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LETTERS

Preparation of Alkenyl Fischer Carbene Complexes via Aldol Condensation with Enolizable Aldehydes

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Abstract: A method for the preparation of alkenyl chromium carbene complexes is described by an aldol condensation of enolizable aldehydes. The aldol condensation of pentacarbonyl methyl(methoxy)methylene chromium is best performed with an aliphatic aldehyde that is precomplexed with tin tetrachloride and the elimination step is optimal with mesyl chloride and triethylamine.

Our investigations of the reactions of carbene complexes with alkynes have led us to prepare complexes of the type **4** and the aldol reaction of the methoxy methyl carbene complex **1** with an α,ω-alkynal seemed the most straightforward approach. The aldol reaction of alkoxy carbene complexes has been known for some time and ostensibly should be useful in the preparation of a variety of alkenyl carbene complexes.[1] We had previously published that aldol addition products **2** could be obtained for a variety of aldehydes and ketones if the carbonyl compound was activated by pre-complexation with a Lewis acid.[2] We also demonstrated that the aldol adducts **2** could be dehydrated to alkenyl complexes although this was only demonstrated for adducts of ketones. We have subsequently found that the procedures that were optimized for the aldol addition / dehydration sequence for ketones are not optimal for aldehydes. Other procedures that have been developed can give good to excellent yields of alkenyl complexes but only from non-enolizable aldehydes.[3] We report here the development of procedures that provide for good overall yields of alkenyl complexes of the type **3** from the aldol addition / elimination sequence from complex **1** and simple aliphatic aldehydes.

We were intrigued by the observation that the aldol reaction of the carbene complex **5** with aliphatic aldehydes could lead to the direct formation of alkenyl carbene complexes if the reaction was carried out in DMF with potassium carbonate.[4] Table I presents our results on extension of this reaction to the complex **1**. We found that the reaction of complex **1** with acetaldehyde led to the rapid consumption of starting material but not

Scheme I

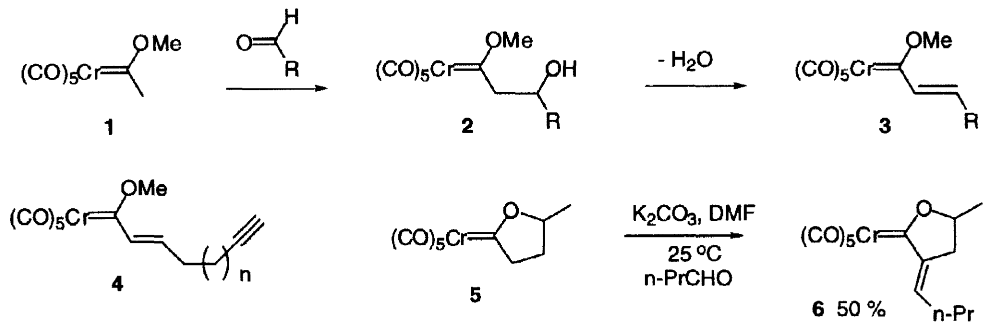

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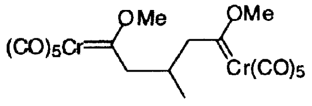
Table I. Aldol Condensation of Complex **1** in DMF.[a]

Entry	R	Temp (°C)	K_2CO_3	Equiv RCHO	Time (h)	Product	% Yield[b] **1**	**3**	**7**	**9**
1	Me	25	1.0	90	1	**3a**	0	0	0	<1
2	Me	25	0.1	90	0.5	**3a**	0	<10	12	15
3	Me	25	0.0	90	0.25	**3a**	15	5	5	10
4	Me	-15	0.0	90	29	**3a**	32	30	2	2
5	Me	-10	0.0	270	96[c]	**3a**	<7	49	- -	- -
6	Et	-10	0.0	270	96	**3b**	10	38		
7	*i*-Pr	-10	0.0	140	96[c]	**3c**	7	41		
8	*t*-Bu	-10	0.0	35	96	**3d**	>75	<10		
9	Ph	-10	0.0	70	72	**3e**	15	29		

[a] All reactions carried out at 0.2 M **1** in DMF. [b] All yields are isolated after silica chromatography. [c] Time includes 18 h at 0 °C.



