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Efficient Access to Cyclic Ureas via Pd-Catalyzed Cyclization

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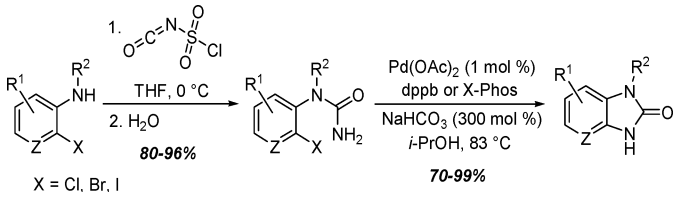
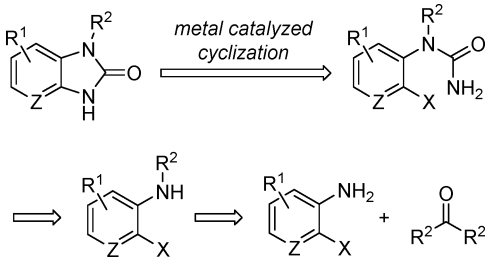
ABSTRACT



An efficient regioselective method for the preparation of structurally diverse imidazopyridinones and benzoimidazolones starting from readily available and economical starting materials is described. High-yielding reductive alkylation of electron-deficient *o*-haloarylamines followed by treatment with inexpensive *N*-chlorosulfonyl isocyanate afforded primary ureas in good overall yields. A Pd-catalyzed urea cyclization reaction furnished imidazopyridinones and benzoimidazolones in excellent yields. Overall, the developed chemistry provides rapid access to pharmaceutically important heterocyclic compounds with high efficiency.

Benzoimidazolones, imidazopyridinones, and the related benzimidazoles/imidazopyridines are heterocyclic substructures embedded in many biologically active molecules with pharmaceutical relevance.[1] As a consequence, the development of efficient methods for the preparation of such compounds constitutes an important area of synthetic research. In particular, the ability to generate these cyclic urea structures in a regioselective fashion, with control of the substituent on each nitrogen atom, is desirable. Current techniques for the synthesis of unsymmetrically substituted benzoimidazolones often rely upon inefficient manipulations of 1,2-diamino compounds followed by carbonyl installation using phosgene or its equivalent.[2] The use of protecting groups is an inevitable feature of such strategies. As part of our ongoing studies in this area, an alternative approach was envisaged, centered around a Pd-catalyzed urea cyclization reaction.

Scheme 1. Regiocontrolled Synthesis of Unsymmetrical Imidazolones



As outlined retrosynthetically in Scheme 1, it was proposed that formation of cyclic ureas could be accomplished via an intramolecular transition-metal-catalyzed amidation reaction. Although this class of reaction has been intensively studied[3] in recent times, examples in which ureas are employed in intramolecular reactions are rare.[4,5] The urea cyclization

(1) For selected examples, see: (a) Kuethe, J. T.; Wong, A.; Davies, I. W. *J. Org. Chem.* **2004**, *69*, 7752−7754 and references cited therein. (b) McClure, K. F.; Abramov, Y. A.; Laird, E. R.; Barberia, J. T.; Cai, W.; Carty, T. J.; Cortina, S. R.; Danley, D. E.; Dipesa, A. J.; Donahue, K. M.; Dombroski, M. A.; Elliott, N. C.; Gabel, C. A.; Han, S.; Hynes, T. R.; LeMotte, P. K.; Mansour, M. N.; Marr, E. S.; Letavic, M. A.; Pandit, J.; Ripin, D. B.; Sweeney, F. J.; Tan, D.; Tao, Y. *J. Med. Chem.* **2005**, *48*, 5728−5737. (c) Terefenko, E. A.; Kern, J.; Fensome, A.; Wrobel, J.; Zhu, Y.; Cohen, J.; Winneker, R.; Zhang, Z.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3600−3603. (d) Li, Q.; Li, T.; Woods, K. W.; Gu, W.-Z.; Cohen, J.; Stoll, V. S.; Galicia, T.; Hutchins, C.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2918−2922. (e) Zuev, D.; Michne, J. A.; Huang, H.; Beno, B. R.; Wu, D.; Gao, Q.; Torrente, J. R.; Xu, C.; Conway, C. M.; Macor, J. E.; Dubowchik, G. M. *Org Lett.* **2005**, *7*, 2465−2468.

