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Rhodium-Complex-Catalyzed Addition Reactions of Chloroacetyl Chlorides to Alkynes

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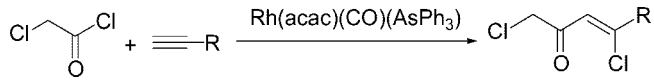
ABSTRACT



The addition reaction of chloroacetyl chloride derivatives with terminal alkynes was found to be catalyzed by Rh(acac)(CO)($AsPh_3$) to afford (*Z*)-1,4-dichloro-3-buten-2-one derivatives, which displayed diverse reactivities in synthetic elaboration.

Addition of acid chloride derivatives with alkynes is a useful reaction, affording β-chloroalkenyl ketones, which allow numerous synthetic applications, in particular, the synthesis of heterocyclic compounds.[1] These reactions have been made possible by using Lewis acids like $AlCl_3$. However, as is anticipated by the use of Lewis acid catalysts, the major products are usually (*E*)-isomers with some exceptions forming mixtures of (*E*)- and (*Z*)-isomers[2] and the selective synthesis of the (*Z*)-isomer still remains to be further scrutinized.

We have reported rhodium-catalyzed addition reactions of chloroformates, ethoxalyl chloride, and perfluorinated acid chlorides to terminal alkynes.[3] The electronegative substituent bound to the carbonyl group appears to play an important role to prevent possible decarbonylation in these reactions. For instance, pioneering work by Nomura, Miura, and coworkers reported the addition reaction of aroyl chlorides with alkynes. However, the reaction is not a neat addition of aroyl chlorides; it proceeds with concomitant decarbonylation, affording formal aryl chloride addition products.[4,5] In view of synthetic application, the products coming from CO-retentive addition are more useful than the formal ArCl adducts since the alkenyl−Cl bond is activated by the α,β-unsaturated carbonyl linkage.[1,6] Our continued study has

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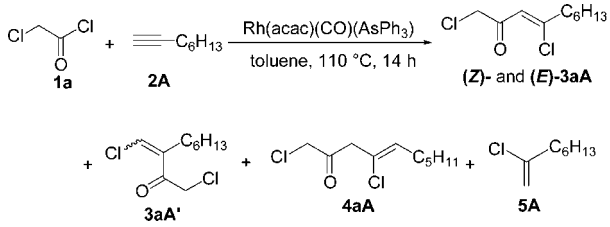
uncovered that even chloroacetyl chloride adds to alkynes to furnish (*Z*)-1,4-dichloro-3-buten-2-ones (Scheme 1) as

Scheme 1



major products, which are even more synthetically versatile, associated with the presence of extra chlorine at the α-position.[7]

In a representative experiment, a mixture of $Rh(acac)(CO)_2$ (0.04 mmol), $AsPh_3$ (0.04 mmol), chloroacetyl chloride **1a** (2.0 mmol), 1-octyne **2A** (2.0 mmol), and toluene (2.0 mL) was heated at 110 °C for 14 h. Analysis of the resulting mixture revealed that **(*Z*)-3aA** and **(*E*)-3aA** were formed in 80 and 6% yield, respectively. HCl adduct **5A** (5%) was also formed in a small quantity. However, possible byproducts such as **3aA′** and **4aA**, which were indeed found in trial experiments (vide infra), were not formed in this particular reaction, thus showing that the addition reaction had taken place regio- and stereoselectively. Routine workup allowed isolation of **(*Z*)-3aA** and **(*E*)-3aA**, which were fully characterized, inclusive of NOE experiment, reduction of **(*Z*)-3aA** to the corresponding alcohol **(*Z*)-3aA-red**, and its characterization and also X-ray crystallography in the case of **(*Z*)-3aI**.[8]

