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Henry reaction of fluorinated nitro compounds

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Dedicated to Professor Wei-Yuan Huang on the occasion of his 90th birthday.

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ABSTRACT

The Henry (nitroaldol) reaction of fluorinated nitro compounds with various aromatic aldehydes and a fluorinated aliphatic aldehyde to give β-fluoro-β-nitroalcohols which bearing a fluorinated quaternary carbon center was reported. The relative configuration of the major diastereoisomer of 2-fluoro-2-nitro-1-(4-nitrophenyl)-3-phenylpropanol (**5bf**) was determined by X-ray single crystal analysis.

1. Introduction

Since its discovery in 1895, the Henry (nitroaldol) reaction becomes one of the most important carbon–carbon bond forming reactions in organic synthesis. The resulted β-nitroalcohol is versatile intermediate in the synthesis of a variety of natural products and medicinally important compounds [1–8]. While the Henry reaction has been extensively studied in numerous synthetic processes, few studies of halogenated nitroalkanes have been reported [9].

Fluorine-containing compounds have attracted considerable attention for introduction of fluorine to organic compounds can drastically change both their biological and physical properties [10–20]. It was reported that as many as 30–40% of agrochemicals and 20% of pharmaceuticals including four of the top ten best-selling drugs on market were estimated to contain fluorine [20,21]. Accordingly, the development of methodologies to incorporate fluorine into organic molecules has attracted great attention recently [10–20]. We envisioned that the addition of α-fluoronitroalkanes to carbonyl compounds to form fluorinated β-hydroxynitroalkanes could represent one of these important methods. Moreover, the Henry reaction of fluoronitroalkane gives rise to fluorinated quaternary carbon center, which is highly desirable motif in numerous drug molecules [22–25]. Fluoronitroalkane is less studied as a monofluorinated synthetic synthon compared to fluoronitroester [26–29]. For a recent example, using α-fluoro-α-nitro esters, Zhao and their coworkers reported an organocatalytic asymmetric Michael addition [28]. In contrast, few reactions of fluoronitroalkane have been reported, to the best of our knowledge [29]. Herein we report the Henry reaction of fluoronitroalkanes to give β-fluoro-β-nitroalcohols with a fluorine-containing quaternary carbon center in high yields.

2. Results and discussion

As shown in Tables 1 and 2, fluoronitroalkanes **3a–3e** were prepared via nitroalkanes **2a–2e** starting from halides **1a** to **1e** [30,31]. Reaction of 1-fluoro-1-nitroheptane **3a** and benzaldehyde **4a** was chosen as the model reaction to optimize the reaction conditions. A variety of bases including organic and inorganic bases were screened as the catalyst (Table 3, entries 1–8). It was found that 1,1,3,3-tetramethylguanidine (TMG) was found to be the most effective, giving product **5aa** in 67% yield with a diastereoselectivity of 30:70. Interestingly, The decrease in dosage of TMG from 50 mol% to 30 mol% resulted similar yield and the same diastereoselectivity (Table 3, entry 8 vs 9). The reaction conditions were further optimized by changing the solvents (Table 4, entries 1–5). Finally, THF (Table 4, entry 2) was found to be the preferential

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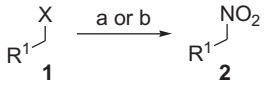
Table 1
Synthesis of nitro compounds.



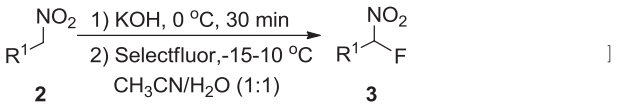
Entry	Substrate	R^1	X	Product	Temp (°C)	Yield (%)
1	**1a**	n-C_6H_{13}	I	**2a**	r.t.	62[a]
2	**1b**	$C_6H_5CH_2$	I	**2b**	60	60[b]
3	**1c**	Ph	Br	**2c**	−18	45[a]
4	**1d**		Br	**2d**	r.t.	35[a]
5	**1e**		Br	**2e**	r.t.	30[a]

[a] $NaNO_2$/urea in DMF.
[b] $AgNO_2$ in H_2O.

solvent in terms of the yield (67%). Reactions in other solvents, such as CH_2Cl_2, EtOH, toluene and MeCN, gave lower yields.

