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Reactions of transition metal carbonyl anions with 2-(1-bromoalkylidene)thiazolidin-4-ones: halogenophilic attack or deprotonation

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ABSTRACT

Bromophilic attack by the transition metal carbonyl anion, $[Re(CO)_5]Na$ ($pK_a = 21.1$), on 2-(1-bromoalkylidene)thiazolidin-4-ones is significantly faster than abstraction of an acidic lactam hydrogen ($pK_a \sim 17$ -18), when the generated carbanion is stabilized by an α -CN or α -PhCO group. The bromophilic reaction of 2-(1-bromoalkylidene)thiazolidin-4-one, having an α -CN electron-withdrawing group, resulted in formation of a new metallacyclic anionic complex. With less reactive vinyl bromides, containing an α -CONHPh or α -CO₂Et group, only deprotonation is observed. The role of the metal carbonyl anion is highlighted by a comparison with the 9-methylfluorenide carbanion (pK_a of 9-methylfluorene is 22.3), which reacts exclusively via a deprotonation pathway.

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Halogen-metal exchange between RLi and RHal, frequently a very fast reaction even at very low temperatures, can be carried out without affecting functional groups, which under ordinary conditions react with RLi. There are numerous examples in which halogen-metal exchange in a polyfunctional organic molecule, containing an acidic hydrogen (OH, COOH, CONH₂) and bromine or iodine, is seemingly faster than deprotonation.¹⁻⁴ On the contrary, reactions of o-, m-, and p-bromo and iodo isomers 1, nondeuterated 2-iodoguinoline (2) and its O-deuterated counterpart with *n*-BuLi, previously examined by Beak et al., 5-7 revealed that proton transfer is the initial process, whereas halogen-metal exchange occurs either in the initially formed deprotonated complex, or in a transient local area of high RLi concentration. Thus, the question whether halogen-metal exchange can be competitive with deprotonation is intriguing, especially because proton transfer is one of the fastest heterolytic reactions.



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Recently, we reported that 2-alkylidene-4-oxothiazolidine vinyl bromides **3a–d** react with a variety of ionic and neutral nucleophiles, leading to (i) the corresponding parent 4-oxothiazolidine **4** as a result of reductive debromination, (ii) bromine substitution, and/or (iii) efficient C(5) functionalization of the thiazolidine ring, all being initiated by bromophilic attack.⁸ Also possessing an acidic site, that is, the lactam hydrogen, they provide a good model for studying the competition between deprotonation and bromine-metal exchange.



a: Z = CN; **b:** Z = CONHPh; **c:** $Z = CO_2Et$; **d:** Z = COPh

Additionally, it has been previously shown that metal carbonyl anions are excellent halogenophilic agents in reactions with selected polyfluorinated^{9,10} and non-fluorinated vinyl and aryl halides.¹¹ Motivated to further explore the elementary processes associated with vinyl bromides **3a–d** and nucleophiles, we now report their reactions with [Re(CO)₅]Na, which, in the cases of compounds **3a** and **3d**, provide unequivocal examples of the bromophilic step being faster than proton transfer.

All reactions of vinyl bromides 3a-d, differing in the electronwithdrawing group Z at the exocyclic C=C bond, with [Re(CO)₅]Na,





carried out in THF at -50 °C, were almost instantaneous. The reaction mixtures were subsequently analysed by NMR and IR methods at room temperature. In studying the fast reactions where two competitive pathways are possible, the order of reagent addition can be important (vide infra).

