

Conjugate Additions of Alkylchromium Reagents mediated by Chromium(III) chloride/ Manganese

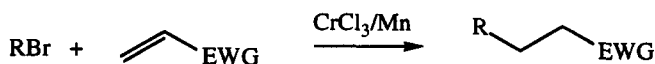
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Abstract: Benzyl and glycosylchromium reagents generated from the corresponding halides and the couple Cr(III)/Mn were added to activated alkenes to afford Michael adducts. The influence of a ligand around the chromium atom as well as the use of a catalytic amount of chromium chloride were investigated. © 1998 Elsevier Science Ltd. All rights reserved.

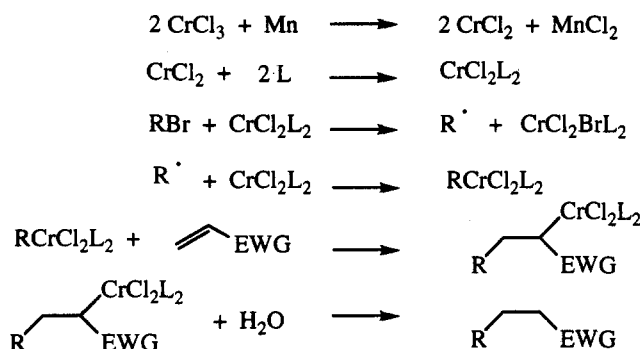
Organochromium reagents have been extensively used in carbon-carbon bond formation reactions.¹ Most of these reactions involve allyl, propargyl, alkenyl, alkynyl or α -acylchromium reagents in Grignard or Reformatsky-type addition to aldehydes.² When alkylchromium reagents are generated from alkyl halides and chromium(II) salts, their reactivity towards aldehydes compete with the cross-coupling reaction³ and with the reduction of alkyl halides to alkanes.⁴ The rate-determining step of the reduction is the formation of the alkyl radicals.⁵ This radical could be stabilized by a sulfur atom; α -thioalkylchromium (III) species prepared by chromium(II) reduction of α -iodosulfides add smoothly and selectively to aldehydes.⁶ A comparison between primary, secondary and tertiary halides in their chromium(II)-mediated tandem coupling reactions with 1,3-dienes and carbonyl compounds has shown that tertiary alkyl iodides are the most active reagents for the sequential generation of radical and anionic species with chromium(II) chloride.⁷ Some additives, catalysts or ligands turned out to be efficient in the determining step, i.e. the reduction of alkyl halides with chromium(II) salts.⁸ One of the main advantages of the ligands is to enhance significantly the reduction potential of Cr(II)/Cr(III) couple. Thus ethylenediamine complexes of chromium(II) are known to efficiently reduce alkyl and aryl halides to the corresponding alkanes^{3,4} as well as to mediate an intermolecular carbon-carbon bond formation between alkyl (or aryl halides) and alkenes.^{9,10} A salient feature in the chromium(II)-mediated reactions is the quality of CrCl₂ which oxidizes rapidly in the presence of moisture. It is well known that the reduction of halides with CrCl₂ fails when the powder turns to a greenish color. An answer could be the *in situ* preparation of CrCl₂ by reduction of chromium(III) by zinc¹¹ or manganese¹². Besides chromium(III) chloride is much less expensive than chromium(II) chloride and the reaction might be catalyzed in chromium.¹² We report herein the use of the couple CrCl₃/Mn in the addition of alkyl halides to activated alkenes.



Scheme 1

With methyl acrylate as the electrophile, 4-*tert*-butylpyridine has the same beneficial influence on the yield of the Michael reaction (74% with the ligand, 53% without it).

