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Novel Applications of Alkyl Fluorides in Organic Synthesis: Versatile Nitrogen Protecting Groups

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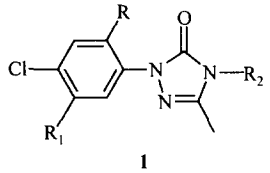
Abstract: The potential of the 2-fluoroethyl group as a nitrogen protecting group was demonstrated. The stability of alkyl fluorides, such as 2-fluoroethyl, to a variety of reaction conditions, makes them attractive nitrogen protecting groups. The 2-fluoroethyl group was easily introduced, in good yields, by the treatment of the NH group with potassium carbonate and 2-bromo-1-fluoroethane. Reaction of the 2-fluoroethyl group with boron tribromide resulted in the replacement of fluorine by bromine, to give the corresponding 2-bromoethyl group which was easily removed by known methods.

Keywords: Protecting group, halogen exchange, alkyl fluorides, N-vinyl, boron tribromide.

Aryl triazolinones **1** are known bioregulators that act by the inhibition of the plant enzyme protoporphyrinogen oxidase.[1] In particular, compound **2,** sulfentrazone, has found broad application in agriculture.[2] Our investigations in this area of chemistry required the synthesis of a wide variety of R, R_1, and R_2 derivatives of **1**.



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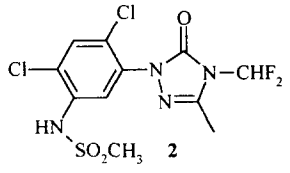

2

Sulfentrazone

The preparation of some of these derivatives, such as compound **11**, required the protection of the heterocyclic nitrogen. The protecting group had to be both chemically stable to a wide range of chemical transformations, such as nitration under strong acidic conditions, catalytic hydrogenation, and alkylation under basic conditions, as well as easily removed by conventional deprotecting procedures[3] such as acidic or basic conditions or catalytic hydrogenation.

Attempts to use commonly used nitrogen protecting groups such as benzyl derivatives,[4] methoxymethyl,[5] and β-ethyl substituted derivatives[6] were not successful; these protecting groups were found to be too unstable to our reaction conditions.

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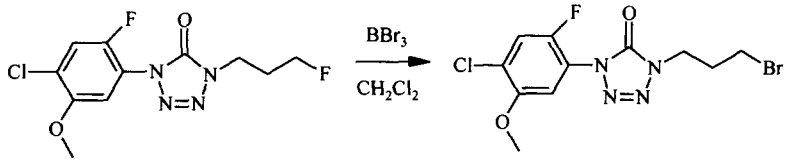
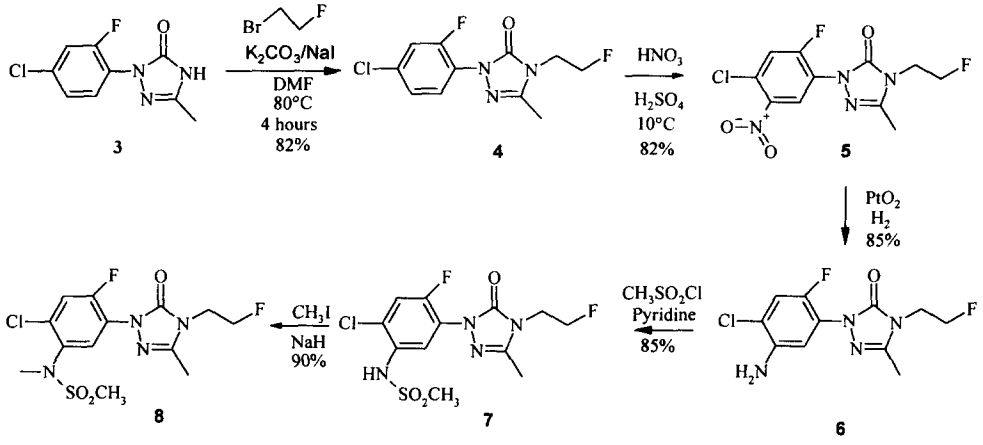
We knew, from literature references[7] and our own previous experience, that alkyl fluorides are resistant to most chemical transformations and reagents,[8] one exception being BBr_3. When alkyl fluorides were treated with Lewis acids such as BBr_3, fluorine was replaced by bromine[9] (scheme 1). This fact allowed us to switch from chemically inert N-alkyl fluorides to chemically labile N-alkyl bromides, which can then easily be removed by known procedures.[6]