Before the $Rh(acac)(CO)_2-AsPh_3$ catalyst system was determined to be the catalyst of choice, we ran a series of trial experiments to look mainly into the ligand effect (Table 1). In general, $AsPh_3$ is far better performing than the other ligands (entries 1−3), although its performance is dependent on the conditions. For instance, under somewhat different conditions (80 °C, 60 h), the reaction using a less selective catalyst $RhCl(CO)(AsPh_3)_2$ afforded, besides **(*Z*)-3aA** (39%) and **(*E*)-3aA** (8%), regioisomer **3aA′** (4%), **5A** (40%), and octyne oligomers. Strikingly different from the addition reaction of heptafluorobutyryl chloride,[3c] PPh_3 complexes display very low performance, although the outcome is variant depending on the particular structure (entries 4−7). The low performance of PPh_3 and other triarylphosphines (entries 8 and 9) is associated mainly with the formation of byproducts **4aA** (vide infra) and **5A**. In the reactions using $RhCl(PPh_3)_3$, RhCl(CO)(dppb), RhCl(CO)(dppp), and $[RhCl(CO)_2]_2$, the conversion of **1a** was low as compared with the conversion of **2A**, indicative of more extensive oligomerization having taken place (entries 6, 10, 11, and 14). On the other hand, $RhCl(CO)(PMe_3)_2$ and RhCl(CO)(dppe) also resulted in low conversion of **1a** due to their intrinsic low activity toward both the desired reaction and the oligomerization (entries 12 and 13).

Table 1. Catalyst Screening for the Reaction of **1a** with **2A**[a]

		yield[b] (%)		
entry	catalyst	**3aA (Z/E)**	**4aA**	**5A**
1	$Rh(acac)(CO)(AsPh_3)$[c]	86 (93/7)	0	5
2	$RhCl(CO)(AsPh_3)_2$[c]	52 (52/48)	14	8
3	$Rh(acac)(AsPh_3)_2$[c]	43 (58/42)	21	9
4	$Rh(acac)(CO)(PPh_3)$[c]	22 (77/23)	19	36
5	$RhCl(CO)(PPh_3)_2$[c]	11 (85/15)	29	23
6	$RhCl(PPh_3)_3$	5 (60/40)	4	10
7	$[Rh(CO)(PPh_3)_2][BF_4]$	4 (75/25)	5	16
8	$RhCl(CO)[P(p\text{-}MeC_6H_4)_3]_2$[c]	15 (67/33)	10	29
9	$RhCl(CO)[P(p\text{-}FC_6H_4)_3]_2$[c]	18 (73/27)	22	24
10	RhCl(CO)(dppb)$_2$[c]	16 (50/50)	8	15
11	RhCl(CO)(dppp)$_2$[c]	14 (64/36)	<1	25
12	RhCl(CO)(dppe)[c]	22 (73/27)	<1	6
13	$RhCl(CO)(PMe_3)_2$	9 (66/34)	3	5
14	$[RhCl(CO)_2]_2$	10 (50/50)	16	10

[a] Reaction conditions: **1a** (2 mmol), **2A** (2 mmol), catalyst (2 mol %), toluene solvent (2 mL), 110 °C, 14 h. [b] Determined by ^1H NMR spectroscopy. [c] Generated in situ by treating $[RhCl(CO)_2]_2$ or $Rh(acac)(CO)_2$ with the respective ligands.

The formation of byproduct **4aA** appears to have come from double-bond isomerization of initially formed **3aA**. Thus, heating a toluene-d_8 solution of pure **(*Z*)-3aA** and $Rh(acac)(CO)(PPh_3)$ (3 mol %) in an NMR tube at 110 °C for 18 h resulted in a mixture comprising **(*Z*)-4aA** (69%) and **(*Z*)-3aA** (31%). Note that **(*E*)-3aA** was not detected at all. The time-course of the $RhCl(CO)(PPh_3)_2$ (5 mol %)-catalyzed reaction at 110 °C further confirmed the isomerization.[9] The formation of **(*E*)-3aA** in the addition reactions and the lack of isomerization of **(*Z*)-3aA** to **(*E*)-3aA** indicates that **(*E*)-3aA** is a genuine product formed as primary product, but not from the isomerization of initially formed **(*Z*)-3aA**.

