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COPPER(I)-PROMOTED SUBSTITUTIONS OF METHOXY AND TETRAHYDRO-2-PYRANYLOXY GROUPS. SYNTHESIS OF ALLENIC AND OLEFINIC ALCOHOLS[1]

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Inspired by some recent progress in Cu(I)-promoted substitution reactions[2] in propargylic[3-5a] and allylic systems[6-8] we have tried to convert the acetylenic and olefinic tetrahydro-2-pyranyloxy (Thp-oxy) and methoxy compounds 1-6 into allenic and olefinic alcohols by reacting them with alkyl Grignard reagents in the presence of Cu(I)I. These reactions, which are reported here, proceeded essentially as desired and constitute novel synthetic methods for α- and β-allenic alcohols with three or four alkyl groups at the propadienyl group, as well as for (E)-alkenols with unusual carbon skeletons.

To our knowledge only one copper(I)-promoted substitution of a Thp-oxy group (allyl-positioned) has been reported.[6] No similar substitutions of alkoxy groups seem to have been reported, but one attempted reaction of an allylic methyl ether with Me_2CuLi failed completely.[8b]

α-Allenic alcohols, alkyl substituted at C-2, are otherwise easily prepared by reaction of organocuprates with appropriately substituted acetylenic oxiranes.[3,4] Analogously substituted β-allenic alcohols, i.e. at C-3, seem to be most conveniently prepared using the alkyllithium reaction of dihalocyclopropanes,[9] the $LiAlH_4$ reduction of enyne alcohols,[10] or the addition of properly substituted propadienyllithium reagents to oxiranes.[11]

Solutions of cuprates were prepared by adding Cu(I)I (1 equiv.) to MeMgI (5 equiv.) in ether at -30^0 under nitrogen atmosphere and stirring for 20-30 min. The acetylenes 1 and 2 were added at the same temperature, the mixtures were brought to room temperature (0.5 h) and stirred for 5 and 2 h, respectively (Method A). Work-up and distillation yielded the allenic and acetylenic alcohols 7, 8 and 9 in the indicated yields. They were accompanied by several by-products (∼ 10 %, GLC).

The methoxy derivative 3 behaved analogously upon treatment with MeMgI-Cu(I)I (4:1) and gave pure (98 %, GLC) α-allenic alcohol 10 upon distillation. When the acetylene 4 was allowed to react with MeMgI-Cu(I)I under the above conditions only slight conversion to products occurred. However, we soon discovered that addition of the Cu(I)I after mixing the starting acetylene and the Grignard reagent (Method B) increased the conversion of 4 into products to 40 % (GLC). When this procedure was combined with a change of solvent to ether:THF (1:3) the conversion was raised to 85 % after 18 h at room temperature. The allenic products 13 and 14 could not be isolated pure by preparative GLC, but GLC-MS gave correct molecular ions. Furthermore, the IR spectrum of the mixture exhibited absorption at 870 cm^{-1} indicating -CH=C=CH-.

Introduction of hydrogen instead of an alkyl group was also a side-reaction in the conversion 3 → 11 using EtMgBr-Cu(I)I (4:1) (Method B) where 12 was formed in 5 % yield (comparison with authentic material) Application of method A instead of B and refluxing of the reaction mixture gave a ratio 11 : 12 of 2:1 (40 % total yield).

In the reaction of 4 with EtMgBr-Cu(I)I (6.1:1.2) the reduction product 14 predominated, and only 6 % of the desired allenic alcohol 15 was isolated.

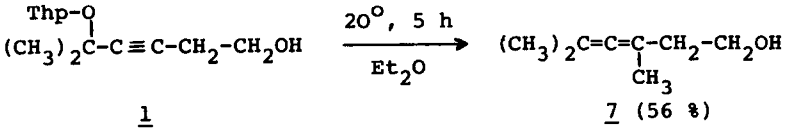
In analogous reactions (Method B) of the olefinic methoxy compounds 5 and 6 (from semi-hydrogenation of the corresponding acetylenes) the alkenols 16 - 18 were isolated in good yields. Grignard reagent and Cu(I)I were used in the ratio 6:1.2. The alcohol 16 seemed better than 98 % pure by GLC on a 0.96 x 600 cm Carbowax 20 M column while 18 contained $\sim$10 % of a product appearing as a shoulder on the front side of the main peak. The 3-alkenol 17 was 93 % pure by GLC on Carbowax, which indicated a contaminant having a longer retention time.