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substrates would ultimately derive from cheaply available *o*-chloroanilines or *o*-chloroaminopyridines. The preceding report from these laboratories described an effective reductive alkylation procedure applicable to either of these electron-poor arylamines, substrates that are normally viewed as inferior partners in this reaction.[6] The present research sought to utilize this reductive alkylation chemistry as a means to prepare various *N*-substituted *o*-chloroarylamines and demonstrate their further elaboration into benzoimidazolones and imidazopyridinones. The results of this work are described herein.

With a series of *N*-substituted *o*-chloroarylamines in hand, attention was focused on their conversion into primary ureas. In this regard, trichloroacetyl isocyanate was shown to deliver the desired ureas in reasonable yield.[7] However, the expense of this reagent and the two-step nature of the process prompted investigation of an alternative reagent.

Chlorosulfonyl isocyanate (CSI) is an extremely inexpensive reagent that converts amines into the corresponding primary ureas.[8] However, the reported yields for this transformation are generally moderate, and detailed experimental procedures are uncommon.[9] Following some experimentation using **1a** (Figure 1), it was determined that the

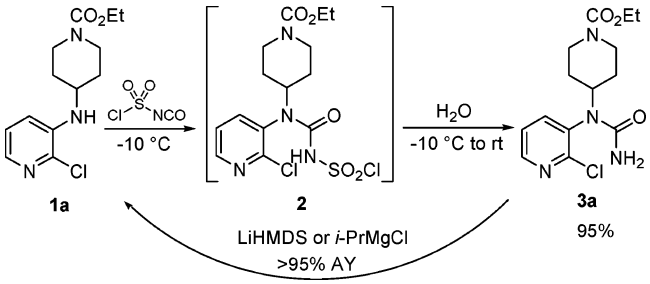
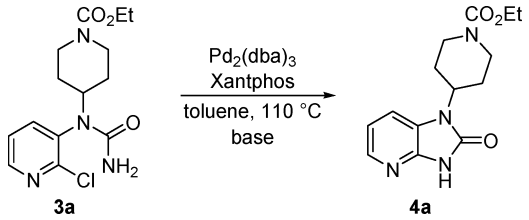


Figure 1. Urea formation using CSI and urea cleavage with strong bases.

order of reagent addition was critical for success when using CSI. Slow addition of CSI to **1a** allowed the intermediate

Table 1. Choice of Base for the Pd-Catalyzed Urea Cyclization[a]



entry	base (mol %)	conversion[b] (%)	assay yield[b] (%)
1	Cs_2CO_3 (300)	99	67
2	K_3PO_4 (300)	90	74
3	K_2CO_3 (300)	99	87
4	$NaHCO_3$ (300)	100	87

[a] Reaction conditions: Urea **3a** (100 mol %), $Pd_2(dba)_3$ (4 mol % Pd), Xantphos (6 mol %), base (300 mol %), toluene (10 mL/g, 150 ppm H_2O), 110 °C, 16 h. [b] Conversion and assay yield determined by LC versus purified standards.

N-chlorosulfonylurea **2** to accumulate in the presence of **1a** and resulted in the formation of dimeric-type species, via further reaction at the chlorosulfonyl group. This problem could be overcome by rapid addition (<1 min) of the CSI, since the secondary reaction was significantly slower. A more practical solution was to adopt an inverse addition protocol, which reproducibly afforded clean conversion to **2**.[10] Hydrolysis of **2** was facile and complete in <10 min upon addition of water to the reaction mixture. Simple extractive workup and subsequent concentration of the organic phase allowed for isolation of pure **3a** in excellent yield by crystallization.

Application of this developed procedure to an array of arylamines delivered high yields without exception. Due to the high efficiency of the previous reductive alkylation step,[6] it was possible to conduct the urea formation directly on the crude stream (Table 4). The exceptional crystallinity of the product ureas enabled facile rejection of impurities during crystallization.

Cyclization of the prepared urea intermediates was initially investigated in the pyridine series. The activated nature of the 2-position of **3a** suggested that an uncatalyzed cyclization process might be feasible; however, tests under both acidic and basic and also thermal conditions met with failure.[11]

(2) (a) Zecchini, G. P.; Torrini, I.; Paradisi, M. P. *J. Heterocycl. Chem.* **1985**, *22*, 1061−1064. (b) Meanwell, N. A.; Sit, S. Y.; Gao, J.; Wong, H. S.; Gao, Q.; St. Laurent, D. R.; Balasubramanian, N. *J. Org. Chem.* **1995**, *60*, 1565−1582 and references cited therein.

