Tetrahedron Letters 53 (2012) 3981–3983

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

CuI/*N*,*N*-dimethylglycine-catalyzed synthesis of *N*-aryloxazolidinones from aryl bromides

Jiaojiao Li [a], Yihua Zhang [a,*], Yongwen Jiang [b], Dawei Ma [b,*]

[a] *Center of Drug Discovery, China Pharmaceutical University, Nanjing 210009, China*
[b] *State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

ARTICLE INFO

Article history:
Received 7 April 2012
Revised 15 May 2012
Accepted 18 May 2012
Available online 26 May 2012

Keyword:
Coupling

ABSTRACT

CuI/*N*,*N*-dimethylglycine catalyzed coupling of aryl bromides with substituted oxazolidinones took place at 120 °C in DMF, affording the corresponding N-arylation products with good to excellent yields. A number of functional groups, such as ketone, nitrile, nitro, methoxy, and hydroxyl were tolerated under these conditions, thereby allowing diversity synthesis of *N*-aryloxazolidinones.

N-Aryloxazolidinone is an important structural motif for pharmaceutical and medicinal utilization. Indeed, several clinically used drugs bearing this moiety have been developed. For example, Linezolid (**1**, Fig. 1)[1] and Eperezolid (**2**)[2] are two antibacterial drugs that are effective against a number of gram-positive bacterial pathogens including methicilin-resistant *Staphylococcus aureas* (MRSA) and vancomycin-resistant *Enterococci* (VRE).[3] Toloxatone (**3**), a selective and reversible inhibitor of monoamine oxidase A, has been approved for the treatment of depression.[4]

Owing to the importance of *N*-aryloxazolidinones in the pharmaceutical field, much attention has been directed to the elaboration of this class of compounds. Formation of oxazolidinones from *N*-aryl aminoalcoholes is the most classical approach for assembling *N*-aryloxazolidinones.[3a] In recent years, metal-catalyzed cross coupling reactions of oxazolidinones with aryl halides, aryl tosylates, or aryl sulfamates open a new avenue to access these compounds. In 2001, Cacchi et al., reported that coupling of aryl halides (both bromides and chlorides) with oxazolidinones could be catalyzed by the combination of $Pd_2(dba)_3$ (or $Pd(OAc)_2$) and Xantphos.[5] Soon after that, a Pfizer group described that a biaryl phosphine ligand could more effectively affect the $Pd_2(dba)_3$-catalyzed coupling of aryl chlorides with oxazolidinones.[6] Quite recently, Ni-catalyzed amination of aryl sulfamates[7] and Pd-catalyzed coupling of hetero-aromatic tosylates[8] with oxazolidinones were reported to be able to afford *N*-aryloxazolidinones with great diversity.

In 2003, Trehan and co-workers[9] and Cacchi et al.,[10] independently described that CuI/*trans*-1,2-diaminocyclohexane could be utilized as the catalyst to promote the N-arylation of oxazolidinones. The usefulness of this catalytic system was further demonstrated by the synthesis of Toloxatone and Linezolid. Although the reaction conditions are compatible with simple and some substituted oxazolidinones, reaction of aryl bromides with sterically hindered and hydroxymethyl-substituted oxazolidinones gave the coupling product in low yields.[9,10] Additionally, comparing with other commonly used ligands, *trans*-1,2-diaminocyclohexane is more expensive. To solve these problems, several groups have explored alternative approaches by using different copper sources and ligands.[11] However, all these catalytic systems were found to be effective only for aryl iodides.[11]

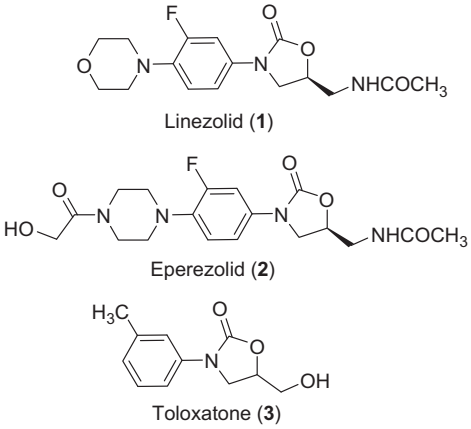


Figure 1. Structures of bioactive *N*-aryloxazolidinones.

