One-Pot, Three-Step Copper-Catalyzed Five-/Four-Component Reaction Constructs Polysubstituted Oxa(Thia)zolidin-2-imines

Chetna Madaan,[a] Shuddham Saraf,[a] Garima Priyadarshani,[a] P. Purushotham Reddy,[b] Sankar K. Guchhait,*[a] A. C. Kunwar,[b] B. Sridhar[c]

[a] Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research (NIPER), S. A. S. Nagar (Mohali) 160062 Punjab, India
Fax +91(172)2214692; E-mail: skguchhait@niper.ac.in

[b] NMR Centre, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

[c] Laboratory of X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

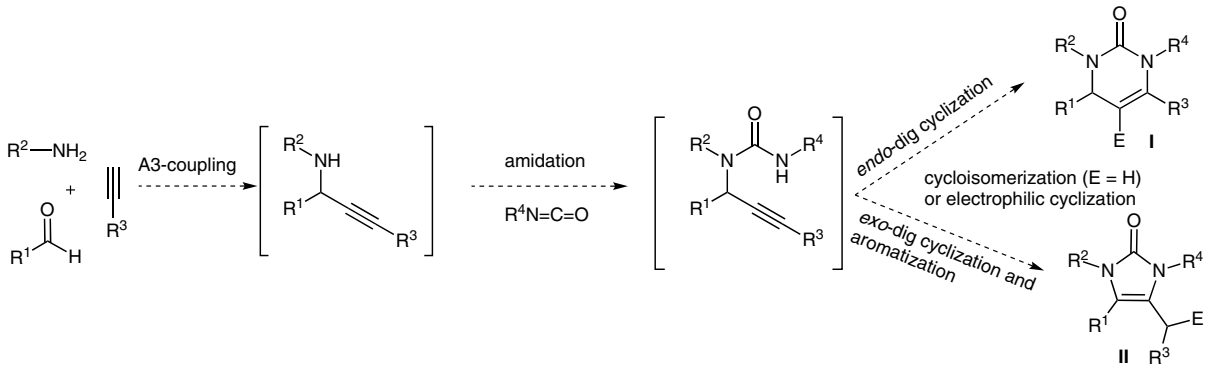
Received: 08.05.2012; Accepted after revision: 05.06.2012

Abstract: A novel one-pot synthesis of polysubstituted oxa(thia)zolidin-2-imines has been developed. It employs A^3-coupling of aldehyde and amine with alkyne to form propargyl amine, which on (thio)amidation with iso(thio)cyanate produces *N*-propargyl(thio)urea, and a cyclization reaction. A 5-*exo*-dig iodocyclization of *N*-propargylurea constructs 5-iodomethyleneoxazolidin-2-imine, while cycloisomerization of the thio analogue provides 5-methylenethiazolidin-2-imine. In this process, CuI catalysis has been found to be crucial, and the cyclization occurs through oxygen/sulfur (not nitrogen) nucleophilic attack to alkyne.

Key words: multicomponent reaction, one-pot, cyclization, copper, heterocycles

The major prescription drugs contain heterocyclic scaffolds. The crucial role played by heterocycles in drug-discovery processes has long been known.[1] Recent in silico investigations on drug database toward exploration of potential 'bioactivity islands' have revealed the importance of heterocyclic scaffolds.[2] The rapid and molecular-diversity-feasible construction of new and 'privileged' heterocyclic scaffolds has gained importance. In this direction, the amalgamation of a multicomponent reaction[3,4] and a consecutive one-pot process (domino, cascade, or tandem),[5] which in many cases gains efficiency under transition-metal catalysis,[6] is a golden nugget for the rapid construction of polysubstituted molecular scaffolds with atom-, step-, and pot-economy.[7] In this approach, variation in reactants can also generate a large number of compounds.

