A Novel Route to 3(5)-Fluoro-1,2,4-triazoles and 8-Fluoropurines by Displacement of the Nitro Group[1]

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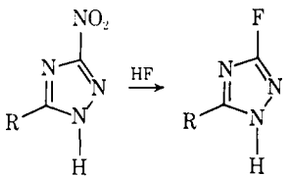
Ring-fluorinated 1,2,4-triazoles have not been previously reported and our interest in 1,2,4-triazoles has prompted us to investigate this class of heterocycles. Conventional synthetic routes to fluoro compounds are notoriously unreliable when applied to new problems. Consequently, a number of novel methods[2] have been introduced for the synthesis of fluoro compounds.

Various methods[3] for preparing fluoro derivatives starting with amino- or chloro-1,2,4-triazoles did not give encouraging results in our hands. As is the case with 7- or 9-unsubstituted purines,[2f] 3(5)-fluoro-1,2,4-triazoles with an ionizable N–H could not be obtained by displacement reactions with fluoride ion in a variety of solvents. Recently the conversion of 3(5)-nitro-1,2,4-triazoles to the corresponding halo derivatives on treatment with halogen acids has been reported.[4] The syntheses of some aromatic fluorine compounds[5] and recently certain fluoro heterocycles[6] by displacement of the nitro group with fluoride ion in high-boiling solvents have been described.

We now report that 3(5)-fluoro-1,2,4-triazoles are obtained in good yield by treatment of the corresponding nitro derivatives with hydrogen fluoride. Liquid hydrogen fluoride was utilized for this purpose to preclude the possibility of hydrolysis of the fluoro compounds at elevated temperatures. Thus, treatment of 3-nitro-1,2,4-triazole with liquid hydrogen fluoride at 150° afforded 3-fluoro-1,2,4-triazole in 80% yield. Several other examples of 3(5)-fluoro-1,2,4-triazoles prepared similarly are given in Table I.

TABLE I

SYNTHESIS OF FLUORO HETEROCYCLES[a] FROM NITRO COMPOUNDS



Registry no.	R	Temp, °C	Time, hr	Yield, %	Mp, °C (solvent of recrystn)	^{19}F nmr, δ^c	Registry no.	Ref for NO_2 compd
42297-29-0	H[b]	150	48	80	131–132 (benzene–ethyl acetate)	124.0	24807-55-4	*d–f*
42297-30-3	Br	100	36	98	113–114 (benzene)	118.3	42297-36-9	*f*
42297-31-4	$COOCH_3$	100	20	70	140–141 (benzene–ethyl acetate)	119.3	26621-28-3	*d*
42297-32-5	OH	100	36	21	125–126 (benzene–ethyl acetate)	118.3	42297-38-1	*g, h*
42297-33-6	8-Fluorotheophylline	60	16	55	245–250 dec (methanol)	106.5	2099-73-2	*i*
42297-34-7	8-Fluorocaffeine	100	20	62	162–163 (methanol)	110.5	42297-40-5	*j*

[a] Satisfactory analytical data (±0.4%) were obtained for C, H (Br), F, and N for all compounds listed in the table. [b] ^{1}H nmr (DMSO-d_6) δ 8.46 (s, 1, H-5). [c] Determined in DMSO-d_6; parts per million relative to CCl_3F as external standard. [d] Reference 4a. [e] E. J. Browne, *Aust. J. Chem.*, **22**, 2251 (1969); C. F. Kroeger and R. Miethchen, *Z. Chem.*, **9**, 378 (1969); L. I. Bagal, M. S. Pevzner, A. N. Frolov, and N. I. Sheludyakova, *Khim. Geterotsikl. Soedin.*, 259 (1970). [f] J. T. Witkowski and R. K. Robins, *J. Org. Chem.*, **35**, 2635 (1970). [g] Reference 4b. [h] W. Manchot and R. Noll, *Justus Liebigs Ann. Chem.*, **343**, 1 (1905); G. I. Chipen, R. P. Bokalder, and V. Ya. Grinshtein, *Khim. Geterotsikl. Soedin.*, 110 (1966). [i] B. F. Duesel, H. Berman, and R. J. Schachter, *J. Amer. Pharm. Ass.*, **43**, 619 (1954). [j] H. Schultzen, *Z. Physiol. Chem.*, 616 (1867).

These heterocycles were characterized by their ^{19}F nmr spectra (Table I).