(3) For examples of intramolecular Pd-catalyzed amidation, see: (a) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35−37. (b) Poondra, R. R.; Turner, N. J. *Org. Lett.* **2005**, *6*, 863−866.

(4) In a study directed toward the sysnthesis of benzothiazoles via cyclization of *o*-bromophenylthioureas, two benzimidazolones were prepared by Pd-catalyzed urea cyclization under relatively harsh conditions/high catalyst loadings; see: Benedi, C.; Bravo, F.; Uriz, P.; Fernández, E.; Claver, C.; Castillón, S. *Tetrahedron Lett.* **2003**, *44*, 6073−6077.

(5) For examples of intermolecular Pd-catalyzed amidation using cyclic ureas, see: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043−6048. For examples of Cu-catalyzed amidation using cyclic and acyclic ureas, see: (b) Trost, B. M.; Stiles, D. T. *Org. Lett.* **2005**, *7*, 2117−2120. (c) Nandakumar, M. V. *Tetrahedron Lett.* **2005**, *45*, 1989−1990. For Pd- and Cu-catalyzed synthesis of 2-aminobenzimidazoles via intramolecular C−N bond formation between an aryl bromide or iodide and a guanidine, see: Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133−136.

(6) See the accompanying paper from these laboratories: McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8*, 3307−3310.

(7) (a) Espino, C. G.; DuBois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600. (b) Kocovsky, P. *Tetrahedron Lett.* **1986**, *27*, 5521−5524.

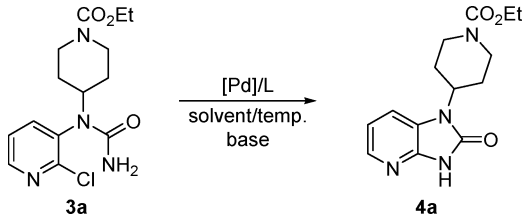
(8) For a review on the use of CSI for various transformations, see: Dhar, D. N.; Murthy, K. S. K. *Synthesis* **1986**, 437−449.

(9) Carril, M.; SanMartin, R.; Churruca, F.; Tellitu, I.; Dominguez, E. *Org. Lett.* **2005**, *7*, 4787−4789 and references cited therein.

(10) Notably, the published procedures advocate a "normal" addition protocol, in which CSI is added to the substrate. Based on the observations from the current work, this could account for the moderate yields obtained in these cases.

(11) Attempted thermal cyclizations in a variety of solvents (DMSO, MeCN, NMP, water, toluene, *i*-PrOH, DMAc, pyridine, *n*-BuOH, and AcOH) were not successful, generally returning unchanged starting material.

Table 2. Optimization of the Pd-Catalyzed Urea Cyclization[a]



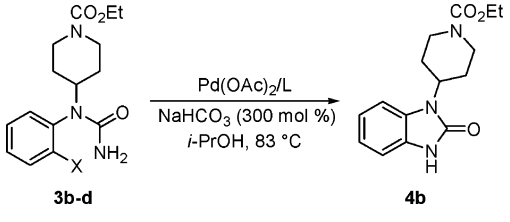
entry	[Pd] (mol %)	L (mol %)	solvent (H_2O)[b]	T (°C)	conv[c] (%)	assay yield[c] (%)
1	$Pd_2(dba)_3$ (4)	Xantphos (6)	toluene (150)	110	99	67
2	Pd/C		toluene (150)	110	30	0
3	$Pd(OAc)_2$ (2)	Ph_3P (8)	toluene (150)	110	20	0
4	$Pd(OAc)_2$ (0.5)		DMAc (285)	110	30	0
5	$Pd(OAc)_2$ (2)	DABCO (4)	DMAc (285)	110	36	0
6	$Pd(OAc)_2$ (2)	dppb (4)	toluene (150)	110	90	90
7	$Pd(OAc)_2$ (2)	dppb (4)	toluene (35)	110	77	70
8	$Pd(OAc)_2$ (2)	dppb (4)	THF (30)	75	64	60
9	$Pd(OAc)_2$ (2)	dppb (4)	THF (725)	75	99	98
10	$Pd(OAc)_2$ (2)	dppb (4)	*i*-PrOH (1250)	83	100	99
11	$Pd(OAc)_2$ (1)	dppb (2)	*i*-PrOH (1250)	83	100	99

[a] Reaction conditions: Urea **3a** (100 mol %) and $NaHCO_3$ (300 mol %) with the indicated catalyst/ligand/solvent (10 mL/g)/temperature for 16 h. [b] Water content values are in ppm, determined by Karl-Fisher titration. [c] Conversion and assay yield determined by LC versus purified standards.

