Synthesis of *N*-Alkoxyindol-2-ones by Copper-Catalyzed Intramolecular N-Arylation of Hydroxamates

Tatyana Kukosha, Nadezhda Trufilkina, Martins Katkevics*

Latvian Institute of Organic Synthesis, Aizkraukles 21, 1006 Riga, Latvia
Fax +37167550338; E-mail: martins@osi.lv

Received 2 June 2011

Abstract: The first example of copper-catalyzed intramolecular N-arylation of hydroxamic acid derivatives is presented. Based on this transformation a new method for the synthesis of *N*-alkoxyindol-2-ones from 2-(2-bromoaryl)acetylhydroxamates has been developed. The reaction conditions tolerate standard hydroxyl protecting groups on the hydroxylamine moiety and are also applicable for the synthesis of six-membered *N*-alkoxybenzolactams.

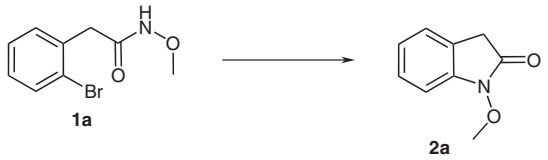
Key words: copper, arylation, cyclization, lactams, hydoxamic acids

Derivatives of 1-alkoxy-1,3-dihydro-indol-2-ones are versatile building blocks for the synthesis of indole derivatives by reduction of the carbonyl group[1] or by conversion of the carbonyl group into triflate followed by cross-coupling reaction. The *N*-hydroxy function in this case serves as the N-protecting group that can be removed under reductive conditions.[1,2] In addition, *N*-alkoxyindol-2-one appears as a core structure in several phytoalexins,[3] gelsedine-type[4] and notoamide-type[5] alkaloids. *N*-Hydroxyindolin-2-one derivatives have been found to be active against multiple sclerosis,[6] as influenza endonuclease inhibitors,[7] and have also been studied as alternative coupling reagents for peptide bond formation.[8]

The title compounds can be prepared by reductive cyclization of (2-nitro-phenyl)acetic acid derivatives[9] or oxidation of 2,3-dihydro-1*H*-indoles.[10] However, both methods suffer from low functional group compatibility and various side reactions. Alternatively, *N*-alkoxyindol-2-ones may be synthesized from 2-arylacethydroxamates by electrophilic cyclization via *N*-alkoxyacylnitrenium anions.[2,11] Although this method is widely used, the outcome is strongly dependent on the substitution pattern of the phenyl ring.

On the other hand, transition-metal-catalyzed cross-coupling reactions are commonly applied to aryl–nitrogen bond formation,[12] although there are only three examples in the literature where this transformation is applied to intra- or intermolecular N-arylation of hydroxamic acid derivatives.[13–15] Yu reported cyclization of 2-arylacethydroxamates to *N*-alkyloxybenzolactams via a Pd-catalyzed C–H activation reaction,[13] but this method is applicable only to α,α-disubstituted hydroxamates. Tomkinson achieved intermolecular N-arylation of O-substituted carbamate derivatives of hydroxylamine using CuI[14] in combination with 1,10-phenanthroline and Cs_2CO_3 in DMF, or $Pd(OAc)_2$[15] with a bis-pyrazole phosphine ligand in toluene. However, hydroxamates were ineffective coupling partners under these conditions.[15]

To expand the substrate scope for the transition-metal-catalyzed amidation reaction and to create a new method for the synthesis of *N*-oxyindolone derivatives, we decided to explore cyclization of 2-(2-bromophenyl)acetylhydroxamate (**1a**) as a model reaction (Scheme 1).



Scheme 1

Initially, we tested several Pd-catalyzed reaction conditions that have been used for cyclization of 2-(2-bromophenyl)acetamide derivatives.[16–18] $Pd(OAc)_2$ in combination with BINAP,[16] X-Phos,[17] or DPEPhos[18] ligand as catalyst systems did not afford product **2a**, nor did reaction conditions used for intermolecular arylation of hydroxylamine carbamate derivatives.[15] However, *N*-methoxybenzolactam **2a** was isolated in 29% yield, if the reaction was carried out in the presence of 10 mol% of CuI, 20 mol% of *N*,*N*′-dimethylethylenediamine (DMEDA) and 2 equivalents of K_2CO_2 in toluene[19] at 80 °C for 2 hours. Addition of molecular sieves[20] to the reaction mixture improved the yield of product **2a** to 40%. This finding indicated that there should be no major limitations for intramolecular N-arylation of hydroxamates and was the starting point for systematic optimization.

