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Palladium-Catalyzed Carbonylative Cross-Coupling with Imines: A Multicomponent Synthesis of Imidazolones

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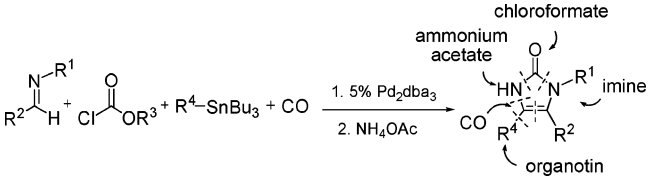
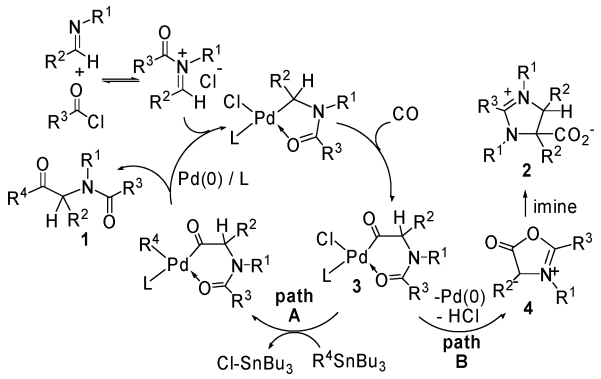


The palladium-catalyzed coupling of imines, chloroformates, organotin reagents, and carbon monoxide leads to the one-pot formation of ketocarbamates in good yields. These products can further be converted to highly substituted imidazolones via a cyclocondensation reaction. Overall, this methodology provides an alternative approach to imidazolones from five simple and readily available building blocks via a one-pot, multicomponent process.

Imidazolones are found in a range of biologically active compounds, including anti-inflammatory,[1a,] anticancer,[1b] and cardioactive agents,[1c] angiotensin II receptor antagonists,[1d] and others.[1e−h] In addition, 2-imidazolones can serve as potential substrates for imidazole synthesis.[2] A variety of methods have been developed to generate and functionalize these heterocycles. These include the condensation of substituted ureas with carbonyl compounds,[3] the coupling of β-amino carbonyl reagents with isocyanates,[4] intramolecular iminium salt cyclizations,[5] as well as more recent metal-catalyzed methods,[6−8] such the rhodium catalyzed N−H insertion of primary ureas with diazo carbonyl compounds,[2a,6] or the ruthenium-catalyzed reaction of substituted ureas with vicinal diols.[7,8]

SCHEME 1. Carbonylative Cross Coupling with Imines



In principle, an attractive approach to imidazolones would be to assemble their core structure directly from multiple, available building blocks. Transition metal catalysis can be a powerful tool in developing such transformations, by activating what are often unreactive substrates toward coupling via metal-based reactions.[9] Toward this end, we have recently reported that imines can undergo a palladium-catalyzed cross-coupling-type reaction with organostannanes by the addition of acid chlorides or chloroformates, to generate α-substituted amides (or carbamates).[10] In addition, preliminary studies showed this reaction could proceed in concert with carbon monoxide insertion, allowing the synthesis of one example of a ketocarbamate (Scheme 1). Considering that ketoamides are known to behave as precursors to imidazoles,[11] we became intrigued with

(1) (a) Sheppeck, J. E., II; Glimore, J. L.; Tebben, A.; Xue, C.-B.; Liu, R.-Q.; Decicco, C. P.; Duan, J. J. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2769−2774. (b) Lai, Z.; Yang. T.; Kim, Y. B.; Sielecki, T. M.; Diamond, M. A.; Strack, P.; Rolfe, M.; Caligiuri, M.; Benfield, P. A.; Auger, K. R.; Copleland, R. A. *PNAS* **2002**, *99*, 14734−14739. (c) Schnettler, R. A.; Dage, R. C.; Grisar, J. M. *J. Med. Chem.* **1982**, *25*, 1477−1481. (d) Bernhart, C. A.; Perreaut, P. M.; Ferrari, B. P.; Muneaux, Y. A.; Assens, J.-L. A.; Clement, J.; Haudricourt, F.; Muneaux, C. F.; Taillades, J. E.; Vignal, M.-A.; Gougat, J.; Guiraudou, P. R.; Lacour, C. A.; Roccon, A.; Cazaubon, C. F.; Breliere, J.-C.; Le Fur, G.; Nisato, D. *J. Med. Chem.* **1993**, *36*, 3371−3380. (e) Naylor, E. M.; Parmee, E. R.; Colandrea, V. J.; Perkins, L.; Brockunier, L.; Candelore, M. R.; Cascieri, M. A.; Colwell, L. F., Jr.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Strader, C. D.; Tota, L.; Wang, P.-R.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 755−758. (f) Reitz, D. B.; Garland, D. J.; Norton, M. B.; Collins, J. T.; Reinhard, E. J.; Manning, R. E.; Olins, G. M.; Chen, S. T.; Palomo, M. A.; McMahon, E. G. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1055−1060. (g) Adres, J. I.; et al. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 653−658. (h) 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*, 2706−2715.

