Russian Journal of Organic Chemistry, Vol. 38, No. 7, 2002, pp. 1030–1034. Translated from Zhurnal Organicheskoi Khimii, Vol. 38, No. 7, 2002, pp. 1073–1077.

Difluoromethylation of Sulfonamides

K. I. Petko, A. A. Tolmachev, and L. M. Yagupol'skii

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, ul. Murmanskaya 5, Kiev, 02094 Ukraine

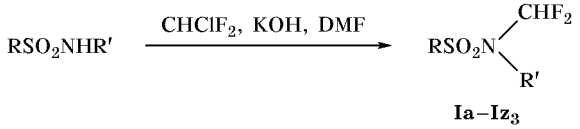
Received June 27, 2001

Abstract—Reactions of sulfonamides RSO_2NHR' with chlorodifluoromethane and solid alkali give the corresponding derivatives $RSO_2N(CHF_2)R'$ containing a difluoromethyl group on the nitrogen atom. Sulfonamides derived from 2-aminobenzothiazole and 2- and 4-aminopyridines react with chlorodifluoromethane at the endocyclic nitrogen atom.

Difluoromethylation of phenols and benzenethiols at the oxygen and sulfur atoms has been well documented [1]. Analogous reactions at the NH group of some heterocyclic compounds have also been reported [2–4]. As a rule, compounds having a difluoromethyl group at exocyclic nitrogen atom readily undergo hydrolysis, so that they were not obtained by direct difluoromethylation [5, 6].

We anticipated that the presence of a strong electron-acceptor group at exocyclic nitrogen atom should enhance the stability of the corresponding *N*-difluoromethyl derivatives, thus making it possible to isolate products of reactions of sulfonamides with difluorocarbene generated from Freon-22 in alkaline medium. The only example of difluoromethylation of *N*-methyl-2-chlorobenzenesulfonamide was reported in patent [7]. We examined this reaction with various sulfonamides **Ia**–**Iz$_3$**, including sterically hindered ones and very weakly nucleophilic *N*-difluoromethylsulfonamides (Table 1). Sulfonamides are weakly nucleophilic substrates; therefore, their reactions with Freon-22 were performed under more severe conditions than those appropriate for phenols and benzenethiols, namely with solid potassium hydroxide in dimethylformamide (Scheme 1). The initial sulfonamides were prepared from accessible *p*-toluenesulfonyl chloride. Under the given conditions, *N*-methyl-*p*-toluenesulfonamide reacted with $CHClF_2$ quite vigorously within 10–15 min, and the reaction mixture spontaneously warmed up to 90–100°C. Some isonitrile was formed as by-product. The reaction of *N*-*tert*-butyl-*p*-toluenesulfonamide was characterized by a weaker exothermic effect, and the yield of the product was higher.

Scheme 1.



Ia–**Iz$_3$**

For R and R′, see Table 1.

Sterically unhindered *N*-aryl-*p*-toluenesulfonamides reacted, as a rule, with self-heating to 60–80°C in 15–20 min, and the yields of the products were high. However, the reactions of *N*-(3-nitrophenyl)- and *N*-(3-trifluoromethylphenyl)-*p*-toluenesulfonamides with $CHClF_2$ were accompanied by strong tarring, and the yields of products **Ig** and **Ih** were poor, 20 and 7%, respectively. We also brought into reaction with $CHClF_2$ derivatives of 2-methyl-5-nitrobenzenesulfonamide. The presence of a nitro group in these substrates also induces appreciable tarring, but the yields of the target products were higher (40–55%) than the yield of **Ig**. No tarring occurred in the reactions with thiophenesulfonamide derivatives, and the yields were good (70–80%).

Sterically hindered *N*-aryl-*p*-toluenesulfonamides having various substituents in the *ortho*-position of the *N*-phenyl ring react with a weak exothermic effect, and in some cases it is necessary to heat the reaction mixture to complete the process. The reaction time increases to 30–40 min. The yields of the target products are fairly high (70–92%); a lower yield was observed only for substrates containing the bulkiest *tert*-butyl group.