Thus, we firstly performed the reactions by adding a slight excess of the corresponding vinyl halide **3** to a solution of $[Re(CO)_5]$ -Na. Initial evidence of the halogenophilic mechanism emerged from the reaction of $[Re(CO)_5]$ Na with **3a** (Table 1, entry 1), giving rise to a product, having IR and ¹³C NMR spectral data characteristic of an anionic oxycarbene Re(CO)₄-complex **5a** (Scheme 1). The patterns are quite similar to those observed for halo(acyl)rhenates, $[Hal(CO)_4Re(CO)R]$ Na, formed in halogenophilic reactions of $[Re(-CO)_5]$ Na with aryl or vinyl halides,^{9–11} and yet have slight but significant differences, such as an upfield chemical shift of the oxycarbene carbon at 248.4 ppm, compared to 256–260 ppm typical for halo(acyl)rhenates. A significant downfield shift (ca. 25–

40 ppm) of both vinylic carbon signals, compared to the typical values for the parent thiazolidine precursors **3**,¹² suggests a quasiaromatic metallacycle structure **5a** for this complex (Scheme 1). The structure was confirmed by comparison of the experimental and calculated (DFT method) chemical shifts and IR frequencies for **5a**. The MALDI and high resolution ESI MS of **5a** also gave a molecular mass consistent with the proposed structure.¹³ The formation of **5a** implies that [Re(CO)₅]Na acts both as a halogenophile abstracting bromine, and as a base, abstracting the acidic NH-proton (Scheme 1). This conclusion is supported by the observation that Re(CO)₅H is present among the reaction products (Table 1, entry 1). Presumably, and in order to explain the formation of complex **5a** together with Re(CO)₅H, the proton and halogen abstractions have to be fast compared to the duration of reagent mixing.

However, at this point, we had only limited information on the reaction kinetics concerning the rates of the halogenophilic and

Table 1

Reactions of [Re(CO)₅]Na with vinyl bromide **3a**, THF, -50 °C

Entry	Reaction conditions	Product yield (%)			
		5a	4a	Re(CO) ₅ Br	Re(CO) ₅ H
1	Direct addition ^a	50	25	$\sim 25^{b}$	20
2	1 equiv NaH, direct addition ^a	90	3	$\sim \! 10^{b}$	_
3	Reverse addition ^c	37	46	${\sim}50^{\mathrm{b}}$	5
4	Reverse addition ^c in the presence of Re(CO) ₅ Br (2 equiv)	60	30	-	<5
5	Reverse addition, ^{c} then 4 equiv Me ₃ SiCl	32 ^d	52	${\sim}50^{ m b}$	7

^a Addition of vinyl bromide **3a** to a solution of $[Re(CO)_5]Na$.

^b Yield estimated from the ¹³C NMR and IR spectra.

^c Addition of [Re(CO)₅]Na solution to a solution of vinyl bromide.

^d Complex **5a** is present, apparently, in silylated form.



Scheme 1.



Entry	Vinyl bromide	Reaction conditions	Product yield (%)						
			Re(CO) ₅ Br	Re(CO) ₅ H	4	6	7	8	
1	3b	Direct addition	$\sim 8^{a}$	90	<1	75	11	_	
2	3d	Direct addition	$\sim 50^{a}$	45	7	_	20	10	
3	3d	Direct addition without Me ₃ SiCl	>90	-	90 ^b	-	-	-	
4	3d	Reverse addition	>90 ^a	<1	42	-	24	7	
5	3b	Reverse addition	<10 ^a	90	-	62	10	_	

Table 2Reactions of $[Re(CO)_5]$ Na with vinyl bromide **3b** (Z = CONHPh) and **3d** (Z = COPh), followed by an excess of Me₃SiCl in THF at $-50 \degree C$

^a Yield estimated from ¹³C NMR and IR spectra.

^b Mainly in NH deprotonated form.

protophilic steps. In order to determine which step occurs first, we next reversed the order of reagent addition. Thus, upon dropwise addition of a solution of $[Re(CO)_5]Na$ to a solution of substrate **3a**, only 5% of $Re(CO)_5H$ was obtained, whereby $Re(CO)_5Br$ and complex **5a**, along with the debrominated 4-oxothiazolidine **4a**, were the main products (Table 1, entry 3). The yield of complex **5a** (Scheme 1) in the reverse addition experiment was only 37%, but in the presence of 2 mol equiv of $Re(CO)_5Br$ it increased to 60% (Table 1, entry 4). The final result illustrates the intermediacy of $Re(CO)_5Br$ as a reactant en route to metallacycle **5a**. It is worth mentioning that deprotonation of **3a** with NaH to give the lactam anion, followed by reaction with $[Re(CO)_5]Na$, led to complex **5a** in excellent yield (Table 1, entry 2).¹³ Thus, in the reaction of vinyl bromide **3a** with $[Re(CO)_5]Na$ the halogenophilic step is apparently faster than deprotonation.