As for the formation of **5A**, we are unable to identify the provenance of HCl. Although H−Rh−Cl species or HCl can be generated through β-hydride elimination from a chloroacetyl−Rh intermediate (vide infra), we have not encountered the formation of chloroketene or its derivatives, which should have been simultaneously formed.

The representative procedure could be successfully applied to a variety of terminal alkynes (Table 2). Besides 1-octyne, other aliphatic alkynes such as *tert*-butylacetylene **2B** (entry 2) and trimethylsilylacetylene **2C** (entry 3) reacted, albeit somewhat slowly due presumably to the steric congestion, to afford high *Z*/*E* ratios, although trimethylsilylacetylene underwent more extensive oligomerization. Alkynes substituted by chloro, cyano, methoxycarbonyl, and siloxy groups **2D**−**G** also formed the corresponding adduct (entries 4−7). However, the *Z*/*E* ratios were less satisfactory (vide infra).

The reaction of benzylacetylene **2H** was also less *Z*-selective, and (*Z*,*Z*)-1,6-diphenyl-2,5-dichloro-2,4-hexadiene

(7) α-Halo ketones are also useful intermediates in organic synthesis. See: (a) *Sci. Synth.* **2005**, *26*, 869. (b) *Sci. Synth.* **2005**, *26*, 745.

(8) For X-ray crystallographic details, see the Supporting Information.

(9) For details, see the Supporting Information.

Table 2. Reaction of **1a** with Terminal Alkynes **2A**−**M**[a]

entry	Product, R =	**3** yield[b] (%)	*Z*/*E*[b]
1[c]	**3aA**, *n*-hexyl	86	93/7
2[d]	**3aB**, *t*-Bu	98	100/0
3[e]	**3aC**, trimethylsilyl	47[f]	100/0
4	**3aD**, 3-chloropropyl	76	82/12
5	**3aE**, 3-cyanopropyl	36	53/47
6[g]	**3aF**, 3-(methoxycarbonyl)propyll	57	58/42
7	**3aG**, *tert*-butyldimethylsiloxyethyl	85	63/37
8	**3aH**, benzyl	35[h]	71/29
9	**3aI**, phenyl	63	87/13
10	**3aJ**, *p*-methoxyphenyl	82	84/16
11	**3aK**, *p*-fluorophenyl	55[f]	85/15
12	**3aL**, 2-thienyl	98	93/7
13	**3aM**, ferrocenyl	42	nd[i]

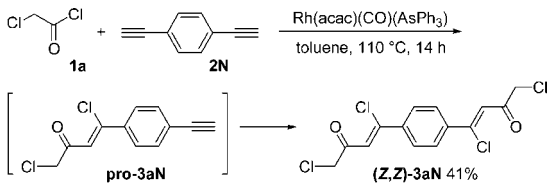
[a] Reaction conditions: **1a** (2 mmol), **2A** (2 mmol), Rh(acac)(CO)($AsPh_3$) (0.1 mmol), toluene solvent (2 mL), 110 °C, 14 h. [b] Determined by ^{1}H NMR spectroscopy. [c] Quantity of Rh(acac)(CO)($AsPh_3$) = 0.04 mmol. [d] Reaction time = 24 h. [e] Reaction time = 18 h. [f] Extensive oligomerization proceeded. [g] Reaction time = 8 h. [h] A large quantity of (*Z*,*Z*)-1,6-diphenyl-2,5-dichloro-2,4-hexadiene was formed. [i] Not determined.

6H was formed as another type of byproduct (entry 8).[10] On the other hand, aromatic and heteroaromatic acetylenes **2I**−**L** (entries 9−12) displayed higher *Z*-selectivities. Note that the nature of the para-substituent displays a distinct effect on the extent of oligomerization, which was more serious for *p*-fluorophenylacetylene as judged by ^{1}H NMR analysis of the reaction mixture. Ferrocenylacetylene **2M** behaved somewhat differently; the color of the reaction mixture was dark purple, and a large quantity of a dark green solid was also formed. This observation and the line-broadening of every ^{1}H NMR signal of the reaction mixture suggest that the ferrocene moiety was oxidized during the catalysis.

