Tetrahedron Letters,Vol.25,No.46,pp 5227-5230,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

A NOVEL SYNTHESIS OF α-FLUOROACETONITRILES.

APPLICATION TO A CONVENIENT PREPARATION OF 2-FLUORO-2-PHENETHYLAMINES

Michael E. LeTourneau and James R. McCarthy*
Merrell Dow Research Institute, Indianapolis, Indiana 46268

Abstract: α-Fluorophenylacetonitriles (3) are readily prepared by the treatment of the corresponding benzaldehyde cyanohydrin trimethylsilylethers (2) with diethylaminosulfur trifluoride (DAST). This method for the introduction of fluorine alpha to a cyano group is also applicable to the cyanohydrin trimethylsilylethers of aromatic ketones. Diborane reduction of the α-fluorophenylacetonitriles (3) yields 2-fluoro-2-phenethylamines (4).

β-Fluoroethylamines have received considerable attention because of the biological activity observed with this class of compounds.[1] Two synthetic methods have been reported for the preparation of β-fluoroamines.[2,3,4,5] A method called "fluorodehydroxylation" converts β-aminoalcohols to β-fluoroamines on treatment with SF_4 and HF in a bomb at low temperatures.[2] Alternatively, aziridines are reported to yield β-fluoroamines by reaction with either HF and an amine[3,4] or with liquid HF.[4] Recently, a synthesis of methyl α,β-aminofluorodeoxypyranosides was reported[5] which utilized a N,N-diallylaziridium cation as an intermediate that was opened with either $Et_4N^+F^-$ or $Et_3N{\cdot}3HF$. Only the method of Wade[3] has been used to prepare 4a. However, these procedures do not provide the flexibility, ease or safety needed for a general synthetic method for introducing fluorine into the benzylic position of a precursor to 4.

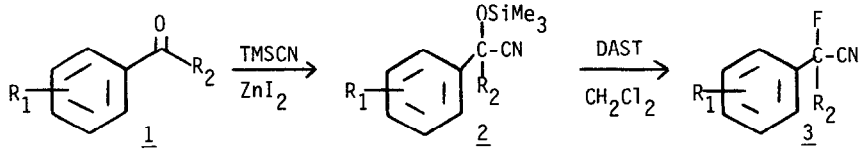
We wish to describe a new facile synthesis of α-fluorophenylacetonitriles (3) which can readily be converted to the corresponding 2-fluoro-2-phenethylamines (4). These potentially versatile intermediates (3) can be prepared from benzaldehydes or aromatic ketones by way of the corresponding cyanohydrin trimethylsilylethers (2).[6] The cyanohydrin ethers (2) are treated directly with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 at 0° to room temperature for 10 min. to 30 min. The α-fluorophenylacetonitriles (3)[7] are obtained in fair to excellent overall yield from the starting benzaldehyde or aromatic ketone (See Table 1).

α-Fluorophenylacetonitrile (3a) has been reported,[8,9,10] however the synthetic routes are not generally efficient. It is interesting to note that an unsuccessful attempt for the preparation of 3a from benzaldehyde cyanohydrin and $PhPF_4$ has been reported.[11] We found that the reaction of 3,4-dimethoxybenzaldehyde cyanohydrin with DAST provided 3c, albeit in about one half the yield obtained from the cyanohydrin trimethylsilylether 2c (43% vs. 82%). The facile reaction of the cyanohydrin trimethylsilylether (2) with DAST can be rationalized by a carbocation type intermediate stabilized by both the conjugative effects of the α-cyano group (demonstrated by Gassman[12]) and the adjacent aromatic ring.

Several of the α-fluorophenylacetonitriles (3) were reduced with diborane[13] to the 2-fluoro-2-phenethylamines[7] (4) in fair to moderate yields (See Table 2). General procedures for the reported transformations are as follows: The method of Evans[6] was followed for the preparation of 2. To a magnetically stirred mixture of ZnI_2 (ca. 10 mg) and benzaldehyde(2.12 g, 20 mmol)[14] in a N_2 atmosphere, cooled to 5° in an ice bath, was added trimethylsilylcyanide

Table 1

α-Fluorophenylacetonitriles Obtained from the Corresponding Benzaldehydes or Aromatic Ketones



1 2 3

Cpd. No.	R_1	R_2	% Yield[a]
3a	H	H	64%
3b	m-OCH_3	H	48%
3c	3,4-dimethoxy	H	82%
3d	m-OAc	H	67%
3e	p-NO_2	H	50%
3f	2-naphthyl[b]	H	46%
3g	3,4-dichloro	H	100%
3h	2,6-dichloro	H	86%
3i	m-fluoro	H	47%
3j	H	CH_3	50%
3k	H	CH_2CH_3	64%

(a) Yields obtained after purification by flash chromatography (overall from 1).

(b) i.e. 2-naphthyl-α-fluoroacetonitrile.

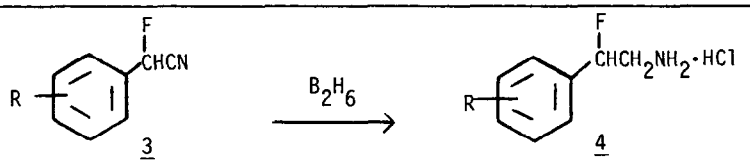
(Aldrich) (1.98 g, 20 mmol) slowly via syringe. The reaction was allowed to come to room temperature and stirred for 10 to 20 min. The mixture was diluted with dry CH_2Cl_2 (25 ml), cooled to 5°, and a solution of DAST (3.54 g, 22 mmol) in CH_2Cl_2 (10 ml) was added dropwise. The reaction was allowed to come to room temperature, stirred for 10 to 30 min. and poured into ice water (150 ml). Additional CH_2Cl_2 (25 ml) was added and the organic layer washed sequentially with H_2O, 0.5 N HCl, H_2O, sat'd. $NaHCO_3$, H_2O, dried ($MgSO_4$) and evaporated *in vacuo* to an oil that was purified by flash chromatography (Baker silica gel) using 10% ethyl acetate in hexane[15] as solvent.

