A Convenient Synthesis of 2-Aryl-3-per(poly)fluoroacylindoles

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2-Aryl-3-per(poly)fluoroacylindoles were synthesized in good yields by the 1,3-dipolar cycloaddition reaction of *C*-aryl-*N*-phenylnitrones with fluorine-containing olefins and the subsequent rearrangement of the adducts. An ionic mechanism was proposed for the formation of the titled compounds.

Keywords 1,3-dipolar cycloaddition, rearrangement, fluorine-containing indole

Introduction

Due to the specific properties imparted by fluorine, the introduction of a fluorine atom or a fluoroalkyl group into lead molecules has been widely used as one of the methods for the development of novel biologically active compounds.[1] Indoles are attractive compounds from the viewpoint of their various biological activities against central nervous system or as a plant hormone,[2] and 2,3-disubstituted indoles are important building blocks for the synthesis of natural products and biologically interesting compounds containing the indole skeleton.[3] So the synthesis of fluorine-containing indoles has aroused much interest in recent years.

1,3-Dipolar cycloaddition of nitrones with olefins was reported for the preparation of isoxazolidines.[4] Cycloadducts of *N*-phenylnitrones and olefins, however, are usually unstable. The known reactivity of the N—O functional group flanked by a π system induces the formation of a number of rearrangement products including indoles from the initial cycloadduct.[5] In our continuous study on developing synthetic strategies to fluorine-containing heterocycles, we found recently a novel pathway leading to 2-aryl-3-per(poly)fluoroacylindoles via 1,3-dipolar cycloaddition of *C*-aryl-*N*-phenyl nitrones to fluorine-containing olefins and the subsequent rearrangement of the adducts.

Results and discussion

C-Aryl-*N*-phenylnitrones (**1**) were prepared by the condensation of aryl aldehydes with *N*-phenylhydroxyamine. Fluorine-containing olefins, *N*-aryl-2-hydropoly(per)fluoroalkenamides (**2** and **3**) and 2-hydropoly(per)fluoroalkenoates (**4**), were prepared by the reported procedure.[6]

The reaction of **1** and fluorine-containing olefin (**2**, **3** or **4**) was carried out in CH_2Cl_2 under refluxing. TLC detection showed that one product was formed predominantly. Isolation by flash chromatography gave pale yellow solids of 2-aryl-3-per(poly)fluoroacylindoles (**5**) (Scheme 1). The results are summarized in Table 1.

The characterizations of known compound, **5aa**, are coincided with those reported in the literature.[5a] The elemental analysis, ^{1}H NMR, ^{19}F NMR, IR and MS spectra of new compounds are in good agreement with the assigned structures. Taking compound **5bc** as an example, the ^{19}F NMR spectrum of **5bc** reveals the presence of a C_3F_7 group. The ^{1}H NMR spectrum of **5bc** shows only the presence of eight aromatic protons at δ 7.31—8.08 and one active hydrogen at δ 9.06. The mass spectrum shows m/z: 425 ($M^+ + 2$), 423 (M^+), 254 ($M^+ - C_3F_7$).

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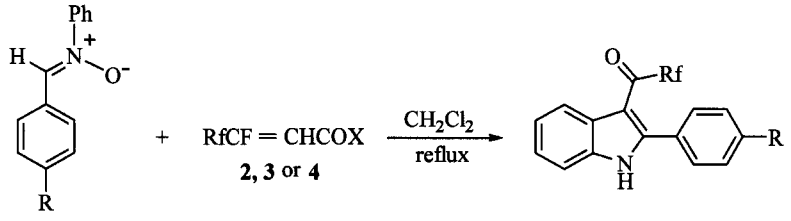
The IR spectrum has an absorption peak at 1653 cm^{-1} for the conjugated carbonyl group.

The formation of compound **5** is assumed to be the results of cycloaddition of **1** with fluorine-containing olefins and the subsequent rearrangement as shown in Scheme 2. Namely, the cycloadduct **A** lost an HF to form compound **B**, which in turn subjected to the cleavage of N—O bond to give an ionic intermediate **C**. Cyclization of **C** followed by the elimination of HCOX gave compound **5** as the final product.