(2) (a) Lee, S.-H.; Yoshida, K.; Matsushita, H.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *J. Org. Chem.* **2004**, *69*, 8829−8835. (b) Plummer, C. W.; Finke, P. E.; Mills, S. G.; Wang, J.; Tong, X.; Doss, G. A.; Fong, T. M.; Lao, J. Z.; Schaeffer, M.-T.; Chen, J.; Shen, C.-P.; Stribling, D. S.; Shearman, L. P.; Strack, A. M.; Van der Ploeg, L. H. T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1441−1446.

(3) For example: (a) Butler, A. R.; Hussain, I. *J. Chem. Soc., Perkin 2* **1981**, 310−316. (b) Patek, M.; Weichsel, A. S.; Drake, B.; Smrcina, M. *Synlett* **2005**, *8*, 1322−1324.

(4) For example: Duschinsky, R.; Dolan, L. A. *J. Am. Chem. Soc.* **1946**, *68*, 2350−2355.

(5) (a) Pesquet, A.; Daïch, A.; van Hijtfe, L. *J. Org. Chem.* **2006**, *71*, 5303−5311. (b) Wendeborn, S.; Winkler, T.; Foisy, I. *Tetrahedron Lett.* **2000**, *41*, 6387−6391. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367−4416. (d) Cheng, J.-F.; Kaiho, C.; Chen, M.; Arrhenius, T. *Tetrahedron Lett.* **2002**, *43*, 4571−4573.

(6) Lee, S.-H.; Clapham, B.; Koch, G.; Zimmermann, J. *Org. Lett.* **2003**, *5*, 511−514.

(7) Kondo, T.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1992**, 1318−1319.

(8) Du, H.; Yuan, W.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 7496−7497.

(9) Representative examples: (a) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786−7787. (b) Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880−2881. (c) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468−469. (d) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050−6051. (e) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081−8082. (f) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473. (g) Wie, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472−1483.

(10) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed* **2004**, *43*, 590−594.

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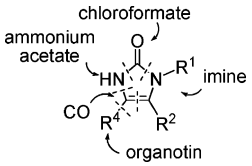
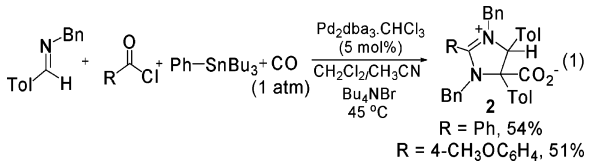


FIGURE 1. A multicomponent approach to imidazolones.

the potential use of this ketocarbamate synthesis in an analogous fashion, to achieve the overall construction of imidazolones. As described below, this can provide a modular route to construct imidazolones from five separate and available building blocks, as shown in Figure 1.

Our initial efforts focused upon the palladium-catalyzed carbonylative cross-coupling reaction with imines. While we have shown that acid chlorides can activate imines toward cross coupling with organostannanes,[10] their use under carbonylative conditions leads instead to the formation of imidazolines **2**

