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Conversion of primary amines to carbamate esters using palladium chloride and di-tert-butyl peroxide. Double carbonylation of secondary amines

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Registry No. PhC≡CPh, 501-65-5; $CH_3O_2CC{\equiv}CCO_2CH_3$, 762-42-5; $C_2H_5C{\equiv}CC_2H_5$, 928-49-4; $HO(CH_3)_2CC{\equiv}CC(CH_3)_2OH$, 142-30-3; $PhC{\equiv}CCH(OC_2H_5)_2$, 6142-95-6; $(C_2H_5O)_2CHC{\equiv}CCH(OC_2H_5)_2$, 3975-08-4; $PhC{\equiv}CCO_2CH_3$, 4891-38-7; (azobenzene–C^2,*N*)$Pd(CH_3CN)_2{}^+BF_4{}^-$, 110294-93-4; (azotoluene-C^2,*N*)$Pd(CH_3NO_2)_2{}^+BF_4{}'$, 110294-95-6; 2,3,4-triphenylcinolinium tetrafluorobroate, 103905-36-8; 3,4-bis(methoxycarbonyl)-2-phenylcinolinium tetrafluoroborate, 103905-40-4; 3,4-diethyl-2-phenylcinolinium tetrafluoroborate, 103905-38-0; 2-phenyl-3,4-(1,1,3,3-tetramethyl-2-oxa-1,3-propanediyl)cinolinium tetrafluoroborate, 110294-97-8; 4-(diethoxymethyl)-2,3-diphenylcinolinium tetrafluoroborate, 110313-44-5; 3,4-bis(diethoxymethyl)-2-phenylcinolinium tetrafluoroborate, 110294-99-0; 2,4-diphenyl-3-(methoxycarbonyl)cinolinium tetrafluoroborate, 110295-01-7; 3,4-diphenyl-6-methyl-2-(4-methylphenyl)cinolinium tetrafluoroborate, 110295-03-9; 3,4-diethyl-6-methyl-2-(4-methylphenyl)cinolinium tetrafluoroborate, 110295-05-1; bis(μ-chloro)bis(azobenzene-C^2,*N*)dipalladium (II), 14873-53-1; (azobenzene-C^2,*N*)$PdnCH_3NO_2)_2{}^+BF_4{}^-$, 110295-07-3; 2,3-diphenyl-1-butene, 22875-84-9; 3-phenyl-1-propene, 300-57-2; 1-phenyl-1-propene, 637-50-3; styrene, 100-42-5; methylacrylate, 96-33-3; phenylacetylene, 536-74-3; bis(trimethylsilyl)acetylene, 14630-40-1; benzenediazoniumcarboxylate, 1608-42-0.

Supplementary Material Available: Figures 1, 2, and 3 showing the structures of 1,2,3-triphenylcinnolinium tetrafluoroborate (I), 2,3-diphenyl-3-(diethoxymethyl)cinnolium tetrafluoroborate (II), and methyl 2,4-diphenylcinnolinium-3-carboxylate tetrafluoroforate (III), respectively, crystallographic data for compounds I–III, tables containing atomic coordinates and isotropic thermal parameters (Tables 1s, 7s, and 13s), bond lengths (Tables 2s, 8s, and 14s), bond angles (Tables 3s, 9s, and 15s), and hydrogen atom coordinates (Tables 5s, 11s, and 16s) for compounds I–III, and tables of anisotropic thermal parameters (Tables 4s and 10s) for compounds I and II (18 pages); listings of observed and calculated structure factors for compounds I–III (Tables 6s, 12s, and 17s) (31 pages). Ordering information is given on any current masthead page.

Conversion of Primary Amines to Carbamate Esters Using Palladium Chloride and Di-*tert*-butyl Peroxide. Double Carbonylation of Secondary Amines

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Primary aliphatic and aromatic amines react with carbon monoxide and di-*tert*-butyl peroxide in alcohol, catalyzed by palladium and copper chlorides, to give carbamate esters in good yields; double carbonylation to oxamate esters, using the peroxide or oxygen, resulted in the case of secondary amines.

