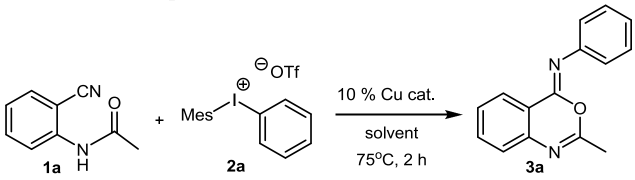


Scheme 1. Arylation - ring closure strategies for the construction of benzoxazine ring via Ar-Cu(III) mediated transformation

For the optimization of the reaction parameters, we chose *N*-(2-cyanophenyl)acetamide **(1a)** as the substrate and phenylmesityliodonium triflate **(2a)** as the arylating agent while the oxidative coupling was performed at 75 °C for 2 hours.[12] Examination of the effect of solvent on the reaction conversion showed that the reaction is slow in DMF, $CHCl_3$, MeOH and provides a complex reaction mixture in toluene (Table 1, Entries 1-4). In contrast, full conversion was reached in 2 hours when the reaction was conducted in THF, DCM, EtOAc or DCE (Entries 5-8.). Comparison of the activity of different copper catalysts revealed that CuCl, CuBr, $(MeCN)_4CuOTf$ and $Cu(OTf)_2$ are suitable for the transformation (Entries 9-15).

After the optimization studies, we aimed to explore the scope and limitations of the developed methodology. First, we reacted *N*-(2-cyanophenyl)acetamide **(1a)** with iodonium salts bearing different R^3 groups using 10 mol% of $Cu(OTf)_2$ in DCE at 75 °C (Scheme 2).

Table 1. Optimization studies of the reaction[a]

