Chromium(II)-Mediated Intermolecular Free-Radical Carbon – Carbon Bond Formation

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Chromium(II) complexes are found to be effective mediators for intermolecular free-radical C – C bond formation. Thus, $Cr(en)_2^{2+}$ species react with alkyl halides to generate the corresponding alkyl radicals which are readily trapped with electron-deficient alkenes to afford the coupling products.

Free-radical carbon – carbon bond-forming addition reactions have been a subject of continuous interest as evidenced by a large number of reports in the recent literature[1–6]. The most important methodology for intermolecular C – C bond formation involves the addition of alkyl radicals to carbon – carbon multiple bonds followed by trapping of the adduct radical. Alkylmercury compounds and alkyl halides with tri-*n*-butyltin hydride have been basic reagents for alkyl radical generation.

In general, chromium(II) salts are known to be effective reducing agents for alkyl and aryl halides[7]. The reaction is believed to proceed by a free-radical mechanism according to Scheme 1. Evidence to support such a mechanism includes the formation of cyclized products from the reduction of 5-hexen-1-yl bromide[7]. The hydrolysis of the alkylchromium species in the last step is presumably a heterolytic process. More recently, chromium(II) complexes have been used in intramolecular free-radical carbon – carbon bond-formation reactions[8,9]. Thus, ω-alkyn-1-yl halides underwent regioselective free-radical cyclizations when reduced with ethylenediamine complexes of Cr^{II} to give substituted methylenecycloalkanes[8]. Similarly, Lübbers and Schäfer have reported that Cr^{II} salts can be effectively used to prepare substituted tetrahydrofurans through radical cyclization of the approporiate alkenyl halides[9].

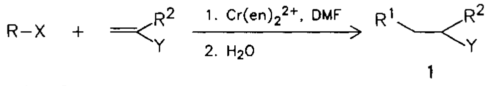
Scheme 1

$$\begin{array}{llllll} R{-}X & + & Cr^{2+} & \longrightarrow R^{\cdot} & + & XCr^{3+} \\ R^{\cdot} & + & Cr^{2+} & \longrightarrow R{-}Cr^{3+} & & \\ R{-}Cr^{3+} & + & H_2O & \longrightarrow RH & + & Cr^{3+} \end{array}$$

As far as we are aware chromium(II) salts have not been used to mediate intermolecular free-radical C – C bond formation[10]. That has stimulated us to investigate the applicability of chromium(II) salts in intermolecular C – C bond-formation reactions. This report presents our first results in this area.

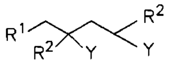
It is found that the ethylenediamine complexes of chromium(II) in dry dimethylformamide (DMF) can effectively mediate an intermolecular carbon – carbon bond formation between alkyl halides and alkenes to afford the corresponding saturated product **1** (Scheme 2). The reactions were performed at room temperature under argon. Dropwise addition of ethylenediamine (2.0 equiv.) in DMF to the green suspension of chromium(II) chloride in DMF led to an immediate color change to pale blue followed by a slower further change to the final dark blue suspension. Addition of the trapping alkene (5.0 equiv.) in one portion was not accompanied by any color change. Dropwise addition of the alkyl halide (0.5 equiv.) in DMF led to a slow color change to pale brown, then to deep brown. The reaction mixtures were stirred at room temperature for several hours after the addition was complete, hydrolyzed with water, and the aqueous solutions were extracted with ether. The reactions were generally complete within a few hours and afforded the coupling products **1** in good to moderate yields. The main products were isolated and identified by GC/MS, ^{1}H-NMR, and compared to those known in the literature.

Scheme 2



R^1, R^2, X, Y: See Table 1.

Primary, secondary, and tertiary alkyl bromides and iodides as well as benzyl bromide were examined, and the results of their reactions with electrophilic alkenes are summarized in Table 1. The coupling of the nucleophilic alkyl radicals, generated from the above-mentioned precursors, with electron-deficient alkenes proceeded smoothly. Thus, treatement of *tert*-butyl bromide with $Cr(en)_2^{2+}$ complexes in the presence of methyl acrylate furnished the coupling product in 72% yield. In addition, a small amount of the double-addition product **2** (R^1 = *t*Bu, R^2 = H, Y = CO_2CH_3) was identified by GC/MS. Other alkyl halides reacted in a similar fashion to afford the coupling products. In general, alkyl iodides reacted faster than alkyl bromides.



2

The results of this study are in full agreement with prior work on the coupling of alkyl radicals with electron-deficient alkenes[1,2]. The use of chromium(II) for the radical generation gave comparable results to those obtained with alkylmercury compounds and tributyltin hydride[11,12], thus extending the present methodology.

The reaction is believed to proceed by a free-radical mechanism and presumably involves the alkyl free radical as an intermediate. The formation of product **1** is consistent with the mechanism given

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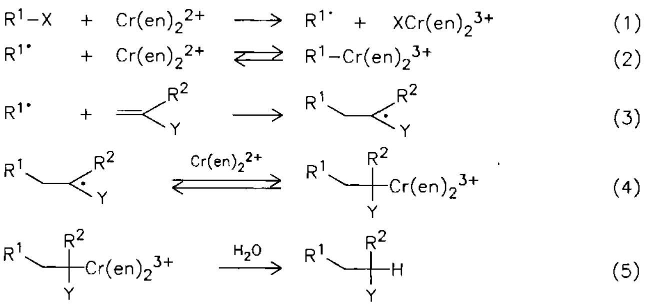
in Scheme 3. The reaction involves a regioselective addition of the radical R to the alkene followed by trapping the adduct radical by another equivalent of chromium(II). The high reduction potential of chromium(II) makes it difficult for the reaction to be a chain one. Thus, two equivalents of chromium(II) salts was needed.