Scheme 1



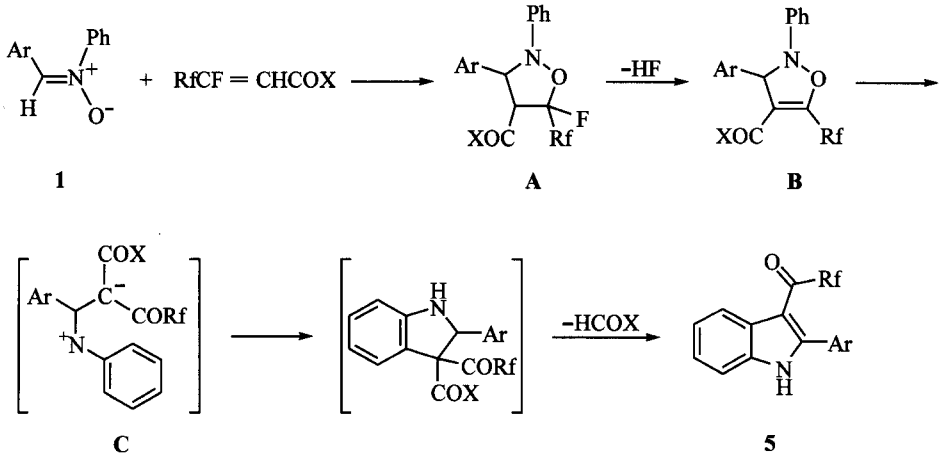
1 **5**

1a: R = H; **1b**: R = Cl;
2a: Rf = CF_3, X = $NHC_6H_4Me(o)$;
2b: Rf = $Cl(CF_2)_3$, X = $NHC_6H_4Me(o)$;
2c: Rf = C_3F_7, X = $NHC_6H_4Me(o)$;
3b: Rf = $Cl(CF_2)_3$, X = $NHC_6H_4NO_2(p)$;
4b: Rf = $Cl(CF_2)_3$, X = OEt

Table 1 Reaction of *C*-aryl-*N*-phenylnitrones (**1**) with fluorine-containing olefins (**2**, **3** or **4**)

Entry	R	Rf	X	Product	Yield (%)
1	H	CF_3	$NHC_6H_4Me(o)$	**5aa**	55.0
2	H	$Cl(CF_2)_3$	OEt	**5ab**	62.3
3	H	$Cl(CF_2)_3$	$NHC_6H_4Me(o)$	**5ab**	70.8
4	H	$Cl(CF_2)_3$	$NHC_6H_4NO_2(p)$	**5ab**	54.5
5	H	$F(CF_2)_3$	$NHC_6H_4Me(o)$	**5ac**	64.5
6	Cl	$Cl(CF_2)_3$	$NHC_6H_4Me(o)$	**5bb**	63.5
7	Cl	$F(CF_2)_3$	$NHC_6H_4Me(o)$	**5bc**	67.0

Scheme 2



1 **A** **B**

C **5**

It was reported that cycloadducts of *C*-aryl-*N*-phenylnitrones (**1**) and olefins may undertake another rearrangement pathway in addition to the above one,[5] resulting in the formation of 3-fluoroalkylindoles as final products in the case of the above olefins (Scheme 3). But no 3-fluoroalkylindole was isolated in the above reactions, and the same product **5ab** was obtained when the same nitrone reacted with three different olefins **4b**, **2b** and **3b** respectively, indicating that the COX group was lost during the reaction and the ionic mechanism shown in Scheme 2 was involved in the rearrangement of the cycloadduct instead of the diradical one. This was further confirmed by the reaction of olefin **2b** with different nitrone (**1a** and **1b**, Entry 3 and Entry 6 in Table 1), which gave different products with the remaining of the *C*-aryl group.

In summary, fluorine-containing heterocyclic compounds, 2-aryl-3-per(poly)fluoroacylindoles (**5**) can be prepared by a new convenient method, namely: 1,3-dipolar cycloaddition reaction of *C*-aryl-*N*-phenylnitrones (**1**) with fluorine-containing olefins and the subsequent rearrangement under mild conditions.

Experimental

Melting points were uncorrected. IR spectra were recorded on a Perkin-Elmer 983G spectrophotometer (KBr pellets). ^{1}H NMR spectra were measured on a Bruker AM 300 (300 MHz) spectrometer (TMS as internal standard). ^{19}F NMR spectra were recorded on a Bruker AM300 spectrometer (282 MHz, TFA as external standard, chemical shifts were reported as δ_{CFCl_3}, $\delta_{CFCl_3} = \delta_{TFA} - 76.8$). Mass spectra were taken on a Finnigan GC-MS 4021 spectrometer. HRMS spectra were taken on a Finnigan MAT 8430 spectrometer. Chromatography was performed on a column packed with silica gel H, particle size 10—40 μm.