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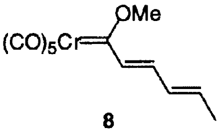

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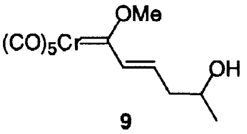

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to the formation of alkenyl complex **3a** with either a catalytic or stoichiometric amount of potassium carbonate. It was discovered that the reaction was rapid in the absence of base (entry 3), however, only small amounts of

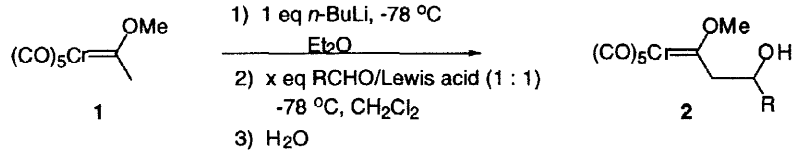

Table II. Aldol Addition of Complex **1** to Aldehydes Mediated by Lewis Acids.[a]

entry	R	Lewis acid	equiv RCHO	Time (h)	Product	% Yield **2**	% Rec **1**
1	*n*-Pr	Et_2AlCl	2	2	**2f**	31[b]	29
2	*n*-Pr	$AlCl_3$	2	2	**2f**	56	- - -[c]
3	*n*-Pr	$SiCl_4$	2	2	**2f**	<15	15
4	Me	Me_3SiOTf	2	2	**2a**	<13	42
5	Me	TiCl(O-i-Pr)$_3$	2	2	**2a**	<6	58
6	Me	$SnCl_4$	2	2	**2a**	62	16
7	*n*-Pr	$SnCl_4$	2	2	**2f**	84[b]	ND
8	*n*-Pr	$TiCl_4$	2	2	**2f**	71[b]	5
9	*n*-Pr	$SnCl_4$	1	2	**2f**	66[b]	ND
10	*n*-Pr	$SnCl_4$	2	1	**2f**	78	ND
11	*n*-Pr	$SnCl_4$	2	4	**2f**	81	ND
12	-$(CH_2)_3C{\equiv}CH$	$SnCl_4$	2	2	**2g**	51	ND
13	*n*-Pr	$TiCl_4$	1	2	**2f**	71[b]	ND
14	-$(CH_2)_3C{\equiv}CH$	$TiCl_4$	2	2	**2g**	- - -[d]	ND

[a] All yields are isolated after silica chromatography. ND indicates yields was not determined. Reactions performed at 0.03 M in **1**. [b] Average of two runs. [c] Complex mixture of side-products formed. [d] A complex mixture of products was formed; yield of **2** could not be determined.

3a were formed along with a large number of other products some of which were isolated and identified as **7** - **9**. It was found that selectivity for the aldol condensation product **3a** could be increased by lowering the temperature but the decrease in rate required an increase in the amount of aldehyde. The optimal procedure (entry 5-9) did provide reasonable yields of alkenyl complexes with enolizable aldehydes but the extended reaction times and the large excesses of aldehyde make the procedure less than desirable.

At this point we reinvestigated the two-step procedure and Table II presents the results of studies directed to the optimization of the conditions for the formation of the aldol addition adduct **2**. The first eight entries reveal that $SnCl_4$ and $TiCl_4$ are the most effective Lewis acids for this reaction. The yield did not improve with the use of excess aldehyde / Lewis acid complex for $TiCl_4$(entries 8 & 13) but a measurable increase in yield is observed with the use of two equivalents of the $SnCl_4$-aldehyde complex (entries 7 & 9). The tin Lewis acid is necessary for the aldol reaction with 6-hexynal since the Ti-mediated reaction gave a mixture of products.

The optimal procedures for the dehydration of aldol adducts from the reaction of complex **1** with ketones involved treatment with Super I alumina column in hexane.[2] As can be seen from the data in Table III, this procedure did not provide particularly useful results with adducts from either acetaldehyde or butyraldehyde. Modest yields could be obtained by treatment with acetyl bromide and triethylamine or with mesyl chloride and pyridine. The best results were obtained with the combination of mesyl chloride (2 equivalents) and triethylamine (2.2 equivalents) which gave the alkenyl complex **3f** in 72 % yield. It is interesting to note that this elimination is much faster than the same reaction with Hunig's base which in turn is much faster than the reaction with pyridine. When DMAP is employed as a co-base in the optimal procedure the yield falls.

With optimization of the procedure for each of the two steps in the aldol condensation of complex **1**, an evaluation of the aldol addition / dehydration sequence with a number of aldehydes was carried out and the results are presented in Table IV. The two protocols A and B differ by whether or not the aldol adduct **2** is purified by silica gel chromatography prior to the dehydration step. The overall yields do not differ substantially between the two, however, purification of **3** can be difficult for procedure B in those cases where separation

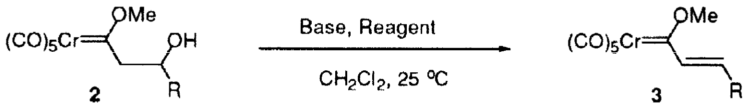

Table III. Dehydration of Aldol Adducts **2**.[a]