We also succeeded in effecting difluoromethylation of sulfonamide having two methyl groups in both *ortho* positions of the *N*-phenyl ring. The reaction

1070-4280/02/3807-1030 $27.00 © 2002 MAIK "Nauka / Interperiodica"

Table 1. Yields, melting points, temperatures of synthesis, ^1H and ^{19}F NMR data, and elemental analyses of *N*-difluoromethylsulfonamides **Ia**–**Iz$_3$**

Comp. no.	R	R′	Yield, %	mp, °C	Reaction temperature, °C	Chemical shifts δ, ppm (*J*, Hz)	
						^1H	^{19}F
Ia	4-MeC_6H_4	Me	57	49–51[a]	90–100	7.00 t (*J* = 60)	–100.05 d (*J* = 60)
Ib	4-MeC_6H_4	*t*-Bu	62	86–88[b]	80–90	7.47 t (*J* = 60)	–89.81 d (*J* = 60)
Ic	4-MeC_6H_4	Ph	95	106–107[c]	60–70	7.49 t (*J* = 60)	–93.52 d (*J* = 60)
Id	4-MeC_6H_4	4-FC_6H_4	54	76–78[a]	60–70	7.56 t (*J* = 60)	–94.02 d (*J* = 60)
Ie	4-MeC_6H_4	4-ClC_6H_4	63	69–70[a]	60–70	7.69 t (*J* = 60)	–92.58 d (*J* = 60)
If	4-MeC_6H_4	4-$MeOC_6H_4$	68	74–76[b]	60–70	7.62 t (*J* = 60)	–93.91 d (*J* = 60)
Ig	4-MeC_6H_4	3-$NO_2C_6H_4$	20	82–83[d]	50–60	7.77 t (*J* = 60)	–93.72 d (*J* = 60)
Ih	4-MeC_6H_4	3-$CF_3C_6H_4$	7	67–68[a]	50–60	7.64 t (*J* = 60)	–93.70 d (*J* = 60)
Ii	4-MeC_6H_4	2-FC_6H_4	77	92–94[b]	50–60	7.58 t (*J* = 60)	–90 to–100[e]
Ij	4-MeC_6H_4	2-MeC_6H_4	78	85–87[b]	70–80	7.64 t (*J* = 60)[f]	–101.39, –100.62 d.d (*J* = 58), –88.92, –88.17 d.d (*J* = 61)
Ik	4-MeC_6H_4	2-$MeOC_6H_4$	72	89–90[b]	70–80	7.54 t (*J* = 60)	–100.41, –99.67 d.d (*J* = 58), –89.22, –88.47 d.d (*J* = 61)
Il	4-MeC_6H_4	2,4-$Me_2C_6H_3$	71	104–105[c]	70–80	7.63 t (*J* = 60)[f]	–101.40, –100.64 d.d (*J* = 58), –89.12, –88.31 d.d (*J* = 61)
Im	4-MeC_6H_4	2-Naphthyl	92	130–131[c]	70–80	7.60 d (*J* = 59), 7.85 d (*J* = 61)	–98.42, –97.29 d.d (*J* = 59), –89.67, –88.48 d.d (*J* = 61)
