Geminal Dialkylation and Alkylative Reduction of Aliphatic Aldehydes

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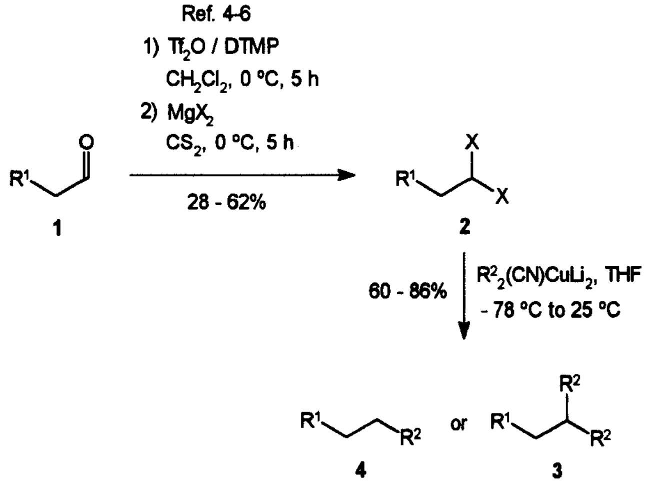
gem-Dialkylation or alkylative reduction of α-unbranched aliphatic aldehydes is easily carried out by replacing the carbonyl oxygen with the *gem*-dihalide functionality followed by substitution of each halogen (bromine or iodine) by two *n*-alkyl groups or one *sec*- or *tert*-alkyl group and one hydrogen atom using higher-order dialkyllithium cyanocuprates.

The aldehyde group is one of the most versatile functional groups used in organic synthesis. However, neither its conversion to a *gem*-dialkyl group nor its alkylative reduction, i.e. transformation of **1** into **4**, is easily accomplished by currently available methods. Thus, the reaction of α,β-unsaturated sulfones, prepared from aldehydes[1] and sulfonomethylphosphonate anions with lithium dialkylcuprates allows effective conversion of **1** into *gem*-dialkylated compounds **3**, but with the limitation that at least one alkyl group must be a methyl group.[1] It should be mentioned that the direct *gem*-dimethylation of carbonyl compounds with dimethyltitanium dichloride fails in the case of aliphatic aldehydes.[2] The alkylative reduction of **1** via selenoacetals allows only the introduction of primary radicals.[3] We and others have worked out straightforward methods for the preparation of *gem*-bistriflates,[4,5] *gem*-dibromides **2** (X = Br)[6,7] and *gem*-diiodides **2** (X = I)[6,8] from aliphatic aldehydes **1**. The substitution of these functionalities by alkyl groups could then be a general method for the transformation of an aldehyde carbonyl group to a tertiary or quaternary alkyl carbon atom. Until now, only the coupling reactions of *gem*-dichlorides and *gem*-dibromocyclopropanes were investigated. Most of the aliphatic *gem*-dichlorides **2** (X = Cl) are unreactive toward lithium organocuprate reagents.[1] The reaction of *gem*-dibromocyclopropanes with di-*n*-alkyllithium cuprates leads to efficient cross coupling, but it is necessary to carry out the reaction in the presence of a high excess of the alkyl halide corresponding to the *n*-alkylcopper reagent.[9] The reactions with di-*sec*-alkyllithium cuprates and di-*tert*-alkyllithium cuprates afford lower yields of dialkylated products.[10] Also, the reactions with dialkylcuprates are occassionally sluggish, requiring long reaction times.[11] Better results are obtained by using higher-order organocuprates.[11,12] In the present paper we report on the reaction of dialkyllithium cyanocuprates[13] with the *gem*-dihalides **2** (X = Br, I), which were prepared by reaction of the corresponding magnesium halides in carbon disulfide with *gem*-bistriflates. The *gem*-bistriflates were synthesized from aldehydes **1** and triflic anhydride as reported by us earlier.[4] The obtained results in the reaction of **2** with dialkyllithium cyanocuprates in tetrahydrofuran are summarized in the Table and Scheme.



DTMP = 2,6-di-*tert*-butyl-4-methylpyridine

3, 4	R^1	R^2	X
a	n-C$_6$H$_{13}$	CH$_3$	I
b	n-C$_6$H$_{13}$	n-C$_4$H$_9$	I
c	C$_6$H$_5$CH$_2$	CH$_3$	Br
d	C$_6$H$_5$CH$_2$	n-C$_4$H$_9$	Br
e	C$_6$H$_5$CH$_2$	s-C$_4$H$_9$	Br
f	C$_6$H$_5$CH$_2$	t-C$_4$H$_9$	Br
g	C$_6$H$_5$CH$_2$	CH$_3$	I
h	C$_6$H$_5$CH$_2$	s-C$_4$H$_9$	I

