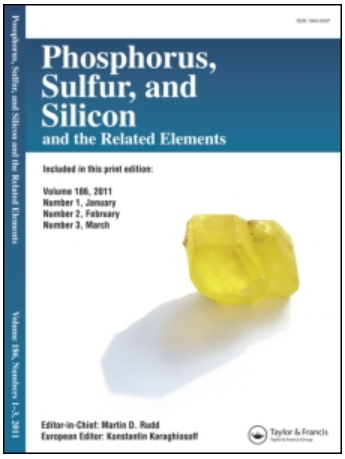

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Chen, Qing-Yun and Chen, Mei-Jin(1992) 'STUDIES ON FLUORINE CONTAINING HETEROCYCLIC COMPOUNDS. 5. A FACILE SYNTHESIS OF 2-SUBSTITUENT-5-TRIFLUOROMETHYL-7-NITROBENZOTHIAZOLES', Phosphorus, Sulfur, and Silicon and the Related Elements, 68: 1, 205 — 210
To link to this Article: DOI: 10.1080/10426509208038385
URL: http://dx.doi.org/10.1080/10426509208038385

Phosphorus, Sulfur, and Silicon, 1992, Vol. 68, pp. 205–210
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STUDIES ON FLUORINE CONTAINING HETEROCYCLIC COMPOUNDS. 5. A FACILE SYNTHESIS OF 2-SUBSTITUENT-5-TRIFLUOROMETHYL-7-NITROBENZOTHIAZOLES

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(Received August 30, 1990; in final form November 5, 1991)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (**1**) reacted with aldehydes and ketones in the presence of **4** equivalent of ammonium sulfide gave rise to the 2-substituted benzothiazolines **3a-k**, of which the 2-monosubstituted products **3a-h** were dehydrogenated by DDQ to give the novel title compounds **4** in high yields.

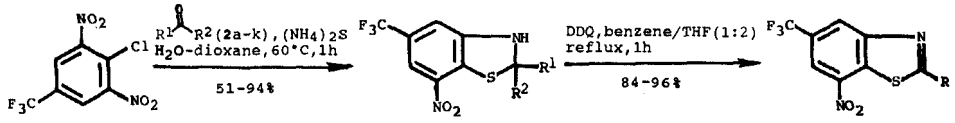
Key words: Heterocycle; organo-fluorine; benzothiazole; aldehyde; DDQ; ammonium sulfide.

INTRODUCTION

Heterocycles containing thiazole ring appear in many drugs such as the thiamine (Vitamin B_1), penicillins,[1] and are widely used as pesticides,[1] fungicides,[2] herbicides[3] and nematocides.[4] Benzothiazole derivatives are important members of this group due to their biological activity,[2,5] and also their applications in industry, *e.g.*, as corrosion inhibitors,[6] antioxidants[7] and vulcanization accelerators.[8] Fluorinated heterocycles have found increasing use in biochemistry[9] and the pharmaceutical industry,[10] as organofluorine compounds exhibit great oxidative and thermal stabilities.[11] Therefore, the synthesis of fluorine containing benzothiazole derivatives is attractive.

The usual methods for the preparation of benzothiazole derivatives are by treatment of *o*-mercaptoaniline either with carboxylic acid, acid chloride or ester, etc.[12] or by oxidation of thioanilides.[12,13] However, the origin of fluorine containing *o*-mercaptoanilines and thioanilides is limited. In a previous paper,[14] we described the facile preparation of 2,2-dimethyl-5-trifluoromethyl-7-nitrobenzothiazole from 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**1**). In continuation of our work on the synthetic applications of 2-monosubstituted benzothiazolines **3**, we report here a new convenient synthesis of 2-substituent-5-trifluoromethyl-7-nitrobenzothiazoles **4** by the dehydrogenation of **3a-h** with the high-potential quinone, 2,3-dichloro-5,6-dicyano-benzoquinone (DDQ).[15]