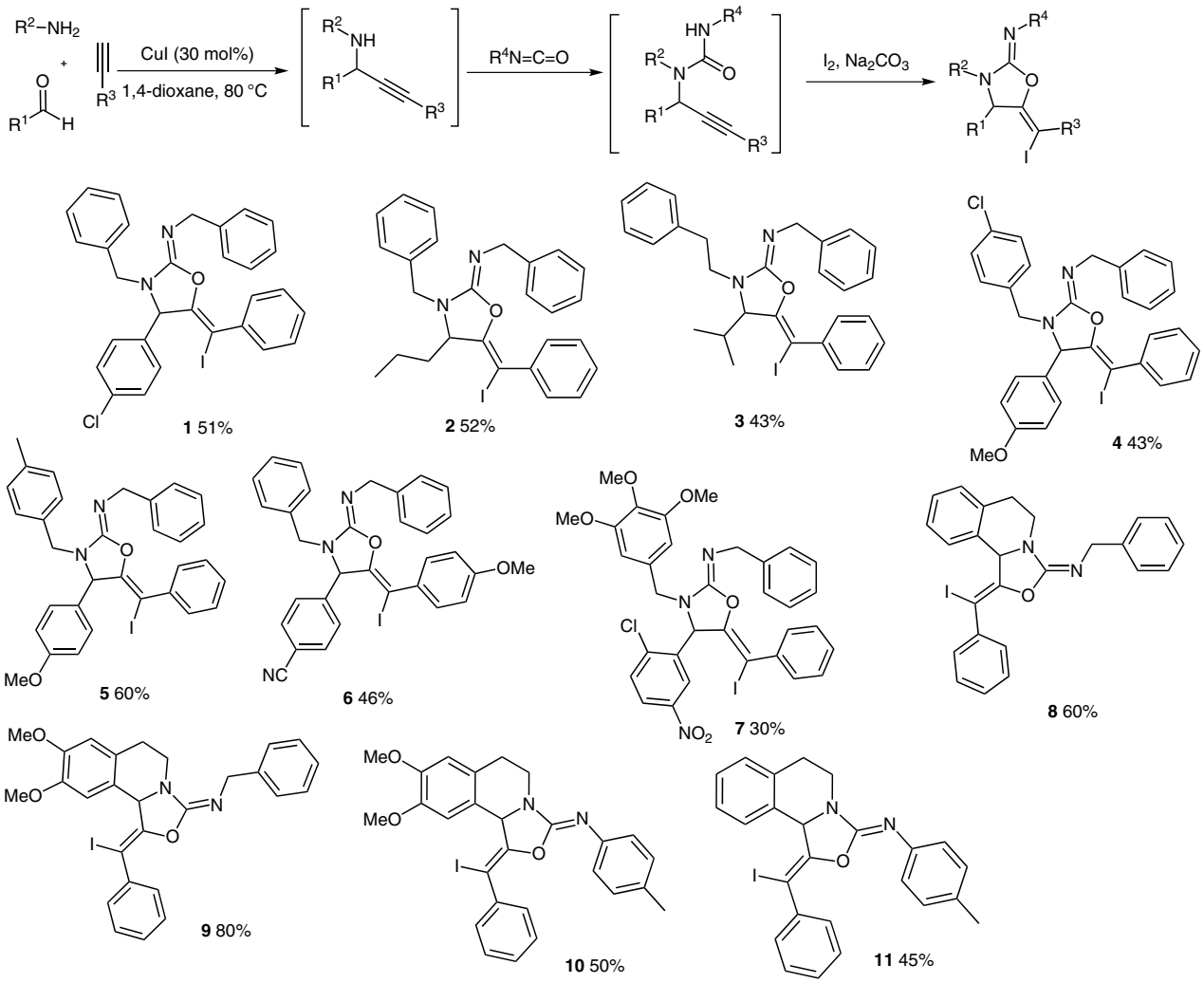
As part of our research program aimed at realizing new leads, we became interested in developing a one-pot, multicomponent reaction that could afford pharmaceutically significant heterocyclic scaffolds. We speculated that a sequence of reactions of a multicomponent condensation of aldehyde, amine, and alkyne (A^3-coupling) to form propargyl amine,[8] which on amidation produces *N*-propargylurea, whose *endo*- or *exo*-dig cycloisomerization with alkyne in the terminal step could produce dihydropyrimidinone **I** or imidazolidinone, respectively (Scheme 1). The later scaffold via isomerization of the double bond might possibly form the aromatic compound imidazolone **II**. Based on known therapeutic importance of these scaffolds[9,10] and the potential efficiency of the synthetic approach, we were interested in exploring the reaction sequence. A one-pot version of this synthesis, which was our endeavor also, is more challenging, because the process requires the catalyst and conditions compatibility and considerably high conversion in each reaction step. Coinage metal (Cu, Ag, or Au) catalyst could be crucial for A^3-coupling and the cycloisomerization with electrophilic activation of alkyne.[11] Cu(I) halide as catalyst was preferentially chosen because of its known



