Nickel(II)-Catalyzed Synthesis of Unsymmetrical Carbodiimides Using Molecular Oxygen as an Oxidant from Isocyanides and Primary Amines

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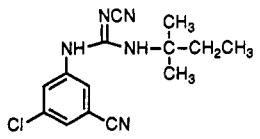
In the course of our studies of a practical synthesis of the antihypertensive drug 1, a general and convenient preparation of *N,N'*-disubstituted carbodiimides **2** was achieved by the nickel(II)-catalyzed reaction of isocyanides with primary amines, using oxygen gas as an oxidant. A palladium(0)/oxygen catalytic system was also useful, giving **2** in good yield, although palladium(II) was inert. A variety of metal oxides and organic peroxides were not effective as the oxidant in the carbodiimide synthesis, with the exception of Ag_2O and HgO. The present synthesis of carbodiimides was applicable to the preparation of *N*-(3-chloro-5-cyanophenyl)-*N'*-*tert*-pentylcarbodiimide (**2a**), a precursor of the antihypertensive drug 1.

Recently, we found that a series of cyanoguanidine derivatives that bear an electron-withdrawing aryl group and a bulky alkyl group have a pronounced vasodilative effect[1] on vascular smooth muscle cells which is based upon potassium channel opening activity.[2] Among them, *N*-(3-chloro-5-cyanophenyl)-*N'*-cyano-*N''*-*tert*-pentylguanidine (1) displays strong activity and minimal side effects. We selected 1 as a hypertensive treatment target and began an investigation of its synthesis.



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Although cyanoguanidine derivatives can be easily prepared from the corresponding carbodiimides,[3] the methods available for the synthesis of unsymmetrical carbodiimides are limited. Most are unapplicable to industrial-scale synthesis due to their high cost and use of toxic reagents and/or complicated procedures.[4,5]

In this paper, we report a general and practical synthesis of *N,N'*-disubstituted carbodiimide from a primary amine and isocyanide using a Ni(II) catalyst and molecular oxygen.

Results and Discussion

Ito *et al.* achieved the synthesis of carbodiimide by the reaction of a primary amine and isocyanide in the presence of a Pd(II) catalyst, a dehydrating agent (molecular sieves or anhydrous Na_2SO_4), and the oxidant Ag_2O (eq 1).[5] This

$$R^1NH_2 + CNR^2 + Ag_2O \xrightarrow[\text{dehydrating agent}\\ \text{benzene}]{\text{10 mol \% } PdCl_2} R^1N{=}C{=}NR^2 + H_2O + 2Ag \quad (1)$$

reaction represents a general preparative method for carbodiimides. Indeed, by using this method, *N*-(3-chloro-5-cyanophenyl)-*N'*-*tert*-pentylcarbodiimide (**2a**), a precursor of 1, was obtained in 83% yield. However, we wished to find less expensive reagents to use in place of $PdCl_2$ and Ag_2O for the industrial synthesis of **2a**.

The synthesis of *N,N'*-disubstituted carbodiimides with a new catalytic system $NiCl_2(II)/O_2$ is summarized in Table I. When 3-amino-5-chlorobenzonitrile (**3a**) was treated in benzene with *tert*-pentyl isocyanide (**4a**) in the presence of 10 mol % of $NiCl_2$ and 4A molecular sieves while O_2 bubbled through the reaction mixture, the coupling reaction proceeded at reflux temperature to afford carbodiimide **2a** in 62% yield (entry 1). It is noted that bubbling air instead of O_2 gas through the $NiCl_2$-catalyzed reaction mixture furnished **2a** in 67% yield (entry 2). One atm of O_2 or air suffices for this reaction. $NiCl_2(PPh_3)_2$ afforded **2a** in good yield as well (entry 3). Bidentate phosphines such as 1,3-bis(diphenylphosphino)propane (dppp) and 1,2-bis(diphenylphosphino)ethane (dppe), however, inactivated the Ni(II) catalyst to afford **2a** in only 4-6% yield.

In contrast to Ni(II), Pd(II) was a relatively poor catalyst: $PdCl_2$ and $PdCl_2(PPh_3)_2$ gave **2a** in only 9 and 5% yield, respectively. On the other hand, Pd(0), which is known to form a peroxo complex with molecular oxygen,[6] afforded **2a** in 61% yield (entry 4).

