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Preliminary Note

Synthesis of bromodifluoromethyl-substituted alkenes. Potassium fluoride supported on alumina as a dehydrobrominating agent

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Abstract

Potassium fluoride supported on alumina is an efficient dehydrobrominating agent. 1,3-Dibromo-1,1-difluoroalkanes – adducts of dibromodifluoromethane and alkenes – give bromodifluoromethyl-substituted alkenes **2** on dehydrobromination with this agent in good to excellent yields. Alkenes **2** were a mixture of *Z*- and *E*-isomers, with the former predominating. Functional groups such as ester, carbonyl, ethylenic and chloromethyl are not affected under such reaction conditions.

Bromodifluoromethyl-substituted alkenes are useful in organic synthesis, as such compounds contain an active allylic bromine atom. They can be utilized in introducing a *gem*-difluoromethylene moiety into organic molecules [1]. Usually bromodifluoromethyl-substituted alkenes have been synthesized by dehydrobromination of 1,3-dibromo-1,1,-difluoroalkanes – adducts of CF_2Br_2 with alkenes – under basic conditions. Refluxing with an alcoholic alkali or with trialkylamine are methods which have been widely adopted [2]. However, under such vigorous conditions, the CF_2Br group or other alkali-sensitive groups could not be kept intact. Seyferth *et al.* reported that dehydrobromination of $CF_2BrCH_2CH_2Br$ in the presence of excess aqueous potassium hydroxide at 120–150 °C gave a *c.* 5:2 mixture of $CH_2{=}CHCF_2Br$ and $CF_2{=}CHCH_2Br$ [3]. In certain cases, high-boiling substances were the main products [4]. Elsheimer *et al.* treated 2-bromo-1-bromodifluoromethylcyclohexane with KOH at 120 °C but only 1-cyclohexylcarboxylic acid was obtained [4, 5]. Thus, the search for a milder dehydrobrominating agent is highly desirable.

Fluoride ion has been shown to be an efficient base, but its low solubility in ordinary organic solvents has hampered its application. Recently, there has been increasing use of alumina coated with potassium fluoride as a reagent or reaction medium in organic synthesis [6]. Fluoride ion has been reported to be *c.* 1000-times more efficient than alkoxides on the basis of dehydrohalogenation experiments [7]. However, there have been few applications of such a base in organofluorine chemistry. Together with dicyclohexyl 18-crown-6, Mielealek *et al.* used KF as a dehydro-iodinating agent to synthesize trifluoromethylacetylene at 120 °C, but the yield was poor and the reaction conditions were considered to be too drastic [8]. Here, we report the synthesis of bromodifluoromethyl-substituted alkenes using potassium fluoride supported on alumina as the dehydrobrominating agent.

The starting materials, 1,3-dibromides (**1**), were prepared by $CrCl_3\cdot6H_2O$/Fe bimetal redox couple-promoted addition of dibromodifluoromethane to alkenes[†]. Treatment with KF/Al_2O_3 [9] (*c.* 2.5 equiv. KF) in acetonitrile (10 ml) at 40–50 °C for several hours of 1,3-dibromides **1** (10 mmol) gave the corresponding bromodifluoromethyl-substituted alkenes **2** (see Table 1).

Compound **2a**: Volatile colourless oil; b.p. 78–82 °C/60 mmHg. ^{19}F NMR ($CDCl_3$/TFA) δ: -39 (s, *Z*-isomer); -34 (s, *E*-isomer) ppm. ^1H NMR ($CDCl_3$/TMS) δ: 6.8–6.6 (m, 2H, $CH{=}CH$); 2.6–2.4 (m, 2H, $CH_2C{=}$); 1.8–0.8 (m, 7H, C_3H_7) ppm. IR $\nu_{max.}$ (cm^{-1}): 2950 (s, C–H); 1650 (m, C=C); 1180 (s, C–F). MS *m/z* (%): 212 (M^+, 0.95); 133 ($M^+ - Br$, 37.6); 77 ($CF_2CH{=}CH_2^+$, 100). (Analysis: Calc. for $C_7H_{11}BrF_2$: C, 39.44; H, 5.16; F, 17.84; Br, 37.56%. Found: C, 39.49; H, 5.17; F, 17.28; Br, 37.60%.)

$$\underset{\textbf{(1a–h)}}{BrCF_2CH_2CHBrR} \xrightarrow[CH_3CN,\ 40–50\ ^\circ C]{KF/Al_2O_3} \underset{\textbf{(2a–h)}}{BrCF_2CH{=}CHR}$$