After examination of different copper sources, bases, and solvent combinations (see Supporting Information), the best reaction conditions [10 mol% $CuBr_2$, 20 mol% DMEDA, 2.0 equiv K_2CO_3, 3 Å MS (100% of weight), toluene, 80 °C, 2 h] that produced *N*-methoxybenzolactam **2a** in 91% yield were identified. Application of other ligands widely used for Cu-catalyzed cross-coupling reactions, for instance proline,[21] *N*,*N*′-dimethylglycine[21b] or 1,10-phenanthroline,[14,22] afforded lower yields of the product **2a** compared to DMEDA, while the use of salicylaldoxime,[20a] 2,2,6,6-tetramethylheptane-3,5-dione,[23] or

SYNLETT 2011, No. 17, pp 2525–2528
Advanced online publication: 22.09.2011
DOI: 10.1055/s-0030-1260328; Art ID: D16811ST

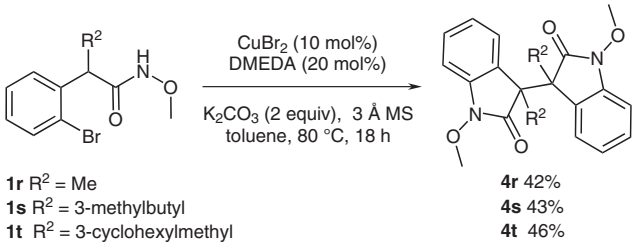
2-isobutyryl-cyclohexanone[23b,24] did not afford **2a** at all. In fact, it appeared that the latter three oxygen-containing ligands might even inhibit the conversion of **1a** into **2a** since, in the absence of the ligands, the reaction proceeded in 9% yield.

In order to explore the scope and limitations of the optimal reaction conditions, cyclization of various hydroxamates **1** was performed, and the results are summarized in Table 1.[25] *N*-Methoxybenzolactam was obtained in a lower yield from the corresponding iodo hydroxamate **1b**,[26] while the cyclization of chloro or trifloromethylsulfonyl derivatives **1c**,**d** did not afford the product **2a** under the same conditions.[27] Standard hydroxyl protecting groups on the hydroxylamine moiety were well tolerated (Table 1, entries 5–9); however, increased temperatures were necessary for full conversion of bulkier benzyl, tetrahydropyranyl, *tert*-butyldimethylsilyl, and *tert*-butyl hydroxamates. The protection of the hydroxamic acid is essential, otherwise the reaction proceeds in only 34% yield (Table 1, entry 10). Interestingly, according to X-ray crystallographic analysis,[28] the product from cyclization of hydroxamic acid **1i** can be regarded as nitrone derivative **3** rather than the cyclic *N*-hydroxyamide in the solid state.

N-Methoxybenzolactams **2k–o** substituted in the phenyl ring (Table 1, entries 11–15) were obtained in moderate to excellent yields, although some reaction time and temperature variations were necessary to achieve the optimal outcome. Since the first step of the catalytic cycle involves formation of Cu amide,[19] the reaction of dibromo derivative **1k** takes place exclusively on the bromine at C-2. The method is applicable also for the synthesis of 3,3-dimethyl and benzylidene derivatives (**2p** and **2q**) of indolones (Table 1, entries 16, 17). However, products **2r–t** monosubstituted at 3-position were obtained in low to moderate yields (Table 1, entries 18–20). The formation of dimerized side products **4r–t** was observed during the course of the reaction and these were isolated in 42–46% yield when the reactions were carried out for 18 hours (Scheme 2). Since the yields of side products **4r–t** did not reach 50%, we assume that half of the starting hydroxamate or *N*-methoxyindolones has been consumed as an internal oxidant[29] and that the side reaction proceeds via radical species.[30]

We have also demonstrated that the reaction conditions are suitable for closure of six-membered rings. 1-Methoxy-3,4-dihydro-1*H*-quinolin-2-one (**5**) was obtained in 93% yield from methyl 3-(2-bromo-phenyl)propionhydroxamate (**1u**) at 100 °C for 18 hours (Table 1, entry 21).

In conclusion, we have demonstrated the potential of copper-catalyzed intramolecular N-arylation of alkyl hydroxamates. This allowed us to develop a new method for the synthesis of *N*-alkoxyindolone derivatives that can be used, with some exceptions, on a broad range of substrates. Further investigations for N-arylation of hydroxamates in an intermolecular manner are in progress.