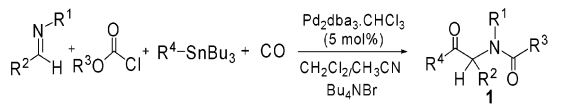


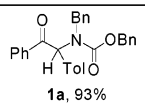
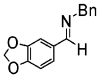
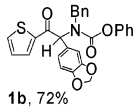
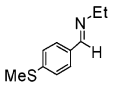
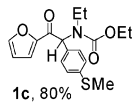
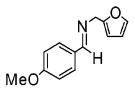
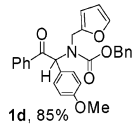
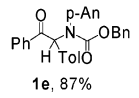
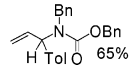
(eq 1, Tol = *p*-tolyl; Bn = benzyl). The latter presumably occurs via a mechanism involving the cyclization of the carbonylated palladium intermediate **3** to form 1,3-oxazolium-5-olate **4** (path B), followed by 1,3-dipolar cycloaddition of an imine (Scheme 1), a reaction we have previously reported.[12] In considering approaches to limit this pathway, we postulated that lowering the basicity of the carbonyl oxygen in intermediate **3** might disfavor cyclization to form **4**, and allow for competitive cross coupling to occur (path A). As shown in Table 1, replacement of the acid chloride with a chloroformate leads to the carbonylative cross-coupling product **1a** in nearly quantitative yield at ambient temperature.[13]

This palladium-catalyzed carbonylative coupling is compatible with a number of chloroformates (entries 1−3). Both aromatic and heteroaromatic organostannanes can participate in the reaction, each providing ketocarbamates in good yields. An even greater variety of imines can participate in this reaction, including those of functionalized aryl-aldehydes (entries 2−4), and *N*-alkyl or *N*-aryl imines (entries 4 and 5). There are certain limitations to this methodology. For example, more reactive transmetalating agents, such as vinylstannanes, appear to transmetalate more rapidly than carbonylation, leading instead to the formation of simple α-substituted carbamate (entry 6). Similarly, alkyl-substituted organostannanes are not sufficiently reactive to participate in this coupling, and enolizable imines lead to side reactions.

Ketoamides are well established to undergo ammonium acetate mediated cyclization to generate imidazoles.[11] However,

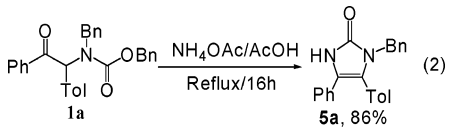
TABLE 1. Palladium-Catalyzed Carbonylative Coupling of Imines, Chloroformates, CO, and Organostannanes[a]



#	Imine	R^3	R^4	Product
1		-Bn	-Ph	 **1a**, 93%
2		-Ph		 **1b**, 72%
3		-Et		 **1c**, 80%
4		-Bn	-Ph	 **1d**, 85%
5		-Bn	-Ph	 **1e**, 87%
6[b]		-Bn		 65%

[a] 0.48 mmol of imine, 1.90 mmol of chloroformate, 0.52 mmol of organotin reagent, $Pd_2dba_3{\cdot}CHCl_3$ (5%), 0.57 mmol of Bu_4NBr, and CO (1 atm) in CH_3CN/CH_2Cl_2 (2:1) at rt for 24-48 h; p-An = 4-$CH_3OC_6H_4$. [b] 50 atm of CO.

to our knowledge ketocarbamates such as **1** have not been employed in similar cyclization reactions. As shown in eq 2, the addition of ammonium acetate to **1a** results in the clean cyclization, along with spontaneous removal of the former chloroformate substituent, leading to the synthesis of imidazolone **5a** in 86% yield.[14]



Considering the high yield cyclization of **1a**, and the ability to access these substrates via carbonylative cross-coupling, we became interested in the potential coupling of these steps in a one-pot format. As shown in Table 2, this can provide an efficient and high-yield synthesis of imidazolones, where the products are assembled overall from five separate and readily available building blocks (imines, chloroformates, organostannanes, carbon monoxide, and ammonium acetate). Notably, much of the same diversity noted in cross-coupling chemistry can be incorporated into these imidazolone products, including the use of variously substituted and functionalized imines, as well as aryl- or heteroaryl-tin reagents. Overall, this allows access to a range of di- and triaryl-substituted imidazolones with independent control over three substituents about the ring.

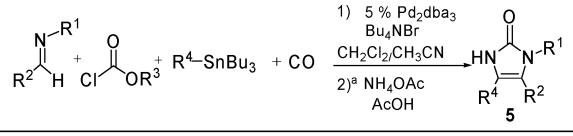
(11) (a) Lee, H. B.; Balasubramanian, B. *Org. Lett.* **2000**, *2*, 323−326. (b) Bleicher, K. H.; Gerber, F.; Wüthrich, Y.; Alanine, A.; Capretta, A. *Tetrahedron Lett.* **2002**, *43*, 7687−7690. (c) Claiborne, C. F.; Liverton, N. J.; Nguyen, K. T. *Tetrahedron. Lett.* **1998**, *39*, 8939−8942. (d) Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. A.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 843−846.