Scheme 1 Design of reaction strategy

SYNLETT 2012, 23, 1955–1959
Advanced online publication: 23.07.2012
DOI: 10.1055/s-0032-1316606; Art ID: ST-2012-B0400-L

efficiency as a π-Lewis acid and less cost. 4-Chlorobenzaldehyde, benzylamine, phenylacetylene, and benzyl isocyanate were used as model substrates. Various experiments were carried out on evaluation of Cu catalyst, base, π-Lewis acid additive, solvent, and reaction temperature. Optimization was focused on stepwise sequential reactions. In every case, A^3-coupling and subsequent amidation provided corresponding *N*-propargylurea in good yield. However, the in situ cycloisomerization towards formation of product **I** or **II** did not materialize. Realizing the inertness of *N*-propargylurea towards cycloisomerization, we then investigated its electrophilic cyclization with iodine and Na_2CO_3. The scaffold that formed was neither dihydropyrimidinone **I** nor imidazolone **II**, rather 5-iodomethyleneoxazolidine-2-imine (compound **1**, Scheme 2).[12] This scaffold structurally resembles the biologically active 2-iminoimidazolines[13] and 2-imidazolones.[14] The compounds containing this scaffold are also known to possess various therapeutic activities.[15] These results incited us to further explore the one-pot synthesis. In A^3-coupling, copper(I) halides (I, Br, and Cl) were found to be more effective catalysts compared to AgOAc and $AuCl_3$. CuBr was most efficient for the A^3-coupling step, while CuI was found to be best for overall process of A^3-coupling, amidation, and iodocyclization. Optimal amount of catalyst was found to be 30 mol%. Among various solvents such as toluene, MeCN, DMSO, THF, and 1,4-dioxane, the later was found to be best. For possible enhancement of reaction conversion of A^3-coupling towards completion, the additional use of various σ-/π-Lewis acids such as $Sc(OTf)_3$, $In(OTf)_3$, AgOTs, AgOTf, or $RuCl_3$, and bases such as pyridine, Et_3N, or *i*-Pr_2EtNH did not help. Increase in reaction temperature from 80 °C to 100 °C or prolonging the reaction did not improve the yields. One-pot reaction of propargylamine with isocyanate underwent with almost quantitative conversion. For iodocyclization, two equivalents of iodine and three equivalents of Na_2CO_3 were found to be optimum. To check the efficiency of one-pot process, the products of the A^3-coupling and amidation step were isolated and subjected to subsequent reactions. They produced the desired intermediate or final product in similar yields. Various iodomethyleneoxazolidine-2-imines with four points of diversity were prepared (Scheme 2). Aliphatic aldehydes and aromatic aldehydes with both electron-withdrawing and electron-donating groups were compatible. However,



Scheme 2 One-pot reactions of A^3-coupling, amidation, and iodocyclization – synthesis of iodomethyleneoxazolidine-2-imines. Reactants (mmol): amine (1 mmol), aldehyde (1 mmol), alkyne (2.2 mmol), isocyanate (1 mmol), iodine (2 mmol), Na_2CO_3 (3 mmol).

aromatic amine and aliphatic alkyne were found to be nonfeasible substrates.

