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ORIGINAL PAPER

Practical and general method for the direct synthesis of alkyl fluorides from alcohols under mild conditions: a reinvestigation

Marco Rupprich · Clemens Decristoforo · Barbara Matuszczak

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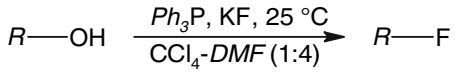
Abstract In contrast to the results presented in a previous report, the direct conversion of alcohols to alkyl fluorides with triphenylphosphine and potassium fluoride in CCl_4/*DMF* under mild conditions failed.

Keywords Alcohols · Alkyl fluorides · Triphenylphosphine · Potassium fluoride

Introduction

Bioactive compounds bearing a fluoromethyl moiety are of great interest, especially in the field of (radio)pharmaceutical chemistry [1]. In a current project of ours, we focused on preparing fluoromethyl-substituted amino acid derivatives, starting from the appropriate hydroxymethylated congeners. In order to circumvent the drawbacks of multistep reactions and the employment of highly reactive fluorination agents such as (diethylamino)sulfur trifluoride (*DAST*), we were interested in a fast, mild and high-yield synthesis.

Recently, Bandgar et al. [2] published a convenient, mild and general method for the direct conversion of alcohols into the corresponding alkyl fluorides in very good yields. This procedure is characterized by the treatment of alcohols with triphenylphosphine (Ph_3P) and potassium fluoride in carbon tetrachloride/*DMF* at room temperature (Scheme 1). Similar conditions have already been described in the literature for the preparation of alkyl fluorides. However, these reactions were performed in the presence of diethyl azodicarboxylate [3] or via alkoxy triphenylphosphonium ions prepared electrochemically from an alcohol and triphenylphosphine [4].



Scheme 1

Surprisingly, although the procedure of Bandgar et al. [2] has been described as exhibiting high chemoselectivity and a wide range of tolerated functional groups, it has never been utilized. Attempts to apply the procedure described above in order to convert our hydroxy compounds into the corresponding fluoro-substituted congeners were not successful. Instead of the expected fluoromethyl derivatives, we only could isolate the corresponding chloro compounds. Based on these findings, we decided to reinvestigate the method of Bandgar et al. [2].

Results and discussion

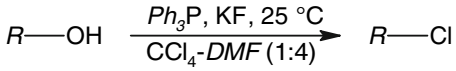
Under the described reaction conditions [2], we repeated the synthetic protocol with 4-methoxybenzylalcohol and 4-hydroxybenzylalcohol. The products obtained were characterized by ^{1}H-NMR spectroscopy and GC/MS spectrometry. In contrast to the results described, we could not find any H–F coupling in the ^{1}H-NMR spectra. However, it was found that (for example) the reaction product of 4-methoxybenzylalcohol with CCl_4/*DMF* (1:4), Ph_3P and KF exhibits *m*/*z* values of 156 and 158 (M^+) in the ratio of 3:1. This, as well as the fragment at *m*/*z* 121,

M. Rupprich (✉) · C. Decristoforo
Department of Nuclear Medicine, Innsbruck Medical University, 6020 Innsbruck, Austria
e-mail: marco.rupprich@i-med.ac.at

M. Rupprich · B. Matuszczak
Department of Pharmacy, University of Innsbruck, 6020 Innsbruck, Austria

indicates the presence of a chlorine atom in the molecule. Thus, these findings (^{1}H-NMR and GC/MS) clearly indicate that fluorine substitution did not occur, and, as expected, the well-known chlorine compound was formed.

In addition to the above mentioned experiments, we performed the reaction (CCl_4/*DMF*; Ph_3P; KF) under microwave irradiation, since it is known that microwave heating results in reduced reaction times and side reactions, increased yields and improved reproducibility [5]. Therefore, we tested whether microwave-induced activation has a positive effect on the system. However, we were able to characterize all of the isolated products from the microwave-accelerated experiments as the corresponding chlorine derivatives (Scheme 2).



Scheme 2

In conclusion, we were not able to reproduce the results described by Bandgar et al. We were only able to isolate the corresponding chlorine compounds. We fully agree with the authors that a one-step conversion of alcohols to the fluorine derivatives under mild conditions is a desirable ambition. However, the protocol given by Bandgar et al. does not allow this goal to be achieved.

Experimental

All reagents and solvents were of analytical grade and were used without further purification. ^{1}H-NMR spectra were recorded on a Varian (Palo Alto, CA, USA) Gemini 200 spectrometer (199.98 MHz for ^{1}H) with the deuterium signal of the solvent used as the lock and *TMS* as internal standard. GC/MS measurements were performed on a HP (Palo Alto, CA, USA) 5890 II gas chromatograph, followed by characterization in a HP 5971 A quadrupole mass spectrometer (EI, 70 eV).

