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Catalytic amination of 5-iodouracil derivatives

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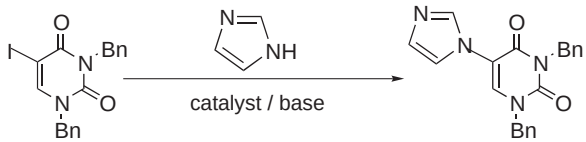
Abstract—Heterocyclic 5-amino uracil derivatives were prepared by catalytic amination of 1,3-dibenzyl-5-iodouracil using $(CuOTf)_2 \cdot PhH$, 1,10-phenanthroline, dibenzylidene acetone, and Cs_2CO_3 as base in xylenes at 95°C. Imidazole and 2-amino thiazoline were problematic using the Cu catalyst, but were effectively coupled using $Ni(COD)_2$, dppf, and Na^{t}OBu in toluene at 100°C. These are the first examples of catalytic amination with a uracil substrate.

Catalytic coupling reactions offer convenient and versatile methods for the synthesis of heterocyclic compounds, and are important tools for drug discovery. A wide variety of catalytic C–C bond forming reactions have been carried out using 5-iodouracil.[1] Catalytic amination of aryl halides is an efficient method for the synthesis of anilines.[2] Relatively few examples of catalytic amination reactions of heterocyclic compounds,[2e–l,3] or nucleosides[4] have been reported, and there are no examples of the catalytic amination of 5-iodouracil. Our interest in synthesizing 5-aminouracil derivatives **2** as potential antiviral compounds[5] led us to investigate various Pd, Cu, and Ni catalytic systems for C–N bond formation between 1,3-dibenzyl-5-iodouracil **1** and a variety of heterocyclic amines.

Our initial experiments were focused on C–N cross coupling of **1** with imidazole. The combination of Pd catalysts with chelating bis-phosphine ligands[3c] or bulky, electron rich biphenyl phosphine ligands[2h] have been shown to be effective for the amination of a variety of aryl and pyridyl halides. None of these examples involved coupling with imidazole, and previous attempts to couple imidazole using palladium catalyst/ligand combinations were reported to be unsuccessful.[6] Our attempts at imidazole amination of **1** using $Pd_2(dba)_3/Cs_2CO_3$ with either BINAP or 2-(dicyclohexylphosphino)biphenyl ligands in toluene at 100°C were similarly unsuccessful. No reaction was evident under these conditions, and starting **1** was recovered.



The copper catalyzed coupling of imidazoles with aryl iodides and bromides using $(CuOTf)_2 \cdot PhH$, 1,10-phenanthroline (phen), dibenzylidene acetone (dba), Cs_2CO_3, in refluxing xylenes was recently reported.[7] Our attempts to couple the 5-iodouracil derivative **1** with imidazole using these conditions were unsuccessful, producing only the deiodinated uracil. However, we were pleasantly surprised to find that this Cu catalyst system was successful for the coupling of **1** with a wide variety of other amines.[8] The results are shown in Table 1. Primary heteroaryl and alkyl amines, and the secondary alkyl amine morpholine all gave satisfactory results and good yields. The temperature of the reaction in xylene was reduced to 95°C in order to minimize competitive deiodination. The concentration of the reagents was also found to be important, and reactions did not proceed to completion when more dilute conditions (<0.09 M Cu catalyst) were used.

In addition to the failure of the Cu catalyst to couple **1** with imidazole, the reaction with 2-aminothiazoline was also unsuccessful, and deiodination was observed (entry 5). Recent reports of Ni catalysts such as Ni(O)/2,2′-bipyridine system for coupling aryl chlorides and 2- and 3-chloropyridines with secondary amines,[2j–l] and the $Ni(COD)_2$/1,1′-bis(diphenylphosphino)ferrocene (dppf) catalytic system for the amination of aryl chlorides with primary, secondary and aryl amines,[2f] and 3-chloropyridine with benzophenone imine,[2g] led us to try a Ni

Keywords: uracil; heterocycle; catalytic amination; copper catalyst; nickel catalyst.