* Corresponding authors.
E-mail addresses: zyhtgd@sohu.com (Y. Zhang), madw@mail.sioc.ac.cn (D. Ma).

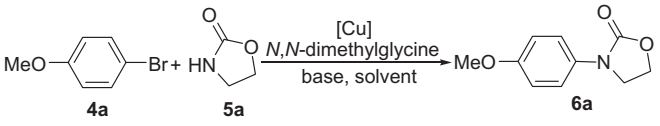
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.05.081

In the past decade, we have demonstrated that some amino acids are useful ligands for promoting copper-catalyzed N-arylation of aryl and vinyl halides.[12] In particular, we found that the combination of CuI and *N*,*N*-dimethylglycine could catalyze coupling of vinyl halides with oxazolidinones.[13] As an extension of this work, we recently discovered that *N*,*N*-dimethylglycine is an excellent ligand for copper-catalyzed coupling of aryl bromides with oxazolidinones. Under the action of this catalytic system, both sterically hindered and hydroxymethyl-substituted oxazolidinones could be used as the coupling partners, providing the corresponding arylation products with good to excellent yields. Herein, we wish to disclose our results.

We started our studies by conducting a coupling reaction of 4-bromoanisole with oxazolidin-2-one using K_2CO_3 as a base. It was found that under the catalysis of 5 mol % CuI and 10 mol % *N*,*N*-dimethylglycine, this reaction completed at 120 °C after 24 h in DMF to afford the desired product **6a** in 88% yield (Table 1, entry 1). Changing solvent to dioxane gave a similar result (entry 2), however, in DMSO only 68% yield was observed (entry 3). The decreasing yields were also found when switching base to K_3PO_4 and Cs_2CO_3 (entries 4 and 5). Further attempts by changing the copper salts to CuCl, CuBr, and Cu_2O failed to give improved results (entries 6–8). However, increasing the catalytic loading could give the best yield even at 110 °C (entry 9). These results give alternative choices when prices of catalytic system and substrates are considered. Without addition of *N*,*N*-dimethylglycine only 9% coupling yield was observed (entry 10), indicating that the presence of the ligand is essential for complete conversion.

Based on the above investigations, we further examined the reaction scope by changing aryl bromides and substituted oxazolidinones (Table 2). We were pleased to observe that a wide range of *N*-aryloxazolidinones could be prepared with good to excellent yields by using our catalytic system. Electron-rich aryl bromides generally required longer reaction time than electron-deficient ones (comparing entries 6 and 10, and 11 and 15). The coupling reaction between 3-methylphenyl bromide and 5-(hydroxymethyl)oxazolidin-2-one also worked well, affording Toloxatone (**3**) directly (entry 16). In contrast with CuI/*trans*-1,2-diaminocyclohexane catalyzed reaction,[9,10] no O-arylation product was observed under our reaction conditions. Similarly, **6q** was obtained in

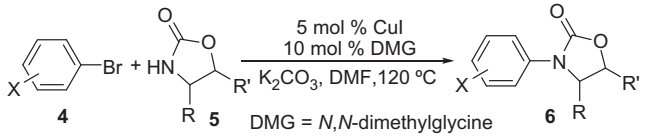
Table 1
Coupling of 4-bromoanisole with oxazolidin-2-one under different conditions[a]



Entry	[Cu]	Solvent	Base	Temp (°C)	Yield[b] (%)
1	CuI	DMF	K_2CO_3	120	88
2	CuI	Dioxane	K_2CO_3	120	83
3	CuI	DMSO	K_2CO_3	120	68
4	CuI	DMF	K_3PO_4	120	44
5	CuI	DMF	Cs_2CO_3	120	21
6	CuCl	DMF	K_2CO_3	120	81
7	CuBr	DMF	K_2CO_3	120	75
8	Cu_2O	DMF	K_2CO_3	120	67
9	CuI	DMF	K_2CO_3	110	94[c]
10	CuI	DMF	K_2CO_3	120	9[d]

[a] Reaction conditions: 4-bromoanisole (1 mmol), oxazolidin-2-one (1.2 mmol), copper salt (0.05 mmol), *N*,*N*-dimethylglycine (0.1 mmol), base (2 mmol), solvent (0.5 mL), 24 h.
[b] Isolated yield.
[c] 0.1 mmol of CuI and 0.2 mmol of *N*,*N*-dimethylglycine were used.
[d] *N*,*N*-dimethyl-glycine was not added.