In 1985, we described the reaction of primary aromatic amines with carbon monoxide, oxygen, alcohol, hydrochloric acid, cupric chloride, and palladium chloride as the catalyst to give the carbamate ester in 16–99% yield.[2] While this reaction occurs at room temperature and atmospheric pressure, it is too slow to be commercially viable, while the use of elevated pressures is unsafe due to the explosive nature of mixtures of carbon monoxide and oxygen. Also, an undesirable side reaction, associated with the coproduction of water, is the conversion of carbon monoxide to carbon dioxide. Therefore, an effort was made to utilize a substitute for oxygen in this process. Recently, di-*tert*-butyl peroxide was found to be effective for the palladium- and copper-catalyzed oxidative carbonylation of methanol to dimethyl oxalate and dimethyl carbonate.[3] We now wish to report (i) that this peroxide is very useful, as an oxygen substitute, in the conversion of both aliphatic and aromatic primary amines to carbamate esters, (ii) that ureas are the principal products at elevated temperatures and pressures, and (iii) that with either oxygen or di-*tert*-butyl peroxide, secondary amines afford products resulting from a novel double as well as monocarbonylation reaction.

Methyl cyclohexylcarbamate (**2**, R = C_6H_{11}, R′ = H, R″ = CH_3) was obtained in 86% yield when cyclohexylamine was carbonylated in methanol by using palladium chloride as the catalyst, hydrochloric acid, di-*tert*-butyl peroxide, and copper(II) chloride at room temperature and 1-atm pressure.

$$\underset{\mathbf{1}}{RR'NH} + CO + R''OH \xrightarrow[{[(CH_3)_3CO]_,\ \text{acid, room temp, 1 atm}}]{PdCl_2,\ CuCl_2} \underset{\mathbf{2}}{RR'NCOOR''} + \underset{\mathbf{3}}{RR'NCOCOOR''}$$

The yield of ester was 17% when the reaction was repeated in the absence of the peroxide while 18% carbamate ester resulted in the absence of acid (but the peroxide was present). Another effective acid was tetrafluoroboric acid, and even the Lewis acid born trifluoride could be used in this reaction. The optimum ratio of substrate/$[(CH_3)_3CO]_2/CuCl_2/PdCl_2$ for these reactions is 5.0/5.0/1.0/0.5, and 1–2 drops of acid were used in all cases.

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[1] Killam Research Fellow, 1986–1988.

[2] Alper, H.; Hartstock, F. W. *J. Chem. Soc., Chem. Commun.* **1985**, 1141.

[3] Morris G.; Oakley, D.; Pippard, D. A.; Smith, D. J. H. *J. Chem. Soc., Chem. Commun.* **1987**, 410, 411.

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Table I. Reaction of Primary Amines with CO/O_2 or $[(CH_3)_3CO]_2/PdCl_2/CuCl_2$/Acid/Alcohol[a]

amine	O_2 (A) or $[(CH_3)_3CO]_2$ (B)	acid	alcohol	yield of 2,[b,c] %
$C_6H_{11}NH_2$	B	HCl	CH_3OH	86
		HCl	CH_3OH	17
	B		CH_3OH	18
$C_{12}H_{25}NH_2$	B	HCl	CH_3OH	79
	B	HBF_4	CH_3OH	72
	B	BF_3	CH_3OH	70
	A	HCl	CH_3OH	99
	A	HCl	C_2H_5OH	99
	A	HCl	$(CH_3)_3COH$	81
	A		$(CH_3)_3COH$	64
n-$C_4H_9NH_2$	B	HBF_4	CH_3OH	88
	A	HCl	CH_3OH	96
	A	HCl	$(CH_3)_3COH$	66
t-$C_4H_9NH_2$	A	HCl	CH_3OH	98
	A	HCl	$(CH_3)_3COH$	40
$PhCH_2NH_2$	B	HCl	CH_3OH	42
	B	HBF_4	CH_3OH	81
	B	BF_3	CH_3OH	85
$PhNH_2$	B	HCl	CH_3OH	60[d]
	B	BF_3	CH_3OH	67
	B	HBF_4	CH_3OH	56
	B		CH_3OH	19
p-$CH_3OC_6H_4NH_2$	B	HCl	CH_3OH	68[e]
2,6-$(CH_3)_2C_6H_3NH_2$	B	HCl	CH_3OH	30[e]

[a] Conditions: amine, 5.0 mmol; $[(CH_3)_3CO]_2$, 5.0 mmol (or O_2); acid, 1–2 drops; $PdCl_2$, 0.5 mmol; $CuCl_2$, 1.0 mmol; alcohol, 60 mL; room temperature, 1 atm. [b] See ref 2 for yields obtained from the $ArNH_2/CO/O_2$ reaction. [c] Physical data [i.e., mp or bp, IR, NMR (^1H, ^{13}C), MS] were in accord with literature results. [d] 38% using CuCl instead of $CuCl_2$. [e] 2.0 mmol of $CuCl_2$.

