COBALT-CATALYZED AMINOCARBONYLATION OF GEMINAL DIHALOALKANES FORMATION OF 2-AMINOAMIDE AND MALONAMIDE DERIVATIVES

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Abstract $Co_2(CO)_8$ catalyzed aminocarbonylation of geminal dihaloalkanes R_2CX_2 (R=H, CH₃, X=Br, Cl) with NHEt₂ affording $R_2C(NEt_2)CONEt_2$ selectively in n-C₆H₁₄ using NEt₃, while the yield of $R_2C(CONEt_2)_2$ fairly increased in THF or benzene in aid of K_2CO_3

Transition metal-catalyzed aminocarbonylation of organic halides converting to more valueadded compounds has drawn considerable attention because of its importance in industrial process ¹ Of particular importance in these areas, selective multifunctionalization of organic halides by transition metal-promoted specific bond activation is current topics in the field of organic synthesis ² On relevance of carbon monoxide activation under mild condition, we previously reported catalytic carbonylation of dibromomethane using transition metal complexes (eq 1), and proposed a possible reaction mechanism involving transition metal ketene intermediates on the basis of isolation of the reaction intermediates 3

$$CH_2Br_2 + CO + HY + Zn \xrightarrow{} MX_2L_2 CH_3COY + ZnBr_2 (1)$$
$$M = Ni, Pd, Pt, L \approx PPh_3 Y = OCH_3, OC_2H_5, N(C_2H_5)_3$$

As a further extension of these studies, we report here $Co_2(CO)_8$ -catalyzed aminocarbonylation of geminal dihaloalkanes to produce 2-aminoamide 1 and malonamide 2 derivatives in addition to amides 3 (eq 2), and describe main controlling factors governing the product selectivity and a possible reaction mechanism

$$R_{2}CX_{2} + CO + NHEt_{2} \xrightarrow{Co_{2}(CO)_{8}} R_{2}C \xrightarrow{NEt_{2}} + R_{2}C \xrightarrow{CONEt_{2}} R_{2}C \xrightarrow{NEt_{2}} R_{2}C \xrightarrow{NEt_{2}} + R_{2}C \xrightarrow{NEt_{2}} R_{2}C \xrightarrow{NEt_{2}} R_{2}C \xrightarrow{NEt_{2}} + R_{2}C \xrightarrow{NEt_{2}} R_{2}C \xrightarrow{NEt_{2}$$

Aminocarbonylation of CH₃CHBr₂ was typically carried out in a stenless steel autoclave(50 ml) containing $Co_2(CO)_8$ (0.4 mmol) and NEt₃ (40 mmol), into which freshly distilled n-C₆H₁₄ (10 ml) was added at room temperature under N₂ Then, addition of CH₃CHBr₂ (10 ml) and NHEt₂ (40 mmol) was followed by introduction of CO (50 atm) The mixture was allowed to react at the specified temperature for the prescribed time. The reaction products were then determined by GLC using an internal standard and identified by NMR, Mass, and IR spectroscopies after isolation with preparative GLC Throughout the reaction in each case, appropriate amount of HCONEt₂, (CONEt₂)₂, and CO(NEt₂)₂ was found to form as by-products

Run	1	Solvent	Base	Products (mol%)			<u>1 + 2 + 3</u>
				2-aminoamide	malonamide	amide	R ₂ CBr ₂
				1	2	3	(%)
CH ₃ CHBr ₂							
	1 2	n-C ₆ H ₁₄	NEt ₃ K ₂ CO ₃	87 18	4	9 82	38 12
	3 4	С ₆ Н ₆	NEt3 K ₂ CO3	9 11	3 67	88 22	35 41
!	5 6	THF	NEt ₃ K ₂ CO ₃	6 6	8 71	86 23	47 39
-	7b)	CH3CHCI2	NEt ₃	56	-	44	15
СН	l ₂ Br ₂	2					
ł	8	n-C6H14	NEt ₃	57	19	24	21
•	9	С ₆ н ₆	к ₂ СО3	29	61	10	15
	10	THF	K ₂ CO3	36	60	4	14
	11 ^{b)}	CH ₂ Cl ₂	K ₂ CO ₃	76	15	9	11

Table I Cobalt-catalyzed Aminocarbonylation of Geminal Dibromoalkanesa)

a) Reaction conditions, CH₃CHBr₂ or CH₂Br₂ (10 mmol), NHEt₂ (40 mmol), base (40 mmol), Co₂(CO)₈ (0 4 mmol), solvent (10 ml), P (CO)= 50 atm, 100 °C, 48 hr b) used as both substrate and solvent