Table 2
CuI/*N*,*N*-dimethylglycine-catalyzed synthesis of *N*-aryloxazolidinones[a]



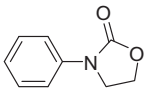
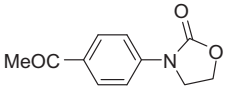
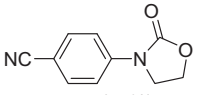
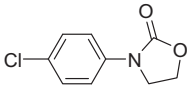
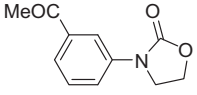
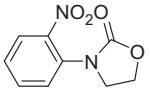
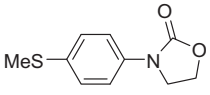
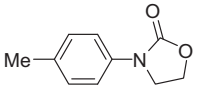
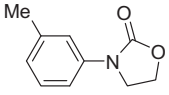
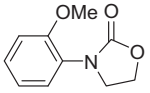
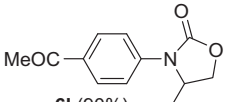
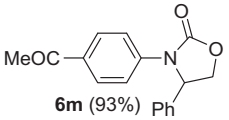
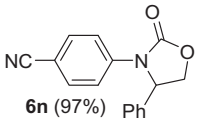
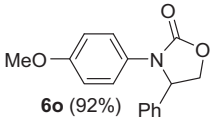
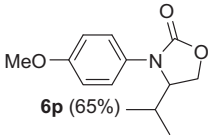
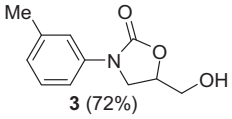
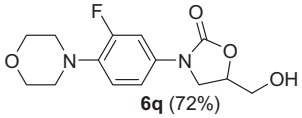
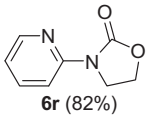
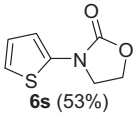
Entry	Time (h)	Product[b] (yield)
1	24	 **6b** (90%)
2	18	 **6c** (95%)
3	18	 **6d** (98%)
4	18	 **6e** (88%)
5	18	 **6f** (91%)
6	18	 **6g** (79%)
7	24	 **6h** (96%)
8	24	 **6i** (68%)
9	24	 **6j** (72%)
10	30	 **6k** (84%)
11	24	 **6l** (90%)
12	24	 **6m** (93%)

Table 2 (*continued*)

Entry	Time (h)	Product[b] (yield)
13	24	 **6n** (97%)
14	50	 **6o** (92%)
15	50	 **6p** (65%)
16	24	 **3** (72%)
17	30	 **6q** (72%)
18	18	 **6r** (82%)
19	24	 **6s** (53%)

[a] Reaction conditions: aryl bromide (1 mmol), substituted oxazolidin-2-one (1.2 mmol), CuI (0.05 mmol), *N*,*N*-dimethylglycine (0.1 mmol), K_2CO_3 (2 mmol), DMF (0.5 mL).

[b] Isolated yield.

72% yield, which could be used for assembling racemic Linezolid (**1**). Additionally, two heteroaryl bromides were found to be applicable, producing **6r** and **6s**, respectively (entries 18 and 19).

In conclusion, we have developed an efficient method for assembling *N*-aryloxazolidinones, which relied on a CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of aryl bromides with substituted oxazolidinones. The economical catalytic system used here, together with good coupling yields and compatibility for a variety of substrates will make this method very competitive in the preparation of bioactive *N*-aryloxazolidinones.

Acknowledgments

The authors are grateful to the Ministry of Science and Technology (Grant 2009ZX09501-00), the Chinese Academy of Sciences and the National Natural Science Foundation of China (Grant 20632050 and 20921091) for their financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.081.