Scheme 3



It is worth mentioning that the benzyl radical can be generated and trapped with electron-deficient alkenes by using a chromium(II) chloride suspension in dry tetrahydrofuran. However, the reaction proceeded slowly at room temperature, but can be dramatically accelerated by heating the reaction mixture under reflux. Thus, addition of benzyl bromide (0.5 equiv.) to the green suspension of chromium(II) chloride (1.0 equiv.) in dry THF (50 ml) and in the presence of methyl acrylate (8.0 equiv.) led to a gradual change to a brown color. Heating the reaction mixture under reflux for 8 hours followed by hydrolysis gave the coupling product **1** (R^1 = $C_6H_5CH_2$, R^2 = H, Y = CO_2CH_3) in 76% yield, in addition to a small amount of bibenzyl (4%). The reaction of benzyl bromide, in general, was accompanied by the formation of the dimeric product, bibenzyl, in low yields. The capability of chromium(II) salts for the reductive coupling of alkyl halides is well documented[13,14]. The reaction of benzyl halides with chromium(II) salts was extensively studied and shown to give benzylchromium complexes, which were identified spectroscopically[15–18]. The latter species reacted in aqueous organic solvents to give either bibenzyl or toluene, and a mechanism for its reactions was given[15]. In one case the trapping of benzylchromium complexes with acrylonitrile in aqueous DMF afforded the coupling product in 40% yield[15].

Attempts to trap the benzyl radical by alkyl-substituted alkenes under these reaction conditions failed. Thus, heating of benzyl bromide and cyclohexene in THF under reflux in the presence of chromium(II) chloride led exclusively to bibenzyl formation (87%; GC), and only a trace of the coupling product was observed.

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Experimental

Materials: Anhydrous chromium(II) chloride was purchased from Aldrich. Alkyl halides and alkenes were obtained from Aldrich and distilled prior to use. DMF was dried as described in the literature[19].

General Procedure: All operations were performed under argon. To the green suspension of chromium(II) chloride (1.84 g, 15.0 mmol) in dry dimethylformamide (50 ml) was added dropwise an ethylenediamine (1.80 g, 30.0 mmol) solution in dimethylformamide (10.0 ml). The color was initially pale blue which then turned to the final deep blue color. The alkene (35.0 mmol) was added in one portion, then the alkyl halide (7.0 mmol) in DMF (10 ml) was added dropwise with continuous stirring. The addition of the alkyl halide was accompanied by an immediate color change to pale brown, then to deep brown. The reaction mixture was stirred at room temperature for several hours after which it was poured into water (100 ml). The aqueous solution was extracted with diethyl ether (3 × 50 ml). The combined ether extracts were washed with water (2 × 30 ml), dried with magnesium sulfate, and filtered. The ether was distilled off, and the residue was distilled under reduced pressure to give the coupling product. Coupling products of entries 1–6 in Table 1 were descried in ref.[11], that of entry 9 in ref.[15], that of entry 10 in ref.[20], and that of entry 11 in ref.[21].

Table 1. Formation of **1** by chromium(II)-mediated coupling reactions of alkyl halides (R^1X) and alkenes ($H_2C{=}CR^2Y$) in DMF at room temperature (Scheme 2)

Entry no.	R^1	X	R^2	Y	Reaction time [h]	Yield (%)[a,b]
1	$(CH_3)_3C$	Br	H	CO_2CH_3	8	72
2	$(CH_3)_3C$	Br	CH_3	CO_2CH_3	8	65
3	c-C_6H_{11}	Br	H	CO_2CH_3	10	56
4	c-C_6H_{11}	I	H	CO_2CH_3	6	66
5	c-C_6H_{11}	I	H	CN	6	68
6	c-C_6H_{11}	I	CH_3	CO_2CH_3	6	50
7	$(CH_3)_2CHCH_2$	I	CH_3	CO_2CH_3	10	45[c]
8	$(CH_3)_2CHCH_2$	Br	CH_3	CO_2CH_3	14	40[c]
9	$C_6H_5CH_2$	Br	H	CN	8	70[d]
10	$C_6H_5CH_2$	Br	H	CO_2CH_3	8	63[d]
11	$C_6H_5CH_2$	Br	CH_3	CO_2CH_3	8	68[d]

[a] Isolated yields of pure products (>90%; GC); all products listed in Table 1 are fully characterized by MS and ^1H NMR. – [b] In addition to the main product, products of double addition were detected by GC and identified by GC/MS (<8% GC yield, correction factor 1). – [c] Polymeric material was detected after distilling the coupling product. – [d] Bibenzyl was detected in 5–10% yield (GC).

Methyl 2,5-Dimethylhexanoate (Entries 7 and 8): B.p. 45–48°/3 Torr. – ^1H NMR ($CDCl_3$): δ = 0.87 [d, J = 6.6 Hz, 6H, $CH(CH_3)$], 1.15 [d, J = 6.9 Hz, 3H, $CH(CH_3)$], 1.18–1.70 [m, 5H, $(CH_2)_2$ and $CH(CH_3)_2$], 2.41 (m, 1H, CH), 3.68 (s, 3H, OCH_3). – MS (70 eV): m/z (%) = 158 (trace) [M^+], 143 (1) [$M^+ - CH_3$], 127 (5) [$M^+ - OCH_3$], 101 (21), 88 (100).

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