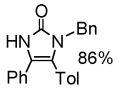
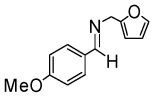
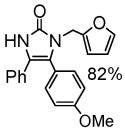
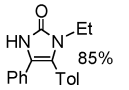
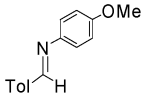
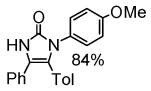
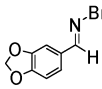
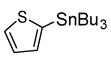
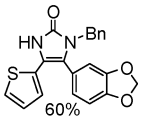
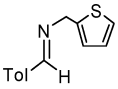
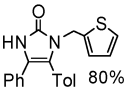
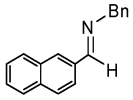
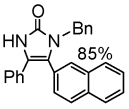
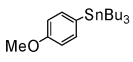
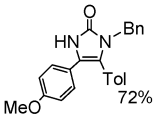
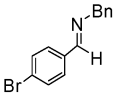
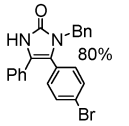
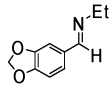
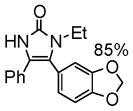
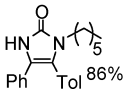
(12) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228−3230.

(13) Bu_4NBr is added in order to keep the ligandless palladium catalyst in solution (see ref 10).

(14) The structure of **5a** was distinguished from its 1*H*-imidazol-2-ol tautomer by means of NOE, and HSQC NMR experiments, as well as IR spectral data; see the Supporting Information for details.

TABLE 2. A One-Pot Synthesis of Imidazolones

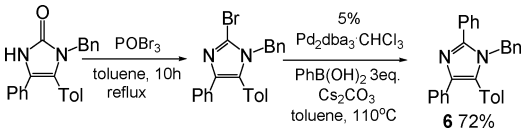


Cpd	Imine	R^3	Tin Reagent	**5** (% yield)
5a		Bn-	Ph-$SnBu_3$	 86%
5b		Bn-	Ph-$SnBu_3$	 82%
5c		Et-	Ph-$SnBu_3$	 85%
5d		Bn-	Ph-$SnBu_3$	 84%
5e[b]		Ph-		 60%
5f		Ph-	Ph-$SnBu_3$	 80%
5g		Ph-	Ph-$SnBu_3$	 85%
5h		Bn-		 72%
5i		Bn-	Ph-$SnBu_3$	 80%
5j		Ph-	Ph-$SnBu_3$	 85%
5k		Bn-	Ph-$SnBu_3$	 86%

[a] Procedure of Table 1, followed by removal of solvent and addition of 15−20 equiv of NH_4OAc in AcOH, reflux 12-16 h. [b] Ketocarbamate was isolated and refluxed in NH_4OAc/AcOH solution for 5 h.

Finally, this synthesis of imidazolones can also be used to access imidazoles. Triaryl-substituted imidazoles have been found to display potent biological activity, including as selective P38 MAP kinase inhibitors.[15] As illustrated in Scheme 2, the coupling of the catalytic formation of imidazolones with the protocol developed by Janda for their bromination and use in palladium-catalyzed cross coupling provides access the triaryl-substituted imidazole core in good yield. Notably, the four substituents in **6** arise overall from two separate cross-coupling reactions (e.g., positions 2- and 4-) and from the imine building block (positions 1- and 5-).

SCHEME 2. Synthesis of Triarylimidazoles



In conclusion, the palladium-catalyzed four-component cross-coupling of imines, chloroformates, organostannane reagents, and carbon monoxide can be utilized to generate ketocarbamates, which are amenable to cyclization to generate imidazolones. Considering the mild conditions (1 atm of carbon monoxide, room temperature) and simple building blocks employed, this provides straightforward access to these heterocycles. Experiments directed toward the use of this multicomponent reaction to generate other targets are underway.