References and notes

1. (a) Brickner, S. J.; Hutchinson, D. K.; Barbachyn, M. R.; Manninen, P. R.; Ulanowicz, D. A.; Garmon, S. A.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. Z.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 673; (b) Renslo, A. R.; Jaishankar, P.; Venkatachalam, R.; Hackbarth, C.; Lopez, S.; Patel, D. V.; Gordeev, M. F. *J. Med. Chem.* **2005**, *48*, 5009; (c) Tucker, J. A.; Allwine, D. A.; Grega, K. C.; Barbachyn, M. R.; Klock, J. L.; Adamski, J. L.; Brickner, S. J.; Hutchinson, D. K.; Ford, C. W.; Zurenko, G. E.; Conradi, R. A.; Burton, P. S.; Jensen, R. M. *J. Med. Chem.* **1998**, *41*, 3727.
2. (a) Xu, G.; Zhou, Y.; Yang, C.; Xie, Y. *Heteroat. Chem.* **2008**, *19*, 316; (b) Lohray, B. B.; Gandhi, N.; Srivastava, B. K.; Lohray, V. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3817; (c) McKee, E. E.; Ferguson, M.; Bentley, A. T.; Marks, T. A. *Antimicrob. Agents Chemother.* **2006**, *50*, 2042.
3. (a) Gregory, W. A.; Brittelli, D. R.; Wang, C. L. J.; Wuonola, M. A.; McRipley, R. J.; Eustice, D. C.; Eberly, V. S.; Bartholomew, P. T.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1989**, *32*, 1673; (b) Park, C. H.; Brittelli, D. R.; Wang, C. L. J.; Marsh, F. D.; Gregory, W. A.; Wuonola, M. A.; McRipley, R. J.; Eberly, V. S.; Slee, A. M.; Forbes, M. *J. Med. Chem.* **1992**, *35*, 1156.
4. (a) Mai, A.; Artico, M.; Esposito, M.; Sbardella, G.; Massa, S.; Befani, O.; Turini, P.; Giovannini, V.; Mondovi, B. *J. Med. Chem.* **2002**, *45*, 1180; (b) Valente, S.; Tomassi, S.; Tempera, G.; Saccoccio, S.; Agostinelli, E.; Mai, A. *J. Med. Chem.* **2011**, *54*, 8228; (c) Moureau, F.; Wouters, J.; Vercauteren, D. P.; Collin, S.; Evrard, G.; Durant, F.; Ducrey, F.; Koenig, J. J.; Jarreau, F. X. *Eur. J. Med. Chem.* **1994**, *29*, 269.
5. Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539.
6. Ghosh, A.; Sieser, J. E.; Riou, M.; Cai, W.; Rivera-Ruiz, L. *Org. Lett.* **2003**, *5*, 2207.
7. Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 2171.
8. Mantel, M. L. H.; Lindhardt, A. T.; Lupp, D.; Skrydstrup, T. *Chem. Eur. J.* **2010**, *16*, 5437.
9. Mallesham, B.; Rajesh, B. M.; Reddy, P. R.; Srinivas, D.; Trehan, S. *Org. Lett.* **2003**, *5*, 963.
10. Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Heterocycles* **2003**, *61*, 505.
11. (a) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J.* **2004**, *10*, 5607; (b) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609; (c) Mino, T.; Harada, Y.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2008**, 614; (d) Phillips, D. P.; Zhu, X.-F.; Lau, T. L.; He, X.; Yang, K.; Liu, H. *Tetrahedron Lett.* **2009**, *50*, 7293; (e) Jammi, S.; Sakthivel, S.; Rout, L.; Mukherjee, T.; Mandal, S.; Mitra, R.; Saha, P.; Punniyamurthy, T. *J. Org. Chem.* **1971**, *2009*, 74; (f) Lin, B.; Liu, M.; Ye, Z.; Ding, J.; Wu, H.; Cheng, J. *Org. Biomol. Chem.* **2009**, *7*, 869; (g) Jammi, S.; Krishnamoorthy, S.; Saha, P.; Kundu, D. S.; Sakthivel, S.; Ali, M. A.; Paul, R.; Punniyamurthy, T. *Synlett* **2009**, *20*, 3323; (h) Ali, M. A.; Saha, P.; Punniyamurthy, T. *Synthesis* **2010**, *6*, 908.
12. Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450.
13. Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **1809**, *2004*, 6.