Unlike the vinyl bromide **3a** which was transformed into the metallacycle **5a**, reactions of substrates **3b** (Z = CONHPh) and **3c** (Z = CO₂Et) with [Re(CO)₅], resulted in proton abstraction, furnishing Re(CO)₅H ($pK_a = 21.1$)^{14,15} as the main product (Scheme 2) The reaction mixtures were relatively unstable at room temperature, but an important finding from the reaction of **3c**, after addition of 18-crown-6, was the complete disappearance of Re(CO)₅H with concomitant formation of 4-oxothiazolidine **4c** (in NH-deprotonated form) and Re(CO)₅Br. In the reaction with **3b** the debromi-

temperature. These results can be interpreted by assuming that a certain amount of $[Re(CO)_5]Na$, present in an acid–base equilibrium, slowly debrominates compounds **3b** or **3c** to the parent sodium salt **4b** or **4c**, respectively.

Importantly, this has been confirmed by the IR detection of a small amount of $[\text{Re}(\text{CO})_5]$ Na remaining in the reaction with a slight excess of **4d**. The equilibrium constant, K = 94 (Eq. 1), was calculated from the IR data. As expected, according to the ACD/Labs program,¹⁶ vinyl bromides **3a–d** are more acidic by $\sim 2 pK_a$ units than the parent thiazolidines **4a–d**. In addition, based on the equilibrium involving neutral and anionic species **3c** and **4c** (Eq. 2), investigated by the IR method, a smaller, but still significant difference of $\geq 1 pK_a$ units between the pK_a s of **3c** and **4c**, was determined. At this point it became obvious that these experiments showed that it was necessary to neutralize the base (the amide anion) in order to determine the true ratio of $\text{Re}(\text{CO})_5\text{Br}$ and $\text{Re}(\text{CO})_5\text{H}$.





nated product **4b** was already present (in 52% yield) after 10 minutes, as indicated by the ¹H NMR spectrum. The amount of **4b** increased with time and reached 82% after 1.5 h at room

Thus, when the vinyl bromide **3b** (Z = CONHPh) was treated with $[Re(CO)_5]Na$, followed by quenching with Me₃SiCl immediately after the reagent mixing at $-50 \degree C$ (Scheme 2), Re(CO)₅H



Scheme 3.





was obtained almost quantitatively, together with the corresponding silyl ether **6b** (Table 2, entry 1). On the other hand, the same quenching procedure applied to the reaction of $[\text{Re}(\text{CO})_5]$ Na with bromide **3d** (Z = COPh) gave a different result: both $\text{Re}(\text{CO})_5$ Br and $\text{Re}(\text{CO})_5$ H were observed in a ~1:1 ratio (Table 2, entry 2). A complex mixture of the thiazolidine-derived products was also formed, in which mono- and bis-silylated derivatives **7d** and **8d** of debrominated 4-oxothiazolidine **4d** were identified (Scheme 3). The mono-silylated product **7d** was almost completely transformed on standing for one day at room temperature into the bis-silylated product **8d**.

In contrast, on repeated direct reaction of **3d** with $[\text{Re}(\text{CO})_5]$ Na in the absence of Me₃SiCl (Table 2, entry 3), the debrominated vinyl compound **4d** (in NH-deprotonated form) and Re(CO)₅Br were formed as the only products. This result strongly indicates that the reaction of **3d** with Re(CO)₅Na is too fast for Re(CO)₅H to be observed without quenching the lactam anion (in the presence of Me₃SiCl) from the equilibrium.