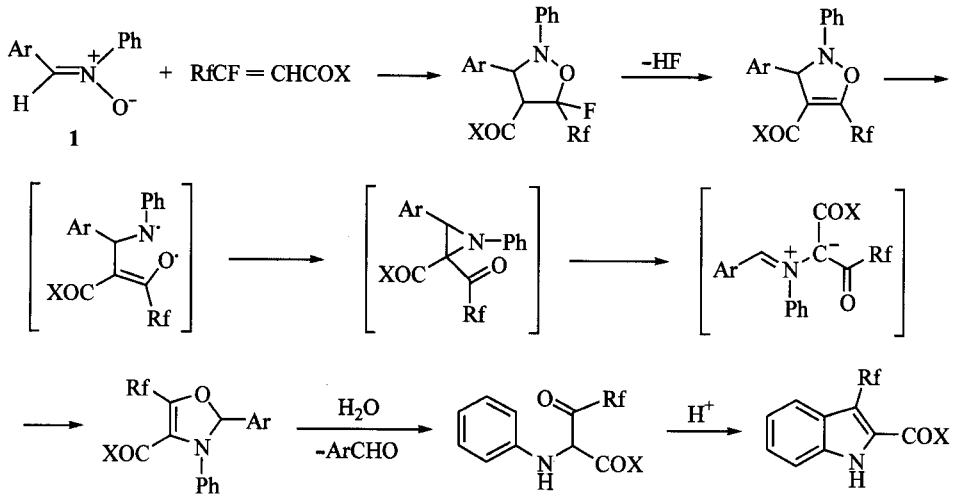
Typical procedure

A mixture of *C*-aryl-*N*-phenylnitrone (**1**) (1.0 mmol) and fluorine-containing olefin (**2**, **3** or **4**) (1.0 mmol) in 10 mL of CH_2Cl_2 was refluxed with stirring for about 20 h (monitored by TLC or ^{19}F NMR). Then the solvent was removed from the reaction mixture and the crude product obtained was purified by flash chromatography using petroleum ether and ethyl acetate (5:1, *V/V*) as eluent to give pale yellow solids of compound **5**.

5aa[5a] M.p. 162—164 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.32—7.38 (m, 2H, ArH), 7.41—7.51 (m, 6H, ArH), 8.07—8.12 (m, 1H, ArH), 8.84 (brs, 1H, NH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −72.5 (s, 3F, CF_3); IR (KBr) ν: 3302, 1653, 1452, 1208, 1136, 935, 755 cm^{-1}; MS *m/z* (%): 289 (M^+, 35.0), 220 ($M^+ - CF_3$, 100.0).

5ab M.p. 147—148 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.33—7.36 (m, 2H, ArH), 7.42—7.54 (m, 6H, ArH), 8.07—8.10 (m, 1H, ArH), 8.83 (brs, 1H, NH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −66.8 (t, 2F, $ClCF_2$), −112.8 (t, 2F, CF_2), −119.0

Scheme 3



(m, 2F, CF_2); IR (KBr) ν: 3226, 1623, 1427, 1189, 1121, 749 cm^{-1}; MS m/z(%): 405 (M^+, 18.0), 407 ($M^+ + 2$, 6.3), 370 ($M^+ - Cl$, 5.8), 220 [$M^+ - Cl(CF_2)_3$, 100.0]. Anal. calcd for $C_{18}H_{10}ClF_6NO$: C 53.29, H 2.48, N 3.45; found C 53.28, H 2.71, N 3.44.

5ac M.p. 145—147 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.32—7.36 (m, 2H, ArH), 7.42—7.55 (m, 6H, ArH), 8.07—8.10 (m, 1H, ArH), 9.01 (brs, 1H, NH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −80.56 (t, 3F, CF_3), −114.79 (t, 2F, CF_2), −125.57 (m, 2F, CF_2); IR (KBr) ν: 3226, 1623, 1427, 1189, 1121, 749 cm^{-1}; MS m/z(%): 389 (M^+, 2.7), 220 ($M^+ - C_3F_7$, 26.7), 93 (100.0). Anal. calcd for $C_{18}H_{10}F_7NO$: C 55.54, H 2.59, N 3.60; found C 55.01, H 2.84, N 3.69.

5bb M.p. 135—136 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.33—7.38 (m, 2H, ArH), 7.42—7.46 (m, 5H, ArH), 8.04—8.07 (m, 1H, ArH), 8.80 (brs, 1H, NH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −67.51 (t, 2F, $ClCF_2$), −113.68 (t, 2F, CF_2), −119.67 (m, 2F, CF_2); IR (KBr) ν: 3249, 1615, 1439, 1191, 1121, 827, 750 cm^{-1}; MS m/z(%): 439 (M^+, 37.5), 441 ($M^+ + 2$, 26.8), 443 ($M^+ + 4$, 5.9), 404 ($M^+ - Cl$, 7.7), 254 [$M^+ - Cl(CF_2)_3$, 100.0], 219 [$M^+ - Cl(CF_2)_3 - Cl$, 25.6]. HRMS calcd for $C_{18}H_9Cl_2F_6NO$ 438.99654, found 438.99512.

5bc M.p. 139—141 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 7.31—7.37 (m, 2H, ArH), 7.39—7.43 (m, 5H, ArH), 8.05—8.08 (m, 1H, ArH), 9.06 (brs, 1H, NH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ: −80.48 (t, 3F, CF_3), −114.85 (t, 2F, CF_2), −125.51 (m, 2F, CF_2); IR (KBr) ν: 3248, 1653, 1439, 1227, 1123, 744 cm^{-1}; MS m/z(%): 423 (M^+, 26.0), 425 ($M^+ + 2$, 8.6), 254 [$M^+ - C_3F_7$, 100.0], 219 [$M^+ - C_3F_7 - Cl$, 25.1]. HRMS calcd for $C_{18}H_9ClF_7NO$ 423.02609, found 423.02689.

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