In	4-MeC_6H_4	2-Morpholinophenyl	64	154–156[c]	90–100	7.26 d (*J* = 58), 7.47 d (*J* = 60)	–99.71, –99.07 d.d (*J* = 58), –88.72, –87.96 d.d (*J* = 60)
Io	4-MeC_6H_4	2-*t*-BuC_6H_4	42	120–121[b]	90–100	7.39 d (*J* = 59), 7.65 d (*J* = 61)	–100.55, –99.42 d.d (*J* = 59), –88.13, –86.98 d.d (*J* = 61)
Ip	4-MeC_6H_4	2,6-$Me_2C_6H_3$	74	87–89[b]	90–100	7.72 t (*J* = 60)	–93.39 d (*J* = 60)
Iq	2-Me-5-$NO_2C_6H_3$	4-ClC_6H_4	48	116–117[d]	40–50	7.78 t (*J* = 60)	–93.10 d (*J* = 60)
Ir	2-Me-5-$NO_2C_6H_3$	4-$MeOC_6H_4$	60	113–114[b]	40–50	7.74 t (*J* = 60)	–93.85 d (*J* = 60)
Is	2-Me-5-$NO_2C_6H_3$	2-$MeOC_6H_4$	62	171–173[c]	40–50	7.52 t (*J* = 60)[g]	–100.45, –99.32 d.d (*J* = 59), –89.13, –88.00 d.d (*J* = 60)
It	2-Me-5-$NO_2C_6H_3$	2-MeC_6H_4	57	112–114[b]	40–50	7.55 t (*J* = 60)[g]	–99.29, –98.18 d.d (*J* = 59), –88.72, –87.96 d.d (*J* = 60)
Iu	2-Me-5-$NO_2C_6H_3$	2-Naphthyl	42	168–169[c]	40–50	7.62 d (*J* = 59), 7.87 s (*J* = 62)	–98.50, –97.35 d.d (*J* = 59), –89.23, –88.18 d.d (*J* = 62)
Iv	2-Thienyl	Ph	72	102–103[c]	50–60	7.49 t (*J* = 60)	–94.02 d (*J* = 60)
Iw	2-Thienyl	2-MeC_6H_4	82	79–81[b]	50–60	7.09 d (*J* = 59), 7.31 d (*J* = 61)	–101.05, –99.86 d.d (*J* = 59), –89.72, –88.69 d.d (*J* = 61)
Ix	2-Thienyl	2-$MeOC_6H_4$	69	76–77[a]	50–60	7.45 t (*J* = 60)	–100.98, –99.80 d.d (*J* = 59), –90.18, –89.02 d.d (*J* = 60)
Iy	2-Thienyl	2-Naphthyl	70	110-111[b]	50–60	7.28 d (*J* = 59), 7.45 d (*J* = 61)	–100.25, –99.48 d.d (*J* = 59), –90.22, –89.44 d.d (*J* = 61)
Iz$_1$	2-Thienyl	2,4-$Me_2C_6H_3$	52	62–63[a]	50–60	7.40 d (*J* = 59), 7.62 d (*J* = 61)	–101.47, –100.64 d.d (*J* = 59), –89.12, –88.31 d.d (*J* = 61)
Iz$_2$	CF_3	4-ClC_6H_4	42	36–37[a]	30–40	6.94 t (*J* = 60)	–90 to –100[e]
Iz$_3$	CF_3	4-BrC_6H_4	54	57–59[a]	30–40	6.94 t (*J* = 60)	–90 to –100[e]