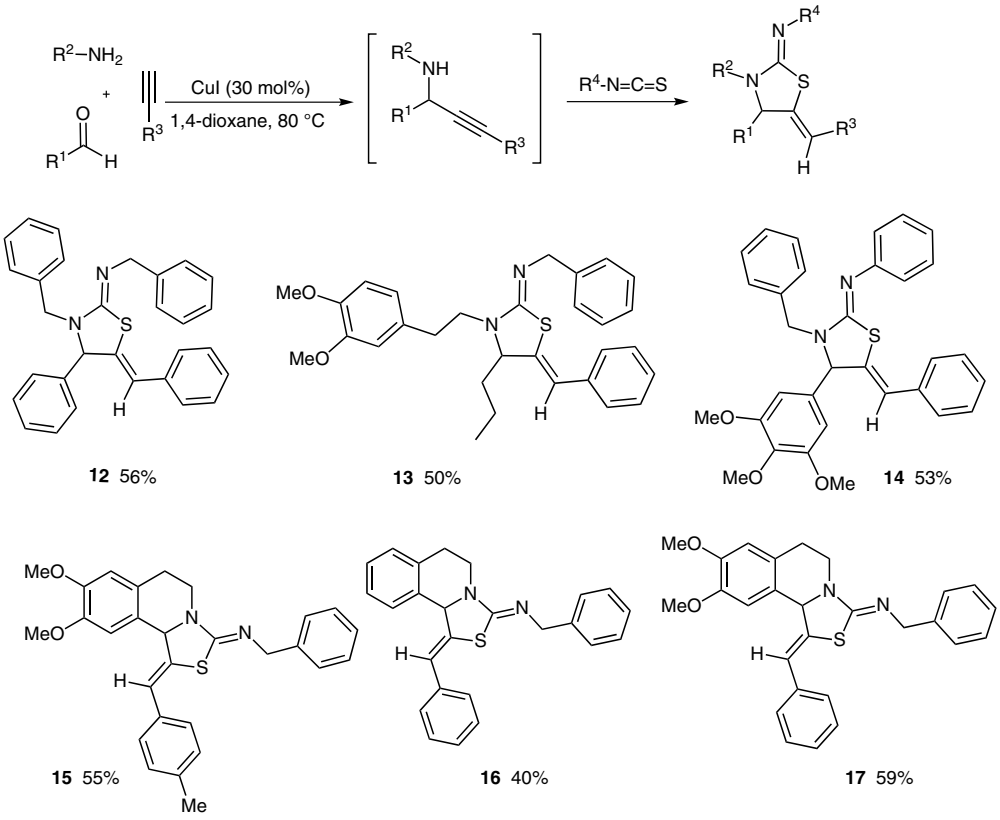
When isothiocyanate was used in place of isocyanate in the process, the thioamidation and cycloisomerization reactions took place in cascade fashion, yielding 5-methylenethiazolidin-2-imines[16] (Scheme 3). Dihydroisoquinolines as imine equivalents underwent reactions with both isocyanate and isothiocyanate in these processes. The experimental procedures were simple and straightforward.[17]

In these one-pot reactions, the 5-*exo*-dig iodocyclization of *N*-propargylurea formed 5-iodomethyleneoxazolidine-2-imine, and the 5-*exo*-dig cycloisomerization of *N*-propargylthiourea provided 5-methylenethiazolidin-2-imine. This implies that the cyclization took place through oxygen/sulfur nucleophilic attack to alkyne. The alternative possible cyclization via nitrogen nucleophilic moiety did not occur. The cycloisomerization of *N*-propargylurea through oxygen, which is less nucleophilic, could not take place. It required a more reactive electrophilic cyclization pathway such as iodocyclization.

The structures of 5-methyleneoxa(thia)zolidin-2-imines were identified by spectroscopic studies (^{1}H, ^{13}C, HSQC, HMBC, DQF-COSY NMR, IR, and MS). For compound **1** (Scheme 2, Figure 1) the proton C8H (δ = 5.10 ppm) showed HMBC correlations with C3 (δ = 74.93 ppm), C4 (δ = 148.27 ppm), C5 (δ = 151.00 ppm), C9 (δ = 134.92 ppm), and C10/C10′ (δ = 130.46 ppm). The C6H/C6′H protons displayed correlations with C5 (δ = 151.00 ppm) whereas C7H/C7′H showed correlation with C5 (δ = 151.00 ppm) as well as C8 (δ = 66.11 ppm). For compound **12** (Scheme 3, Figure 1) the olefinic proton C3H appeared as a doublet at δ = 6.21 ppm and showed a vinylic coupling ($^4J_{C3H–C8H}$) of 1.4 Hz with C8H. In the HMBC experiments C3H showed correlations with C1/C1′ (δ = 128.03 ppm), C2 (δ = 133.83 ppm), C4 (δ = 140.28 ppm), and C8 (δ = 70.20 ppm), while C8H depicted correlations with C3 (δ = 122.40 ppm), C4 (δ = 140.28 ppm), C5 (δ = 155.75 ppm), C9 (δ = 141.38 ppm), and C10/C10′ (δ = 127.51 ppm) whereas C6H/C6H′ showed correlation with C5 (δ = 155.75 ppm) and C7H/C7H′ depicted correlations with C5 (δ = 155.75 ppm) and C8 (δ = 70.20 ppm).

