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PRELIMINARY NOTE

A Facile Preparation of Gem-Difluorohomoallylic Alcohols[1]

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SUMMARY

The reaction of 3-bromo-3,3-difluoropropene with zinc powder in THF at 0°C to room temperature in the presence of aldehydes and ketones provides a useful, easily scaled up route to gem-difluorohomoallylic alcohols. α,β-Unsaturated aldehydes and ketones give exclusively the 1,2-addition product. In all cases, only the α-gem-difluorohomoallyl regioisomer was observed.

In recent years, bioactive compounds that contain the difluoromethylene group alpha to a reactive functionality have been the focus of many research efforts [2]. The most widely used method for the introduction of such functionality has been the Reformatsky reaction employing halodifluoroacetates [3]. More recently, difluoroketene silyl acetals have also been utilized for the preparation of difluoromethylene functionalized compounds [4].

Methodology which could also provide useful precursors to this type of functionality is a gem-difluoroallylation reaction,

$$>C{=}O \quad + \quad [CH_2{=}CHCF_2]M \longrightarrow >C(OH)CF_2CH{=}CH_2$$

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since elaboration of the resultant gem-difluorohomoallylic alcohol would provide an entry to a wide variety of difluoromethylene functionalized derivatives. Although such types of allylation processes have been extensively investigated with non-fluorinated precursors [5], only two examples of gem-difluoroallylation of carbonyl substrates have been reported. Seyferth generated gem-difluoroallyl-lithium at low temperature (-95°C) in the presence of the carbonyl component. Although this procedure gave reasonable yields with dialkyl ketones, aryl alkyl ketones and aliphatic aldehydes, low yields of the gem-difluorohomoallylic alcohol were obtained with aromatic aldehydes, α,β-unsaturated aldehydes and diaryl ketones [6]. Hiyama obtained somewhat better results by generation of the gem-difluoroallyl anion *via* reaction of γ,γ-difluoroallylsilanes [7] or α,α-difluoroallylsilanes [8] with fluoride ion in the presence of the carbonyl substrates. However, this procedure necessitated the prior preparation of the requisite difluoroallylsilane.

We have now developed a direct allylation of aldehydes and ketones via the *in situ* reaction of 3-bromo-3,3-difluoropropene* with acid-washed zinc powder and the carbonyl substrate. This methodology avoids the use of thermally unstable intermediates [6], the problem of competitive reaction of the carbonyl substrates

$$Zn + R^1C(O)R^2 + CH_2{=}CHCF_2Br \xrightarrow[0^\circ \text{ to RT}\\ \text{overnight}]{\text{THF}} R^1R^2C(OH)CF_2CH{=}CH_2$$

with the alkyl lithium bases [6] and the prior preparation of allylation precursors [7,8]. Table I summarizes representative examples of aldehydes and ketones utilized in this approach. The

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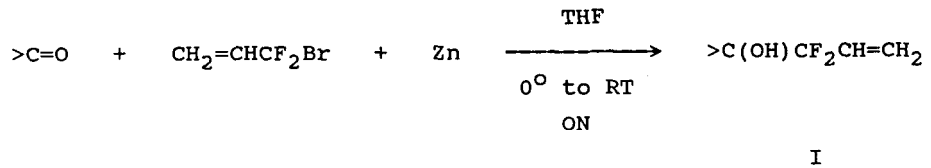
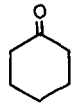
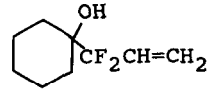
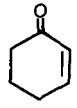
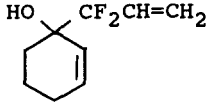
* 3-bromo-3,3-difluoropropene is available commercially from Japan Halon and Fluorochem Limited.