Compounds **3** were obtained in medium to excellent yields by the reaction in 1,4-dioxane-H_2O of aldehydes **2a-h** and ketones **2i-k** with 2-mercapto-3-nitro-5-trifluoromethyl aniline, which was thought to be the intermediate, generated *in situ* by reaction of **1**, through both chlorine displacement and nitro reduction,[14] with **4** equivalent of aqueous ammonium sulfide containing 8% of sulfur (Scheme I). Thus, the aldehydes **2a-h** and 3-heptanone (**2i**) gave corresponding **3a-h** and **3i**,



1 **3** a-k **4** a-h

2,3	R^1	R^2	2,3	R^1	R^2
a	H	C_2H_5	g	H	4-$CH_3C_6H_4$
b	H	C_3H_7-n	h	H	4-$CH_3OC_6H_4$
c	H	C_3H_7-i	i	C_2H_5	C_4H_9-n
d	H	C_4H_9-n	j	$CH_2(CH_2)_2CH_2$	
e	H	C_6H_{13}-n	k	$CH_2(CH_2)_3CH_2$	
f	H	C_6H_5			

4	R	4	R
a	C_2H_5	e	C_6H_{13}-n
b	C_3H_7-n	f	C_6H_5
c	C_3H_7-i	g	4-$CH_3C_6H_4$
d	C_4H_9-n	h	4-$CH_3OC_6H_4$

SCHEME I

the products with monoalkyl (or aryl) and dialkyl in 2-position. While cyclopentanone (**2j**) and cyclohexanone (**2k**) resulted in the formation of spiro compounds **3j** and **3k** respectively. The benzothiazolines **3** easily precipitate from the aqueous solution of reaction mixtures and are obtained by filtration. The sulfur powder formed in reactions is readily removed either by flash chromatography (silica gel) or by filtration and the products are sufficiently pure to be used in the next step. The high-potential quinone DDQ, commercially available, is a powerful dehydrogenating agent which has found extensive application in synthetic organic chemistry.[15,16] Thus, the benzothiazoles **4** are prepared by hydrogen transfer of **3a-h** in refluxing dry benzene-THF (1:2) in the presence of one equivalent of DDQ. That is, **3a-e** react with DDQ to give the corresponding 2-alkyl products **4a-e**, and **3f-h** undergo rapid dehydrogenation to result in 2-aryl compounds **4f-h** respectively (Tables I and II). The yields are excellent and are higher than those from the usual methods, e.g., by the dehydrogenation with sulfur powder.[17] The isolation is generally convenient, since the dichlorodicyano-hydroquinone ($DDQH_2$) formed in the hydrogen transfer process is rather insoluable and can be removed either by filtration or by percolation of the solution of the crude products through a short column of silica gel (see Experimental). Of interest in oxidation is the fact that aromatisation of the benzothiazolines **3a-h** to the benzothiazoles **4a-h** occurs readily to form a C=N bond.

The assignment of the products prepared is based on their elemental analyses, mass spectra, infrared and nuclear magnetic resonances. The mass spectra give the molecular ion peaks, which as well as the microanalyses and the nuclear magnetic resonances are in agreement with their constitutions (see Table I). In the infrared spectra of **3a-k**, the NH stretching vibrations are observed in the region of 3350 cm^{-1} (see Table II). The bands of **4a-h** at 1450 cm^{-1}, which are totally absent in the infrared spectra of compounds **3a-k** are assigned to the vibrations arising from heterocyclic benzothiazole system, indicating the successful dehydrogenation of **3a-h** to form a C=N bond.

The procedure described here, establishes a facile method for the preparation of 2-substituent-5-trifluoromethyl-7-nitrobenzothiazoles from 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**1**). The simplicity of the operations and the high yields of reactions are among obvious advantages over the previously described routes.