The reactions of conjugated alkynes such as methyl propiolate, dimethyl acetylenedicarboxylate, and 1-ethynylcyclohexene were not successful; the major event was oligo- or polymerization. 4-Octyne having an internal triple bond gave only a trace of oligomers.

1,4-Di(ethynyl)benzene **2N** reacted with **1a** (2 equiv) to afford the corresponding diketone (Scheme 2). The somewhat

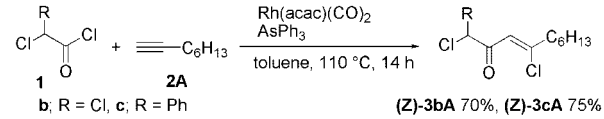
Scheme 2



low yield may stem from the ease of oligomerization of the initially formed adduct **pro-3aN** rather than the second addition reaction. Intermediate **pro-3aN** is an aromatic alkyne having an electronegative group at the para-position. In view of the extensive oligomerization found in the *p*-fluorophenylacetylene reaction, one can expect the formation of oligomers, which were indeed found in the reaction of **2N**.

The reactivity of chloroacetyl chloride derivatives having substituents at the α-position is highly dependent on the nature of the substituent. Dichloroacetyl chloride **1b** and phenylchloroacetyl chloride **1c** reacted with **2A** normally (Scheme 3). However, α-chlorobutyryl chloride **1d** and

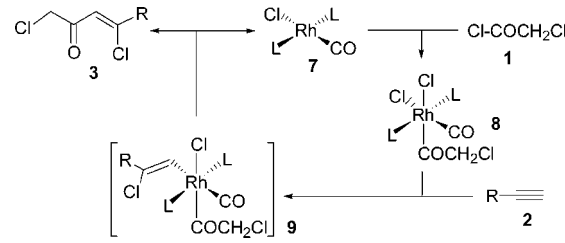
Scheme 3



trichloroacetyl chloride **1e** did not form the corresponding adducts at all, and instead, (*Z*,*Z*)-7,10-dichlorohexadeca-7,9-diene **6A** was formed in 42 and 63% yield, respectively.[10] In the reaction of **1d**, 1,1-dichloropropane (10%) and 1-propenyl chloride (18%) were also formed, suggesting that decarbonylation and *β*-hydride elimination processes were also taking place.

The present catalysis is most likely to proceed through three processes: oxidative addition of the C(O)−Cl bond of **1** to Rh(I), insertion of alkyne into the Rh−Cl bond, and subsequent C−C reductive elimination (Scheme 4, illustrated

Scheme 4



for $RhCl(CO)L_2$-type catalysts). The following observations substantiate the proposal, albeit partially.

Attempted oxidative addition of **1a** with Rh(acac)(CO)($AsPh_3$) did not proceed cleanly (room temperature in toluene, 3 h); the yellow solid obtained did not display satisfactory IR or ^{13}C and ^{1}H NMR spectra. However, the reaction with $RhCl(CO)(AsPh_3)_2$ **7-AsPh$_3$** (room temperature in benzene, 3 h) took place neatly to give $RhCl_2(CO)(AsPh_3)_2(COCH_2Cl)$ **8-AsPh$_3$** (88%). Although **8-AsPh$_3$** was totally insoluble in any common solvents, we were able isolate an analytically pure sample, the structure of which was unequivocally verified by X-ray analysis.[8] $RhCl(CO)L_2$ (**7-PMe$_3$**: L = PMe_3, **7-PMePh$_2$**: L = $PMePh_2$) also reacted cleanly to form $RhCl_2(CO)L_2(COCH_2Cl)$ (**8-PMe$_3$**, 92%; **8-PMePh$_2$**, >99%).[8] Thus, oxidative addition of **1a** is a clean and facile process

(10) Details will be reported separately.