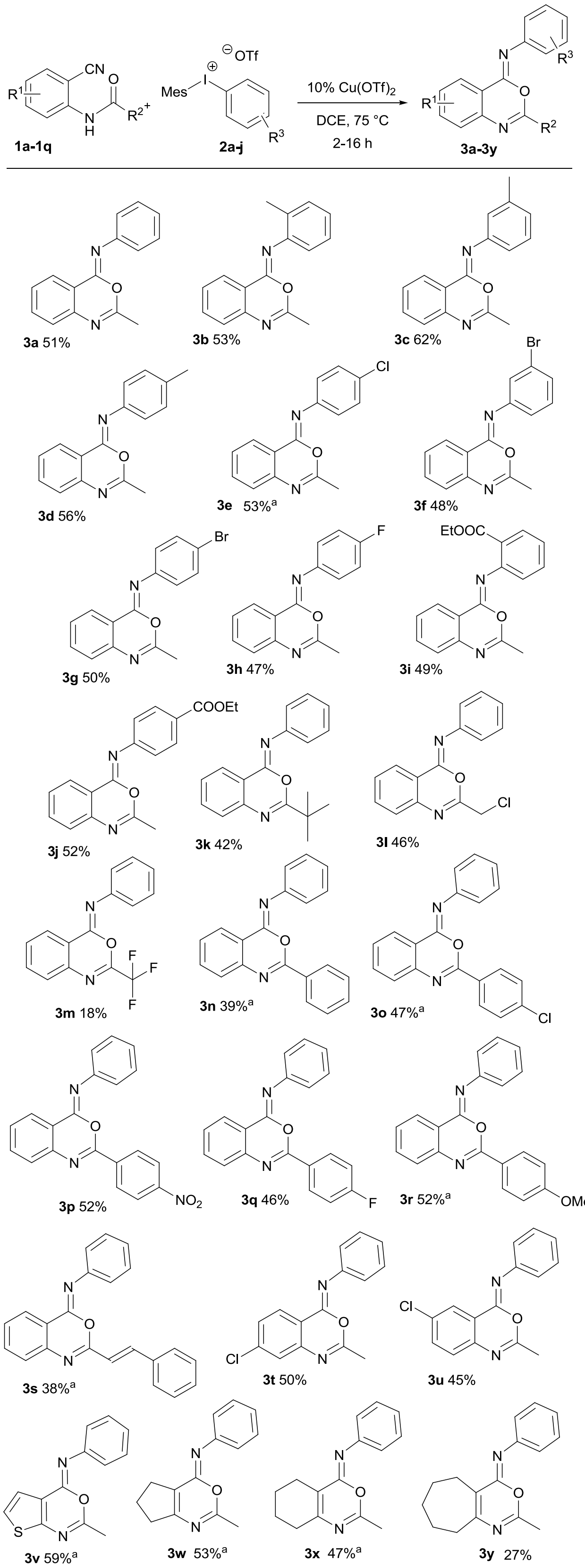


Entry	Catalyst	Solvent	Conv. [%]
1	$Cu(OTf)_2$	DMF	9[b]
2	$Cu(OTf)_2$	$CHCl_3$	52
3	$Cu(OTf)_2$	MeOH	56[b]
4	$Cu(OTf)_2$	PhMe	decomp[b]
5	$Cu(OTf)_2$	THF	100
6	$Cu(OTf)_2$	DCM	100
7	$Cu(OTf)_2$	EtOAc	100
8	$Cu(OTf)_2$	DCE	100
9	CuCl	EtOAc	100
10	CuBr	EtOAc	100
11	CuI	EtOAc	35
12	CuO	EtOAc	5
13	$CuSO_4$	EtOAc	16
14	$Cu(acac)_2$	EtOAc	16
15	$(MeCN)_4Cu(OTf)$	EtOAc	100

[a] *N*-(2-cyanophenyl)acetamide (0.125 mmol), diaryliodonium salt (0.150 mmol), $Cu(OTf)_2$ (0.013 mmol); solvent (250 μl), argon atmosphere, 75°C, 2h. [b] 8 h reaction time

When a methyl substituent was present in any position of the phenyl group of the iodonium salt, we obtained the desired compounds **(3b, 3c** and **3d)** in 53%, 62% and 56% yields, respectively. When the aryl part of the iodonium salt contained halogen atom (F, Cl, or Br) ortho to the iodine, the ring closing reaction was retarded and the desired compounds were detected only with GC-MS (0-17% GC-MS conversion, not shown). When the reaction was attempted with diaryliodonium salts containing halogens (F, Cl, Br) in the meta and para positions, **1a** was transformed to the desired iminobenzoxazines **(3e-3h)** in 53%, 48%, 50% and 47% yields. Diaryliodonium salts bearing COOEt group provided the desired products (**3i** and **3j**) with the similar efficiency (49 and 52% yields).

After examining the applicability of different arylmesityliodonium salts, we studied the reactivity of different amides in the ring closing reaction. The amides **(1b-1k)** were reacted with phenylmesityliodonium triflate **(2a)** to prepare the desired iminobenzoxazines **(3k-3s)**. When alkyl-substituted anilide derivatives **(1b**, **1d**, **1e)** were reacted in DCE, the desired products (**3k**, **3l**, **3m**) were isolated in 42%, 46% and 18% yields. When aromatic anilide **(1c)** was used compound **3n** was isolated in 39%. When the reaction was performed with aromatic amides bearing EWG or EDG groups **(1f-1i)** in the para position, the desired iminobenzoxazines (**3o**, **3p**, **3q** and **3r**) were obtained in 47%, 52%, 46% and 52% yields, respectively.

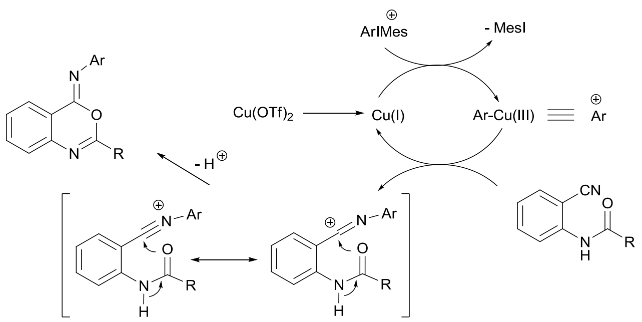


Scheme 2. Substrate scope of the copper-catalyzed transformation. *Reaction conditions:* *N*-(2-cyanophenyl)amide (0.500 mmol), diaryl iodonium salt (0.600 mmol), $Cu(OTf)_2$ (0.050 mmol); solvent (1000 μl), argon atmosphere, 75°C, 2-16h. [a] reaction was conducted in EtOAc.