Table 1. (Contd.)

Compound no.	Found, %			Formula	Calculated, %		
	C	H	N (S)		C	H	N (S)
Ia	45.26	4.82	5.96	$C_9H_{11}F_2NO_2S$	45.93	4.71	5.98
Ib	51.82	6.11	5.19	$C_{12}H_{17}F_2NO_2S$	51.96	6.18	5.05
Ic	56.27	4.40	4.84	$C_{14}H_{13}F_2NO_2S$	56.56	4.41	4.71
Id	52.98	3.72	(10.45)	$C_{14}H_{12}F_3NO_2S$	53.33	3.84	(10.17)
Ie	50.71	3.65	4.56	$C_{14}H_{12}C_1F_2NO_2S$	50.68	3.65	4.22
If	55.02	4.57	4.46	$C_{15}H_{15}F_2NO_3S$	55.04	4.62	4.28
Ig	48.98	3.54	8.21	$C_{14}H_{12}F_2N_2O_4S$	49.12	3.53	8.18
Ih	49.30	3.38	(8.96)	$C_{15}H_{12}F_5NO_2S$	49.32	3.31	(8.76)
Ii	53.41	3.70	(10.54)	$C_{14}H_{12}F_3NO_2S$	53.33	3.84	(10.17)
Ij	57.90	5.06	(10.49)	$C_{15}H_{15}F_2NO_2S$	57.87	4.86	(10.30)
Ik	55.01	4.86	4.49	$C_{15}H_{15}F_2NO_2S$	55.04	4.62	4.28
Il	58.69	5.26	4.43	$C_{16}H_{17}F_2NO_2S$	59.06	5.26	4.30
Im	62.52	4.67	(9.32)	$C_{18}H_{15}F_2NO_2S$	62.24	4.35	(9.23)
In	56.83	5.28	(8.42)	$C_{18}H_{20}F_2N_2O_3S$	56.53	5.27	(8.38)
Io	61.15	6.05	4.03	$C_{18}H_{21}F_2NO_2S$	61.17	5.99	3.96
Ip	59.23	5.00	4.40	$C_{16}H_{17}F_2NO_2S$	59.06	5.26	4.30
Iq	44.52	3.00	7.58	$C_{14}H_{11}ClF_2N_2O_4S$	44.63	2.94	7.44
Ir	48.56	3.98	7.46	$C_{15}H_{14}F_2N_2O_5S$	48.39	3.79	7.52
Is	50.03	4.08	7.48	$C_{15}H_{14}F_2N_2O_5S$	48.39	3.79	7.52
It	50.51	3.77	7.77	$C_{15}H_{14}F_2N_2O_4S$	50.56	3.96	7.86
Iu	54.86	3.75	6.79	$C_{18}H_{14}F_2N_2O_4S$	55.10	3.60	7.14
Iv	45.74	3.17	5.00	$C_{11}H_9F_2NO_2S_2$	45.67	3.14	4.84
Iw	47.70	3.57	4.57	$C_{12}H_{11}F_2NO_2S_2$	47.51	3.66	4.62
Ix	45.20	3.41	(20.48)	$C_{12}H_{11}F_2NO_3S_2$	45.13	3.47	(20.08)
Iy	53.25	3.20	(19.09)	$C_{15}H_{11}F_2NO_2S_2$	53.09	3.27	(18.90)
Iz_1	49.18	4.19	(20.09)	$C_{13}H_{13}F_2NO_2S_2$	49.20	4.13	(20.21)
Iz_2	31.22	1.72	4.37	$C_8H_5C_1F_5NO_2S$	31.03	1.63	4.52
Iz_3	27.08	1.39		$C_8H_5BrF_5NO_2S$	27.14	1.39	

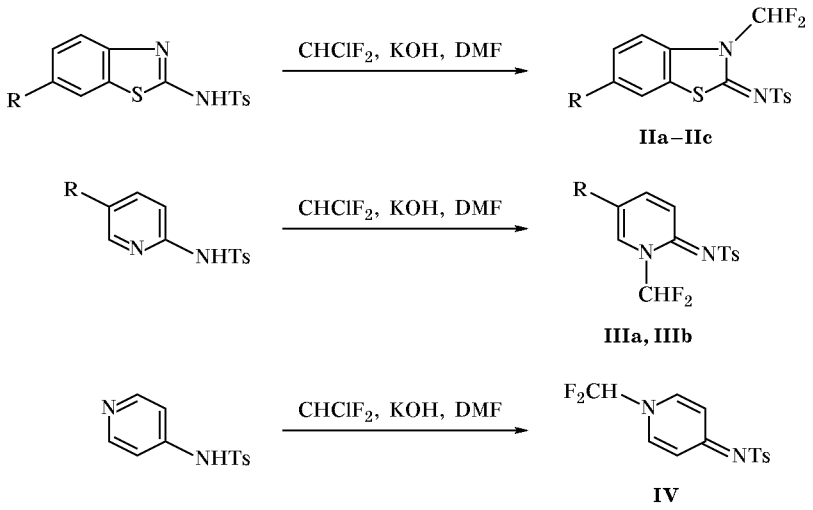
[a] From hexane.
[b] From 2-propanol–hexane (1 : 1).
[c] From 2-propanol.
[d] From carbon tetrachloride.
[e] Broadened signal.
[f] The central component is broadened.
[g] The central component is broadened and doubled.

took 1 h at 90–100°C, and the yield of product **Ip** was 74%. However, more sterically hindered *N*-(2,4,6-tribromophenyl)-*p*-toluenesulfonamide failed to react with chlorodifluoromethane.