The structures of 16, 17 and 18 were proved by NMR.[12] 16: δ = 5.82 - 5.05 (m,2H), 3.40 (d,2H), 2.80 (s,1H), 2.6 - 1.8 (m,3H), 1.40 (sext.,2H), 0.97 and 0.90 (d and t,6H), 17: δ = 5.50 - 5.30 (m,2H), 3.65 (t,2H), 2.5 - 1.8 and 2.18 (m and s,4H), 1.7 - 1.0 (m,4H), 0.99 and 0.90 (d and t,6H). Decoupling of the C-1 protons induced changes in the multiplet between 1.7 - 1.0 ppm. This procedure was also applied to prove the structure of 18: δ = 5.45 - 5.12 (m,2H), 3.60 (t,2H), 2.90 (s,1H), 2.4 - 1.8 (m,3H), 1.7 - 1.0 (m,6H), 0.90 (two t,6H). The IR spectra of the alkenols 16 - 18 showed strong absorption around 965 cm^{-1}, indicating predominant (E) configuration, in accordance with the cuprate reactions of allylic acetates.[8b] The reactions of 5 and 6 gave no compounds derived from hydrogen introduction instead of alkyl ($<$ 1 %), which is a serious side-reaction in the conversions of the acetylene 4 to allenes. Other authors have reacted propargylic acetates[5] and oxiranes[3-4] with various cuprate reagents and in some cases reported hydrogen introduction.[3,5b] In analogous reactions of allylic acetates [8a,b] and oxiranes[8c,d] no by-products of this kind have been reported. The source of the hydrogen in the above reactions is most probably the copper-bound alkyl groups.[13]

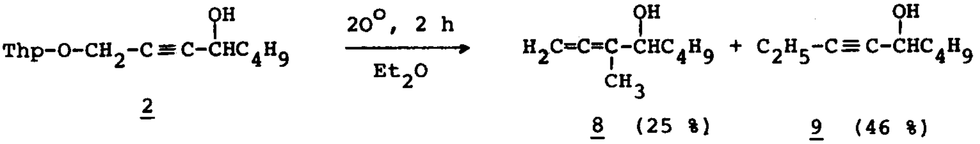
Direct substitution of the Thp-oxy and methoxy groups, i.e. without a double bond shift, does not seem to be a problem, except for 2, as long as Method B is used, e.g. when 1 was reacted with MeMgI-Cu(I)I (4:0.25) using Method A an acetylenic compound $t\text{-}C_4H_9\text{-}C{\equiv}C\text{-}CH_2\text{-}CH_2\text{-}OH$ was formed (16 %; 50 % total yield) and we have observed the same tendency in other preliminary experiments. Method B gave less than 7 % of direct substitution.

The acetylenic compound 2 does not react with MeMgI alone in refluxing ether. However, the methyl ether 3 reacts with butyllithium without added Cu(I), but not methyllithium, to give an allenic alcohol corresponding to 10 and 11.[14] The analogous reaction of 5 should also be performable as alkyllithium reagents add to the double bond of allyl alcohol itself.[15]

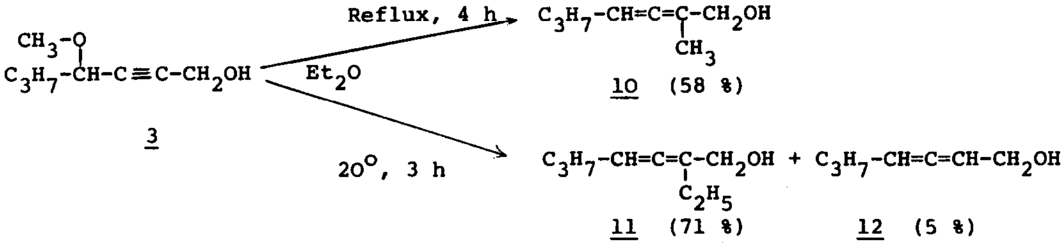
Preliminary results indicate that the hydroxy group is not essential in some of the copper-promoted reactions, since 3-(Thp-oxy)-1-hexene gives a product, tentatively identified as 4-decene, when allowed to react with C_4H_9MgBr-Cu(I)I (15% after 1 h at 20^{o}).



$$\underset{\underline{1}}{(CH_3)_2\overset{Thp\text{-}O}{C}\text{-}C\equiv C\text{-}CH_2\text{-}CH_2OH} \xrightarrow[Et_2O]{20^{o},\ 5\ h} \underset{\underline{7}\ (56\ \%)}{(CH_3)_2C{=}C{=}\underset{CH_3}{C}\text{-}CH_2\text{-}CH_2OH}$$

