N,*N*-Dialkylcarbodiimide synthesis by palladium-catalysed coupling of amines with isonitriles

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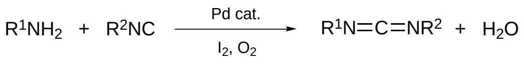
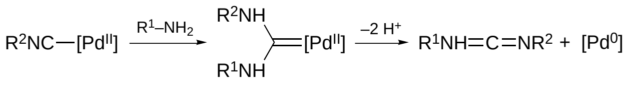
Catalytic condensation of amines and isonitriles can be accomplished efficiently at 100 °C using a palladium complex catalyst, oxygen, and iodine to give *N*,*N*-dialkylcarbodiimides.

We recently reported[1] that I_2 can promote the homogeneous carbonylation of amines to urethanes using a palladium complex catalyst in an alcohol,† and we suggested that an *N*-iodoamine intermediate was involved. Isonitriles are isoelectronic with carbon monoxide, and we now wish to report that amines will condense with isonitriles, under conditions similar to those noted for amine carbonylation, to give good yields of *N*,*N*-dialkylcarbodiimides. This I_2-promoted reaction provides an alternative to conventional syntheses of carbodiimides which are accomplished *via* phosgenation of thiourea,[2] thermal coupling of isocyanates (for which synthesis also entails phosgene),[3] or catalytic dehydration of ureas.[4] Furthermore, this new route, which uses O_2, seems advantageous compared with another palladium complex catalysed procedure that uses silver oxide as a stoichiometric oxidant.[5]

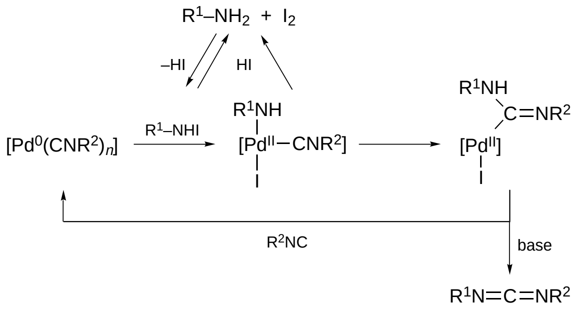


$$R^1NH_2 + R^2NC \xrightarrow[I_2,\ O_2]{\text{Pd cat.}} R^1N{=}C{=}NR^2 + H_2O$$

Scheme 1



Scheme 2



Scheme 3

In a typical procedure (Scheme 1), palladium acetate (22 mg, 0.1 mmol), iodine (50 mg, 0.2 mmol), and anhydrous sodium carbonate (320 mg, 3.0 mmol) were placed in a pressure vessel. Cyclohexylamine (0.11 ml, 1.0 mmol) and cyclohexyl isocyanide (0.1 ml, 0.8 mmol) were dissolved in acetonitrile (10 ml) and added to the reaction mixture which was then pressurized with O_2 (40 psi) and heated to 100 °C for 3 h. The initially deep-red reaction mixture turned yellow– orange; no Pd black precipitation was observed. (There was no obvious reaction rate dependence on O_2 pressure.) The mixture was cooled to ambient temperature, depressurized, filtered, and analysed by GC. Carbodiimide isolation was accomplished by evaporative removal of solvent and residual amine, followed by vacuum distillation. Representative results are given in Table 1.

As shown in Table 1, aliphatic amines give some carbodiimide when O_2 is used as the sole oxidizing reagent (entries 2, 7). This may derive from a process (Scheme 2) which is similar to that reported[5] for a palladium complex-catalysed carbodiimide synthesis *via* a palladium(ii) carbene complex; here, O_2 replaces Ag_2O as the oxidant. Indeed, the initial rate of carbodiimide synthesis increases with increasing O_2 pressure. However, in the absence of iodine, the carbodiimide product undergoes subsequent hydrolysis to the urea.