In all the difluoromethylation products obtained from sterically hindered sulfonamides the fluorine atoms in the CHF_2 group become magnetically non-equivalent. Their ^{19}F NMR spectra display an *AB* part of *ABX* spin system: two doublets of doublets with different spin–spin coupling constants. In the ^1H NMR spectra of the products having bulkier substituents (such as *tert*-butyl, morpholino, and fused benzene ring), the CHF_2 proton appears as two doublets with the corresponding coupling constants. The CHF_2 group in 2-methyl and 2-methoxy derivatives gives rise to a triplet with broadened middle component in the ^1H NMR spectra.

The ^{19}F NMR spectrum of **Ii** contains a broadened signal between –90 and –100 ppm, and in the ^1H NMR spectrum a triplet with a coupling constant of

Scheme 2.



II, R = H (**a**), MeO (**b**), $MeSO_2$ (**c**); **III**, R = H (**a**), Cl (**b**).

59.5 Hz is observed. This inconsistence between the ^1H and ^{19}F NMR spectra is explained by different relaxation periods of the ^1H and ^{19}F nuclei.

The reactions of trifluoromethanesulfonamides with $CHClF_2$ and solid alkali should be performed on cooling, for the initial sulfonamide undergoes partial hydrolysis in strongly alkaline medium above 40°C and further reaction with Freon-22 leads to formation of the corresponding isonitrile.

The $N(CHF_2)SO_2CF_3$ group gives in the ^{19}F NMR spectrum a narrow singlet from the trifluoromethyl group and a broadened diffuse signal from the CHF_2 group between –90 and –100 ppm. In the ^1H NMR spectra of such compounds, the difluoromethyl group appears as a triplet with a coupling constant of 59 Hz.

We also examined difluoromethylation of sulfonamides containing a heterocyclic fragment on the nitrogen atom, i.e., an additional nucleophilic center. The reactions of *N*-(2-benzothiazolyl)- and *N*-(2- or 4-pyridyl)sulfonamides with $CHClF_2$ and KOH in DMF involved mainly the heterocyclic nitrogen atom (Table 2). In the ^{19}F NMR spectra of crude reaction products we observed only small signals (2–3%) belonging to isomeric compounds with a CHF_2 group on the exocyclic nitrogen atom (Scheme 2). Heterocyclic derivatives **IIa**–**IIc**, **IIIa**, **IIIb**, and **IV** are yellow–orange substances with higher melting points than those of products **Ia**–**Iz$_3$**. The signal from the difluoromethyl group in the ^{19}F NMR spectra of **IIa**–**IIc**, **IIIa**, **IIIb**, and **IV** is located in a stronger field

Table 2. Yields, melting points, ^1H and ^{19}F NMR chemical shifts, and elemental analyses of compounds **IIa**–**IIc**, **IIIa**, **IIIb**, and **IV**[a]