Unlike the case with Ag_2O, 2.4-3.0 molar equiv of the isocyanide **4a** was required in the Ni or Pd/O_2 system

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(1) (a) Morita, T.; Yoshiizumi, K.; Nishimura, N.; Goto, K.; Sukamoto, T.; Yoshino, K. Japanese Patent 31250, 1991. Independently, similar studies were reported by other laboratories. (b) Atwal, K. S.; McCullough, J. R.; Grover, G. J. Eur. Patent Appl. EP 354553, 1990. (c) Evans, J. M.; Stemp, G.; Hadley, M. S. Eur. Patent Appl. EP 392802, 1990.

(2) Recent reviews on potassium channel openers: (a) Robertson, D. W.; Steinberg, M. I. *J. Med. Chem.* **1990**, *33*, 1529. (b) Longman, S. D.; Hamilton, T. C. *Med. Res. Rev.* **1992**, *12*, 73.

(3) Petersen, H. J. *J. Med. Chem.* **1978**, *21*, 773.

(4) Generally, carbodiimides are prepared by the desulfurization of *N,N'*-disubstituted thioureas. However, toxic reagents such as HgO, PbO, and phosgene[1c] are often used for the desulfurization. (a) Schmidt, E.; Striewsky, W.; Hitzler, F. *Ann.* **1948**, *560*, 222. (b) Kurzer, F.; Douraghi-Zadeh, K. *Chem. Rev.* **1967**, *67*, 107. Moreover, isothiocyanate, a precursor of thiourea, is synthesized from a primary amine and thiophosgene, which is a highly toxic reagent (see ref 1a,c).

(5) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1975**, *40*, 2981.

(6) Valentine, J. S. *Chem. Rev.* **1973**, *73*, 235.

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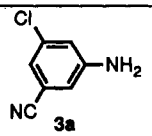
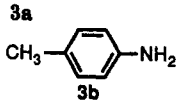
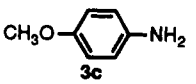
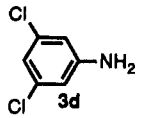
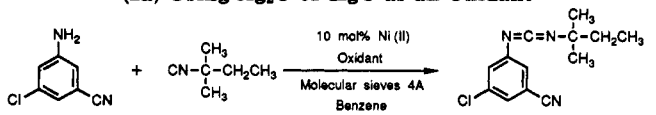
Table I. Nickel- or Palladium-Catalyzed Synthesis of Carbodiimides Using O_2 as an Oxidant[a]

$$R^1NH_2 \ (3) + CNR^2 \ (4) \xrightarrow[\text{dehydrating agent (molecular sieves 4A or } Na_2SO_4)]{\text{10 mol \% catalyst, } O_2 \text{ or air, benzene}} R^1N{=}C{=}NR^2 \ (2)$$

entry	amine	isocyanide	catalyst	4/3	oxidant	product	yield,[b] %
1	 **3a**	$CNC(CH_3)_2CH_2CH_3$ **4a**	$NiCl_2$	2.4	O_2	**2a**	(62)
2	**3a**	**4a**	$NiCl_2$	3.0	air	**2a**	65 (67)
3	**3a**	**4a**	$NiCl_2(PPh_3)_2$	2.4	O_2	**2a**	(67)
4	**3a**	**4a**	$Pd(PPh_3)_4$	3.0	O_2	**2a**	55 (61)
5	 **3b**	**4a**	$NiCl_2$	2.0	O_2	**2b**	88
6	 **3c**	**4a**	$NiCl_2$	1.4	O_2	**2c**	77
7[c]	 **3d**	$CNC(CH_3)_3$ **4b**	$NiCl_2$	3.0	O_2	**2d**	43
8	n-$C_7H_{15}NH_2$ **3e**	**4a**	$NiCl_2$	1.2	O_2	**2e**	71

[a] General conditions: **3** (10.0 mmol), catalyst (10.0 mol %), O_2 or air (1.0 atm), molecular sieves 4A (3.0 g) (except for entry 7) in benzene (25–30 mL), at the reflux temperature for 1.0–3.0 h. [b] Isolated yields. The values in parentheses are the GC yields based on an internal standard. [c] Anhydrous Na_2SO_4 (1.0 g) was used as a dehydrating agent.