The structures of **9** (Scheme 2) and **17** (Scheme 3) were also deduced from detailed NMR studies (see Supporting Information), which have been duly confirmed from single-crystal X-ray diffraction studies (Figure 2).[18]

In conclusion, we have developed a novel method of CuI-catalyzed four-component, one-pot, three-step reaction towards construction of 5-iodomethyleneoxazolidin-2-imines, 5-methylenethiazolidin-2-imines, and their tetrahydroisoquinoline-fused analogues. The process employs the readily available starting materials aldehyde, amine, alkyne, and iso(thio)cyanate.



Scheme 3 One-pot reactions of A^3-coupling, thioamidation, and cycloisomerization – synthesis of 5-methylenethiazolidin-2-imines

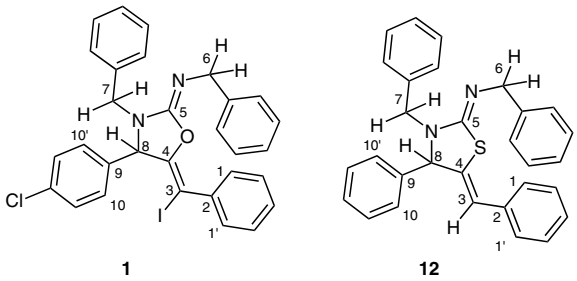


Figure 1 2D NMR: Deduced Structure of **1** and **12**

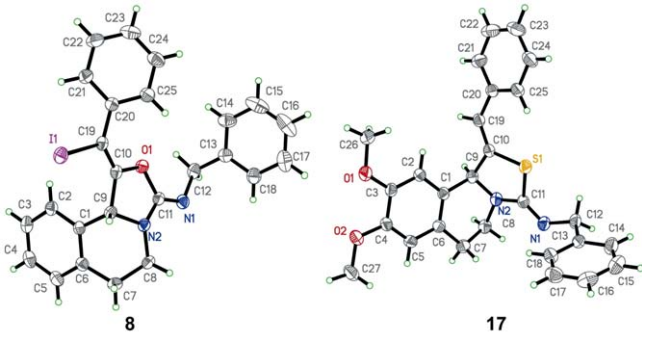


Figure 2 ORTEP structures

Acknowledgment

We gratefully acknowledge financial support from DST, New Delhi for this investigation. P.P.R. is thankful to CSIR for senior research fellowship.

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

References and Notes

(1) (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A.; Rees, C.-W.; Scriven, E.-F.-V., Eds.; Elsevier Science: Oxford, **1996**. (b) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329. (c) Bon, R. S.; Waldmann, H. *Acc. Chem. Res.* **2010**, *43*, 1103. (d) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095. (e) Berlinck, R. G. S.; Burtoloso, A. C. B.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919. (f) Berlinck, R. G. S.; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516.

(2) (a) Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17272. (b) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. *Drug Discovery Today* **2011**, *16*, 164. (c) Reymond, J. L.; Deursen, R. V.; Blum, L. C.; Ruddigkeit, L. *Med. Chem. Commun.* **2010**, *1*, 30. (d) Ertl, P.; Jelfs, S.; Mühlbacher, J.; Schuffenhauer, A.; Selzer, P. *J. Med. Chem.* **2006**, *49*, 4568. (e) Bemis, G. W.; Murcko, M. A. *J. Med. Chem.* **1996**, *39*, 2887. (f) Broughton, H. B.; Watson, I. A. *J. Mol. Graphics Modell.* **2005**, *23*, 51.

(3) (a) *Multicomponent Reactions*; Zhu, J.; Bienaymé, H., Eds.; Wiley-VCH: Weinheim, **2005**. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

(4) For our publications, see: (a) Guchhait, S. K.; Chandgude, A. L.; Priyadarshani, G. *J. Org. Chem.* **2012**, *77*, 4438. (b) Guchhait, S. K.; Madaan, C. *Synlett* **2009**, 628. (c) Guchhait, S. K.; Madaan, C.; Thakkar, B. S. *Synthesis* **2009**, 3293. (d) Guchhait, S. K.; Madaan, C. *Org. Biomol. Chem.* **2010**, *8*, 3631. (e) Guchhait, S. K.; Jadeja, K.; Madaan, C. *Tetrahedron Lett.* **2009**, *50*, 6861. (f) Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. *J. Med. Chem.* **2011**, *54*, 5013.