Based on previous assumptions,¹⁰ the mechanism of the reaction is outlined in Scheme 3:



Scheme 3

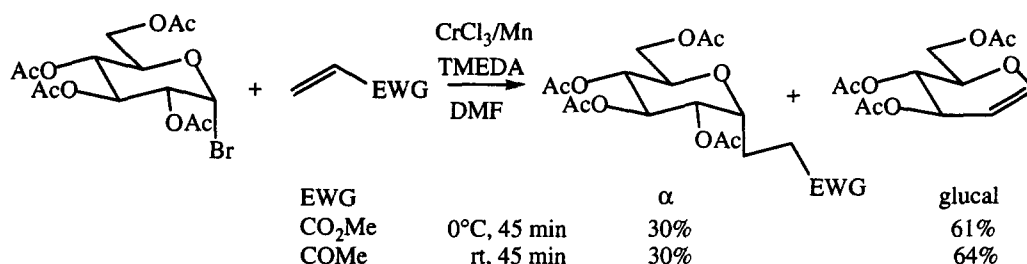
The Michael adduct is formed after trapping of the organometallic species by water, which liberates a chromium(III) species. If we postulate that such a species could be reduced with manganese, then the addition of a small amount of water could facilitate the regeneration of chromium. As a matter of fact, our studies showed that the reaction could be catalytic in chromium (Table 3), although the turnover is small and the amount of water must be severely controlled. The addition of a concentrated addition of HCl could be an alternative, but the combination of trimethylsilyl chloride (TMSCl) and isopropanol which generates HCl in an anhydrous medium turned out to be a more promising way (runs 7 and 8 in Table 3).

Table 3: Reaction with benzyl bromide, acrylonitrile (5 eq.), Mn (1 eq.) in THF (r.t., 13 h)

Run	CrCl ₃ (eq.)	Additive (eq.)	Isolated yield (1)	Isolated yield (2)
1	2	H ₂ O (0.42)	67%	2%
2	1	H ₂ O (0.42)	70%	traces
3	0.5	H ₂ O (1)	63%	7%
4	0.5	HCl 12 N (0.42)	67%	2%
5	0.5	C ₂ H ₅ OH (1)	54%	4%
6	0.25	HCl 12 N (0.42)	38%	5%
7	0.25	TMSCl + iPrOH (1)	62%	traces
8	0.1	TMSCl + iPrOH (1)	48%	traces

At this stage of the discussion, it is interesting to examine if glycosyl chromium species which could be prepared as intermediates¹⁵ can react with electrophiles. Indeed, preliminary results showed that the reaction between acetobromoglucose and methyl acrylate (20 eq.) in the presence of chromium(III) chloride (4 eq.), manganese and TMEDA as the ligand gave 30% of the α -C-glucoside and 61% of glucal (Scheme 4). Only the α configuration of the C-glycoside was obtained. No rearrangement of the acetyl group affording 2-deoxyglucopyranose¹⁶ occurred, which precludes an anomeric radical as a long-lived intermediate. On the

other hand, the importance of the elimination of the acetyl group at the C-2 position of the carbohydrate ring indicates the transient formation of an anomeric carbon-chromium bond.



Scheme 4

We are now investigating the possibility to apply this methodology to prepare C-glycosides from carbohydrates devoid of leaving groups at the C-2 position of the ring.

References and notes

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- In a typical experiment, manganese (0.087g, 1.57 mmol) and anhydrous CrCl₃ (0.499g, 3.15 mmol) were put together and were stirring under nitrogen. THF (4 mL) was then added to the solid mixture. A solution of 4-tBuPy (0.925 mL, 6.3 mmol) in THF (5mL) was added dropwise to the suspension. To the resulting green solution were introduced acrylonitrile (0.398g, 7.5 mmol) and then benzyl bromide (0.257g, 1.5 mmol). After 13 h, the mixture was hydrolyzed with a solution of ammonium chloride, extracted with diethyl ether. The organic layers were washed with sodium hydrogen sulfate and sodium hydrogen carbonate solutions, then dried over magnesium sulfate. After evaporation, the residue was purified by chromatography on silica gel (cyclohexane/ ethyl acetate: 9/1) to afford 0.185g of the Michael adduct (85%).
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