

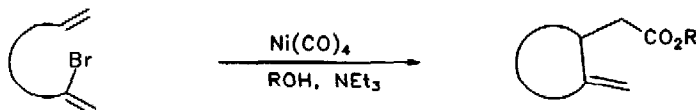
Nickel-promoted Intramolecular Cyclization of Vinyl bromides with Alkenes and Alkynes

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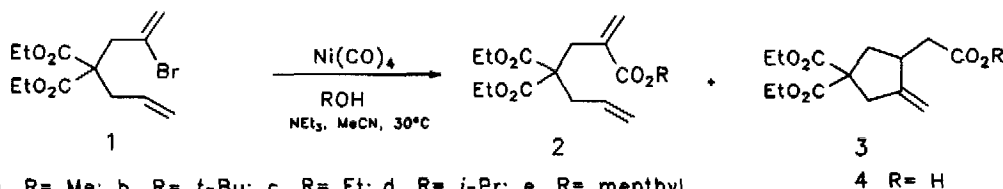
Abstract: The reaction of vinyl bromides bearing distal olefin or acetylene functionalities with tetracarbonylnickel in the presence of alcohols and triethylamine results in the formation of exo-methylene cyclic esters in a regioselective process. High influence of the bulkiness of the alcohol is found.

Synthesis of cyclic compounds is a strategic goal in organic chemistry¹ and, consequently, development of new methodologies towards this type of compounds is the subject of current extensive work in organic synthesis. In this context, transition-metal based methods increase the synthetic efficiency by forming more than one C-C bond with high selectivity². In connection with our work on tetracarbonylnickel induced cyclization reactions³ we have found that exo-methylene carbocyclic compounds could be obtained from bromovinyl substrates bearing olefin or acetylene functionalities in a linear chain according to scheme 1.



Scheme 1

When substrate 1 was treated⁴ with tetracarbonylnickel (CAUTION!)⁵ in the presence of methanol and triethylamine we obtained the corresponding linear ester 2a as a single isolated product in yields ranging from 65-90 %⁶. This linear ester was the main product obtained regardless of the $\text{MeOH}/1$ ratio used. After methanol was replaced by a bulkier alcohol, such as *t*-BuOH, we found two new compounds in a 3.2 to 1 ratio and 85 % overall isolated yield that according to their spectral data we assigned structures 3b and 4.



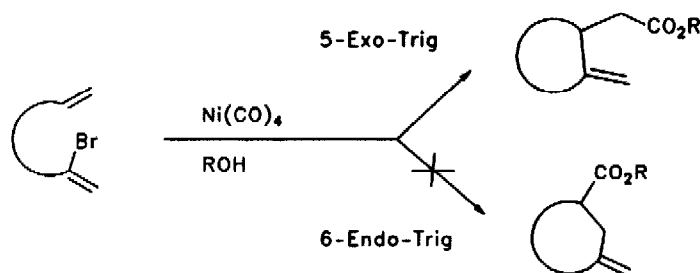
The effect of the size of the group R in the alcohol on product distribution was studied and the results obtained are summarized in table I. As it can be seen, the ratio of cyclic *versus* non cyclic products parallels the bulkiness of the alkyl group in ROH. Acid 4 was obtained mainly using *t*-BuOH and its formation may be explained by hydrolysis of the corresponding *t*-butyl ester during work up or purification. In the case of using L-menthol the corresponding esters 3e were obtained as a 1:1 mixture of diastereomers.

Table I. Influence of the alcohol in the cyclization of 1.

R in ROH	ROH/1 ^a	PRODUCTS (Isolated yield %)		
		2	3	4
Me	10	89	--	--
Me	5	78	--	--
Me	2	66	6	4
Me	0.5	42	traces	--
<i>t</i> -Bu	10	--	65	20
<i>t</i> -Bu	3	--	57	12
Et	3	60	28	--
<i>i</i> -Pr	3	35	61	--
L-menthyl	1.2	--	92	--

^a molar ratio alcohol/substrate

The results so far obtained show that this cyclization occurs under very mild conditions with high selectivity through a 5-Exo-Trig pathway with no products arising from the competitive 6-Endo-Trig process. In addition, no isomerization of the exocyclic double bond was observed in any of the reactions carried out.



The same regioselectivity was found when other substrates related to 1 were reacted under similar conditions to give cyclic exomethylene esters as described in table II. Formation of seven member cyclic compounds was not observed in spite of decreasing the alcohol/substrate ratio employed, the product obtained being always the corresponding linear ester.

Table II. Cyclization reactions of bromovinyl derivatives.

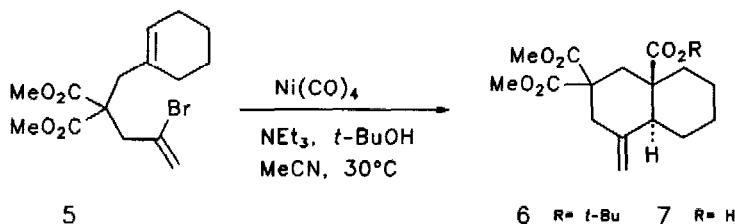
Substrate	ROH	Products (isolated yields %)	ester/acid ^a
	<i>t</i> -BuOH	(79)	7:1
	<i>t</i> -BuOH	(77)	1.5:1
	MeOH	(71)	-- ^b
	<i>t</i> -BuOH	(75)	40:1
	<i>t</i> -BuOH	(46)	-- ^b

^a molar ratio *t*-butyl ester (R = *t*-Bu) to acid (R = H). ^b Only ester was obtained.

These results agree with those obtained in other transition metal promoted cyclization processes from similar substrates. Thus, Grigg *et al.*⁸ reported a general preference for the 5-Exo-Trig versus 6-Endo-Trig cyclization in a series of studies of non carbonylative Heck type reaction mediated by palladium catalysts. Negishi⁹ and Oppolzer¹⁰ showed the feasibility of inducing ester formation by carbonylation in related palladium catalyzed cyclization reactions but usually higher pressures and temperatures than those used in the present Ni-promoted process are required.

When the reaction was performed on compound 5 in the presence of *t*-BuOH a mixture of two related compounds, *t*-butyl ester 6 and the corresponding acid 7, were exclusively produced in a 2:1 ratio and 77% overall yield. The structure of these products was deduced from spectroscopic data including COSY, HETCOR, COLOC and NOE difference experiments; 6 and 7 arise from a 6-Endo-Trig cyclization that, unexpectedly, took place to give the interesting *trans* fused decalin system. This change in the cyclization trends can be tentatively explained by considering the conformational constraints imposed by the six member

cyclic olefin⁸. Work is in progress to gain further insight on factors influencing the selectivity of this process.



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References and notes

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4. Typical Experimental Procedure: To a solution of starting bromide (1 mmol) in acetonitrile (10 mL) containing the alcohol and NEt₃ (3 mmol) Ni(CO)₄ (2 mmol) was added. When the reaction was complete a stream of Ar was passed through the reaction mixture and the volatiles were condensed in a cold trap containing iodine to destroy any unreacted nickel complex. Flash chromatography of the residue gave the products for which correct analytical and spectroscopic data were secured.
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11. We have found independently that competition between the 6-Endo-Trig cyclization process and the, in general, more feasible 5-Exo-Trig one in a Ni-promoted spirocyclic annulation (see reference 3c) only took place when using six member cyclic allyl halides.