Reaction of conjugated amide **(1k)** with phenylmesityliodonium triflate **(2a)** afforded the appropriate iminobenzoxazine **(3s)** in 38% yield.

Finally, the ring closure reaction was performed with substrates bearing chloro substituents on the anilide moiety **(1l**, **1m)**, with heteroaromatic derivative (thiophene, **1n**) and non-aromatic systems (**1o-1q**). The presence of halogens on the aromatic ring of anilide were well-tolerated, both in meta and para positions, and the desired benzoxazines (**3t** and **3u**) were isolated in 50% and 45% yields. The ring closure reaction of *N*-(3-cyanothiophen-2-yl)-acetamide **(1n)** provided the desired sulfur-containing heteroaromatic system **3v** in 59% yield. Non-aromatic condensed iminooxazine systems containing cyclopentene, cyclohexene and cycloheptene rings (**3w**, **3x** and **3y**) were obtained in 53%, 47% and 27% yields, respectively.

Regarding a possible mechanism of the transformation, on the basis of similar copper(III)-catalyzed oxidative couplings, we propose that the reaction starts with the formation of the Cu(I) species from $Cu(OTf)_2$ (Scheme 3).[5] In the following step, the Cu(I) catalyst is oxidized by the iodonium salt resulting the formation of the Ar-Cu(III) intermediate. We suppose that this highly electrophilic Cu(III) interacts with the nitrile function resulting the formation of a cationic species and Cu(I). The formed N-arylnitrilium intermediate readily undergoes cyclization with the participation of the amide group via nucleophilic attack of the carbonyl oxygen providing the iminobenzoxazine product.



Scheme 3. Proposed mechanistic steps for the transformation

In conclusion, we have demonstrated on a novel reaction that the concept of ring closing strategy based on electrophilic Ar-Cu(III) activation of triple bonds provides an efficient tool for the transformation of nitrile derivatives. Herein, we report the development of a new copper-catalyzed oxidative transformation for the construction of iminobenzoxazine derivatives from ortho-cyanoanilides and diaryliodonium salts. The overall transformation includes a *6-exo-dig* cyclization which is accompanied by the formation of new C-O and C-N bonds. The developed methodology enables the synthesis of benzoxazine derivatives with high modularity due to the easily variable functional groups built in the reaction. Further applications of the oxidative ring closure-arylation concept for the construction of novel heterocyclic systems are in progress in our laboratory.

Experimental Section

General Procedure

N-(2-cyanophenyl)acetamide **(1a)** (80.1 mg, 0.500 mmol), diaryliodonium salt (0.600 mmol, 1.2 eq.) and copper(II)triflate (18.08 mg; 0.050 mmol, 10 mol%) were added to a 4 ml vial then the system was charged with argon. Solvent (1,2-dichloroethane or ethyl acetate, 1000 µl) was added under argon atmosphere then the reaction mixture was stirred at 75°C for the appropriate time. Saturated sodium hydrogen carbonate solution (10 ml) was added to the mixture, the aqueous layer was extracted with dichloromethane (4 x 10 ml) the combined organics were dried over anhydrous sodium sulfate, filtered and evaporated. Purification of the crude products by column chromatography on silica gel afforded the products as solids.

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References

[1] a) M. Meldal, C. W. Tornoe, *Chem. Rev.* **2008**, *108*, 2952; b) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337-3015; c) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651-2710; d) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054-3131; e) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954-6971; f) A. Alexakis, J. E. Backvall, N. Krause, O. Pamies, M. Diéguez, *Chem. Rev.* **2008**, *108*, 2796-2823; g) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem. Int. Ed.* **2011**, *50*, 11062-11087; h) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464-3484; i) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926-1936; j) S. Cacchi, G. Fabrizi, A. Goggiamani, *Org. Biomol. Chem.* **2011**, *9*, 641-652; k) R. T. Gephart, T. H. Warren, *Organometallics* **2012**, *31*, 7728-7752.

[2] Á. Sinai, Á. Mészáros, T. Gáti, V. Kudar, A. Palló, Z. Novák, *Org. Lett.* **2013**, *15*, 5654-5657.