(5) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3605. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Huang, C.; Fu, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. Commun.* **2008**, 6333. (e) Fields, W. H.; Khan, A. K.; Sabat, M.; Chruma, J. J. *Org. Lett.* **2008**, *10*, 5131. (f) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103.

(6) (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127.

(7) (a) For atom-economy, see:Trost, B. M. *Science* **1991**, *254*, 1471. (b) Step-economy:Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Pot-economy:Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438.

(8) (a) Bariwal, J. B.; Ermilat'ev, D. S.; Van der Eycken, E. V. *Chem.–Eur. J.* **2010**, *16*, 3281. (b) Kouvatsos, N.; Meldrum, J. K.; Searle, M. S.; Thomas, N. R. *Chem. Commun.* **2006**, 4623. (c) Zhang, Y.; Li, P.; Wang, M.; Wang, L. *J. Org. Chem.* **2009**, *74*, 4364. (d) Li, C.; Wei, C. *Chem. Commun.* **2002**, 268.

(9) (a) Brown, L. E.; Dai, P.; Porco, J. A.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 4228. (b) Tale, R. H.; Rodge, A. H.; Hatnapure, G. D.; Keche, A. P. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4648.

(10) Gong, X.; Yang, H.; Liu, H.; Jiang, Y.; Zhao, Y.; Fu, H. *Org. Lett.* **2010**, *12*, 3128.

(11) (a) Bruneau, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 2328. (b) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654.

(12) During the progress of this work, a method of amidation of propargylamine and AgOTf-catalyzed cycloisomerization towards the synthesis of imidazolone was reported. See:Peshkov, V. A.; Pereshivko, O. P.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2011**, *76*, 5867.

(13) Ermolat'ev, D. S.; Bariwal, J. B.; Steenackers, H. P. L.; De Keersmaecker, S. C. J.; Van der Eycken, E. V. *Angew. Chem. Int. Ed.* **2010**, *49*, 9465.

(14) Carling, R. W.; Moore, K. W.; Moyes, C. R.; Jones, E. A.; Bonner, K.; Emms, F.; Marwood, R.; Patel, S.; Patel, S.; Fletcher, A. E.; Beer, M.; Sohal, B.; Pike, A.; Leeson, P. D. *J. Med. Chem.* **1999**, *42*, 2706.

(15) (a) Wollweber, H.; Hiltmann, R.; Stoepel, K.; Kroneberg, H. G. *Eur. J. Med. Chem.* **1980**, *15*, 111. (b) Shibuya, A. US 20040191679 A1 20040930, **2004**.

(16) Frost, J. M.; Latshaw, S. P.; Dart, M. J.; Carroll, W. A.; Perez-Medrano, A.; Kolasa, T.; Patel, M.; Nelson, D. W.; Li, T.; Peddi, S.; Wang, X.; Lui, B. PCT Int. Appl. WO 2010071783 A1 20100624, **2010**.

(17) **Representative Experimental Procedure for the Synthesis of (*E*,*Z*)-*N*,*N*′-Dibenzyl-4-(4′-chlorophenyl)-5-(1′,1′-iodophenylmethylene)oxazolidin-2-imine (Compound 1, Scheme 2)**
To a magnetically stirred solution of 4-chlorobenzaldehyde (140 mg, 1.0 mmol) and benzylamine (107 mg, 1 mmol) in anhyd 1,4-dioxane (2.5 mL) were added phenylacetylene (224 mg, 2.2 mmol) and CuI (30 mol%) under nitrogen. The reaction mixture was heated at 80 °C for 5 h (monitored by