The experimental results were summarized in Table I. The yield and selectivity of N,Ndiethyl-2-diethylaminopropionamide 1 substantially reached to the best particularly in n-C₆H₁₄ (Run 1). In most of cobalt-catalyzed carbonylation of organic halides,^{1,2} it is general that sort of additives and polarity of reaction medium change selectivity of the products and even affect the course of the reactions. It is worth noting that N,N,N',N'-tetraethyl-methylmalonamide 2 was produced increasingly in C₆H₆ or THF by using inorganic base such as K₂CO₃ (Run 4 and 6), although 2 was little obtained in n-C₆H₁₄. Only 3 was yielded in polar solvent such as acetonitrile and pyridine in which quaternary reaction of dibromide with NHEt₂ took place predominantly instead 1,1-Dichloroethane was not carbonylated effectively at least under the reaction employed as in Table I (Run 7).

On the other hand, the similar reaction mode in aminocarbonylation of CH_2Br_2 was observed although quaternary side reaction took place rather predominantly. In THF and benzene, N,N,N',N'-tetraethylmalonamide appears to form rather mainly in K_2CO_3 (Run 9 and 10). Interestingly, N,N-diethyl-2-diethylaminoacetamide was yielded rather exclusively on aminocarbonylation of CH_2Cl_2 without the formation of quaternary salt in spite of slow reaction (Run 11).

In Table II, catalyst activities of some metal carbonyls toward aminocarbonylation of 1,1dibromoethane were investigated under the same reaction conditions. It is apparent that $Co_2(CO)_8$ effectively promoted the aminoamidation to yield 2-aminopropionamide 1, while $Ru_3(CO)_{12}$ was found to be effective for affording propionamide selectively in THF

Catalyst	P	1 + 2 + 3		
	2-aminoamide	malonamide	amide	CH ₃ CHBr ₂
	1	2	3	(%)
Co ₂ (CO) ₈	87	4	9	38
ir ₄ (CO) ₁₂	-	-	100	22
Ru ₃ (CO) ₁₂	-	-	100	24
Ru3(CO)12 ^{b)}	6	-	94	53
M(ČO) ₆ (M,Cr,Mo,W)	-		-	0

Table II Comparison of Catalyst Activity for Aminocarbonyaltion of CH₃CHBr₂a)

a) The same reaction conditions were employed as in Table 1 except using n-hexane (10ml) as solvent b) in THF

Although multifarious factors affecting on these particular reactions derive some difficulties to rationalize the reaction conditions governing the course of the reactions and the product selectivities, it is clear that $Co_2(CO)_8$ catalyzed aminocarbonylation of geminal dihaloalkanes yielding 2-aminoamide and malonamide derivatives in the presence of base, whereas acetamide derivatives were only obtained by $Co_2(CO)_8$ -Zn systems as previously reported 3

To better define mechanisms of these reactions, THF solution of $Co_2(CO)_8$ was treated with 5-fold NHEt₂ in a glass pressure bottle initially at -75 °C. The reaction mixture was then allowed to react with CO (6 atm) by raising the reaction temperature slowly to 20 °C. After passing the resulting solution through a short column of neutral Al₂O₃, off-yellow crystalline solid of $Co(CONEt_2)(CO)_4$ was isolated with 27% yield ⁴ Although $Co_2(CO)_8$ is known to react with the secondary amines to yield the formamides together with the disproportionation products, the cobalt-carbamoyl species as the key intermediate remains unexplored ⁵

$$Co_2(CO)_8$$
 + NHEt₂ ------ $Co(CONEt_2)(CO)_4$ + $[Co(CO)_4]NH_2Et_2$ (3)
4

Interesting feature of 4 was its catalytic activity toward aminocarbonylation of geminal dihaloalkanes. It was found that 4 promoted aminocarbonylation of 1,1-dibromoethane with NHEt₂/CO (50 atm) giving 2-aminopropionamide 1 (480%/4), malonamide 2 (18%), and propionamide (38%) in n-C₆H₁₄ at 100 °C in the presence of NEt₃, while in THF was selectively formed propionamide 3 (710%/4) in addition to malonamide 2 (169%). These stoichiometric model reactions suggest that a cobalt-carbamoyl intermediate 4 likely plays a key role in these catalytic aminocarbonylation. More detailed studies for elucidating a possible reaction mechanism particularly to answer the questions how the substituent of R₂CBr₂ affects the product selectivity, are now actively investigated.

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References and Notes

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- 4, IR (KBr), 2995m, 2960m cm⁻¹ (v_{C-H}), 2045-1870vs (v_{C=O}), 1640s (v_{C=O}), MS(EI, 70ev), 271 (M⁺) Cryoscopic molecular weight measurement in benzene, found 255, calcd 271 Acidolysis of 4 with dry HCl in THF yielded N,N-diethylformamide in 58% yield
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