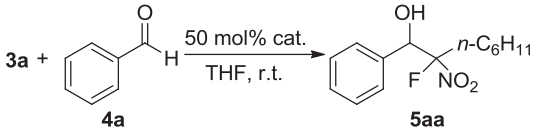
After the optimal reaction condition was found (30 mol% of TMG in THF), the diastereoselective Henry reactions of α-fluoronitroalkanes **3a–3e** and various aldehydes **4a–4h** were investigated. As summarized in Table 5, the Henry reaction between α-fluoronitroalkanes **3a/3b** and different aromatic aldehydes in the presence of 30 mol% TMG in THF at room temperature led to desired products in moderate to good yield (40–80%) (Table 5, entries 1–10). In general, aromatic aldehydes bearing electron-withdrawing groups showed higher reactivity than those with electron-donating groups. In contrast to α-fluoronitroalkanes **3a/3b**, compound **3c–3e** seemed to be more reactive since the reactions at ambient atmosphere produced a complex mixture. However, when the reactions of **3c–3e** were carried out at a lower temperature (approximately −30 °C), the reactions went smoothly to afford the nitroaldol products in 60–85% yields (Table 5, entries 11–15). Interestingly, some of the nitroaldol products were unstable when subjecting to silica gel chromatograph. The products **3c** and aromatic aldehydes (e.g. *p*-nitrobenzaldehyde) of retro Henry reaction were isolated. The Henry reaction of fluoroalkylaldehyde was studied. 1-Fluoro-1-phenyl-1-nitromethane **3c** reacted smoothly with 5-chloro-2,2,3,3,4,4,5,5-octafluoropentanal **4i** (Table 5, entry 12) under

Table 2
Monofluorination of nitro compounds.



Entry	Substrate	R^1	Product	Yield (%)
1	**2a**	n-C_6H_{13}	**3a**	82
2	**2b**	$C_6H_5CH_2$	**3b**	80
3	**2c**	Ph	**3c**	75
4	**2d**		**3d**	76
5	**2e**		**3e**	73

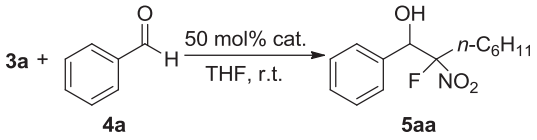
Table 3
Effects of base catalysts.



Entry	Cat.	Yield (%)[a]	Syn:anti[a]
1	K_2CO_3	38	26:74
2	Cs_2CO_3	36	26:74
3	f-BuONa	45	23:77
4	Et_3N	35	46:54
5	DBU	60	31:69
6	DABCO·$6H_2O$	26	57:43
7	DIPEA	29	44:56
8	TMG	67	30:70
9[b]	TMG	70	30:70

DABCO, triethylenediamine; DIPEA, ethyldiisopropylamine, TMG, tetramethylguanidine.
[a] Yields and Syn:anti determined by ^{19}F NMR.
[b] 30% TMG was used.

Table 4
Effects of the solvent.



Entry	Solvent	Yield (%)[a]	Syn:anti[a]
1	CH_2CL_2	32	33:67
2	THF	67	30:70
3	EtOH	60	31:69
4	toluene	45	37:63
5	MeCN	34	29:71

[a] Determined by ^{19}F NMR.

the same reaction conditions, giving a 73% yield of the nitroaldol product in a 27:73 diastereoselectivity. Both isomers except **5df** of nitroaldol products were obtained and fully characterized after a careful separation by column chromatography on silica gel. Owing

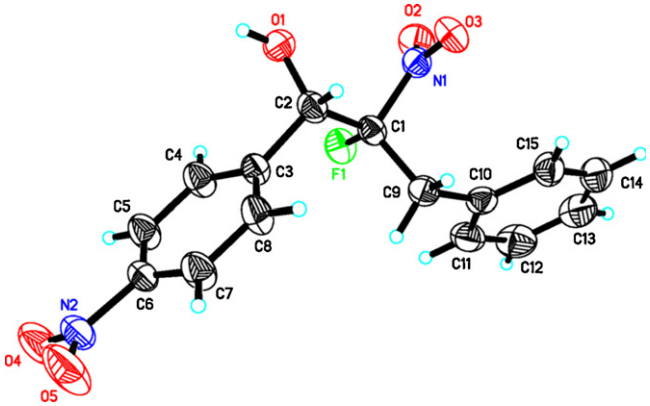


Fig. 1. X-ray structure of *anti*-**5bf**. Selected bond lengths (Å) and (torsion) angles (°): F(1)–C(1) 1.358(19), N(1)–O(2) 1.209(2), N(1)–O(3) 1.216(2), N(1)–C(1) 1.542(2), O(1)–C(2) 1.419(2), C(1)–C(9) 1.512(2), C(1)–C(2) 1.527(2); O(2)–N(1)–C(1) 118.85(16), O(3)–N(1)–C(1) 15.71(13), F(1)–C(1)–C(9) 110.32(15), F(1)–C(1)–C(2) 109.25(14), C(9)–C(1)–C(2) 117.09(14), F(1)–C(1)–N(1) 105.24(12), C(9)–C(1)–N(1) 108.35(13), C(2)–C(1)–N(1) 105.84(14), O(1)–C(2)–C(3) 111.90(15), O(1)–C(2)–C(1) 104.72(14), C(3)–C(2)–C(1) 112.81(15), C(1)–C(9)–C(10) 112.89(13); F(1)–C(1)–C(2)–O(1) −60.1(2).