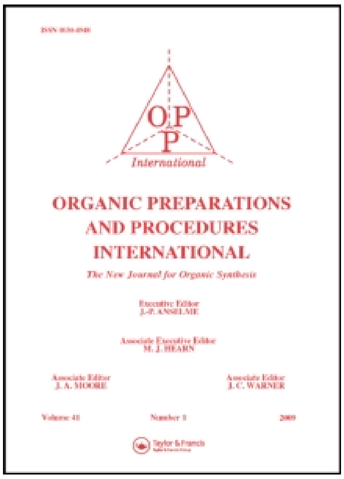

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A CONVENIENT SYNTHESIS OF POLYFLUORINATED α, ω-DIAMINES

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A CONVENIENT SYNTHESIS OF POLYFLUORINATED α, ω-DIAMINES

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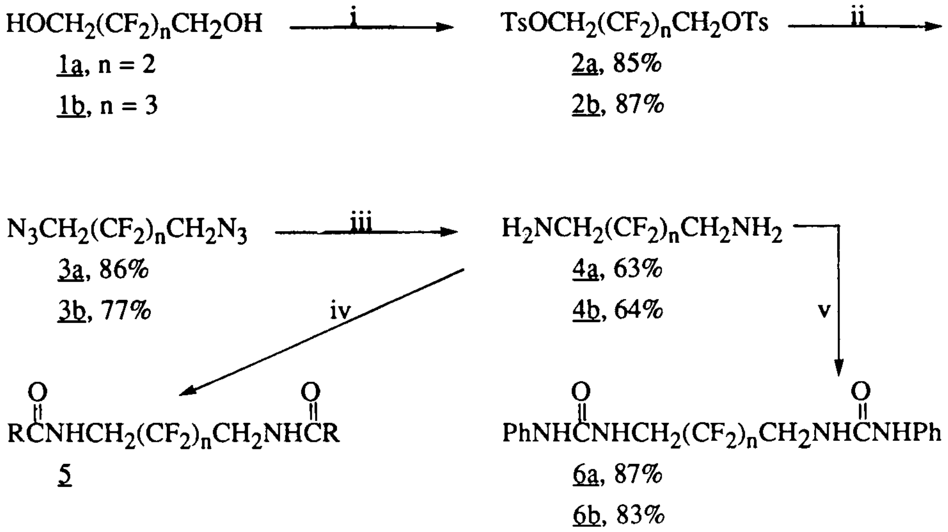
Recent reports of the synthesis of fluorinated diamines[1,2] coupled with their particular interest as non-invasive tumor imaging agents[2] prompt us to communicate our own convenient preparation of symmetrically fluorinated putrescine (4a) and cadaverine (4b) analogs as well as some of their bisamide and bisurea derivatives, 5 and 6, respectively.

In the evaluation of synthetic methodology toward the preparation of 4, three pathways were considered: 1) hydride reduction of perfluorosuccinamide and perfluoroglutaramide, 2) reduction of the corresponding perfluoro-α, ω-dinitriles, and 3) reduction of the dia- zides 3. Although the lithium aluminum hydride (LAH) reduction of perfluoroglutar- amide[3,4] has been reported to yield 4b, explosions have occurred using this procedure.[5] Use of borane-THF apparently cirvuments this hazard, although low yields of 4a were reported for the reduction of perfluorosuccinamide.[1] Catalytic reduction of perfluoroglutaronitrile requires high temperatures and pressures[6,7] making this method unsuitable for laboratory preparations. Catalytic reduction of diazide 3b was reported to be facile, but its synthesis required the carcinogenic HMPA (hexamethylphosphoramide) as solvent.[8,9] We elected to explore the latter route employing the non-carcinogenic DMPU (1,3-dimethyl-3,4,5,6- tetrahydro-2(1H)-pyrimidinone)[10] instead of HMPA for the reaction of ditosylate 2 with azide ion.



i) TsCl, pyridine; ii) NaN_3, DMPU, 100-110°, 48 hrs; iii) H_2, 10% Pd/C, EtOH, 6 hrs; iv) RCOCl, Et_3N, Et_2O; v) PhNCO, 2-butanone.

The polyfluorinated α,ω-diols 1 are readily available either commercially (1b) or by the LAH reduction of the corresponding diesters.[11] The ditosylates 2 were prepared easily as reported for the nonfluorinated α, ω-diols.[12,13] Displacement of both tosylate groups of 2 with a 2-fold excess of sodium azide occurred in DMPU at 100-110°; after 48 hrs, reactions were generally ca. 95% complete as judged by integration of the ^1H nmr spectra of the crude isolated products (cf. ca. 90% displacement in HMPA[8]). Crude 3 were hydrogenated over 10% Pd/C using a Parr shaker to afford the desired polyfluorinated diamines 4 in 63-64% yield after vacuum distillation. The overall yields of 4 from 1 ranged from 43-46%, which are equal to or better than those obtained by the literature methods mentioned above.