Application of this procedure to the synthesis of some 8-fluoropurines was also successful. 8-Fluorocaffeine and 8-fluorotheophylline were obtained from the corresponding 8-nitropurines (Table I).

Analogous to 7- or 9-unsubstituted 6-fluoropurines,[2e] the 3(5)-fluoro-1,2,4-triazoles in Table I are stable to base but are hydrolyzed in acidic solution. 8-Fluorocaffeine and 8-fluorotheophylline, like 6-fluoropurines[2e]

(1) Presented in part at the Fourth International Congress of Heterocyclic Chemistry, Salt Lake City, Utah, July 1973, Abstract No. B-4.

(2) (a) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**,3060 (1971); (b) K. L. Kirk and L. A. Cohen, *ibid.*, **95**, 4619 (1973); (c) M. J. Robins and S. R. Naik, *ibid.*, **93**, 5277 (1971); (d) D. H. R. Barton, R. H. Hesse, H. T. Toh, and M. M. Pechet, *J. Org. Chem.*, **37**, 329 (1972); (e) J. Kiburis and J. H. Lister, *J. Chem. Soc. C*, 3942 (1971); (f) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963); (g) M. Ikehara and S. Yamada, *Chem. Pharm. Bull.*, **19**, 104 (1971).

(3) (a) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, New York, N. Y., 1969; (b) M. Hudlicky, "Organic Fluorine Chemistry," Plenum Press, New York, N. Y., 1971.

(4) (a) L. I. Bagal, M. S. Pevzner, and V. A. Lopyrev, *Khim. Geterotsikl. Soedin., Sb. 1: Azotsoderzhashchie Geterotsikly*, 180 (1967); *Chem. Abstr.*, **70**, 77876t (1969); (b) C. F. Kroeger, R. Miethchen, H. Frank, M. Siemer, and S. Pilz, *Chem. Ber.*, **102**, 755 (1969); (c) L. I. Bagal, M. S. Pevzner, V. Ya. Samarenko, and A. P. Egorov, *Khim. Geterotsikl. Soedin.*, 702 (1970); (d) L. I. Bagal, M. S. Pevzner, V. Ya. Samarenko, and A. P. Egorov, *ibid.*, 1701 (1970).

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(6) G. Bartoli, A. Latrofa, F. Naso, and P. E. Todesco, *J. Chem. Soc., Perkin Trans. 1*, 2671 (1972).

and other 8-fluoropurines,[2g] are readily hydrolyzed in dilute acid.

Since both 3(5)-nitro-1,2,4-triazoles and certain 8-nitropurines[7] are readily available, this method should provide a general route to the corresponding fluoro heterocycles.

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were recorded at 60 MHz for ^1H and at 56.4 MHz for ^{19}F with a Hitachi Perkin-Elmer R20A spectrometer in DMSO-d_6 solutions. Analytical data were determined by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedure.—The nitro heterocycle (20 mmol) was heated with excess (*ca.* 30 ml) liquid hydrogen fluoride in a Monel or Teflon-lined bomb under the conditions given in Table I. At the end of the reaction the bomb was cooled and volatile material was removed under a stream of nitrogen. The residue was dried in a plastic vacuum desiccator over potassium hydroxide pellets. The products were crystallized directly or in some cases were purified by chromatography over silica gel as follows. The crude product (2 g) was dissolved in methanol, and silica gel (10 g) was added to the solution. The mixture was evaporated to dryness under reduced pressure and the silica gel mixture was slurried in chloroform and applied to a small silica gel column packed in chloroform. Elution with chloroform containing 1–10% methanol provided the pure products.

Completion of the reaction and purity of the products were determined by tlc on silica gel using 9:1 chloroform–methanol. The nitro compounds and the purines were visualized under a uv light. The fluoro-1,2,4-triazoles were detected as purple spots by spraying the tlc plate first with a 1% solution of *tert*-butyl hypochlorite[8] in cyclohexane, drying the plate at room temperature, and then spraying with potassium iodide–starch solution.

(7) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **82**, 3773 (1960).

(8) Available as Unispray Aerosol Reagent from Nutritional Biochemicals Corp.; this reagent detects NH compounds.

Communications

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

Synthesis of 1-Hydroxybicyclo[*n*.1.0]alkanes from Silyl Alkenyl Ethers. A Novel Class of Cyclopropanols[1]

Summary: The reaction of trimethylsilyl cycloalkenyl ethers (**1**) with Simmons–Smith reagent gave the corresponding silyl cyclopropyl ethers (**2**), which on hydrolysis afforded 1-hydroxybicyclo[*n*.1.0]alkanes (**3**, n = 3–5) which are a novel class of cyclopropanols having the hydroxy groups at the bridgehead carbon.

