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I_2-Promoted Palladium-Catalyzed Carbonylation of Amines

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Palladium-catalyzed carbonylation of amines in the presence of iodide is well known for the preparation of isocyanate precursors.[1] This process is of practical significance because it avoids phosgenation, but it proceeds only under high pressure (>75 atm CO; 5−10 atm of O_2) and at elevated temperature (150−180 °C).[1,2] Significant conversion of CO to CO_2 also occurs.[3] It is believed that I^- is converted to I_2 under these reaction conditions.[1,2] Since an initial charge of I_2 (used stoichiometrically) will promote Pd-catalyzed carbonylation of amines to urea derivatives under milder conditions (40 psi, 95 °C; Scheme 1, a),[4] we wanted to determine if I_2 could similarly initiate Pd-catalyzed amine carbonylation in the context of urethane synthesis; if iodide thus produced could be recycled using a simple oxidant, only a catalytic amount of I_2 would be required. We found that fast amine carbonylation did take place, either when a stoichiometric amount of I_2 was added to a mixture of aniline and a catalytic amount of palladium acetate under CO or when a catalytic amount of I_2 was used instead under a mixture of CO and O_2 (Scheme 1, b). However, it was surprising that *no* carbonylation occurred when aniline was treated similarly with palladium acetate under CO/O_2, but using an initial charge of iodide salts instead of I_2.

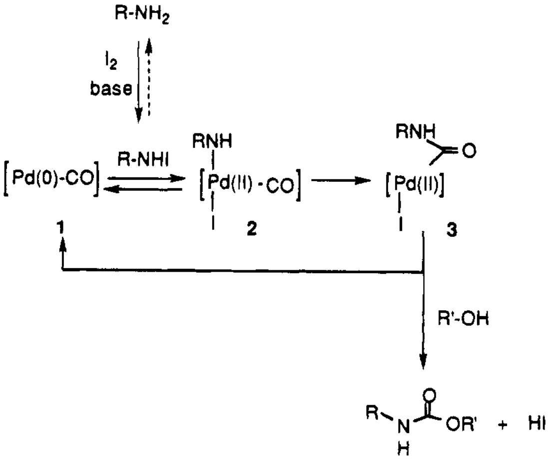
Scheme 1

(a) $R^1R^2NH + I_2 + CO \rightarrow (R^1R^2N)_2CO + 2HI$

(b) $ArNH_2 + I_2 + CO + R^1OH \rightarrow ArNHCO_2R^1 + 2HI$

We note that added base is essential for efficient carbonylation of aniline, yet strong base, such as NaOH, enhances competitive *p*-iodination of aniline, ultimately leading to 4-aminobenzoate. Prolonged stirring of aniline and I_2 with K_2CO_3 prior to addition of CO also gave substantial 4-aminobenzoate, but this side reaction could be suppressed by reducing the interval between addition of base and CO pressurization. In a typical procedure, palladium acetate (22 mg; 0.1 mmol), iodine (254 mg; 1.0 mmol), and K_2CO_3 (276 mg, 2.0 mmol) were placed in a pressure vessel. Aniline (92 mg; 1.0 mmol) was dissolved in methanol (10 mL), the solution was cooled to 0 °C, and it was added to the reaction vessel, which was then pressurized with CO at this temperature. The reaction mixture was then heated at 100 °C for about 30 min. Carbonylation was usually complete in less than 10 min, at which time Pd black precipitated.[5] The reaction mixture was cooled back to 0 °C, depressurized, filtered, and analyzed. Carbamate isolation was accomplished by distillative removal of the alcohol and extraction of the residue with ether. Iodine could be recovered by aqueous acidification, treatment with H_2O_2, and extraction. In an alternate route, aniline (92 mg, 1.0 mmol), palladium acetate (22 mg, 0.1 mmol), I_2 (76 mg, 0.3 mmol), and potassium percarbonate (344 mg, 1.0 mmol) were heated in methanol under CO, which also gave the urethane in good yield. In no case did carbonylation occur when the reaction mixture was charged with iodide, even under conditions where iodide is presumably oxidized to iodine rapidly *in situ*. Heterocyclic amines are less basic than aniline and are poorer nucleophiles. Nonetheless, 2-aminopyridine and 2-aminopyrimidine underwent rapid, high yield, Pd-catalyzed carbonylation to the corresponding carbamates under our standard conditions.

Scheme 2



Commonly accepted mechanistic proposals for amine carbonylation involve direct attack on a Pd(II)-coordinated CO ligand, but we believe the requirement for initial I_2 use belies this suggestion for our system. Instead, we propose that carbamate may be produced in our system by oxidative addition of an *N*-iodoamine intermediate to an *in situ* prepared, low-valent Pd species **1** to give an amido complex, **2** (Scheme 2). Significantly, when aniline was treated with I_2 under the carbonylation reaction conditions, but in the absence of Pd or O_2, azobenzene was produced (15%), consistent with the intermediate formation of *N*-iodoaniline.[6,7] Relative rates for amine carbonylation were determined by competition experiments: $p\text{-}Me_2NC_6H_4NH_2$ (4.8) > $p\text{-}MeOC_6H_4NH_2$ (2.5) > $C_6H_5NH_2$ (1.0) > $p\text{-}ClC_6H_4NH_2$ (0.4) > $p\text{-}MeO_2CC_6H_4NH_2$ (0.1). On the basis of studies involving formation of carbodiimides under similar circumstances,[8] it is unlikely that amine iodination is rate determining (the iodoamine might even be formed reversibly). We suggest either that the oxidative addition of the *N*-iodoamine is rate determining or that it can occur

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(1) (a) Fukuoka, S.; Chono, M.; Khono, M. *J. Chem. Soc., Chem. Commun.* **1984**, 399. (b) Fukuoka, S.; Chono, M.; Khono, M. *J. Org. Chem.* **1984**, *49*, 1458. (c) Fukuoka, S.; Chono, M.; Khono, M. *Chemtech* **1984**, 670.