1r R^2 = Me
1s R^2 = 3-methylbutyl
1t R^2 = 3-cyclohexylmethyl

4r 42%
4s 43%
4t 46%

Scheme 2

Table 1 $CuBr_2$/DMEDA-Catalyzed Cyclization of Different Hydroxamates[a]

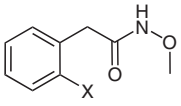
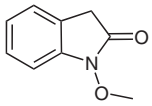
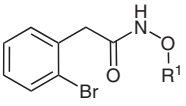
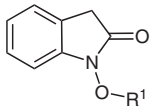
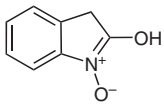
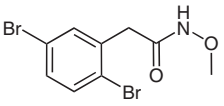
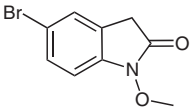
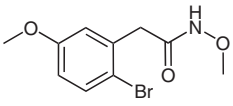
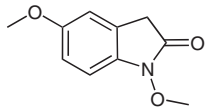
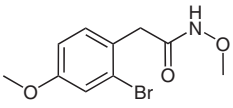
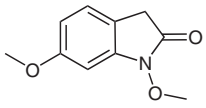
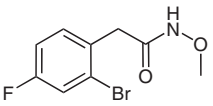
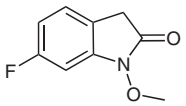
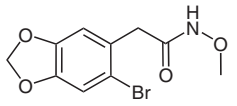
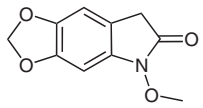
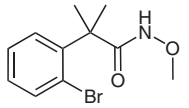
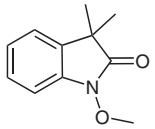
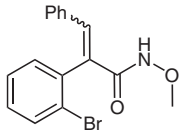
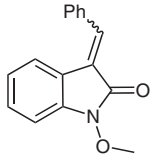
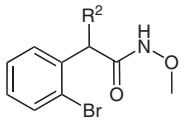
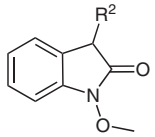
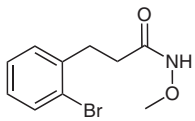
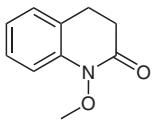
Entry	Hydroxamate	Product	Yield (%)
1	 **1a** X = Br	 **2a**	91
2	**1b** X = I	**2a**	39
3	**1c** X = Cl	**2a**	0
4	**1d** X = OTf	**2a**	0
5	 **1e** R^1 = All	 **2e**	92
6	**1f** R^1 = Bn	**2f**	67, 84[b]
7	**1g** R^1 = THP	**2g**	83[b]
8	**1h** R^1 = TBDMS	**2h**	81[b]
9	**1j** R^1 = *t*-Bu	**2j**	82[b]
10	**1i** R^1 = H	 **3**	34
11	 **1k**	 **2k**	94
12	 **1l**	 **2l**	92
13	 **1m**	 **2m**	68[c], 76[d]
14	 **1n**	 **2n**	72

Table 1 $CuBr_2$/DMEDA-Catalyzed Cyclization of Different Hydroxamates[a] (continued)

Entry	Hydroxamate	Product	Yield (%)
15	 **1o**	 **2o**	45[e]
16	 **1p**	 **2p**	82[e]
17	 **1q**	 **2q**	68[e]
18	 **1r** R^2 = Me	 **2r**	60
19	**1s** R^2 = 3-methylbutyl	**2s**	11, 32[c]
20	**1t** R^2 = 3-cyclohexylmethyl	**2t**	25
21	 **1u**	 **5**	93[b,e]

[a] *Reaction conditions*: $CuBr_2$ (10 mol%), DMEDA (20 mol%), K_2CO_3 (2.0 equiv), 3 Å MS (100 wt%), toluene, 80 °C, 2 h, *c* 0.1 mmol/mL, isolated yields.
[b] At 100 °C.
[c] 5 h.
[d] Cu_2O (10 mol%) instead of $CuBr_2$.
[e] 18 h.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was supported by the European Social Fund (No.2009/0203/1DP/1.1.1.2.0/09/APIA/VIAA/023).

