Tetrahedron Letters,Vol.24,No.12,pp 1255-1258,1983 0040-4039/83/121255-04$03.00/0
Printed in Great Britain

TETRACARBONYL NICKEL INDUCED REACTION OF gem-DIBROMOCYCLOPROPANES WITH ALCOHOLS OR AMINES. VERSATILE SYNTHESIS OF CYCLOPROPANECARBOXYLIC ACID DERIVATIVES

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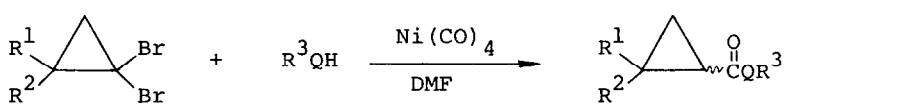
Summary: Treatment of gem-dibromocyclopropanes with alcohols or amines in the presence of tetracarbonyl nickel affords the corresponding cyclopropanecarboxylates or -carboxamides, respectively.

Tetracarbonyl nickel mediated reactions have provided a variety of methods in organic synthesis. Earlier work in our laboratory has shown a new ring formation in the reaction of heterocumulenes with acetylenic compounds,[1] or diphenylcyclopropenone[2] in the presence of tetracarbonyl nickel. In this report, we wish to describe the tetracarbonyl nickel induced carboxylation of gem-dibromocyclopropanes. Though some carboxylation reactions of organic halides with tetracarbonyl nickel have been reported, the substrates are generally limited to allyl, vinyl, and aryl halides.[3] The present process provides the facile transformation of gem-dibromocyclopropanes to the corresponding cyclopropanecarboxylic acid derivatives.



1 2 Q=O, NH, NR4

General procedure is as follows. To a mixture of a gem-dibromocyclopropane (1 mmol) and an alcohol (or an amine) (2.5 mmol) in DMF (2.4 mL) was added tetracarbonyl nickel (6 mmol) at room temperature under nitrogen. The mixture was stirred at 70°C for 3 h. After removal of tetracarbonyl nickel under reduced pressure, 30 mL of 5% aqueous HCl solution was added to the resultant mixture, which was extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated. The product was isolated by silica gel column chromatography. Some results are summarized in Table 1.

An interesting feature of the present reaction is that reduction of the bromine atom takes place. The reaction did not occur without tetracarbonyl nickel,

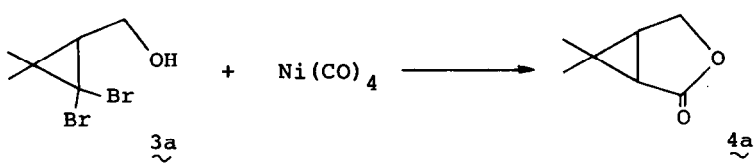
and monobromocyclopropanes are not subjected to carboxylation under the similar conditions. The molar ratio of tetracarbonyl nickel to the dibromocyclopropane 1 affected the yield of the product. The reaction was suppressed under the pressure of CO gas. Cyano and methoxycarbonyl groups are inert to tetracarbonyl nickel, which makes this carboxylation general and efficient.

Table 1. Preparation of Cyclopropanecarboxylic Acid Derivatives[a)]

R^1	1	R^2		R^3QH (molar eq.)	$Ni(CO)_4$ (molar eq.)	2 Yield %	(trans:cis)
Ph		H	1a	n-PrOH (2.5)	6	62	(34:66)
	1a			PhOH (2.5)	6	57	
	1a			m-Cl-C_6H_4OH (2.5)	6	56	
Me		CO_2Me	1b	n-PrOH (2.5)	6	75	
Me		CN		n-PrOH (2.5)	6	51	
	1a			n-$PrNH_2$ (2.5)	6	78	(45:55)
	1a			n-$PrNH_2$ (2.5)	1	52	
	1a			n-$PrNH_2$ (1)	1	52	
	1a			n-$PrNH_2$ (1)	1[b)]	0	
	1a			$PhNH_2$ (2.5)	6	63	(50:50)
	1a			 (2.5)	6	66	
	1a			 (2.5)	6	56	
	1b			 (2.5)	6	44	

a) Reaction was carried out at 70°C for 3 h. b) CO, 20 Kg/cm^2.