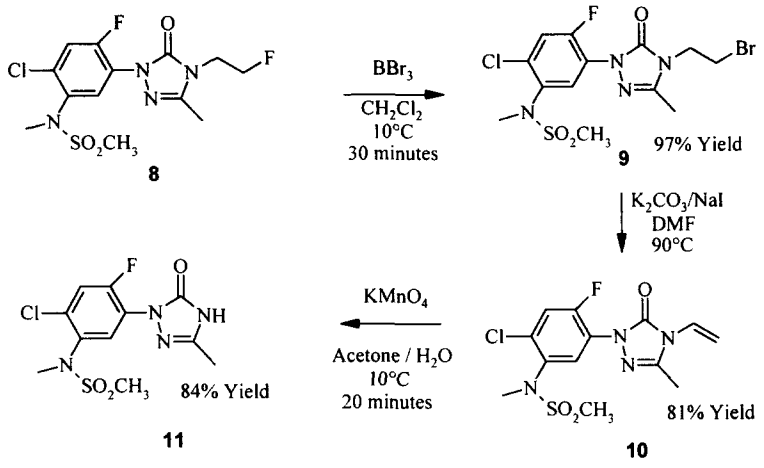
Scheme 1. Halogen exchange reaction with boron tribromide.

Treatment of compound **3** with 1-bromo-2-fluoroethane in the presence of potassium carbonate and sodium iodide in DMF, at 80°C, gave the corresponding N-2-fluoroethyl derivative **4** in good yields.[10] In the absence of sodium iodide, reaction times were longer. The N-protected 2-fluoroethyl compound **4** was successfully nitrated with 70% nitric acid, in sulfuric acid, in 82 % yield, and hydrogenated with H_2/ PtO_2 in ethanol to give the corresponding 1-(4-chloro-2-fluoro-5-aminophenyl)-4-(2-fluoroethyl)-4,5-dihydro-3-methyl-1,2,4-triazolin-5(1H)-one **6** in 85 % yield. The amino group of this compound was then reacted with methanesulfonyl chloride, and alkylated with NaH/CH_3I to give compound **8** in good overall yields[11] (scheme 2).



Scheme 2. Protection of the triazolinone nitrogen with 2-fluoroethyl group.

The N-2-fluoroethyl group in compound **8** was removed by the procedure[12] described in scheme **3.** Halogen exchange with BBr_3 in CH_2Cl_2, at 10°C was fast, giving the desired N-2-bromoethyl compound **9** in good yields. Halogen elimination was accomplished by heating **9** with potassium carbonate in DMF as a solvent. The N-vinyl group in compound **10** was readily removed by oxidation with potassium permanganate in an acetone/water solution at 10°C.



Scheme 3. Deprotection of N-(2-fluoroethyl) triazolinone.

In summary, 2-fluoroethyl is a novel nitrogen protecting group, which combines both chemical stability to a wide range of chemical transformations and ease of removal upon treatment with BBr_3. In addition to acting as a nitrogen protecting group, alkyl fluorides can be used to introduce carbon-carbon double bonds in molecules such as compound **8**, following several chemical manipulations such as hydrogenation, treatment with sulfuric acid, etc., that olefins would not normally survive. In this sense, alkyl fluorides can be viewed as protected or masked olefins.