Interestingly, when **3a** was treated with LiHMDS or *i*-PrMgCl smooth cleavage of the urea occurred and returned the precursor **1a**, presumably via elimination of cyanate ion (Figure 1).

At this stage, the use of transition-metal catalysis was examined, and palladium was chosen as the starting point.[12] An initial encouraging result was obtained using $Pd_2(dba)_3$ and Xantphos with Cs_2CO_3 as the base in toluene at 110 °C. Under these conditions, the conversion of starting material was high while the assay yield was only moderate (Table 1, entry 1). The mass balance was accounted for in urea cleavage, returning **1a**, as observed previously under more strongly basic conditions. After screening several bases, both K_2CO_3 and $NaHCO_3$ emerged as suitable candidates (Table 1, entries 3 and 4), and $NaHCO_3$ was chosen for further study owing to its extremely mild nature.[13]

Table 3. *o*-Haloaniline Urea Cyclizations[a]



entry	X	[Pd] (mol %)	L (mol %)	conv[b] (%)	assay yield[b] (%)
1	Cl (**3b**)	$Pd(OAc)_2$ (2)	dppb (4)	0	0
2	Cl (**3b**)	$Pd(OAc)_2$ (1)	X-Phos (3)	99	99 (89)[c]
3	Br (**3c**)	$Pd(OAc)_2$ (2)	dppb (4)	0	0
4	Br (**3c**)	$Pd(OAc)_2$ (1)	X-Phos (3)	72[d]	70[d]
5	I (**3d**)	$Pd(OAc)_2$ (2)	dppb (4)	5	5
6	I (**3d**)	$Pd(OAc)_2$ (1)	X-Phos (3)	100[c]	99[c]

[a] Reaction conditions: Urea **3b**−**d** (100 mol %) and $NaHCO_3$ (300 mol %) with the indicated catalyst/ligand in *i*-PrOH (10 mL/g) at 83 °C. [b] Conversion and assay yield determined by LC versus purified standards. [c] Yield in parentheses refers to isolated material. [d] After 72 h.

Although good yields were obtained under these conditions, further exploration of the reaction variables ultimately led to a superior catalytic system (Table 2). An attempt to employ a heterogeneous catalyst for this reaction was unsuccessful (Table 2, entry 2). With respect to homogeneous systems, ligand-free conditions met with failure (Table 2, entry 4). Monodentate Ph_3P and DABCO were also ineffectual (Table 2, entries 3 and 5). Having demonstrated that Xantphos promoted the reaction, attention was focused on alternative, less expensive bidentate phosphines, and bis-(diphenylphosphino)butane (dppb) surfaced as a good ligand for this reaction. Seeking to gain control of the urea hydrolysis problem, the reaction was conducted in the presence of varying amounts of water (Table 2, entries 6 and 7). When the water content of the system was reduced to 35 ppm, the reaction stalled at 77% conversion whereas an increased water content gave better results. The exact role played by water in this case is unknown at present. The temperature could be reduced to 75−85 °C and a reasonable reaction rate maintained (complete conversion within 16 h). Significantly, the urea cleavage side-reaction was completely suppressed at the lower temperature. The reaction functioned in alternative solvents, and ultimately, *i*-PrOH was chosen as the optimum solvent. Catalyst loading was reduced to 1 mol % of $Pd(OAc)_2$ and 2 mol % of dppb, routinely affording >99% conversion and 99% assay yield.

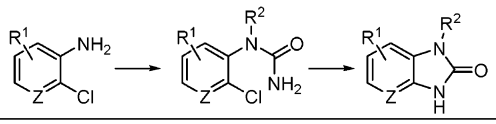
These conditions proved effective throughout the pyridine series, and essentially quantitative yields were obtained with all substrates (Table 4).