The product (3a) was obtained as a light yellow oil (1.73 g, 64%); ^1H NMR ($CDCl_3$) δ 6.05 (d, J=47 Hz, 1), 7.5 ppm (s,5); MS (CI/CH_4) m/e 136 (MH^+), 116 ($M^+-F^\cdot$); 109 ($M^+-CN^\cdot$); IR (thin film) 1490, 1450, 1350, 1300, 1280, 1190, 1000, 940 $cm.^{-1}$ Anal. Calcd for C_8H_6FN: C, 71.10; H, 4.48; N, 10.37. Found: C, 71.09; H, 4.62; N, 10.01.

To a solution of 3a (11.6 g, 85.5 mmol) in dry THF (170 ml), cooled in an ice bath to 5° under a N_2 atmosphere was added 1M borane-THF (Aldrich) (340 ml, 340 mmol). The reaction was

Table 2

2-Fluoro-2-Phenethylamines Obtained from 3



Cpd. No.	R	m.p., °C[a]	% Yield[b]
4a	H	170-172[c]	49%
4b	m-OCH_3	127-129.5	49%
4c	3,4-dichloro	178-181	41%
4d	2,6-dichloro	239-240	50%
4e	m-fluoro	148-151	46%

(a) Crystallized from CH_3CN or EtOH-CH_3CN.

(b) Based on recrystallized analytically pure material.

(c) Lit.[3] m.p. 169°C.

stirred in the ice bath for 40 min. and quenched by the dropwise addition of ethanol (430 ml). The mixture was acidified with ethanolic HCl and concentrated in vacuo. The residue was triturated with cold CH_3CN (ether in other examples) and recrystallized from ethanol-acetonitrile yielding colorless crystals of 4a (7.4 g, 49%), m.p. 170-172° (Lit.[3] m.p. 169°). The above sequence can be completed in only a few hours on a multigram scale.

It should be noted that the reduction failed when a strong electron donating group was present in the 4-position of the phenyl ring (i.e. 3c). This reaction sequence was successful utilizing phenylacetaldehyde as the starting material but problems with the formation of olefins were observed with several nonaromatic ketones. This was not unexpected, since examples of the dehydration of alcohols by DAST have been reported.[17,18] Additional work is under way on the transformations of 3.

Acknowledgements:

The authors wish to thank Dr. Donald L. Trepanier for his advice and interest in this work, and Robert J. Barbuch for spectral data and discussion on fluorine coupling constants.

References and Notes

1. J. Kollonitsch, Isr. Jr. Chem., 17, 53 (1978); Biomedicinal Aspects of Fluorine Chemistry, R. Filler, Y. Kobayashi, eds., Elsevier Biomedical Press, New York, 1982. The dramatic increase in stability of β-fluoroamines over the corresponding β-chloroamines has been noted.[3]
2. J. Kollonitsch, S. Marburg, L.M. Perkins, J. Org. Chem., 44, 771 (1979).
3. T.N. Wade, J. Org. Chem., 45, 5328 (1980).
4. G.M. Alvernhe, C.M. Ennakoua, S.M. Lacombe, A.J. Laurent, J. Org. Chem., 46, 4938 (1981).
5. D. Picq, D. Anker, C. Rousset, A. Laurent, Tetrahedron Lett., 24, 5619 (1983).
6. D.A. Evans, Chem. Commun., 55 (1973); P.G. Gassman, J.J. Talley, Tetrahedron Lett. 3773 (1978).
7. All new compounds are fully supported by IR; ^1H NMR and mass spectroscopy. All compounds except 3g and 3h gave satisfactory C, H, N analysis, including the 2-fluoro-2-phenethylamines which were prepared from 3g and 3h.
8. B. Cavalleri, B. Bellasio, G.G. Gallo, E. Testa, Farmaco-Ed. Sci., 23, 1127 (1968).
9. R.C. Petry, C.O. Parker, F.A. Johnson, T.E. Stevens, J.P. Freeman, J. Org. Chem., 32, 1534 (1967).
10. A.V. Fokin, V.A. Komarov, S.M. Davydova, K.V. Frosina, Izv, Akad. Nauk SSSR, Ser. Khim 113 (1973); Chem. Abstract, 78, 135783p. (1973).
11. D.J. Costa, N.E. Boutin, J.G. Riess, Tetrahedron, 30, 3793 (1974).
12. P.G. Gassman, T.L. Guggenheim, J. Org. Chem., 47, 3023 (1982).
13. We have found diborane to be a satisfactory reducing agent for other halonitriles: C.E. Reineke, J.R. McCarthy, J. Amer. Chem. Soc., 92, 6376 (1970), while $LiAlH_4$ gave polymeric materials.
14. A minimum volume of CH_2Cl_2 was added to solid aldehydes or ketones to obtain a solution.
15. Ethyl acetate (10% to 33%) in hexane proved satisfactory as a solvent for all purifications.
16. A.L. Johnson, J. Org. Chem., 47, 5220 (1982).
17. L. Somekh, A. Shanzer, J. Org. Chem. 48, 907 (1983), and references cited therein.
18. K. Boutlon, B.E. Cross. J. Chem. Soc., Perkin Trans. I, 1293 (1981).

(Received in USA 2 July 1984)