(2) Gupte, S. P.; Chaudhari, R. V. *J. Catal.* **1988**, *114*, 246.

(3) Kanagasabapathy, S.; Thangaraj, A.; Gupte, S. P.; Chaudhari, R. V. *Catal. Lett.* **1994**, *25*, 361.

(4) Pri-Bar, I.; Alper, H. *Can. J. Chem.* **1990**, *68*, 1544.

(5) Carbonylation is apparently catalyzed by a homogeneous Pd species which decomposes to Pd black once the amine concentration decreases to *ca.* 5%. However, *p*-iodoaniline seems also to react with Pd black to give the aminobenzoate.

(6) Millar, I. T.; Springall, H. D. *A Shorter Sidgwick's Organic Chemistry of Nitrogen*; Clarendon Press: Oxford, 1969; p 102.

(7) *N*-Iodo derivatives of aromatic and heterocyclic amines are known. For example, see: (a) Lauransan, J.; Corset, J. *Ann. Chim. (Paris)* **1969**, *4*, 475. (b) Fratiello, A. *J. Chem. Phys.* **1964**, *41*, 2204.

(8) Pri-Bar, I.; Schwartz, J. Unpublished results.

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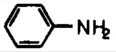
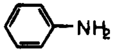
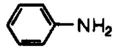
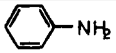
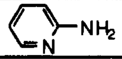
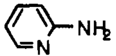
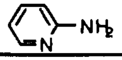
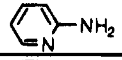
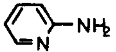
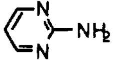
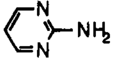
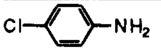
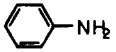
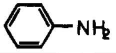
Table 1. Carbonylation of Amines

	Amine (1.0 mmol)	Alcohol (10 ml)	Promoter (mmol)	K_2CO_3 (mmol)	pCO (psi)	pO_2 (psi)	Yield[a] (%)
1		MeOH	KI (2.0)	(2.0)	50	30	NR
2		MeOH	I_2 (1.0)	(2.0)	50	---	74[b]
3		MeOH	I_2 (1.0)	NaOH (2.0)	50	---	trace[c]
4		MeOH	I_2 (0.3)	(1.0)[d]	50	---[d]	65[e]
5		EtOH	I_2 (1.0)	(2.0)	50	---	7
6		EtOH	I_2 (1.5)	(2.0)	40	10	90[f]
7		EtOH	I_2 (1.5)	---	40	10	24
8		EtOH	I_2 (0.1)	(0.2)	40	40	85
9		EtOH	I_2 (0.4)	(0.8)	40	10	66
10		MeOH	I_2 (1.0)	(2.0)	50	---	NR
11		MeOH	I_2 (0.1)	(0.2)	40	40	80[f]
12		MeOH	I_2 (1.0)	(2.0)	50	---	65
13		None[g]	I_2 (1.0)	(2.0)	50	---	NR
14	*n*-$BuNH_2$	MeOH	I_2 (1.0)	(2.0)	50	---	85
15	*tert*-$BuNH_2$	MeOH	I_2 (1.0)	(2.0)	50	---	35
16		MeOH	I_2 (1.0)	(2.0)[h]	50	---	0[i]

[a] Carbamate yields are based on amine and were determined by gc using authentic samples. [b] Methyl 4-aminobenzoate, 3%. [c] Methyl 4-aminobenzoate, 45%. [d] Potassium percarbonate (1.0 mmol) used. [e] Methyl 4-aminobenzoate, 15%. [f] Isolated yields. [g] 1,2-Dimethoxyethane was used as solvent. [h] No Pd complex was present. [i] Azobenzene, 15%.

reversibly to a Pd(0)(carbonyl) complex.[9] In this latter scheme (Scheme 2), migratory "insertion" of the amido ligand is rate determining: relative rates of insertion[10] *vs* reversion to starting materials would determine the overall success of the synthetic procedure. Urethane might be formed by *β*-hydride elimination in **3**, giving isocyanate which is then trapped by solvent.[11,12] Alternatively, **3** could undergo direct alcoholysis by solvent attack at the carbonyl group. Further studies of scope and mechanism of this new I_2-initiated route are now in progress.

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[9] For oxidative addition to a Pd(0) carbonyl, see: Cowell, A.; Stille, J. K. *Tetrahedron Lett.* **1979**, 133.

[10] For example, see: Sugita, N.; Minkiewicz, J. V.; Heck, R. F. *Inorg. Chem.* **1978**, *10*, 2809.

[11] Isocyanates can be formed by reaction between certain amines and CO in the presence of Pd(II) in an inert solvent. See: Henry, P. M. U. S. Patent 3,641,092, 1972; *Chem. Abstr.* **1972**, *76*, 141704.

[12] We also note that some dimethyl carbonate can be formed as a byproduct, which might arise by simple methanol carbonylation by Pd(II) species.