Table II. Reaction of Secondary Amines with CO/O_2 or $[(CH_3)_3CO]_2/PdCl_2/CuCl_2/HCl/CH_3OH$[a]

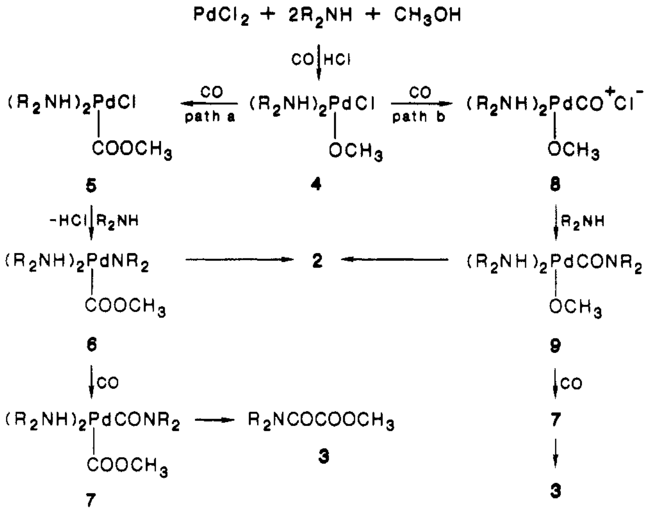
amine	O_2 (A) or $[(CH_3)_3CO]_2$ (B)	O_2/CO ratio	products,[b] % 2	3
$(C_6H_{11})_2NH$	A	2	2	25
	A	3	11	7
	A	4	20	6
	A	0.2	6	16
$C_6H_{11}NHCH_3$	A	2	12	4
	B		17	43
$(C_2H_5)_2NH$	A	2	44	14[c]
$(i$-$C_3H_7)_2NH$	A	2	31	6
	B		20	35
$(i$-$C_4H_9)_2NH$	B		32	27
piperidine	A	2	16	12
	B		64	16

[a] Conditions: amine, 5.0 mmol; $[(CH_3)_3CO]_2$, 5.0 mmol (or O_2); $PdCl_2$, 0.5 mmol; $CuCl_2$, 1.0 mmol; HCl, 0.1 mmol; CH_3OH, 60 mL. [b] Products were identified by comparison of spectral results with literature data and/or by independent synthesis. [c] 2 and 3 were obtained in 49% and 8% yields, respectively, using $(C_2H_5)_2NH/PdCl_2/CuCl/LiCl/[(CH_3)_3CO]_2/CH_3OH$ at 90 °C and 5.9 atm for 3.5 h.

Carbamate esters were obtained in good yields from either primary aliphatic or aromatic amines, and the results are listed in Table I (yields are also reported for aliphatic primary amines using oxygen—not described previously). Note that, unlike aromatic amines and oxygen, acid is beneficial but not essential in the case of primary aliphatic amines. Di-*tert*-butyl peroxide is also useful when primary aliphatic amines are employed as reactants.

Elevated temperatures and pressures have a significant influence on the reaction of aromatic but not aliphatic amines (e.g., n-butylamine still affords the carbamate ester as the main product at 7–8 atm and 92 °C). For example, aniline reacts with cuprous chloride, palladium chloride, and an equimolar amount of di-*tert*-butyl peroxide in methanol at 8.9 atm and 78 °C for 2 h, to give diphenylurea (carbanilide) in 56% yield and N-phenylmethylcarbamate in 6% yield. Only diphenylurea is formed (50% yield) if the reaction is repeated in the presence of added lithium chloride for 2.5 h. However, after a reaction time of 15.5 h, the urea was isolated in 88% yield and **2**, R = Ph, R′ = H, R″ = CH_3, was obtained in 6% yield, and some dimethyl carbonate formation was detected. Note that little or no carbonate ester of the solvent alcohol is produced until all the amine has been consumed.

Scheme I

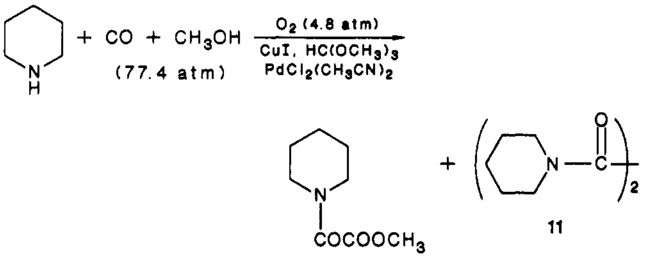


Extension of the carbonylation reaction to secondary amines using either di-*tert*-butyl peroxide or oxygen afforded not only the carbamate ester **2** but also the oxamate ester **3**, arising from a novel double carbonylation reaction. Varying amounts of **2** and **3** were isolated, depending on the nature of the substrate (Table II). Although amines containing relatively bulky R groups do give appreciable quantities of the oxamic acid ester, one cannot attribute the results to steric effects alone. Also, the ratio of **2**/**3** is quite different when one compares the results obtained by using oxygen with di-*tert*-butyl peroxide. Furthermore the product ratio, in the case of oxygen, is sensitive to the proportion of O_2/CO (see results for dicyclohexylamine) with the oxamate most favored by using a 2/1 O_2/CO ratio.