References

1. a. Theodoridis, G.; Baum, J.S.; Hotzman, F.W.; Manfredi, M.C.; Maravetz, L.L.; Lyga, J.W.; Tymonko, J.M.; Wilson, K.R.; Poss, K.M.; Wyle, M.J. Synthesis and herbicidal properties of aryltriazolinones, ed. D.R. Baker, J.G. Fenyes, and G.S. Basarak, *Synthesis and Chemistry of Agrochemicals III*, ACS Symposium Series **504**, 1992, 134-146. b. Matringe, M.; Scalla, R. *Pest. Biochem. Physiol.* **1988**, *32*, 164. c. Witkoski, D.A.; Halling, B.P. *Plant Physiol.* **1989**, *90*, 1239.
2. Theodoridis, G., FMC Corporation, U.S. Patent 4,818,275, 1989.
3. a. Kocienski, P.J. *Protecting Groups*, Georg Thieme Verlag, Stuttgart, 1994. b. Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, J. Wiley, New York, 1991.
4. a. Suzuki, H.; Tsukuda, A.; Kondo, M.; Aizawa, M.; Senon, Y.; Nakajima, M.; Watanabe, T.; Yokoyama, Y. *Synthesis* **1984**, 738. b. Evans, D.A.; Lundy, K.M. *J.Am.Chem.Soc.* **1992**, *114*, 1495.
5. Kirby, G.W.; Robins, D.J.; Stark, W.M. *J.Chem.Soc., Chem. Commun.* **1983**, 812.
6. Gonzalez, C.; Greenhouse, R.; Tallabs, R.; Muchowski, J.M. *Can.J.Chem.* **1983**, *61*, 1697.
7. Hudlicky, M.; Pavlath, A.E. *Chemistry of Organic Fluorine Compounds II*, ACS Monograph 187, 1995.
8. Theodoridis, G.; Hotzman, W.H.; Scherer, L.W.; Smith, B.A.; Tymonko, J.M.; Wyle, M.J. *Pestic. Sci.* **1990**, *30*, 259.
9. a. Theodoridis, G.; Hotzman, W.H.; Scherer, L.W.; Smith, B.A.; Tymonko, J.M.; Wyle, M.J. ed. D.R. Baker, J.G. Fenyes, and G.S. Basarak, *Synthesis and Chemistry of Agrochemicals III*, ACS Symposium Series **504**, 1992, 126. b. Namavary, M.; Satyamurthy N.; Barrio, J.R. *Journal of Fluorine Chemistry* **1995**, *72*, 89.
10. **Synthesis of compound 4.** To a solution of 1-(4-chloro-2-fluorophenyl)-4,5-dihydro-3-methyl-1,2,4-triazolin-5(1H)-one **3**[2] (9.10 g, 0.040 mol) in DMF (80 mL), was added 1-bromo-2-fluoroethane (6.35 g, 0.050 mol), K_2CO_3

(6.90 g, 0.050 mol), and NaI (1.0 g, 0.0066 mol). After 4 hours at 80°C the solution was poured into water (200 mL) and extracted with three portions of ether (150 mL). The combined organics were dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2/ethyl acetate (90/10 v/v) as eluent to give compound **4** (8.84 g, 81% yield) as white needles: mp 68-69°C (heptane/ethyl acetate, 85/15 v/v). ^{1}HNMR ($CDCl_3$) δ 2.31 (3H, s), 3.97 (1H, dt, J_{HF}= 27 Hz), 4.67 (1H, dt, J_{HF}= 47 Hz), 7.20-7.50 (3H, m). Anal. Calcd. for $C_{11}H_{10}ClF_2N_3O$: C, 48.27; H, 3.68; N, 15.35; Cl, 12.95. Found: C, 48.27; H, 3.63; N, 15.25; Cl, 12.75.

11. **Analytical data, compound 5**, mp 97-98°C. ^{1}HNMR ($CDCl_3$) δ 2.35 (3H, s), 4.00 (1H, dt, J_{HF}= 27 Hz), 4.69 (1H, dt, J_{HF}= 47 Hz), 7.44 (1H, d, J= 9.6 Hz), 8.30 (1H, d, J= 6.9 Hz). Anal. Calcd. for $C_{11}H_9ClF_2N_4O_3$: C, 41.46; H, 2.84; N, 17.58; Cl, 11.12. Found: C, 41.68; H, 2.79; N, 17.52; Cl, 11.33.

Compound 6, mp 121-122°C. ^{1}HNMR ($CDCl_3$) δ 2.31 (3H, s), 3.99 (1H, dt, J_{HF}= 27 Hz), 4.67 (1H, dt, J_{HF}= 47 Hz), 6.92 (1H, d, J= 7.2 Hz), 7.15 (1H, d, J= 9.6Hz). Anal. Calcd. for $C_{11}H_{11}ClF_2N_4O$: C, 45.76; H, 3.84; N, 19.40; Cl, 12.28. Found: C, 45.99; H, 3.71; N, 19.46; Cl, 12.09.

Compound 7, mp 188-189°C. ^{1}HNMR ($CDCl_3$) δ 2.33 (3H, s), 3.04 (3H, s), 3.94 (1H, dt, J_{HF}= 27 Hz), 4.68 (1H, dt, J_{HF}= 47 Hz), 6.79 (1H, s), 7.29 (1H, d, J= 9.3 Hz), 7.87 (1H, d, J= 6.9Hz). Anal. Calcd. for $C_{12}H_{13}ClF_2N_4O_3S$: C, 39.29; H, 3.57; N, 15.27; Cl, 9.66. Found: C, 39.33; H, 3.45; N, 15.16; Cl, 9.57.