Scheme

No significant differences were found in the reaction of dialkyllithium cyanocuprates (R^2_2(CN)CuLi$_2$) with **2** when X = Br or I. The alkane **3c** is obtained in 82% yield from **2c** and in 80% from **2g** showing that, in this reaction, the higher intrinsic reactivity of the C–I bond in relation to the C–Br bond is compensated for by the steric hindrance of the iodine atom. The steric hindrance of the alkyl chains of the cuprates and of the substrates **2** also plays a very important role in the course of the reaction. Thus, if unbranched groups R^2 are employed, geminal alkylation takes place in good yield, giving products **3**. When R^2 is α-substituted the reaction also takes place in good yield, although leading to the products **4**, which are formed by alkylative reduction. This process is initiated by radical substitution of an halogen atom by hydrogen giving a mono halogenated derivative,[14] which then is transformed into the product **4**. No reaction takes place when α-alkyl substituted dihalides **2** are used.

Table. Alkylation of *gem*-Dihalides **2** with $R_2^2(CN)CuLi_2$

Product	Yield (%)[a]	bp (°C)/mbar found[b]	bp (°C)/mbar reported	^{13}C NMR ($CDCl_3$/TMS)[c] δ
3a	80	170/1010	166/1010[15]	14.02 (C-9), 22.55 (C-1, C-1′), 22.61 (C-8), 27.35 (C-4), 27.89 (C-2), 29.32 (C-6), 29.84 (C-5), 31.86 (C-7), 38.99 (C-3)
3b	65	170/40	156/33[16]	13.95 (C-1, C-1′, C-12), 22.52 (C-2, C-2′, C-11), 26.71 (C-7), 29.18 (C-3, C-3′, C-8, C-9), 30.77 (C-10), 31.79 (C-4, C-4′, C-6), 32.66 (C-5)
3c	82	100/40	94–96/37[17]	28.40 (C-3), 22.60 (C-4, C-4′), 34.60 (C-1), 41.66 (C-2), 126.33, 129.10, 143.85 (C-ar.)
3d[d]	75	150/7		14.07 (C-7, C-7′), 23.05 (C-6, C-6′), 28.76 (C-5, C-5′), 33.07 (C-3, C-4, C-4′), 35.62 (C-1), 37.05 (C-2), 125.37, 128.20, 143.21 (C-ar.)
4e	78	100/66	85–86/40[18]	11.53 (C-6), 19.05 (C-5′), 28.88 (C-3), 29.27 (C-2), 34.23 (C-5), 36.49 (C-1, C-4), 125.76, 128.91, 142.77 (C-ar)
4f	86	80/66	227/1010[19]	26.66 (C-2), 29.31 (C-5, C-5′), 36.70 (C-1), 43.85 (C-3), 125.50, 128.34, 142.76 (C-ar)
3c	80	100/40	94–96/37[17]	
4h	60	100/66	85–86/40[18]	

[a] Yield of isolated product.

[b] Refers to oven temperature for Kugelrohr distillation.

[c] Recorded in a Varian VX-300S.

[d] New compound.
HRMS:[e] found, 232.219108. Calc. for $C_{17}H_{28}$, 232.219101.
IR (film): $\nu = 1600, 1460, 1380\ cm^{-1}$.
^1H NMR[c] ($CDCl_3$/TMS): $\delta = 0.89$ (t, 6H, CH_3, $J = 6$ Hz), 1.20–1.34 (m, 14H, CH_2), 1.50–1.60 (m, 1H, CH), 2.54–2.60 (m, 2H, Ph–C$\underline{H}_2$), 7.10–7.30 (m, 5H, H_{arom}).
MS[e] (100 eV): m/z (%) = 232 ($M^{\bullet +}$, 12), 175 ($M - C_4H_9$, 24), 91 ($C_7H_7^+$, 100).

[e] Recorded in a Varian Mat 711 at 100 eV.

In summary, we have demonstrated for the first time a very suitable method for the stepwise elaboration of a carbon framework through *gem*-dialkylation or reductive alkylation of α-unbranched aliphatic aldehydes.

Alkylation of *gem*-Dihalides 2; General Procedure:
CuCN (0.89 g, 10 mmol) was suspended in anhydrous THF (10 mL). The corresponding alkyllithium (20 mmol) was added dropwise to the cooled slurry (−78 °C). The dihalogenated compound (5 mmol) in THF (100 mL) was introduced and the reaction mixture allowed to warm to r.t. and stirred overnight. The mixture was hydrolyzed with a 10% aqueous NH_4Cl in conc. NH_4OH (100 mL) and extracted with pentane (3 × 50 mL). The organic layer was dried ($MgSO_4$), the solvent removed in vacuo and the residue distilled to afford the alkylated products **3** or **4**. All the products were fully characterized by spectroscopic methods.

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