These results, together with those reported earlier for the oxidative carbonylation of methanol with di-*tert*-butyl peroxide,[3] are consistent with carbonylation occurring mainly at a palladium center while copper activates the peroxide (formation of a copper alkoxide intermediate) and reoxidizes the palladium.

A possible mechanism to account for the role of palladium in the conversion of amines to **2** and **3** is outlined in Scheme I (illustrated for a secondary amine and methanol). Interaction of the amine, alcohol, palladium chloride, and acid may generate the chloroalkoxypalladium compound **4**. Insertion of carbon monoxide (CO binding to Pd followed by ligand migration—path a) would give **5** which, on reaction with additional amine, affords **6**. Reductive elimination from **6** would generate the carbamate ester **2**. An alternative pathway (path b) for formation of **2** involves CO displacement of chloride **8**, followed by reaction with amine to give **9** and then reductive elimination. The oxamate ester **3** can arise by CO insertion into either **6** or **9** to give **7** and subsequent reductive elimination. It is conceivable that the conversion of **6** to **7** is assisted by the presence of a bulky R_2 unit. It is not obvious why **9**, if formed, should afford only **2** in the case of a primary amine and **2** and **3** when a secondary amine is used as the substrate. In the case of the CO/O_2 reaction, use of greater than a 2/1 ratio of O_2/CO gives the carbamate ester as the major product, and this may be a consequence of oxygen retarding CO insertion into **6** (but not **4**). Note that most of the steps in paths a and b (e.g., **6** → **7** → **3**; **8** → **9**) are analogous to mechanisms proposed for the double carbonylation of halides to α-keto amides.[4-8]

There has been considerable interest in recent years in the palladium complex catalyzed double carbonylation of halides to α-keto amides, acids, and esters.[4-8] α–Keto amides are obtained in good yields when quite bulky amines such as di-*n*-propylamine are used, but only monocarbonylation occurs for diisopropylamine or diisobutylamine. Finally, a recent report described the reaction of piperidine with a catalytic amount of $PdCl_2(CH_3CN)_2$, cuprous iodide, trimethyl orthoformate, carbon monoxide, and oxygen to give the oxamate **10** in 29% yield and 1,1′-oxalyldipiperidine (**11**) in 44% yield. However, a very high pressure of carbon monoxide (77.4 atm or 80 kg/cm²) is required, while no double carbonylation occurs with 1/1 CO/O_2 (1 atm).[9]



10 **11**

In conclusion, while this research raises a number of questions concerning the mechanism of the above reactions [e.g., what is the precise role of acid, O_2, and $((CH_3)_3CO)_2$?], the following significant findings have resulted from this work: (i) di-*tert*-butyl peroxide can be employed as an oxygen substitute for the conversion of primary amines to carbamate esters in good yields; (ii) Lewis or protonic acids can be used in these reactions; (iii) with oxygen or the peroxide, secondary amines afford both carbamate and oxamate esters (albeit in modest yields), the latter arising from a double carbonylation reaction. This approach to the synthesis of carbamate esters is superior to others[10] in terms of mildness and simplicity, and the oxamate ester preparation compares favorably with the alkyloxalyl chloride–amine reaction.

Experimental Section

General Data. All of the chemicals used were purchased from commercial suppliers and were used as received. Gas chromatographic determinations were made on a Varian Vista 6000 gas chromatograph (FID detector) equipped with a 2-m 5% Carbowax 20m (or OV–17) on Chromosorb W column. A Perkin-Elmer 783 spectrometer was used for infrared spectral determinations and Varian EM-360 and XL-300 instruments were used to record nuclear magnetic resonance spectra, while mass spectral determinations were made by using a VG 5050 micromass spectrometer.

General Procedure for the Palladium Chloride Catalyzed Carbonylation of Amines with Di-*tert*-butyl Peroxide. Carbon monoxide was bubbled through methanol (60 mL) for 15 min. Palladium chloride (0.5 mmol) was added followed, 3 min later, by the acid (1–2 drops). The mixture was stirred under carbon monoxide for 10 min, and $CuCl_2$ (1.0 mmol) was added, followed by the amine (5.0 mmol) and then di-*tert*-butyl peroxide (5.0 mmol). The reaction mixture was stirred overnight at room temperature and 1 atm and filtered, and the filtrate was concentrated by rotary evaporation. Compounds **2** and **3** (if formed) were separated and isolated by ether extraction, and then the ether extract was subjected to preparative thin-layer chromatography (ether–hexane), affording products in yields given in Tables I and II.