Comp. no.	Yield, %	mp,[b] °C	Chemical shifts δ ($J_{H,F}$, Hz)		Found, %			Formula	Calculated, %		
			^1H	^{19}F	C	H	S		C	H	S
IIa	55	150–151	8.11 t (57)	–104.83 d (57)	50.64	3.23	18.17	$C_{15}H_{12}F_2N_2O_2S_2$	50.83	3.41	18.09
IIb	48	130–132	8.00 t (58)	–104.37 d (58)	49.84	3.61	16.35	$C_{16}H_{14}F_2N_2O_3S_2$	50.00	3.67	16.68
IIc	53	245–247	8.14 t (58)	–104.42 d (58)	44.45	3.30	22.31	$C_{16}H_{14}F_2N_2O_4S_3$	44.44	3.26	22.24
IIIa	25	147–149	7.99 t (59)	–104.74 d (59)	52.17	4.27	11.03	$C_{13}H_{12}F_2N_2O_2S$	52.34	4.05	10.75
IIIb	30	174–176	8.02 t (59)	–104.18 d (59)	46.95	3.29	9.46	$C_{13}H_{11}ClF_2N_2O_2S$	46.92	3.33	9.64
IV	57	210–212	7.94 t (58)	–102.76 d (59)	52.23	3.99	10.74	$C_{13}H_{12}F_2N_2O_2S$	52.34	4.05	10.75

[a] The difluoromethylation was carried out at 50–60°C.

[b] From 2-propanol.

(δ_F –104 to –107 ppm), and in the ^{1}H NMR spectra, in a weaker field (δ ~8 ppm), as compared to the corresponding signals of **Ia**–**Iz$_3$**.

Thus the difluoromethylation of sulfonamides derived from aliphatic, aromatic, and heterocyclic amines is a general reaction ensuring preparation of various compounds with a difluoromethyl group on the nitrogen atom.

EXPERIMENTAL

The ^{1}H (in DMSO-d_6) and ^{19}F NMR spectra (in CCl_4) were recorded on a Varian VXR-300 spectrometer (300 MHz for ^{1}H) using tetramethylsilane and chlorotrifluoromethane as internal references.

Difluoromethylation of sulfonamides (*general procedure***).** A solution of 0.01 mol of sulfonamide in 10 ml of distilled DMF was saturated with Freon-22 at room temperature, and 0.05 mol of finely powdered potassium hydroxide was added under vigorous stirring. Bubbling of Freon-22 through the mixture was continued under vigorous stirring until the gas was no longer absorbed. In the synthesis of compounds **Iz$_2$** and **Iz$_3$**, the mixture was cooled; in the synthesis of **Ij**–**Ip**, the mixture was maintained at a temperature specified in Table 1 for each particular compound. The mixture was diluted with 150 ml of water, and the precipitate was filtered off, dried in air, and recrystallized from appropriate solvent. Compound **Ia** separated as an oily substance which was extracted with diethyl ether (2×50 ml), the extract was dried over $MgSO_4$, the solvent was evaporated, and the residue was distilled under reduced pressure. A fraction with bp 95–97°C (0.1 mm) was collected and was then crystallized from hexane.

REFERENCES

1. Yagupol'skii, L.M., *Aromaticheskie i geterotsiklicheskie soedineniya s ftorsoderzhashchimi zamestitelyami* (Aromatic and Heterocyclic Compounds with Fluorine-Containing Substituents), Kiev: Naukova Dumka, 1988, p. 318.
2. Poludnenko, V.G., Didinskaya, O.B., and Pozharskii, A.F., *Khim. Geterotsikl. Soedin.*, 1984, no. 4, pp. 520–524.
3. Petko, K.I. and Yagupolskii, L.M., *J. Fluorine Chem.*, 2001, vol. 108, no. 2, pp. 211–214.
4. Lyga, J.V. and Patera, R.M., *J. Fluorine Chem.*, 1998, vol. 92, no. 2, pp. 141–145.
5. Brauer, D.J., Burger, H., Grunwald, M., Pawelke, G., and Wilke, J., *Z. Anorg. Allg. Chem.*, 1986, vol. 537, no. 1, pp. 63–78.
6. Yagupolskii, L.M., Petko, K.I., Maletina, I.I., and Retchitskii, A.N., *J. Fluorine Chem.*, 1996, vol. 76, no. 1, pp. 95–98.
7. US Patent no. 4 652 304, 1987; *Chem. Abstr.*, 1987, vol. 107, no. 178 272 y.