TABLE I

Characteristics, physical and MS data of **3** and **4** prepared

Product	Appearance[a]	Yield[b] (%)	m.p.[a,c] (°C)	Formula[d] (F.W.)	MS[e] (m/e,%)
3a	red grains	62	151.5-152	$C_{10}H_9N_2F_3O_2S$ (278.3)	278 (25.76)
3b	red grains	63	130-130.5	$C_{11}H_{11}N_2F_3O_2S$ (292.3)	292 (30.18)
3c	red grains	53	150-150.6	$C_{11}H_{11}N_2F_3O_2S$ (292.3)	292 (10.51)
3d	red grains	70	127-127.5	$C_{12}H_{13}N_2F_3O_2S$ (306.3)	306 (12.00)
3e	red grains	94	120-121	$C_{14}H_{17}N_2F_3O_2S$ (334.4)	334 (10.49)
3f	red grains	58	128-129	$C_{14}H_9N_2F_3O_2S$ (326.3)	326 (66.10)
3g	red grains	81	144-144.5	$C_{15}H_{11}N_2F_3O_2S$ (340.3)	340 (58.72)
3h	red grains	68	147-148	$C_{15}H_{11}N_2F_3O_3S$ (356.0446)	356.0443 (87.22)
3i	red grains	51	105-106	$C_{14}H_7N_2F_3O_2S$ (334.3)	334 (27.16)
3j	brown grains	71	203-204	$C_{12}H_{11}N_2F_3O_2S$ (304.3)	304 (48.46)
3k	brown needles	67	230-230.5	$C_{13}H_{13}N_2F_3O_2S$ (318.3)	318 (59.43)
4a	white plates	84	52-52.5	$C_{10}H_7N_2F_3O_2S$ (276.2)	276 (85.77)
4b	white needles	91	49-50	$C_{11}H_9N_2F_3O_2S$ (290.3)	291(M^++1) (26.40)
4c	white needles	91	50-51	$C_{11}H_9N_2F_3O_2S$ (290.3)	290 (42.65)
4d	white needles	92	40-41	$C_{14}H_{11}N_2F_3O_2S$ (304.3)	304 (3.05)
4e	whites needles	96	30-30.5	$C_{14}H_{15}N_2F_3O_2S$ (332.3)	332 (12.43)
4f	white needles	86	160-160.5	$C_{14}H_7N_2F_3O_2S$ (324.3)	324 (100.00)
4g	white needles	87	183-183.5	$C_{15}H_9N_2F_3O_2S$ (338.3)	338 (73.54)
4h	yellow needles	94	186-186.5	$C_{15}H_9N_2F_3O_3S$ (354.3)	354 (100.00)

[a] Recrystallized from ethanol.

[b] Yield of isolated **3** on **1** and **4** on **3**.

[c] Uncorrected, measured on open glass capilliaries.

[d] Satisfactory microanalysis obtained: C±0.45, H±0.44, N±0.23, F±0.29, S±0.32.

[e] Obtained on Finnigan-402 spectrometer except **3h** on Mat-711 HRMS spectrometer.