Formation of Re(CO)₅H and Re(CO)₅Br in $\approx 1:1$ ratio (entry 2, Table 2) suggests that the ratio is not kinetically controlled, but both, the halogenophilic and protophilic reactions with **3d** are fast compared to the duration of reagent mixing. The reverse order of reagent addition can indicate which of the reactions is faster and takes place first. When a solution of [Re(CO)₅]Na was added dropwise to a solution of **3d**, followed by the addition of Me₃SiCl, only Re(CO)₅Br was obtained (Table 2, entry 4 and Scheme 3) and minute amounts of Re(CO)₅H (<1%). The reaction with **3a** performed in the same manner resulted in only 7% of Re(CO)₅H, giving Re(CO)₅Br and complex **5a** as the main products (Table 1 entry 5). On the other hand, reversing the order of reagent addition had no effect on the reaction of **3b**, and Re(CO)₅H was formed almost quantitatively (Table 2, entry 5), just as in the case of direct addition (Table 2, entry 1).

Thus, the reverse addition experiments have finally confirmed that vinyl bromides **3a** and **3d** are first attacked on the halogen by $[\text{Re}(\text{CO})_5]$ Na. Deprotonation is, on the other hand, the fastest process for compounds **3b** and **3c**. Such dichotomy can be explained by the much higher reactivity of **3a** and **3d** in halogenophilic reactions compared to **3b** and **3c**. The α -substituents in **3a** and **3d**, CN and PhCO, respectively, being stronger electron-acceptors than CONHPh (for **3b**) and CO₂Et (for **3c**), can better stabilize the incipient vinyl carbanion. This is also in agreement with the qualitative reactivity order of vinyl bromides, **3a**, **3d** \gg **3b** > **3c**, towards [CpMo(CO)₃]K, when CpMo(CO)₃Br was the only organometallic product.

How fast are the halogenophilic reactions of **3a** and **3d** with $[\text{Re}(\text{CO})_5]$ Na? The available data on the kinetic acidity of metal carbonyl hydrides allows an estimation to be made.^{14,15} Vinyl bromides are by 3–4 pK_a units more acidic than $\text{Re}(\text{CO})_5$ H (see Eqs. 1 and 2). An expected rate constant for proton transfer from an NH-acid to a metal carbonyl anion is at least ~10⁶ l/mol s at such pK_a difference. Since only the halogenophilic reaction is observed in the case of **3d** its rate should be not less than 10⁸ l/mol s, which is quite near to the diffusion limit. The preferred attack on the

halogen in vinyl bromides **3a** and **3d** is possible because of the exceedingly high rate of the halogenophilic reaction with [Re(- CO_{3}]Na. It is worth mentioning that the role of the metal carbonyl anion has been further highlighted by comparison with a carbanion of comparable basicity. Thus, the reaction of **3a** with 9-methyl-fluorenide lithium (pK_a of 9-methylfluorene is 22.3) resulted only in deprotonation of the NH group and quantitative recovery of the starting bromide **3a** after silylation and hydrolysis (Scheme 4).

Carbanions are usually considered as good halogenophi-les,^{17,18} but the results of the current study lead us to the conclusion that metal carbonyl anions show even higher tendency towards attack on halogen with respect to carbanions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.112.

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1695 m, 1510 s. Spectra of **5a** in the presence of 18-crown-6: ¹H NMR (THF): δ = 3.88 s (**CH**₂). ¹³C NMR (THF): δ = 240.48 (Re=**C**-O), 193.44 (**C**O, 1C), 192.79 (**C**O, 1C), 191.94 (**C**O, 2C), 116.83 (**C**N), 37.40 (**C**H₂), the signals of the quaternary carbons of the thiazolidinone backbone were not observed due to the low signal-to-noise ratio. IR (THF): v = 2193 s (CN), 2072 s (CO), 1975 sh (CO), 1958 vs (CO), 1925 s (CO), 1685 m, 1510 s. To record the NMR spectra in undeuterated THF the sample in a sealed thin-walled glass capillary (\sim 3.5 mm

diameter) was placed inside a standard 5 mm NMR tube containing acetone-d₆ for the lock signal.

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