entry	R	Base (eq)	Reagent (eq)	Time (h)	% Yield **3**
1	Me	Et_3N (2.3)	AcBr (2.4)	3	46 [b]
2	Me	none	Alumina, Super I [c,d]	4	25
3	*n*-Pr	none	Alumina, Super I [c,e]	2	40
4	*n*-Pr	none	DDC (1.2), $CuCl_2$(0.1)	5	- - - [f]
5	*n*-Pr	Et_3N (2.2)	$(TfO)_2O$ (2)	12	- - - [g]
6	*n*-Pr	Et_3N (2.2)	TsCl (2)	12	- - - [g]
7	*n*-Pr	pyridine (2.2)	MsCl (2)	36	43
8	*n*-Pr	$(i\text{-}Pr)_2EtN$ (2.2)	MsCl (2)	5	61
9	*n*-Pr	Et_3N (2.2), DMAP (1)	MsCl (2)	16	- - - h
10	*n*-Pr	Et_3N (2.2)	MsCl (2) i	0.1	72
11	*n*-Pr	Et_3N (1.1)	MsCl (1.1)	- - -	- - - [j]
12	*n*-Pr	Et_3N (5)	MsCl (2)	0.1	36 [b]

[a] All yields are isolated after silica chromatography. All reaction performed at 0.02 M in **2**. [b] Only trace of **2** remaining. [c] Hexane solvent. [d] 12 weight equivalents. [e] 4.4 weight equivalents. [f] Complex **2** was consumed and no significant amounts of **3** detected. [g] Complex **2** is still present but a complex mixture of products is formed. [h] Complex **2** was consumed within 15 min but the elimination of the mesylate was slow. Warming to 25 °C for 16 h led to the formation of **3** along with a side product. [i] Temperature was 0 °C. [j] Mesylate formation was not complete and addition of additional mesyl chloride and Et_3N did not result in complete consumption of **2**.

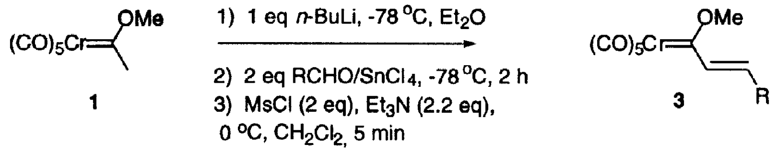

Table IV. Preparation of Alkenyl Carbene Complexes by Aldol condensation of Complex **1**.[a]

entry	R	Product	Yield of **3** Procedure A [b]	Yield of **3** Procedure B [b]
1	*Me*	**3a**	56	61 [c]
2	*n*-Pr	**3f**	63	57
3	*i*-Pr	**3c**	54 [d]	
4	t-Bu	**3d**	8 [e]	4 [f]
5	E-$CH_3CH=CH$	**3h**	36	44 [c]
6	Ph	**3e**	47	39
7	E-PhCH=CH	**3i**	9	23
8	$-(CH_2)_6C\equiv CH$	**3j**	53	57

[a] All yields are isolated after silica chromatography. Reactions performed at 0.03 M in **1**. [b] See text. [c] Final product **3** cannot be separated from residual amount of **1**. [d] Reaction time is 15 min. [e] Reaction warmed to 25 °C and stirred for 16 h before quench. [f] 2 h reaction time for elimination.

from unconsumed methyl methoxy complex **1** is difficult. In each case only the trans-isomer of **3** is obtained and detectable amounts of the cis-isomer were not seen for the examples in Table IV. It is not clear why the yields are lower with unsaturated aldehydes and thus the present method[5] is complementary to existing methods[3] for the preparation of alkenyl complexes by the aldol reaction.

General Procedure A: Complex **1** (1 mmol) was dissolved in 30 mL of ether and deprotonated with 1 eq of *n*-BuLi under argon at -78 °C for 30 min. In a separate flask, a solution of the aldehyde (2 mmol) in 10 mL of CH_2Cl_2 was cooled to - 78 °C and $SnCl_4$ (2 mmol) was added. After 30 min, the solution of the enolate of complex **1** was transferred to the aldehyde/Lewis acid complex via cannula. The aldol reaction was allowed to proceed for two hours at -78 °C, before it was quenched by rapid addition to 50 mL of water. The organic layer was separated, washed with brine and dried over anhyd $MgSO_4$. The solvent was removed and the aldol adduct was purified by chromatography on silica gel. Elution with pentane removed unreacted **1** and subsequent elution with a 1:1:3 mixture of ether, CH_2Cl_2 and hexane as eluent gave **2**. The purified aldol adduct **2** was dissolved in CH_2Cl_2 to make a 0.02 M solution and two equivalents of MsCl and 2.2 equivalents of Et_3N were added at 0 °C. When the reaction was complete (usually 5 min) as indicated by TLC, satd $NaHCO_3$ was added to quench the reaction mixture. The organic layer was separated, and the aqueous phase was extracted with ether (3 x 20 mL). The combined organic layer was washed with aq $NaHCO_3$ and brine and then dried over anhyd magnesium sulfate. The product alkenyl carbene complex **3** was purified by chromatography on silica gel by elution with hexane. *Procedure B* is identical to the above procedure except that the aldol adduct **2** is not purified. The crude adduct is dissolved in CH_2Cl_2 and treated to the same dehydration procedure.

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