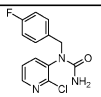
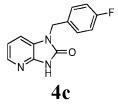
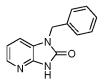
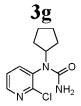
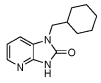
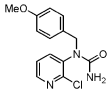
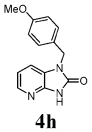
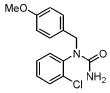
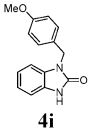
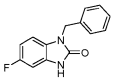
As anticipated, for the haloaniline series the $Pd(OAc)_2$/dppb system was ineffective with the *o*-chloroanilines. More

(12) Cu-catalyzed conditions were less successful for this reaction, affording only 67% conversion of starting material. See: Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729.

(13) Again, the mass balance was found in the urea cleavage side reaction, apparently suppressed under the less basic conditions.

Table 4. Urea Formation[a] and Pd-Catalyzed Cyclization[b]



entry	urea	urea yield (%)[c]	cond.	cyclized product	cyclic urea yield (%)[c]
1	 **3e**	88	**A**	 **4c**	94
2	 **3f**	86	**A**	 **4d**	95
3	 **3g**	85	**A**	 **4e**	93
4	 **3h**	83	**A**	 **4f**	94
5	 **3i**	85	**A**	 **4g**	95
6	 **3j**	84	**A**	 **4h**	95
7	 **3k**	85	**B**	 **4i**	92
8	 **3l**	80	**B**	 **4j**	90
9	 **3m**	81	**B**	 **4k**	91

[a] Reaction conditions: reductive alkylation, *o*-chloroarylamine (100 mol %), carbonyl (110 mol %), TFA (200 mol %), and STAB (120 mol %) in *i*-PrOAc at rt; urea formation, CSI (120 mol %), THF/*i*-PrOAc, −10 °C, then H_2O. [b] Reaction conditions: (A) urea (100 mol %), $Pd(OAc)_2$ (1 mol %), dppb (2 mol %), and $NaHCO_3$ (300 mol %) in *i*-PrOH (10 mL/g) at 83 °C; (B) urea (100 mol %), $Pd(OAc)_2$ (1 mol %), X-Phos (3 mol %), and $NaHCO_3$ (300 mol %) in *i*-PrOH (10 mL/g) at 83 °C. [c] Yields refer to isolated material.

surprising was the lack of reactivity with both the *o*-bromo and *o*-iodo derivatives. This situation was partially remedied when dppb was replaced with Buchwald's highly active X-Phos ligand. Under these conditions, the chloroaniline derivative reacted smoothly while both the bromo and iodo compounds were less efficient. In fact, the iodoaniline required 72 h at 83 °C to reach completion, and the bromoaniline only reached 72% conversion before stalling.[14] The reasons for this unusual trend in reactivity across the halogen series are unclear at this time (Table 3).

Table 4 illustrates the substrate scope for this chemistry and displays the isolated yields for both the CSI-mediated urea formation and the Pd-catalyzed cyclization. In all cases, the efficiency of the urea cyclization reaction combined with the lack of byproducts rendered product isolation a straighforward task. Dilution with a suitable extraction solvent and an aqueous wash to remove inorganics leaves a solution from which the product can be crystallized in high purity.

In summary, we have demonstrated an efficient conversion of *o*-chloro-*N*-substituted arylamine products into benzoimidazolones and imidazopyridinones via a novel method. The use of readily available CSI for the formation of primary ureas was studied, and a high-yielding, reproducible procedure was developed. Critical to the success of this step was the use of an inverse addition protocol. Further, a Pd-catalyzed cyclization of these ureas was optimized to proceed in generally excellent yields. The $Pd(OAc)_2$/dppb catalyst system is simple, economical, and effective for the 2-chloropyridine series. For the less reactive *o*-chloroanilines, the more active X-Phos ligand produced the desired result. Overall, the described chemistry represents a method by which inexpensive starting materials can be rapidly elaborated into more complex heterocyclic structures of pharmaceutical importance.

Acknowledgment. We thank Robert A. Reamer and Tom J. Novak (Department of Process Research, Merck and Co. Inc.) for assistance with NMR data and mass spectrometry data acquisition, respectively.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Xantphos/$Pd(OAc)_2$ was also ineffective in attempts to cyclize the bromoaniline substrate.