Derivatives of 4 could be prepared in a straight forward manner from various acid chlorides to give 5 or from phenylisocyanate providing 6 (Table). ^{19}F nmr signals of the diamines and derivatives are listed in the Table. This methodology should be applicable to the preparation of a variety of α,ω-diamines of general formula $H_2NCH_2(CF_2)_nCH_2NH_2$.

EXPERIMENTAL SECTION

WARNING. Although we have experienced no problem with diazides 3, organic azides are generally recognized as potentially explosive and should be handled with due care behind appropriate shielding.

TABLE. Physical Data for Diamines 4 and Derivatives 5 and 6.

Compound No.	n	R	Yield (%)[a]	Purification[b]	bp/mm (mp),°C	^{19}F nmr[c]
4a	2	--	46[d]	dist.	58-60/7	-122.9
4b	3	--	43[d]	dist.	42-44/1	-121.9 -126.4
5a	2	CH_3	70	recr.	(214-216)	-119.1[e]
5b	3	CH_3	77	recr.	(175-178)	-117.5[e] -126.2
5c	2	Ph	86	recr.	(242-244)	-118.6[e]
5d	3	Ph	78	recr.	(208-210)	-112.5 -121.5
5e	2	PhCH=CH	83	recr.	(274-276)	-118.7[e]
5f	3	PhCH=CH	81	recr.	(225-227)	-117.1[e] -125.9
6a	2	PhNH	87	recr.	(257-258)	-115.0
6b	3	PhNH	83	recr.	(201-203)	-118.1[e] -126.1

a) All yields refer to pure isolated products. b) Recrystallization from $CHCl_3$. c) In $CDCl_3$. d) Overall yield, 1--> 4. e) In DMSO-d_6.

Ditosylates 2 were prepared using the literature procedure[12,13] in 83-89% yield after recrystallization from MeOH.

2a, mp. 89-91°.

Anal. Calcd for $C_{18}H_{18}F_4O_6S_2$: C, 45.95; H, 3.83; S, 13.63; F, 16.15
Found : C, 45.86; H, 4.05; S, 13.67; F, 15.99

2b, mp. 92-94°.

Anal. Calcd for $C_{19}H_{18}F_6O_6S_2$: C, 43.85; H, 3.49; S, 12.32; F, 21.90
Found : C, 43.74; H, 3.42; S, 12.57; F, 21.74

Preparation of Diazides 3. Typical Procedure.- A mixture of 31.0 mmol of 2 and 8.00 g (123 mmol) of sodium azide in 70 ml of DMPU was heated to 100-110° for 48 hrs under nitrogen. Water (300 mL) was added and the product extracted with ether. The ether extracts were washed with water and brine, and dried over magnesium sulfate. Evaporation *in vacuo* provided crude 3 as yellow to amber liquids in 77-86% yields (ca. 95% pure by ^{1}H nmr; ca. 5% starting 2). Crude diazides 3 were reduced directly to diamines 4 without purification.

Preparation of Diamines 4. Typical Procedure.- A mixture of 21 mmol of crude 3, 0.5 g of 10% Pd/C, and 80 mL of absolute ethanol was hydrogenated at 50 psi on a Parr shaker apparatus for 6 hrs, evacuating periodically and recharging with hydrogen to remove the nitrogen formed in the reaction. After filtration through diatomaceous earth and examining the filtrate carefully by ir for the absence of azide, the ethanol was removed in vacuo and the liquid distilled in vacuo (Table) to provide 63-64% of pure 4.

Anal. Calcd for 4a, $C_4H_8F_4N_2$: C, 31.01; H, 5.04; N, 17.50
Found: C, 30.97; H, 4.89; N, 17.54

Anal. Calcd for 4b, $C_5H_8F_6N_2$: C, 28.58; H, 3.84; N, 13.33
Found : C, 28.55; H, 3.64; N, 13.64

Diamides 5 were prepared from one equivalent of diamine 4 and 2.2 equivalents of the acid chloride in the presence of 2.2 equivalents of triethylamine in ether at room temperature. The solid products were recrystallized from chloroform.

Bisureas 6, were prepared from 2.5 mmol of diamine 4 and 5.5 mmol of phenylisocyanate in 25 mL of 2-butanone at room temperature, and the products recrystallized from chloroform.

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