The reactions involving oxygen instead of di-*tert*-butyl peroxide were also effected at ambient temperature and 1 atm, with a flowmeter used to control the proportions of carbon monoxide and oxygen. The procedure was, except for the noted change, identical with that described for di-*tert*-butyl peroxide.

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Registry No. **1** ($R = C_6H_{11}$, $R' = H$), 108-91-8; **1** ($R = C_{12}H_{25}$, $R' = H$), 124-22-1; **1** ($R = C_4H_9$, $R' = H$), 109-73-9; **1** ($R = t\text{-}C_4H_9$, $R' = H$), 75-64-9; **1** ($R = PhCH_2$, $R' = H$), 100-46-9; **1** ($R = Ph$, $R' = H$), 56-41-7; **1** ($R = 4\text{-}CH_3OC_6H_4$, $R' = H$), 104-94-9; **1** ($R = 2,3\text{-}(CH_3)_2C_6H_3$, $R' = H$), 87-62-7; **1** ($R = R' = C_6H_{11}$), 101-83-7; **1** ($R = C_6H_{11}$, $R' = CH_3$), 98-94-2; **1** ($R = R' = C_2H_5$), 109-89-7; **1** ($R = R' = C_3H_7\text{-}i$), 108-18-9; **1** ($R = R' = C_4H_9\text{-}i$), 110-96-3; **1** ($R = R' = (CH_2)_5$), 110-89-4; **2** ($R = C_6H_{11}$, $R' = H$, $R'' = CH_3$), 5817-68-5; **2** ($R = C_{12}H_{25}$, $R' = H$, $R'' = CH_3$), 66769-57-1; **2** ($R = C_{12}H_{25}$, $R' = H$, $R'' = C_2H_5$), 6268-50-4; **2** ($R = C_{12}H_{25}$, $R' = H$, $R'' = C(CH_3)_3$), 106810-56-4; **2** ($R = C_4H_9$, $R' = H$, $R'' = CH_3$), 2594-21-0; **2** ($R = C_4H_9$, $R' = H$, $R'' = C(CH_3)_3$), 59256-58-2; **2** ($R = t\text{-}C_4H_9$, $R' = H$, $R'' = CH_3$), 27701-01-5; **2** ($R = t\text{-}C_4H_9$ $R' = H$, $R'' = C(CH_3)_3$), 71872-03-2; **2** ($R = PhCH_2$, $R' = H$, $R'' = CH_3$), 5817-70-9; **2** ($R = Ph$, $R' = H$, $R'' = CH_3$), 2603-10-3; **2** ($R = H_3COC_6H_4$, $R' = H$, $R'' = CH_3$), 14803-72-6; **2** ($R = 2,6\text{-}(CH_3)_2C_6H_3$, $R' = H$, $R'' = CH_3$), 20642-93-7; **2** ($R = R' = C_6H_{11}$, $R'' = CH_3$), 6946-78-7; **2** ($R = C_6H_{11}$, $R' = CH_3$, $R'' = CH_3$), 56475-81-1; **2** ($R = R' = C_2H_5$, $R'' = CH_3$), 4652-44-2; **2** ($R = R' = C_3H_7\text{-}i$, $R'' = CH_3$), 31603-49-3; **2** ($R = R' = C_4H_9\text{-}i$, $R'' = CH_3$), 83487-24-5; **2** ($R = R' = (CH_2)_5$, $R'' = CH_3$), 1796-27-6; **3** ($R = R'' = C_6H_{11}$, $R'' = CH_3$), 110193-54-9; **3** ($R = C_6H_{11}$, $R' = CH_3$, $R'' = CH_3$), 110193-55-0; **3** ($R = R' = C_2H_5$, $R'' = CH_3$), 110193-56-1; **3** ($R = R' = C_3H_7\text{-}c$, $R'' = CH_3$), 110193-57-2; **3** ($R = R' = C_4H_9\text{-}c$, $R'' = CH_3$), 110193-58-3; **3** ($R = R' = (CH_2)_5$, $R'' = CH_3$), 20173-02-8; CH_3OH, 67-56-1; C_2H_5OH, 64-17-5; $(CH_3)_3COH$, 75-65-0; $PdCl_2$, 7647-10-1; $((CH_3)_3CO)_2$, 110-05-4; $C_6H_5NHCONHC_6H_5$, 26763-63-3.

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