Table II. The Ni(II)-Catalyzed Synthesis of Carbodiimide (2a) Using Ag_2O or HgO as an Oxidant



3a **4a** **2a**

entry	catalyst	oxidant	yield,[a] %
1	$NiCl_2$	Ag_2O	86 (84)
2	$NiCl_2(PBu_3)_2$	Ag_2O	(89)
3	$NiCl_2$dppp	Ag_2O	(85)
4	$NiCl_2$dppe	Ag_2O	(73)
5	$NiCl_2(PBu_3)_2$	HgO	(69)

[a] Isolated yield. The values in parentheses are the GC yields based on an internal standard.

because of the concurrent oligomerization[7] of **4a**. It was more effective to add isocyanide in two or three portions during the course of the reaction in order to avoid the oligomerization.

The present method is applicable to the synthesis of aromatic and aliphatic unsymmetrically *N,N'*-disubstituted carbodiimides. In particular, aniline derivatives bearing electron-donating groups such as *p*-toluidine and *p*-anisidine afforded the corresponding carbodiimides in good yields (entries 5 and 6). An unsymmetrical *N,N'*-dialkylcarbodiimide was obtained by the reaction of a primary alkylamine with an alkyl isocyanide (entry 8). In these cases, no significant oligomerization of isocyanide was observed, and accordingly the amount of isocyanide used could by diminished.

Although O_2 is a most attractive oxidant in the present carbodiimide synthesis, the use of a stoichiometric amount of Ag_2O and HgO in combination with $NiCl_2$ or $NiCl_2$ phosphine complexes also afforded **2a** in good yield (Table II). Noteworthy is that the bidentate phosphine scarcely inactivated the $NiCl_2/Ag_2O$ catalytic system. However, some other metal oxides and organic peroxides were disappointing.[8]

A mechanistic study of the present Ni(II)-catalyzed synthesis of carbodiimide using O_2 has not yet been carried out. Based upon the mechanism proposed for the previously reported Pd(II)-catalyzed synthesis of carbodiimides,[5] a mechanism involving an oxonickel(II) carbene complex as a key intermediate can be proposed.

Finally, carbodiimides bearing electron-withdrawing aryl groups were easily converted to the corresponding cyanoguanidine derivatives (eq 2), which have remarkable

$$R^1N{=}C{=}NR^2 + H_2NCN \xrightarrow[\text{DMF}]{\text{cat. } i\text{-Pr}_2\text{EtN}} R^1NH{-}C(=NCN){-}NHR^2 \quad (2)$$

1 65%
R^1 = 3-chloro-5-cyanophenyl, R^2 = *tert*-pentyl
5 55%
R^1 = 3,5-dichlorophenyl, R^2 = *tert*-butyl

vasodilative action.[1a] For instance, the treatment of **2a** with cyanamide using a catalytic amount of *i*-Pr_2EtN in DMF gave **1** in 65% yield after recrystallization. *N*-*tert*-Butyl-*N'*-cyano-*N''*-(3,5-dichlorophenyl)guanidine (**5**) was obtained from **2d** in the same manner.

In summary, a number of unsymmetrical carbodiimides can be synthesized by the reaction of primary amines with isocyanides in the presence of a Ni(II) catalyst and molecular oxygen. This reaction represents a convenient

(7) Nolte, R. J. M.; Zwikker, J. W.; Reedijk, J.; Drenth, W. *J. Mol. Catal.* **1978**, *4*, 423.

(8) Though a number of oxidants such as CuO, PbO, RuO_2, Ni_2O_3, V_2O_5, *t*-BuOOH, and *m*-CPBA were examined, these reagents did not afford the carbodiimide efficiently.

and inexpensive synthesis of **2a**, a precursor of antihypertensive drug **1**.