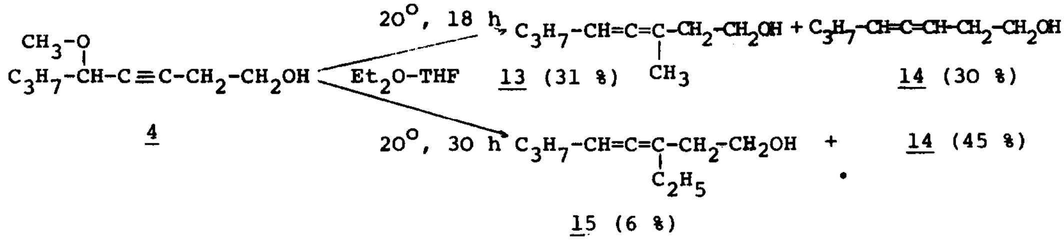


$$\underset{\underline{2}}{Thp\text{-}O\text{-}CH_2\text{-}C\equiv C\text{-}\overset{OH}{C}HC_4H_9} \xrightarrow[Et_2O]{20^{o},\ 2\ h} \underset{\underline{8}\ (25\ \%)}{H_2C{=}C{=}\underset{CH_3}{C}\text{-}\overset{OH}{C}HC_4H_9} + \underset{\underline{9}\ (46\ \%)}{C_2H_5\text{-}C\equiv C\text{-}\overset{OH}{C}HC_4H_9}$$



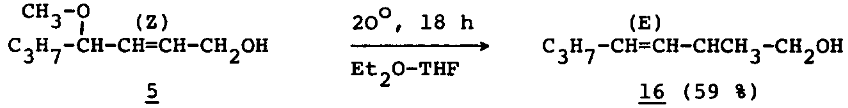
$$\underset{\underline{3}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}C\equiv C\text{-}CH_2OH} \xrightarrow[Et_2O]{Reflux,\ 4\ h} \underset{\underline{10}\ (58\ \%)}{C_3H_7\text{-}CH{=}C{=}\underset{CH_3}{C}\text{-}CH_2OH}$$

$$\underset{\underline{3}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}C\equiv C\text{-}CH_2OH} \xrightarrow[20^{o},\ 3\ h]{Et_2O} \underset{\underline{11}\ (71\ \%)}{C_3H_7\text{-}CH{=}C{=}\underset{C_2H_5}{C}\text{-}CH_2OH} + \underset{\underline{12}\ (5\ \%)}{C_3H_7\text{-}CH{=}C{=}CH\text{-}CH_2OH}$$

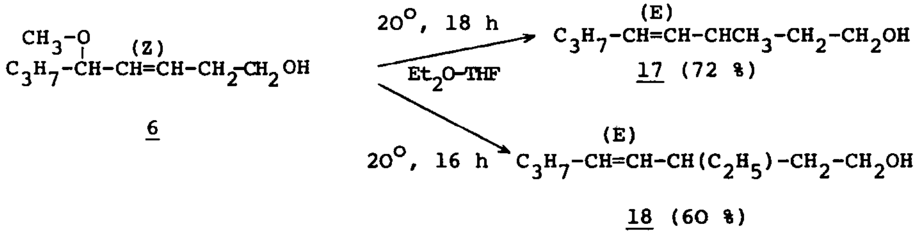


$$\underset{\underline{4}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}C\equiv C\text{-}CH_2\text{-}CH_2OH} \xrightarrow[Et_2O\text{-}THF]{20^{o},\ 18\ h} \underset{\underline{13}\ (31\ \%)}{C_3H_7\text{-}CH{=}C{=}\underset{CH_3}{C}\text{-}CH_2\text{-}CH_2OH} + \underset{\underline{14}\ (30\ \%)}{C_3H_7\text{-}CH{=}C{=}CH\text{-}CH_2\text{-}CH_2OH}$$

$$\underset{\underline{4}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}C\equiv C\text{-}CH_2\text{-}CH_2OH} \xrightarrow[20^{o},\ 30\ h]{Et_2O\text{-}THF} \underset{\underline{15}\ (6\ \%)}{C_3H_7\text{-}CH{=}C{=}\underset{C_2H_5}{C}\text{-}CH_2\text{-}CH_2OH} + \underline{14}\ (45\ \%)$$



$$\underset{\underline{5}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}\overset{(Z)}{CH{=}CH}\text{-}CH_2OH} \xrightarrow[Et_2O\text{-}THF]{20^{o},\ 18\ h} \underset{\underline{16}\ (59\ \%)}{C_3H_7\text{-}\overset{(E)}{CH{=}CH}\text{-}CHCH_3\text{-}CH_2OH}$$



$$\underset{\underline{6}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}\overset{(Z)}{CH{=}CH}\text{-}CH_2\text{-}CH_2OH} \xrightarrow[Et_2O\text{-}THF]{20^{o},\ 18\ h} \underset{\underline{17}\ (72\ \%)}{C_3H_7\text{-}\overset{(E)}{CH{=}CH}\text{-}CHCH_3\text{-}CH_2\text{-}CH_2OH}$$

$$\underset{\underline{6}}{C_3H_7\text{-}\overset{CH_3\text{-}O}{C}H\text{-}\overset{(Z)}{CH{=}CH}\text{-}CH_2\text{-}CH_2OH} \xrightarrow{20^{o},\ 16\ h} \underset{\underline{18}\ (60\ \%)}{C_3H_7\text{-}\overset{(E)}{CH{=}CH}\text{-}CH(C_2H_5)\text{-}CH_2\text{-}CH_2OH}$$

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