Compound 8, mp 157-158°C. ^{1}HNMR ($CDCl_3$) δ 2.32 (3H, s), 3.02 (3H, s), 3.28 (3H, s), 3.98 (1H, dt, J_{HF}= 27 Hz), 4.68 (1H, dt, J_{HF}= 47 Hz), 7.36 (1H, d, J= 9.6 Hz), 7.73 (1H, d, J= 7.5Hz). Anal. Calcd. for $C_{13}H_{15}ClF_2N_4O_3S$: C, 41.00; H, 3.97; N, 14.71; Cl, 9.31. Found: C, 41.13; H, 4.02; N, 14.50; Cl, 9.60.

12. **Nitrogen deprotection. Halogen exchange, compound 9**. A solution of boron tribromide (1 Mole solution in methylene chloride, 20 cc, 0.020 mol) was slowly added dropwise to a solution of compound **8** (3.80 g, 0.010 mol) in methylene chloride (60 mL) under nitrogen at 10°C. The solution was stirred at 10°C for 30 minutes, and quenched with water. The organic layer was dried over magnesium sulfate and concentrated. The residue was chromatographed on silica gel with CH_2Cl_2/ethyl acetate as eluent (70/30 v/v) to give compound **9** (4.28g, 97% yield) as small prisms: mp 158-160°C (heptane/ethyl acetate, 70/30 v/v). ^{1}HNMR ($CDCl_3$) δ 2.38 (3H, s), 3.03 (3H, s), 3.29 (3H, s), 3.69 (2H, t), 4.08 (2H, t), 7.37 (1H, d, J= 9.6 Hz), 7.74 (1H, d, J= 7.5 Hz). Anal. Calcd. for $C_{13}H_{15}BrClFN_4O_3S$: C, 35.35; H, 3.42; N, 12.68; Cl, 8.02. Found: C, 35.37; H, 3.24; N, 12.50; Cl, 8.26.

N-Olefin formation, compound 10. To a solution of compound **9** (3.0 g, 0.0068 mol) in DMF (60 mL) was added potassium carbonate (1.87g, 0.0136 mol), and sodium iodide (0.5g, 0.003 mol). After 18 hours at 80°C the solution was poured into water and extracted with ether. The combined organics were dried over magnesium sulfate and concentrated. The residue was chromatographed in silica gel with CH_2Cl_2/heptane as eluent (80/20 v/v), to give compound **10** (1.98 g, 81% yield). mp 92-93. 1HNMR ($CDCl_3$) δ 2.37 (3H, s), 3.03 (3H, s), 3.29 (3H, s), 5.14 (1H, d, J= 9.59 Hz), 5.90 (1H, d, J= 16.0 Hz), 6.52-6.6 (1H, m), 7.35 (1H, d, J= 9.6 Hz), 7.72 (1H, d, J= 7.0 Hz). Anal. Calcd. for $C_{13}H_{14}ClFN_4O_3S$: C, 43.27; H, 3.91; N, 15.52; Cl, 9.82. Found: C, 41.32; H, 3.50; N, 14.81; Cl, 9.87.

N-Olefin cleavage, compound 11. Compound **10** (1.26g, 0.0050 mol) was dissolved in acetone (40 mL), water (40 mL) was added and the solution cooled to 0°C. Potassium permanganate (2.76 g, 0.0175 mol) was slowly added and the solution stirred at 5°C for 20 minutes. The solution was filtered through Celite and the aqueous solution extracted with ether (200 mL). The organic layer was dried over magnesium sulfate and concentrated. The residue was chromatographed in silica gel with methylene chloride/ethyl acetate as eluent (70/30 v/v)to give compound **11** (0.90 g, 82% yield) mp 189-191°C. 1HNMR ($CDCl_3$) δ 2.12 (3H, s), 7.35-7.63 (3H, m), 11.77 (1H,s). Anal. Calcd. for $C_{13}H_{14}ClFN_4O_3S$: C, 43.27; H, 3.91; N, 15.52; Cl, 9.82. Found: C, 41.32; H, 3.50; N, 14.81; Cl, 9.87.