(R: **a**, C_4H_9; **b**, C_6H_{13}; **c**, $CH_2CH_2COCH_3$; **d**, $CH_2CH_2CH{=}CH_2$; **e**, CH_2Cl; **f**, CH_2OAc; **g**, $(CH_2)_8CO_2Me$; **h**, $-(CH_2)_4-$)

Elimination proceeded smoothly to give the corresponding alkenes **2** in good to excellent yield. Acetonitrile and *N,N*-dimethylformamide were suitable

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[†] A mixture consisting of 2 mmol of $CrCl_3\cdot6H_2O$, 15 mmol of iron powder, 12 mmol of dibromodifluoromethane and 10 mmol of alkene in 20 ml of commercially available absolute ethanol was stirred at 60–70 °C for *c.* 10 h. Usual work-up gave the starting materials **1** in *c.* 60–95% isolated yield.

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TABLE 1. Dehydrobromination of 1,3-dibromides **1** with KF/Al_2O_3[a]

Run No.	1,3-Dibromides	Time (h)	Product	E/Z ratio[b]	Yield (%)[c]
1	$CF_2BrCH_2CHBrC_4H_9$ (**1a**)	4	$CF_2BrCH{=}CHC_4H_9$ (**2a**)	95:5	87
2	**1a**	4	$CF_2BrCH{=}CHC_4H_9$ (**2a**)	94:6	94[d]
3	**1a**	28	$CF_2BrCH{=}CHC_4H_9$ (**2a**)	1:1	70[e]
4	$CF_2BrCH_2CHBrC_6H_{13}$ (**1b**)	4	$CF_2BrCH{=}CHC_6H_{13}$ (**2b**)	92:8	84
5	$CF_2BrCH_2CHBrC_2H_4Ac$ (**1c**)	4	$CF_2BrCH{=}CHC_2H_4Ac$ (**2c**)	84:16	74
6	$CF_2BrCH_2CHBrC_2H_4CH{=}CH_2$ (**1d**)	4	$CF_2BrCH{=}CHC_2H_4CH{=}CH_2$ (**2d**)	88:12	74
7	$CF_2BrCH_2CHBrCH_2Cl$ (**1e**)	5	$CF_2BrCH{=}CHCH_2Cl$ (**2e**)	–	74
8	$CF_2BrCH_2CHBrCH_2OAc$ (**1f**)	4	$CF_2BrCH{=}CHCH_2OAc$ (**2f**)	95:5	65
9	$CF_2BrCH_2CHBr(CH_2)_8CO_2Me$ (**1g**)	6	$CF_2BrCH{=}CH(CH_2)_8CO_2Me$ (**2g**)	88:12	90
10	2-Bromo-1-bromodifluoromethylcyclohexane (**1h**)	8	1-Bromodifluoromethylcyclohexene (**2h**)	–	40

[a] All reactions were carried out in CH_3CN at 40–50 °C with 2.5 equiv. of KF/Al_2O_3, unless otherwise indicated. All products had satisfactory ^{19}F NMR, ^1H NMR, MS and IR spectra, analysis or HRMS data.

[b] Estimated by ^{19}F NMR spectroscopy.

[c] Isolated yields.

[d] *N,N*-Dimethylformamide was used as the solvent.

[e] Reaction was carried out with refluxing triethylamine as the dehydrobrominating agent.

solvents. The alkenes obtained were a mixture of *E*- and *Z*-isomers with the former predominating. The ^{19}F NMR of an *E*-isomer CF_2Br appeared at δ −35 ppm, while the *Z*-isomer CF_2Br absorption was at δ −39 ppm (CF_3CO_2H as external standard, with upfield positive). In contrast to the refluxing aqueous alkaline system, the present reaction conditions were milder and the product was simpler. Functional groups such as alkyl, ester, carbonyl or chloromethyl etc. could be tolerated under such reaction conditions and did not affect the elimination reaction.

Under these conditions, the *cis* isomer of 2-bromo-1-bromodifluoromethylcyclohexane (**1h**) could be easily dehydrobrominated, while the *trans* isomer could not, even under more drastic conditions (Run 10). This result might give a clue about the pathway of the dehydrobromination, i.e. such reactions usually proceed via an *E*2 elimination procedure [5].

In summary, KF supported on alumina in acetonitrile or *N,N*-dimethylformamide is an effective dehydrobrominating agent. The simplicity of the experimental procedure, the ready availability of the base and the good yields make this approach a useful route for synthesizing various bromodifluoromethyl-substituted alkenes. Furthermore, such alkenes bearing an allylic bromine atom are potential difluoromethylene-introducing building blocks in organic synthesis.

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