TABLE I

Gem-difluoroallylation of aldehydes and ketones



I

Entry	Aldehyde or Ketone	I[a]	% Yield[b]
1	C_6H_5CHO	$C_6H_5CH(OH)CF_2CH=CH_2$	67
2	$n\text{-}C_6H_{13}CHO$	$n\text{-}C_6H_{13}CH(OH)CF_2CH=CH_2$	53
3	$C_6H_5CH=CHCHO$	$C_6H_5CH=CHCH(OH)CF_2CH=CH_2$[c]	74
4	$C_6H_5C(O)CH_3$	$C_6H_5(CH_3)C(OH)CF_2CH=CH_2$	47
5	$C_6H_5C(O)CF_3$	$C_6H_5(CF_3)C(OH)CF_2CH=CH_2$	67
6			54
7			40

a all products gave satisfactory ^{19}F, ^{1}H, and MS data

b isolated yields

c isolated by flash chromatography

reaction worked well with aromatic aldehydes, aliphatic aldehydes, and ketones. The α,β-unsaturated aldehyde and ketones gave exclusive formation of the 1,2-addition product; no 1,4-addition product was observed - even when the reaction was carried out in the presence of CuI. As indicated by the products listed in Table I, only the regioisomer with the gem-difluoromethylene group alpha to the alcohol function was observed.

A typical experimental procedure is as follows: a two-necked flask fitted with a pressure equalizing addition funnel, a nitrogen inlet tube and a Teflon coated magnetic stir bar was charged with 2.6 g (40 mmol) of acid-washed zinc powder, 2.1 g (20 mmol) of benzaldehyde and 20 ml of dry THF. The reaction mixture was cooled to 0°C with an ice bath, and a mixture of 3.3 g (21 mmol) of 3-bromo-3,3-difluoropropene in 10 ml of THF was slowly added to the zinc/aldehyde mixture via the addition funnel. After the addition was completed, the reaction mixture was warmed with stirring to room temperature over a period of 4.5 hours and then stirred at room temperature overnight. Then, 30 ml of 5% hydrochloric acid was added to the reaction mixture, and the mixture was stirred for five minutes. Excess zinc was removed by suction filtration, and the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 ml), and the ether extracts combined with the organic layer. The organic material was washed with 50 ml of a saturated sodium bicarbonate solution, water (2 x 50 ml), and then dried over anhydrous $MgSO_4$. After evaporation of the solvents, the residue (3.4 g) was distilled to give 2.5 g (67%) of the gem-difluoroalcohol product, bp 56-57° C/0.5 mm Hg, 99% GLPC purity.

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2 J.T. Welch, Tetrahedron, 43 (1987) 3123.

3 E.A. Hallinan and J. Fried, Tetrahedron Lett., (1984) 2301; J. Fried, E.A. Hallinan and M.J. Szwedo, J. Am. Chem. Soc., 106 (1984) 3871; M.H. Gelb, J.P. Svaren and R.H. Abeles, Biochemistry, 24 (1985) 1813; D.A. Trainor and M.M. Stein, Eur. Pat. Appl. 0 204 571 (1985); S. Thaisrivongs, D.T. Pals, W.M. Kati, S.R. Turner, and L.M. Thomasco, J. Medicinal Chem., 28 (1985) 1553; S. Thaisrivongs, D.T. Pals, W.M. Kati, S.R. Turner, L.M. Thomasco and W. Watt, J. Medicinal Chem., 29 (1986) 2080; D.J. Burton and J.C. Easdon, J. Fluorine Chem., 38 (1988) 125; R.W. Lang, and B. Schaub, Tetrahedron Lett., (1988) 2943.

4 D.J. Burton and J.C. Easdon, 190th National Meeting of the American Chemical Society, Chicago, Illinois, September 1985, Abstract Fluo 016; D.J. Burton and J.C. Easdon, 12th International Symposium on Fluorine Chemistry, Santa Cruz, California, August 1988, Abstract #110; O. Kitagawa, T. Taguchi and Y. Kobayashi, Tetrahedron Lett., (1988) 1803.

5 For recent allylation of carbonyl substrates using metallic Zn, Sn, Mn or Cd cf.: C. Petrier and J.L. Luche, J. Org. Chem., 50 (1985) 910; J. Nokami, J. Otera, T. Sudo and R. Okawara, Organometallics, 2 (1983) 191; T. Hiyama, M. Sawahata and M. Obayashi, Chem. Letters, (1983) 1237; S. Araki, H. Ito and Y. Butsugan, J. Organometall. Chem., 347 (1988) 5.

6 D. Seyferth, R.M. Simon, D.J. Sepelak and H.A. Klein, J. Am. Chem. Soc., 105 (1983) 4634.

7 T. Hiyama, M. Obayashi and M. Sawahata, Tetrahedron Lett., (1983) 4113.

8 M. Fujita and T. Hiyama, J. Am. Chem. Soc., 107 (1985) 4085.