References and Notes

(1) Henmi, T.; Sakamoto, T.; Kikugawa, Y. *Heterocycles* **1997**, *44*, 157.
(2) Kikugawa, Y.; Shimada, M.; Matsumoto, K. *Heterocycles* **1994**, *37*, 293.
(3) Pedras, M. S. C.; Chumala, P. B.; Suchy, M. *Phytochemistry* **2003**, *64*, 949.
(4) Kitajima, M.; Nakamura, T.; Kogure, N.; Ogawa, M.; Mitsuno, Y.; Ono, K.; Yano, S.; Aimi, N.; Takayama, H. *J. Nat. Prod.* **2006**, *69*, 715.
(5) (a) Kato, H.; Yoshida, T.; Tokue, T.; Nojiri, Y.; Hirota, H.; Ohta, T.; Williams, R. M.; Tsukamoto, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 2254. (b) Tsukamoto, S.; Kato, H.; Samizo, M.; Nojiri, Y.; Onuki, H.; Hirota, H.; Ohta, T. *J. Nat. Prod.* **2008**, *71*, 2064.
(6) (a) Bouerat, L.; Fensholdt, J.; Liang, X.; Havez, S.; Nielsen, S. F.; Hansen, J. R.; Bolvig, S.; Andersson, C. *J. Med. Chem.* **2005**, *48*, 5412. (b) Bouerat, L. M. E.; Fensholdt, J.; Nielsen, S. F.; Liang, X.; Havez, S. E.; Andersson, E. C.; Jensen, L.; Hansen, J. R. WO 2005058309, **2005**; *Chem. Abstr*. **2005**, *143*, 97259.
(7) Parkes, K. E. B.; Ermert, P.; Fässler, J.; Ives, J.; Martin, J. A.; Merrett, J. H.; Obrecht, D.; Williams, G.; Klumpp, K. *J. Med. Chem.* **2003**, *46*, 1153.
(8) El-Faham, A.; Albericio, F. *Eur. J. Org. Chem.* **2009**, 1499.
(9) (a) Di Carlo, F. J. *J. Am. Chem. Soc.* **1944**, *66*, 1420. (b) Wright, W. B. Jr.; Collins, K. H. *J. Am. Chem. Soc.* **1956**, *78*, 221. (c) Somei, M.; Sato, H.; Kaneko, C. *Heterocycles* **1983**, *20*, 1797. (d) Kende, A. S.; Thurston, J. *Synth. Commun.* **1990**, *20*, 2133.
(10) Neset, S. M.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1993**, *47*, 1141.
(11) (a) Kikugawa, Y.; Kawase, M. *J. Am. Chem. Soc.* **1984**, *106*, 5728. (b) Kawase, M.; Kitamura, T.; Kikugawa, Y. *J. Org. Chem.* **1989**, *54*, 3394. (c) Kikugawa, Y.; Shimada, M. *Chem. Lett.* **1987**, 1771. (d) For a review, see: Kikugawa, Y. *Heterocycles* **2009**, *78*, 571.
(12) For reviews on copper-catalyzed cross-couplings, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. For selected reviews on palladium-catalyzed cross-couplings, see: (d) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (e) Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 6338. (f) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27.
(13) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058.
(14) Jones, K. L.; Porzelle, A.; Hall, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2008**, *10*, 797.
(15) Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. *Org. Lett.* **2009**, *11*, 233.
(16) Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099.
(17) van den Hoogenband, A.; den Hartog, J. A. J.; Lange, J. H. M.; Terpstra, J. W. *Tetrahedron Lett.* **2004**, *45*, 8535.
(18) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35.
(19) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
(20) For reports of the benefit of molecular sieves in the copper-catalyzed cross-coupling reaction, see: (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607. (b) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. *Chem. Commun.* **2009**, 953. (c) Yao, B.; Zhang, Y.; Li, Y. *J. Org. Chem.* **2010**, *75*, 4554.
(21) (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (b) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164.
(22) Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Mehdinejad, H. *Synlett* **2004**, 1517.
(23) (a) Altman, R. A.; Buchwald, S. L. *Org.Lett.* **2007**, *9*, 643. (b) de Lange, B.; Lambers-Verstappen, M. H.; Schmieder-van de Vondervoot, L.; Sereinig, N.; de Rijk, R.; de Vries, A. H. M.; de Vries, J. G. *Synlett* **2006**, 3105.
(24) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742.

(25) **General Procedure**
To an oven-dried vial equipped with a stirrer bar, hydroxamate (1.0 equiv, 0.2 mmol), copper(II) bromide (10 mol%), K_2CO_3 (2.0 equiv, 0.4 mmol) and 3 Å MS (100 wt%) were added. The vial was closed using an aluminium open-top seal with PTFE-faced septum, flushed with argon before addition of dry toluene (2 mL) and DMEDA (20 mol%) and stirred at the appropriate temperature for the appropriate time (Table 1). After cooling the reaction mixture was diluted with EtOAc (5 mL) then filtered through a short silica plug and washed with EtOAc. The solvent was removed in vacuo, and the crude product was purified by flash column chromatography on silica gel eluting with EtOAc–hexane (1:5) to give the product.

(26) Compound **2a** was obtained in 61% yield from iodo hydroxamate **1b** if K_3PO_4 was used as base. For a report of the advantage of K_3PO_4 as compared to K_2CO_3 in copper-catalyzed amidation of aryliodides, see ref. 19.

(27) Product **2a** from chloro hydroxamate **1c** was obtained in 43% yield if reaction was carried out for 1 h in MeCN at sample concentration 0.2 mmol/mL.

(28) Crystallographic data for **3** have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-827122, and may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CD2 1EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk.

(29) For recent examples where the hydoxamate N–O moiety serves as an internal oxidant, see: (a) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (b) Patureau, F. W.; Glorius, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1977.

(30) For a review on oxidative homocoupling reactions, see: Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, 353.