Experimental Section

General Procedure for the Synthesis of Ketocarbamates 1. In a drybox, imine (0.48 mmol) and chloroformate (1.91 mmol) were dissolved in acetonitrile (10 mL) then the solution was stirred for 15 min in a 50 mL reaction bomb. To this solution was added Pd_2dba_3·$CHCl_3$ (25 mg, 0.024 mmol) and the mixture was stirred for 30 min until the Pd_2dba_3·$CHCl_3$ was dissolved. Tetrabutylammonium bromide (186 mg, 0.576 mmol) in methylene chloride (5 mL) and the organostannane (0.53 mmol) in methylene chloride (5 mL) were added to the reaction mixture. The solution was frozen in liquid nitrogen then degassed, and carbon monoxide (15 psi) was added. The mixture was stirred at room temperature for 24 h. After the reaction period was completed, solvents were removed in vacuo. The product was dissolved in 50 mL of ethyl acetate, then 25 mL of saturated KF solution was added and the mixture was stirred for 5 h. This solution was filtered over celite and extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and dried over $MgSO_4$ then solvent was evaporated under reduced pressure and the product was purified by silica gel chromatography with hexane:ethylacetate as eluent.

Synthesis of 1a. The above procedure was followed, yielding **1a** as a yellow oil (93%). ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ 7.8 (s, br, 2H), 7.47−7.43 (t, 1H), 7.34−7.27 (t, 2H), 7.27−7.25 (m, 3H), 7.18−7.15 (m, 4H), 7.13−7.11 (m, 4H), 7.04−7.02 (d, 2H), 6.92 (s, br, 2H), 5.25−5.16 (dd, 2H), 4.95−4.91 (d, 1H), 4.33−4.29 (d, 1H), 2.27 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C): δ 197.6, 157.6, 139.4, 138.9, 136.5, 135.8, 133.3, 131.1, 130.7, 129.9, 129.0, 128.7, 128.6, 128.4, 128.1, 128.0, 127.3, 126.6, 67.9, 65.9, 49.0, 21.3. IR (KBr): ν_{CO} 1703, 1698 cm^{-1}. HRMS: calcd for $C_{30}H_{28}NO_3^+$ 450.2069, found 450. 2063.

General Procedure for the Synthesis of Imidazolones 5. In a drybox, imine (0.48 mmol) and chloroformate (1.91 mmol) were dissolved in acetonitrile (10 mL) and stirred for 15 min in a 50 mL reaction bomb. To this solution was added Pd_2dba_3·$CHCl_3$ (25 mg, 0.024 mmol) and the mixture was stirred for 30 min until the Pd_2dba_3·$CHCl_3$ was dissolved. Tetrabutylammonium bromide (186 mg, 0.576 mmol) in methylene chloride (5 mL) and the organostannane (0.53 mmol) in methylene chloride (5 mL) were added to the reaction mixture. The solution was frozen in liquid nitrogen and degassed, then carbon monoxide (15 psi) was added. The mixture was stirred at room temperature for 24 h. After the reaction period was completed, solvents were removed in vacuo. To this was added 25 mL of acetic acid and 15 equiv of ammonium acetate, and the mixture was refluxed for 16 h. The resulting deep yellow solution

(15) For review: Jackson, P. F.; Bullington, J. L. *Curr. Top. Med. Chem.* **2002**, *2*, 1011−1020.

was quenched with saturated Na_2CO_3 solution, the pH was adjusted to 7−8, and the product was extracted with methylene chloride (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, and filtered. The yellow residue was further purified by silica gel chromatography with hexane:ethylacetate as eluent.

Synthesis of 5a. The above procedure was followed, yielding **5a** as a white solid (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.24 (s, 1H), 7.26 (s, 2H), 7.21−7.17 (m, 5H), 7.15−7.13 (m, 3H), 7.08−7.04 (m, 4H), 4.77 (s, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.3, 138.8, 137.7, 130.9, 129.7, 129.5, 128.5, 128.3, 127.4, 127.1, 126.6, 126.4, 125.4, 121.9, 118.3, 44.7, 21.4. IR (KBr): ν_{NH} 3435 cm^{-1}; ν_{CO} 1684 cm^{-1}. HRMS: calcd for $C_{23}H_{21}N_2O^+$ 341.1648, found 341.1648.

Acknowledgment. We thank NSERC, FQRNT, and CFI for financial support of this research.

Supporting Information Available: Synthetic details and characterization of the compounds in eq 1and Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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