Experimental Section

3-Chloro-5-aminobenzonitrile (**3a**),[9] *tert*-pentyl isocyanide (**4a**),[10] and $NiCl_2(PPh_3)_2$[11] were prepared according to literature procedures. *tert*-Pentyl isocyanide (**4a**) was prepared in benzene and used for the synthesis of carbodiimides as an azeotropic mixture with benzene. The concentration of **4a** was measured by ^1H NMR integration. Other amines, catalysts, oxidants, and *tert*-butyl isocyanide were commercially available materials. The structures of all compounds were supported by their IR (Hitachi 270-50) and 300-MHz ^1H NMR (Bruker AM 300) spectra. Cyanoguanidine derivatives **1** and **5** and carbodiimide **2e**[12] were analyzed for C, H, N, and the results were within 0.4% of the calculated theoretical values. Melting points were taken on a capillary melting point apparatus (Büchi 535).

Preparation of *N*-(3-Chloro-5-cyanophenyl)-*N'*-*tert*-pentylcarbodiimide (2a) Using 10 mol % of $NiCl_2$ and Air. To a solution of 583 mg (6.00 mmol) of *tert*-pentyl isocyanide (**4a**) in benzene (5.0 mL) were added 3-amino-5-chlorobenzonitrile (**3a**) (763 mg, 5.00 mmol), $NiCl_2$ (65 mg, 0.50 mmol), and 1.5 g of molecular sieves 4A. The mixture was refluxed for 20 min with air bubbling through it. Then, to the reaction mixture was added a solution of 583 mg (6.00 mmol) of *tert*-pentyl isocyanide (**4a**) in benzene (5.0 mL), and the mixture was refluxed for 30 min. Next, a solution of 291 mg (3.00 mmol) of *tert*-pentyl isocyanide (**4a**) in benzene (2.5 mL) was added, and the mixture was again refluxed for 30 min. Throughout, air was bubbled through the mixture. After being cooled to room temperature, the mixture was filtered and the filtrate was concentrated. The resulting residue was purified by distillation to give **2a** as a brown oil (Kugelrohr, bp 200–230 °C (0.2 mmHg) 806 mg, 65% yield): IR (neat) 2976, 2240, 2152, 1574, 858 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (t, J = 7.2 Hz, 3 H), 1.39 (s, 6 H), 1.65 (q, J = 7.2 Hz, 2H), 7.15–7.35 (m, 3H).

Preparation of *N*-(4-Methylphenyl)-*N'*-*tert*-pentylcarbodiimide (2b). To a solution of 1.17 g (12.0 mmol) of *tert*-pentyl isocyanide (**4a**) in benzene (10.0 mL) were added *p*-toluidine (**3b**) (1.07 g, 10.0 mmol), $NiCl_2$ (130 mg, 1.00 mmol), and 3.0 g of molecular sieves 4A. The mixture was refluxed for 30 min while O_2 bubbled through the mixture. To the reaction mixture was added a solution of 777 mg (8.00 mmol) of *tert*-pentyl isocyanide (**4a**) in benzene (7.5 mL), and the mixture was refluxed for 30 min. Again, O_2 was bubbled through the mixture. After being cooled to room temperature, the mixture was filtered and the filtrate was concentrated. The resulting residue was purified by column chromatography (cyclohexane/ethyl acetate = 50/1 (v/v)) to afford **2b** as a brown oil (1.79 g, 88% yield): IR (neat) 2976, 2112, 1516, 816 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3 H), 1.33 (s, 6 H), 1.60 (q, J = 7.4 Hz, 2 H), 2.29 (s, 3 H), 6.98 (d, J = 8.3 Hz, 2 H), 7.08 (d, J = 8.3 Hz, 2 H).

Carbodiimides **2c–2e** were similarly prepared.

***N*-(4-Methoxyphenyl)-*N'*-*tert*-pentylcarbodiimide (2c).** A brown oil: IR (neat) 2972, 2112, 1514, 832 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (t, J = 7.4 Hz, 3 H), 1.34 (s, 6 H), 1.60 (q, J = 7.4 Hz, 2 H), 3.77 (s, 3 H), 6.82 (d, J = 8.9 Hz, 2 H), 7.02 (d, J = 8.9 Hz, 2 H).

***N*-*tert*-Butyl-*N'*-(3,5-dichlorophenyl)carbodiimide (2d).** A brown oil: IR (neat) 2976, 2152, 1194, 908, 842 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 6.94 (d, J = 1.9 Hz, 2 H), 7.08 (t, J = 1.9 Hz, 1 H).