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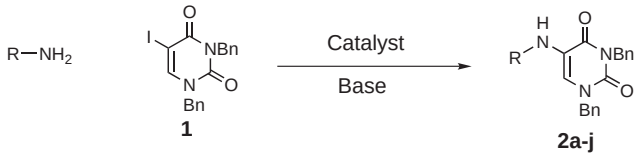
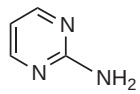
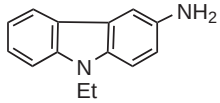
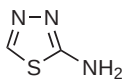
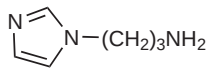
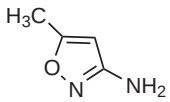
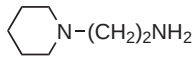
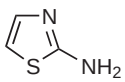
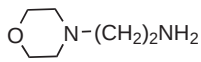
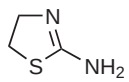
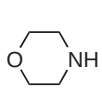
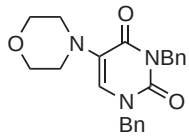
Table 1. Amination of 1,3-dibenzyl-5-iodouracil



Entry	Amine	Yield **2a-e**, (%)[c]	Entry	Amine	Yield **2f-j**, (%)[c]
1		**2a**, 71%[a]	6		**2f**, 42%[a]
2		**2b**, 64%[a]	7		**2g**, 76%[a]
3		**2c**, 72%[a]	8		**2h**, 78%[a]
4		**2d**, 73%[a]	9		**2i**, 77%[a]
5		**2e**, 0%[a] **2e**, 61%[b]	10		 **2j**, 73%[a]

[a]Reactions were carried out with 1.43 mmol **1**, 2.15 mmol amine, 1.57 mmol Cs_2CO_3, 0.07 mmol $(CuOTf)_2$.PhH, 1.43 mmol 1,10 phenanthroline (phen), 0.07 mmol dibenzylidene acetone (dba) in *p*-xylene 1.5 ml, 95° C, 24 h. [b]Reactions were carried out with 1.43 mmol **1**, 2.15 mmol amine, 2 mmol of Na^{t}OBu, 0.07 mmol $Ni(COD)_2$, 0.14 mmol 1,1-bis (diphenyl phospino) ferrocene (dppf), in toluene (2 mL), 100° C, 24 h. [c]Products were purified by silica gel column chromatography. All compounds were characterized by NMR (^{1}H, ^{13}C) and HRMS.

catalyst for these substrates. We found that **1** undergoes amination with imidazole (1) and 2-amino thiazoline (entry 5) in 52 and 61% yields, respectively, using catalyst $Ni(COD)_2$/dppf/Na^{t}OBu/toluene at 100°C for 24 h.[9] Competing deiodination was evident in both cases under these conditions, and the isolated 1,3-dibenzyluracil can be recycled by iodination.

In summary, the catalytic amination of 5-iodouracil has been demonstrated for the first time using copper or nickel catalysts. A variety of heterocyclic derivatives were obtained in moderate to very good yields. Further studies using $Ni(COD)_2$/dppf for heterocycle-amine coupling are in progress.

Acknowledgements

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8. Representative procedure: In a dry box a Schlenk tube was charged with **1** (1.43 mmol), morpholine (2.15 mmol), $(CuOTf)_2 \cdot PhH$ (0.07 mmol), dba (0.07 mmol), phen (1.43 mmol), Cs_2CO_3 (1.57 mmol), and *p*-xylene (1.5 mL). The reaction was heated at 95°C for 24 h. The reaction mixture was poured into saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The organic layer was separated, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (2:1 hexanes–ethyl acetate eluent) to obtain the pure product **2j** as a viscous oil in 73% yield; IR (KBr) 1700, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.70–2.92 (m, 4H), 3.65–3.8 (m, 4H), 4.90 (s, 2H), 5.15 (s, 2H), 6.52 (s, 1H), 7.15–7.55 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 44.80, 50.42, 52.12, 66.50, 126.69, 127.37, 127.59, 127.80, 128.17, 128.58, 128.87, 135.37, 136.65, 150.40, 160.27; FAB MS *m*/*z* 378.12 ($C_{22}H_{23}N_3O_3$+H, calcd 378.18).
9. Representative procedure: A Schlenk tube was charged with **1** (1.43 mmol), 2-aminothiazoline (2.15 mmol), $Ni(COD)_2$ (0.07 mmol), dppf (0.14 mmol), Na′OBu (2 mmol), and toluene (2 mL). The reaction was heated at 100°C for 24 h. The reaction mixture was diluted with CH_2Cl_2, then filtered (2×10 mL). The volatiles were removed in vacuo, and the crude product was recrytallized (EtOAc–hexane) to obtain the pure **2e** in 61% yield; mp 175–178°C; IR (KBr) 1700, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.31 (t, J=7.3 Hz, 2H), 4.05 (t, J=7.3 Hz, 2H), 4.92 (s, 2H), 5.18 (s, 2H), 7.2–7.6 (m, 10H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.67, 45.04, 52.75, 60.20, 117.86, 126.43, 127.58, 127.77, 128.06, 128.30, 128.78, 135.60, 136.36, 149.60, 156.78, 159.56; FAB MS *m*/*z* 393.48 ($C_{21}H_{20}N_4O_2$+H, calcd 393.14).