Sir: Very recently Rubottom and Lopez have reported in this journal[2] the synthesis of silyl cyclopropyl ethers and cyclopropanols by the reaction of silyl alkenyl ethers with Simmons–Smith reagent. This note has prompted us to disclose our results on the synthesis of 1-hydroxybicyclo[*n*.1.0]alkanes. The synthetic method is operationally simpler and much more useful than one might evaluate it from the result of Rubottom and Lopez.

Although there has been a good deal of interest in the chemistry of cyclopropanols,[3] little has been known about 1-hydroxybicyclo[*n*.1.0]alkanes, which are a novel class of cyclopropanols having the hydroxy group at the bridgehead carbon. Aside from having intrinsic interest, this class of cyclopropanols is important as the intermediate in the Clemmensen reduction of difunctional ketones[4] and in some other rearrangements.[5] Only several isolated examples of more highly substituted, but not the parent, 1-hydroxybicyclo[*n*.1.0]alkanes have been reported in the literature,[6] except those described by Rubottom and Lopez[2] which will be mentioned later. Although a wide variety of methods have been developed for the synthesis of cyclopropanols,[3,7] most of them are not suitable or inherently not applicable for the synthesis of such cyclopropanols as 1-hydroxybicyclo[*n*.1.0]alkanes.[8]

We have now established that the transformation shown in eq 1 is an exceedingly convenient way of

(1) Synthesis *via* Silyl Alkenyl Ethers. IV. For part III see S. Murai, Y. Kuroki, K. Hasegawa, and S. Tsutsumi, *J. Chem. Soc., Chem. Commun.*, 946 (1972). A part of this work has been presented at the Symposium on Small Ring Compounds, Oct 1972, Nagoya, Japan.

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(5) R. H. Eastman and A. V. Winn, *J. Amer. Chem. Soc.*, **82**, 5908 (1960); W. von E. Doering, M. R. Willcott, III, and M. Jones, Jr., *ibid.*, **84**, 1224 (1962); W. F. Erman, R. S. Treptow, P. Bakuzis, and E. Wenkert, *ibid.*, **93**, 657 (1971); M. L. Rueppel and H. Rapoport, *ibid.*, **94**, 3877 (1972).

(6) (a) A. J. Birch and R. Keeton, *Aust. J. Chem.*, **24**, 331 (1971); (b) J. F. Templeton and W. Wie, *Tetrahedron Lett.*, 3955 (1971); (c) W. Reusch and D. P. Priddy, *J. Amer. Chem. Soc.*, **91**, 3677 (1969); (d) P. S. Venkataramani, J. E. Karoglan, and W. Reusch, *ibid.*, **93**, 269 (1971); (e) I. T. Harrison, R. J. Rawson, P. Turnbull, and J. H. Fried, *J. Org. Chem.*, **36**, 3515 (1971); (f) J. V. Paukstelis and J. Kao, *J. Amer. Chem. Soc.*, **94**, 4784 (1972).

(7) J. L. Magrane, Jr., and D. L. Cottle, *J. Amer. Chem. Soc.*, **64**, 484 (1942); J. P. Freeman, *J. Org. Chem.*, **29**, 1379 (1964); H. H. Wasserman and D. C. Clagett, *Tetrahedron Lett.*, 341 (1964), and *J. Amer. Chem. Soc.*, **88**, (1966); D. T. Longone and W. D. Wright, *Tetrahedron Lett.*, 2859 (1969); H. C. Brown and S. P. Rhodes, *J. Amer. Chem. Soc.*, **91**, 4306 (1969); R. Köster, S. Arora, and P. Binger, *Angew. Chem., Int. Ed. Engl.*, **8**, 205 (1969); C. H. DePuy and R. A. Klein, *Org. Syn.*, **47**, 108 (1967); U. Schöllkopf, J. Paust, and M. R. Patsch, *ibid.*, **49**, 88 (1969).

(8) Two interesting approaches to substituted 1-hydroxybicyclo[4.1.0]-heptanes starting from alkyl enol ethers have been reported. In these studies, tetrahydropyranyl[6a] and β-chloroethyl[6b] groups were employed as the "removable" alkyl groups.