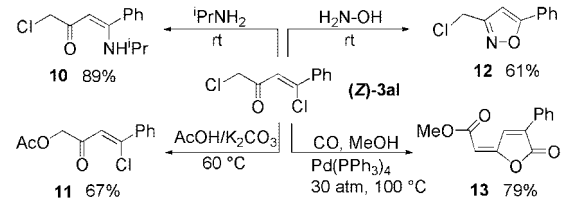
as far as the Vaska type rhodium complexes are concerned, as was reported by Cole-Hamilton and a co-worker.[11]

To gain information of the insertion process, **8-AsPh$_3$** was treated with 2 equiv of **2A** in toluene-d_8. Although **8-AsPh$_3$** was insoluble, the mixture became homogeneous at 110 °C. ^{1}H NMR analysis of the mixture after 12 h revealed quantitative reductive elimination back to **1a** having taken place. The reaction of **8-PMe$_3$** with **2A** under identical conditions also resulted in extensive reductive elimination (61%) with **8-PMe$_3$** (33%) remaining unchanged. Another attempted reaction using **8-PMePh$_2$** and **2A** was not informative of the details of the insertion process either.

Although the foregoing attempts to confirm insertion of alkyne failed due to the facile reductive elimination, we presume that the insertion does take place during the catalysis in the presence of a large quantity of **1a**. In closely related reactions of chloroformate, ethoxalyl chloride, and perfluorinated acid chloride,[3] we have proposed that the insertion takes place through chloro-rhodation (vs acyl-rhodation), which agrees with *cis*-insertion forming a (*Z*)-isomer as near a sole product. In contrast, the present reaction is somewhat different in that the *Z*/*E* ratios are low, in particular, when functional groups are introduced to the alkyne molecules (entries 5−7, Table 2). The low ratio is not due to the *Z*-to-*E* isomerization since **(*Z*)-3aA** did not isomerize to **(*E*)-3aA** when exposed to Rh(acac)(CO)(PPh$_3$) (vide supra). Moreover, the *Z*/*E* ratio in the reaction of **2F** (entry 6, Table 2) was basically constant throughout the time course, suggesting that **(*E*)-3aF** is, at least partially, a genuine initial product formed from the main event, not through possible secondary processes like isomerization. Accordingly, we may have to admit that there is possible involvement of *trans*-insertion via external nucleophilic attack of chloride, as far as polar alkynes are concerned.[12] *trans*-Chlororhodation has not been documented, but *trans*-chloropalladation is a well-known process.[13]

Synthetic utility of the products is exemplified for **3aI** (Scheme 5). The reaction with isopropylamine took place

Scheme 5



exclusively at the β-chlorine but acetic acid replaced the α-chlorine. Cyclization with hydroxylamine involved both carbonyl group and the β-chlorine to afford isoxazole **12**, while another type cyclization involving both chlorine atoms was possible in the palladium-catalyzed carbonylation, affording **13**.[14]

In conclusion, Rh(acac)(CO)(AsPh$_3$) catalyzes the addition reaction of chloroacetyl chloride with terminal alkynes to furnish 1,4-dichloro-3-butene-2-ones, which are envisioned to serve as versatile intermediates in organic synthesis. Further extension to other acid chloride derivatives is in progress.

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Supporting Information Available: Experimental details, spectral data of all new compounds, and details of the X-ray analysis of (*Z*)-**3aI**, **8-AsPh$_3$**, **8-PMe$_3$**, and **8-PMePh$_2$**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Weston, S. W.; Cole-Hamilton, D. J. *Inorg. Chim. Acta* **1998**, *280*, 99.

(12) A solvent effect study to look into *cis*-/*trans*-insertion using polar solvents like acetone and THF for the reaction of 1-octyne was hampered by very low yields, which did not furnish reliable data of the *Z*/*E* ratio. However, a lower *Z*/*E* ratio was observed when the reaction of entry 6 (Table 2) was repeated in the presence of (*n*-octyl)$_3$MeNCl, although the reaction was messy. For details, see the Supporting Information.

(13) Lu, X. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; John Wiley & Sons: New York, 2002; Vol. II, pp 2267−2287.

(14) For γ-alkylidenebutenolides in pharmaceutical applications, see: Ahmed, Z.; Langer, P. *J. Org. Chem.* **2004**, *69*, 3753, and references cited therein.