Experiment 1: Reaction of 4-hydroxybenzylalcohol in CCl_4/DMF (1:4) in the presence of Ph_3P and KF

Three hundred and ten milligrams of 4-hydroxybenzylalcohol (2.5 mmol) and 1.64 g triphenylphosphine (6.25 mmol) were dissolved in a mixture of 3 cm^3 of CCl_4/*DMF* (1:4), followed by the addition of 290 mg KF (5 mmol). The resulting mixture was stirred at room temperature for 0.5 h. The mixture was extracted with *n*-hexane (2 × 5 cm^3) and the combined organic phases were dried over sodium sulfate. The solvent was removed in vacuo and the remaining residue was purified by column chromatography (ethyl acetate/*n*-hexane; 1:9) to obtain the chlorine compound with a yield of 72%; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 7.13$ (d, 2H, $J = 8.6$ Hz), 6.87 (d, 2H, $J = 8.6$ Hz), 4.54 (s, 2H); GC/MS (EI, 70 eV): $m/z = 144$ (M^+, 2.5%), 142 (M^+, 7.8%), 107 ($[M\text{-}Cl]^+$, 100%), 91 (20.5%).

Experiment 2: Reaction of 4-hydroxybenzylalcohol in CCl_4/DMF (1:4) in the presence of Ph_3P and KF under microwave irradiation

Sixty milligrams of 4-hydroxybenzylalcohol (0.5 mmol) and 320 mg triphenylphosphine (1.2 mmol) were dissolved in mixture of 2 cm^3 of CCl_4/*DMF* (1:4) followed by the addition of 59 mg KF (1.0 mmol). The resulting mixture was heated in a microwave synthesizer (CEM Discover, Matthews, NC, USA) with an irradiation power of 50 W for 5 min at 50 °C. After the reaction (TLC), the mixture was extracted with *n*-hexane (2 × 5 cm^3) and the combined organic phases were dried over sodium sulfate. The solvent was removed in vacuo and the remaining residue was purified by column chromatography (ethyl acetate/*n*-hexane; 1:9) to obtain the chlorine compound with a yield of 81%.

^{1}H-NMR and mass spectra were found to be identical to those described in "Experiment 1."

Experiment 3: Reaction of 4-methoxybenzylalcohol in CCl_4/DMF (1:4) in the presence of Ph_3P and KF

Six hundred and ninety milligrams of 4-methoxybenzylalcohol (5.0 mmol) and 3.28 g triphenylphosphine (12.5 mmol) were dissolved in a mixture of 5 cm^3 of CCl_4/*DMF* (1:4), followed by the addition of 580 mg KF (10.0 mmol). The resulting mixture was stirred at room temperature for 1.5 h. The mixture was extracted with *n*-hexane (2 × 5 cm^3) and the combined organic phases were dried over sodium sulfate. The solvent was removed in vacuo, and the remaining residue was purified by column chromatography (ethyl acetate/*n*-hexane; 1:9) to afford the chlorine compound in 79% yield; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 7.32$ (d, 2H, $J = 8.4$ Hz), 6.92 (d, 2H, $J = 8.4$ Hz), 4.55 (s, 2H), 3.78 (s, 3H); GC/MS (EI, 70 eV): $m/z = 158$ (M^+, 4.2%), 156 (M^+, 13.2%), 121 ($[M\text{–}Cl]^+$, 100%), 91 (9.8%), 78 (20.3%), 77 (21.8%).

Experiment 4: Reaction of 4-methoxybenzylalcohol in CCl_4/DMF (1:4) in the presence of Ph_3P and KF under microwave irradiation

Fifty-two milligrams of 4-methoxybenzylalcohol (0.37 mmol) and 235 mg triphenylphosphine (0.90 mmol) were dissolved in mixture of 2 cm^3 of CCl_4/*DMF* (1:4)

followed by the addition of 41 mg KF (0.71 mmol). The resulting mixture was heated in a microwave synthesizer (CEM Discover) with an irradiation power of 50 W for 5 min at 50 °C. After the reaction (TLC), the mixture was extracted with *n*-hexane (2×5 cm^3) and the combined organic phases were dried over sodium sulfate. The solvent was removed in vacuo and the remaining residue was purified by column chromatography (ethyl acetate/*n*-hexane; 1:9) to obtain the chlorine compound in 89% yield.

^{1}H-NMR and mass spectra were found to be identical to those described in "Experiment 3."

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