***N*-*n*-Heptyl-*N'*-*tert*-pentylcarbodiimide (2e).** A colorless oil: IR (neat) 2968, 2928, 2128, 1464 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 6.9 Hz, 3 H), 0.93 (t, J = 7.4 Hz, 3 H), 1.23 (s, 6 H), 1.25–1.40 (m, 8 H), 1.50 (q, J = 7.4 Hz, 2 H), 1.50–1.65 (m, 2 H), 3.19 (t, J = 6.9 Hz, 2 H). Anal. Calcd for $C_{13}H_{26}N_2$: C, 74.23; H, 12.46; N, 13.32. Found: C, 74.39; H, 12.57; N, 13.14.

Preparation of *N*-(3-Chloro-5-cyanophenyl)-*N'*-*tert*-pentylcarbodiimide (2a) using 10 mol % of $NiCl_2$ and Ag_2O. To a solution of 2.11 g (21.7 mmol) of *tert*-pentyl isocyanide (**4a**) in benzene (35 mL) were added 3-amino-5-chlorobenzonitrile (**3a**) (2.76 g, 18.1 mmol), $NiCl_2$ (235 mg, 1.81 mmol), 6.6 g of molecular sieves 4A, and Ag_2O (4.19 g, 18.1 mmol), and the mixture was refluxed for 1 h. After being cooled to room temperature, the mixture was filtered and the filtrate was concentrated. The resulting residue was column chromatographed on silica gel (cyclohexane/ethyl acetate = 10/1 (v/v)) to afford **2a** as a brown oil (3.86 g, 86% yield).

Preparation of *N*-(3-chloro-5-cyanophenyl)-*N'*-cyano-*N''*-*tert*-pentylguanidine (1). Diisopropylethylamine (319 mg, 2.47 mmol) was added to a mixture of **2a** (7.5 g, 30.3 mmol) and cyanamide (6.5 g, 154 mmol) in DMF (40 mL), and the solution was stirred at 90–95 °C for 2 h. After being cooled to room temperature, the solution was poured into 400 mL of water. The resulting precipitates were collected and purified by recrystallization from ethanol to give **1** as colorless crystals (5.7 g, 65% yield): mp 181.0–183.0 °C; IR (KBr) 3316, 2246, 2168, 1598, 874 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.83 (t, J = 7.4 Hz, 3 H), 1.29 (s, 6 H), 1.70 (q, J = 7.4 Hz, 2H), 7.29 (bs, 1H), 7.40–7.50 (m, 2 H), 7.60–7.70 (m, 1 H), 9.43 (bs, 1 H). Anal. Calcd for $C_{14}H_{16}ClN_5$: C, 58.03; H, 5.57; N, 24.17. Found: C, 58.06; H, 5.55; N, 24.19.

Cyanoguanidine derivative **5** was similarly prepared by the above procedure.

***N*-*tert*-Butyl-*N'*-cyano-*N''*-(3,5-dichlorophenyl)guanidine (5).** Colorless crystals: mp 191.0–192.5 °C; IR (KBr) 3284, 2164, 1574, 842 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (s, 9 H), 7.09 (d, J = 1.7 Hz, 2 H), 7.25 (t, J = 1.7 Hz, 1 H), 7.39 (bs, 1 H), 9.29 (bs, 1 H). Anal. Calcd for $C_{12}H_{14}Cl_2N_4$: C, 50.54; H, 4.95; N, 19.65. Found: C, 50.58; H, 4.96; N, 19.57.

Supplementary Material Available: ^1H NMR (300 MHz) spectra of **2a–2d** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Mahood, S. A.; Schaffner, P. V. L. *Organic Synthesis*; John Wiley and Sons, Inc.: New York, 1943; Collect. Vol. II, p 160.

(10) Ugi, I.; Meyr, R. *Organic Synthesis*, John Wiley and Sons, Inc.: New York, 1973; Collect. Vol. V, p 1060.

(11) Cotton, F. A.; Faut, O. D.; Goodgame, D. M. L. *J. Am. Chem. Soc.* **1961**, *83*, 344.

(12) The purities of other carbodiimides that are too sensitive to moisture to be analyzed were confirmed by the ^1H NMR spectra.