2,2-Dibromo-3,3-dimethylcyclopropanemethanol (3a) derived from prenyl alcohol[4)] was treated with tetracarbonyl nickel in DMF at 75°C for 3 h to give 6,6-dimethylbicyclo[3.1.0]-3-oxahexan-2-one (4a) in 73% yield. The thus obtained

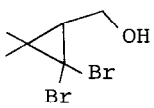
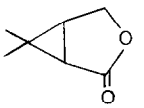
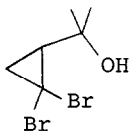
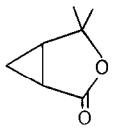
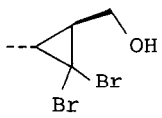
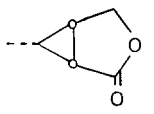
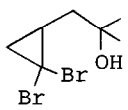
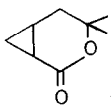


3a 4a

bicyclic γ-lactone 4a can be easily transformed to cis-chrysanthemic acid.[5)] In the reaction of 3a with 2.2 molar equivalent of tetracarbonyl nickel, cis-2-bromo-3,3-dimethylcyclopropanemethanol (10%) was obtained as a byproduct. This monobromocyclopropanemethanol is derived from reduction of the bromine atom trans to the hydroxymethyl group of 3a. The gem-dichlorocyclopropanemethanol did not react even if the reaction temperature was raised (75°C, 5h or 120°C, 7h). Starting

from 2,2-dibromo-trans-3-methylcyclopropanemethanol, trans-6-methylbicyclo[3.1.0]-3-oxahexan-2-one (4b)[6] was produced. It is of interest that t-alcohol worked well as a nucleophile. This intramolecular reaction was applied to the preparation of the bicyclic δ-lactone 4c[7] as shown in Table 2.

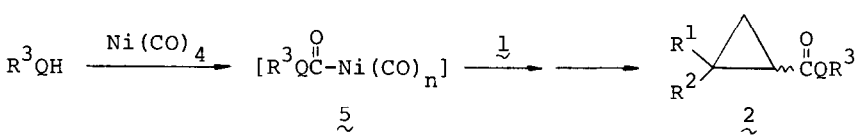
Table 2. Preparation of Bicyclic Lactones

2,2-Dibromocyclopropanealkanol 3	$Ni(CO)_4$ (molar eq.)	Reaction Temp.(°C)	Time(h)	Bicyclic Lactone 4	Yield %
	2.2	80	11	 4a	37[a]
	7	75	3		73
	7	75	3		70
	1.2	80	11	 4b	43[b]
	7	75	3	 4c	51

a) cis-2-Bromo-3,3-dimethylcyclopropanemethanol was produced as a byproduct (10%).

b) cis-6-Methylbicyclo[3.1.0]-3-oxahexan-2-one was not obtained and cis-2-bromo--trans-3-methylcyclopropanemethanol[6] was produced as a byproduct (24%).

The reaction mechanism has not been clarified yet. As one of the plausible paths, tetracarbonyl nickel is considered to contact with a nucleophile at the first stage to generate the complex 5. Then, the complex 5 reacts with the gem-dibromocyclopropane 1 to form the carbon-carbon bond of carboxylates or carboxamides. The similar mechanism involving 5 has been proposed in carboxylation of



vinyl halides.[8] Another possibility that the reaction is initiated by oxidative addition of the gem-dibromocyclopropane 1 to tetracarbonyl nickel might be excluded because 1a was recovered (>90%) after being treated with tetracarbonyl nickel in

DMF at 70°C for 3 h.

It has not been proven in which step a bromine atom is reduced. It is likely that tetracarbonyl nickel serves an important role in the reduction reaction. The reaction of 1a with tetracarbonyl nickel was carried out in the presence of n-propanol-d to give the corresponding α-deuteriocyclopropanecarboxylate. This result shows that a hydrogen atom is introduced from an alcohol. Tetracarbonyl nickel was found to reduce α-bromo-β-methyl-γ-butyrolactone into β-methyl-γ-butyrolactone in the presence of a small amount of water. A relative reduction with tetracarbonyl nickel has been reported in debromination of tribromomethyl group.[9] From these facts, α-bromocyclopropanecarboxylates might be intermediates which are reduced with tetracarbonyl nickel.

Inter- or intramolecular carboxylation reaction of gem-dibromocyclopropanes has been scarcely known.[10] The present procedure provides a convenient method for the preparation of cyclopropanecarboxylates and -carboxamides. Further studies involving the mechanism are being investigated.

Acknowledgement This work was partly supported with Grant-in-Aid for Scientific Research from the Ministry of Education.

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6) 4b: IR (neat) 1765 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.1-1.4 (m, 4H), 1.79 (dd, 1H, J=5.9, 2.8 Hz), 1.9-2.1 (m, 1H), 4.1-4.4 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 16.0 (q), 21.0 (d), 25.1 (d), 25.2 (d), 69.5 (t), 175.9 (s). cis-2-Bromo-trans-3-methylcyclopropanemethanol: IR (neat) 3340 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.8-1.3 (m, 2H), 1.27 (d, 3H, J=6.3 Hz), 1.62 (s, 1H), 2.97 (dd, 1H, J=7.7, 3.6 Hz), 3.59 (d, 2H, J=6.1 Hz).
7) 4c: IR (neat) 1725 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.77 (q, 1H, J=4.3 Hz), 1.1-2.3 (m, 5H), 1.34 (s, 3H), 1.47 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 11.9 (d), 12.5 (d), 18.8 (t), 27.5 (q), 29.1 (q), 35.8 (t), 83.1 (s), 172.4 (s).
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(Received in Japan 26 November 1982)