TLC). To the resultant mixture was added benzyl isocyanate (0.12 mL, 1.0 mmol). The mixture was stirred at 80 °C for 2 h (monitored by TLC). Then I_2 (506 mg, 2 mmol) and Na_2CO_3 (315 mg, 3 mmol) were added, and the reaction was continued at 80 °C for further 3 h (monitored by TLC). The resultant mixture was extracted with EtOAc. The combined organic solution was washed with H_2O, dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The column chromatographic purification of crude mass on silica gel (100–200 mesh) eluting with EtOAc–PE provided (*E*,*Z*)-*N*,*N*′-dibenzyl-4-(4′-chlorophenyl)-5-(1′,1′-iodophenylmethylene)oxazolidin-2-imine (301 mg, 51% yield); brown viscous liquid. MS (APCI): *m/z* = 591 [M(^{35}Cl) + H]$^+$. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.50 (d, *J* = 15.3 Hz, 1 H), 4.51 (d, *J* = 14.7 Hz, 1 H), 4.49 (d, *J* = 14.7 Hz, 1 H), 4.99 (d, *J* = 15.3 Hz, 1 H), 5.10 (s, 1 H), 7.16–7.37 (m, 17 H) 7.45 (d, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 46.00, 49.94, 65.97, 74.81, 126.44, 127.40, 127.82, 128.09, 128.21, 128.31, 128.74, 129.13, 129.67, 130.34, 134.43, 134.54, 134.80, 135.63, 137.55, 141.26, 148.15, 150.89 ppm. IR (KBr): ν_{max} = 2932, 2853, 2369, 2335, 1712, 1645, 691 cm^{-1}. HRMS: *m/z* calcd for $C_{30}H_{24}ClIN_2O$: 591.0702 [M(^{35}Cl) + H]$^+$; found: 591.0685.
All reactions (Scheme 2) were carried out following the representative procedure.

Representative Experimental Procedure for the Synthesis of (*Z*,*Z*)-*N*,*N*′-Dibenzyl-5-benzylidene-4-phenylthiazolidin-2-imine (Compound 12, Scheme 3)

To a magnetically stirred solution of benzaldehyde (106 mg, 1.0 mmol) and benzyl amine (107 mg, 1 mmol) in anhyd 1,4-dioxane (2.5 mL) were added phenylacetylene (224 mg, 2.2 mmol) and CuI (30 mol%) under nitrogen. The mixture was heated at 80 °C for 5 h (monitored by TLC). Benzyl isothiocyanate (0.14 mL, 1.0 mmol) was then added. The reaction was continued at 80 °C till completion (3 h, monitored by TLC). The resultant mixture was extracted with EtOAc. The combined organic solution was washed with H_2O, dried over anhyd Na_2SO_4, filtered, and concentrated under vacuum. The column chromatographic purification of crude mass on silica gel (100–200 mesh) eluting with EtOAc–PE provided (*Z*,*Z*)-*N*,*N*′-dibenzyl-5-benzylidene-4-phenylthiazolidin-2-imine (250 mg, 56% yield); light yellow solid; mp 106–109 °C. MS (APCI): *m/z* = 447 [M + H]$^+$. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.66 (d, *J* = 15.1 Hz, 1 H), 4.67 (d, *J* = 15.2 Hz, 1 H), 4.64 (d, *J* = 15.2 Hz, 1 H), 5.23 (d, *J* = 1.7 Hz, 1 H), 5.42 (d, *J* = 15.1 Hz, 1 H), 6.21 (d, *J* = 1.7 Hz, 1 H), 7.17–7.42 (m, 20 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 47.31, 58.18, 70.05, 122.29, 126.50, 127.05, 127.31, 127.34, 127.56, 128.02, 128.26, 128.47, 128.47, 128.48, 128.55, 129.01, 133.82, 136.01, 136.96, 140.27, 141.04, 155.81 ppm. IR (KBr): ν_{max} = 3032, 2919, 1751, 1645, 1619, 695 cm^{-1}. HRMS: *m/z* calcd for $C_{30}H_{26}N_2S$: 447.1897 [M + H]$^+$; found: 447.1902.
All reactions (Scheme 3) were carried out following the representative procedure: When 3,4-dihydroisoquinoline or 6,7-dimethoxy-3,4-dihydroisoquinoline was used as imine equivalent (Schemes 2 and 3), the reactions were done by using 10 mol% of CuI (in place of 30 mol%) keeping all other conditions the same.

(18) Complete crystallographic X-ray data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336 033; email: deposit@ccdc.cam.ac.uk]. CCDC 879707 contains the supplementary crystallographic data for Compound **8**, Scheme 2. CCDC 857504 contains the supplementary crystallographic data for Compound **17**, Scheme 3.