[3] a) J. Collette, D. McGreer, R. Crawford, F. Chubb, R. B. Sandin, *J. Amer. Chem. Soc.* **1956**, 78, 3819-3820; b) G. F. Koser, R. H. Wettach, C. S. Smith, *J. Org. Chem.* **1980**, *45*, 1543-1544; c) P. J. Stang, V. V. Zhdankin, R. Tykwinski, *Tetrahedron Lett.* **1992**, *33*, 1419-1422; d) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052-9070; e) J. M. Bouma, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14242-14245; (f) M. Bielawski, B. Olofsson, *Chem. Commun.* **2007**, *25*, 2521-2523; g) M. S. Yusubov, A. V. Maskaev, V. V. Zhdankin, *ARKIVOC* **2011**, 370-409; h) L. F. Silva, Jr., B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722-1754; i) V. V. Zhdankin, *Hypervalent Iodine Chemistry:*

Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds, Wiley **2013**.

[4] a) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172-8174; b) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593-1597; c) R. J. Phipps, L. Mc Murray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773-10776; d) A. Bigot, A. E. Williamson, M. J. Gaunt, *J. Am. Chem. Soc.* **2011**, *133*, 13778-13781; e) M. G. Suero, E. D. Bayle, B. S. L. Collins, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 5332-5335; f) A. J. Walkinshaw, W. Xu, M. G. Suero, M. J. Gaunt, *J. Am. Chem. Soc.* **2013**, *135*, 12532-12535; g) E. Cahard, N. Bremeyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2013**, *52*, 9284-9288; h) F. Zhang, S. Das, A. J. Walkinshaw, A. Casitas, M. Taylor, M. G. Suero, M. J. Gaunt, *J. Am. Chem. Soc.* **2014**, *136*, 8851-8854; i) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc*. **2011**, *133*, 4260-4263; j) J. H. Ryan, P. J. Stang, *Tetrahedron Lett.* **1997**, *38*, 5061-5064; k) A. Casitas, X. Ribas, *Chem. Sci.* **2013**, *4*, 2301-2318.

[5] a) Y. Wang, C. Chen, S. Zhang, Z. Lou, X. Su, L. Wen, M. Li, *Org. Lett.* **2013**, *15*, 4794-4797; b) X. Su, C. Chen, Y. Wang, J. Chen, Z. Lou, M. Li, *Chem. Commun.* **2013**, *49*, 6752-6754; c) Y. Wang, C. Chen, J. Peng, M. Li, *Angew. Chem. Int. Ed.* **2013**, *52*, 5323-5327.

[6] a) R. Mazurkiewicz, *Monatsch. Chem.* **1989**, *120*, 973-980; b) D. Bonne, M. Dekhane, J. Zhu, *Org. Lett.* **2005**, *7*, 5285-5288.

[7] a) D. J. Hart, N. A. Magomedov, *J. Am. Chem. Soc.* **2001**, *123*, 5892-5899; b) H. Wang, A. Ganesan, *J. Org. Chem.* **2000**, *65*, 1022-1030; c) F. He, B. B. Snider, *J. Org. Chem.* **1999**, *64*, 1397-1399; d) H. Wang, A. J. Ganesan, *J. Comb. Chem.* **2000**, *2*, 186-194.

[8] S. Yamamoto, S. Hashiguchi, S. Miki, Y. Igata, T. Watanabe, M. Shirashi, *Chem. Pharm. Bull.* **1996**, *44*, 734-745.

[9] H. Tawada, Y. Sugiyama, H. Ikeda, Y. Yamamoto, K. Meguro, *Chem. Pharm. Bull.* **1990**, *38*, 1238-1245.

[10] K. Waisser, J. Matyk, H. Divišová, P. Husáková, J. Kuneš, V. Klimešová, K. Palát, J. Kaustová, *Archiv der Pharmazie* **2007**, *5*, 264-267.

[11] T. B. Selby, L. D. Birch, WO Patent 03/032731 A1, 2003, *Chem. Abstr.* **2003**, 138:316207.

[12] For detailed optimization results see Supporting Information

COMMUNICATION

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