We have proposed[1] that oxidative addition of an *in situ* generated *N*-iodoamine intermediate to a low-valent palladium species occurs in the context of carbamate synthesis.‡ Donor substituents could contribute to the stability of such oxidized amine intermediates and, by concentration enhancement, favour overall reaction with Pd^0. Relative rates for amine carbonylation were: $p\text{-}Me_2NC_6H_4NH_2 > p\text{-}MeOC_6H_4NH_2 \gg PhNH_2 > p\text{-}ClC_6H_4NH_2 > p\text{-}MeO_2CC_6H_4NH_2$; aliphatic amines were

Table 1 Oxidative coupling of amines with isonitriles

Entry	Amine/mmol	Isonitrile/mmol	I_2/mmol	Yield[a]
1	$C_6H_{11}NH_2$ (1.4)	$C_6H_{11}NC$ (0.8)	(0.2)	67[b]
2	$C_6H_{11}NH_2$ (1.4)	$C_6H_{11}NC$ (0.8)	—	35[c]
3	$C_6H_{11}NH_2$ (1.4)	Me_3CNC (0.9)	(0.2)	41[5]
4	Me_3CNH_2 (1.4)	$C_6H_{11}NC$ (0.9)	(0.2)	46[5]
5	Me_3CNH_2 (19)	$C_6H_{11}NC$ (1.2)	(0.2)	76[5]
6	Me_3CNH_2[d] (38)	Me_3CNC (0.9)	(0.2)	86, 70[e]
7	Me_3CNH_2[d] (10)	Me_3CNC (0.9)	—	31[f]
8	$p\text{-}MeOC_6H_4NH_2$ (1.4)	$C_6H_{11}NC$ (0.9)	(0.2)	67[6]
9	Me_3CNH_2 (1.4) $n\text{-}C_4H_9NH_2$ (1.4)	Me_3CNC (0.9)	(0.2)	4 (sym)[g] 63 (asym)[g,5]

[a] Carbodiimide yield determined by GC; yield based on added isonitrile. [b] An unknown byproduct was also formed; no urea was produced. [c] Dicyclohexyl urea was also formed (10%) in the absence of I_2. [d] Reaction performed in neat amine. [e] No Na_2CO_3 added. [f] Di-*tert*-butyl urea was also formed (30%) in the absence of I_2. [g] Sym = *N*,*N*-di-*tert*-butylcarbodiimide; asym = *N*-*tert*-butyl-*N*-*n*-butylcarbodiimide.

the most reactive. Carbodiimide synthesis was slower than carbonylation for each amine investigated, and only aliphatic amines and *p*-methoxyaniline were especially reactive.[§] Highest yields of carbodiimide were realized when excess amine was employed (Table 1, entries 4, 5, 6). A mechanistic alternative for the I_2-enhanced pathway involves oxidative addition of the *N*-iodoamine to a palladium(0) isonitrile complex,[¶] which may be rate determining, or reversible. In this latter proposal (Scheme 3), migratory 'insertion' of the amido ligand[‖] could be rate determining, and relative rates for insertion[**] *vs*. reversion to the starting amine would contribute to the overall success of the synthetic procedure, as would the presence of base, such as carbonate or excess amine. The preferred formation of the asymmetrical carbodiimide from a mixture of *tert*-butylamine and *n*-butylamine and *tert*-butyl isocyanide (Table 1, entry 9) is likely sterically controlled.

Footnotes

[†] For example, palladium acetate (22 mg, 0.1 mmol), iodine (254 mg, 1.0 mmol), Na_2CO_3 (276 mg, 2.0 mmol), aniline (92 mg, 1.0 mmol), methanol (10 ml) 50 psi CO; 100 °C; 30 min yields methyl phenylcarbamate (74%).

[‡] Aniline treated with I_2 under carbonylation reaction conditions (ref. 1), but in the absence of Pd or O_2, gave azobenzene (15%), consistent with the intermediate formation of *N*-iodoaniline.

[§] A small amount of carbodiimide was produced, as determined by GC–MS, by reaction between *p*-$ClC_6H_4NH_2$ and $C_6H_{11}NC$.

[¶] For oxidative addition to $(RNC)_2Pd^0$, see L. Malatesta, *J. Chem. Soc*., 1955, 3924. Relative rate trends for oxidative addition of a series of *N*-iodoamines to either $(RNC)_2Pd^0$ or $Pd^0\,(CO)_n$ species could be similar.

[‖] Deprotonation of a palladium(ii)-coordinated amine to give an amido complex has been reported using strong bases such as disilylamide (J. Louie, F. Paul and J. F. Hartwig, *Organometallics*, 1996, **15**, 2794) or *tert*-butoxide (see, for example, R. A. Widenhoefer and S. L. Buchwald, *Organometallics*, 1996, **15**, 3534). No similarly strong base is present in the system described herein.

[**] The rate of alkyl group 'insertion' in a $Pd^{II}(RNC)$ complex increases with increasing nucleophilicity of the migrating carbon. See S. Otsuka and K. Ataka, *J. Chem. Soc., Dalton Trans*., 1976, 327. Relative rates for amido group insertion might also follow this trend.

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