TABLE II

IR, ^{1}H-, ^{19}F-NMR data of **3** and **4** prepared

Product	IR(KCl)[a] ν(cm^{-1})	^{1}H($CDCl_3$,TMS)[b,c] δ,J(Hz)	^{19}F($CDCl_3$,TFA)[c,d] δ,J(Hz)
3a	1160(C-F) 1320(NO_2) 3360(NH)	1.05(t,3H,J=7.2,CH_3),1.76-2.16(h,2H,J_1=J_2=7.2,CH_2),4.70(s,1H,NH),5.40(t,1H,J=7.2,SCH),6.80(s,1H,ArH,p- to NO_2),7.76(s,1H,ArH,o- to NO_2),	-14.0
3b	1160(C-F) 1310(NO_2) 3360(NH)	1.00(t,3H,J=7.2, CH_3), 1.50(m,2H,$MeCH_2$), 1.84(m,2H, $SCCH_2$), 4.70(s,1H,NH), 7.44(t,1H,J=7.2, SCH), 6.78(s,1H, ArH,p- to NO_2),7.76(s,1H,ArH,o- to NO_2)	-14.0
3c	1160(C-F) 1320(NO_2) 3350(NH)	1.00-1.15(d,6H,J=7.2,2xCH_3), 1.90-2.18(oct, 1H,J_1=7.2, J_2=6.3,MeCH),4.70(s,1H,NH), 5.28-5.36(d,1H, J=6.3,SCH), 6.76(s,1H,ArH,p- to NO_2),7.74(s,1H,ArH,o- to NO_2)	-13.5
3d	1160(C-F) 1320(NO_2) 3350(NH)	0.86(t,3H,J=7.2, CH_3), 1.40(m,4H, 2xCH_2), 1.85(m,2H,$SCCH_2$), 4.65(s,1H,NH), 5.42(t,1H,J=7.0, SCH), 6.76(d,1H,J=1.8, ArH, p- to NO_2),7.74(d,1H,ArH,o- to NO_2)	-14.6
3e	1160(C-F) 1320(NO_2) 3350(NH)	0.88(t,3H,J=7.2, CH_3), 1.32(m,8H,4xCH_2), 1.84(m, 2H, J=6.3, $SCCH_2$), 4.70(s,1H,NH), 5.42(t,1H,J=6.3,SCH), 6.76(d, 1H,J=1.8, ArH,p- to NO_2), 7.74(d, 1H, J=1.8, ArH, o- to NO_2)	-14.6
3f	1125(C-F) 1320(NO_2) 3380(NH)	4.87(s,1H,NH), 6.45(s,1H, SCH), 6.82(d,1H,J=1.8, ArH,p- to NO_2), 7.40(m,5H,ArH),7.80(d,1H,J=1.8,ArH,o- to NO_2)	-14.6
3g	1160(C-F) 1320(NO_2) 3360(NH)	2.36(s,3H,CH_3),4.85(s,1H,NH),6.46(s,1H,SCH),6.84(s,1H,ArH, p- to NO_2),7.12-7.24(d,2H,J=9.0,ArH,o- to CH_3),7.32-7.40(d, 2H,J=8.1,ArH,m- to CH_3),7.80(s,1H,ArH,o- to NO_2)	-14.6
3h	1175(C-F) 1320(NO_2) 3350(NH)	3.80(s,3H,OCH_3),4.85(s,1H,NH),6.48(s,1H,SCH),6.82(s,1H,ArH, p- to NO_2),6.84-6.94(d,2H,J=8.1,ArH,p- to OCH_3),7.36-7.45 (d,2H,J=8.1,ArH,o- to OCH_3),7.80(s,1H,ArH,o- to NO_2)	-14.6
3i	1160(C-F) 1330(NO_2) 3320(NH)	0.90-1.12(q,6H,J_1=7.2,J_2=5.4,2xCH_3),1.40(m,4H,J=5.4,2xCH_2), 1.80-1.96(t,4H,J=7.2,2x$SCCH_2$),4.44(s,1H,NH),6.76(s,1H,ArH, p- to NO_2),7.76(s,1H,ArH,o- to NO_2)	-14.0

3j	1140(C-F) 1320(NO_2) 3320(NH)	1.80-1.85(t,4H,J=5.4,2xCH_2),2.12-2.18(t,4H,J=5.4, $C(CH_2)_2$), 4.70(s,1H, NH), 6.80(s,1H,ArH,p- to NO_2), 7.80(s,1H,ArH,o- to NO_2)	-14.6
3k	1160(C-F) 1320(NO_2) 3320(NH)	1.56(s,2H,CH_2), 1.65(s,4H,2xCH_2), 2.16(s,4H,$C(CH_2)_2$), 4.60 (s,1H,NH),6.80(s,1H,ArH,p- to NO_2),7.80(s,1H,ArH,o- to NO_2)	-14.0
4a	1160(C-F) 1320(NO_2) 1460(C=N)	1.52(t,3H,J=7.2,CH_3), 3.24(q,2H,J=7.2,CH_2), 8.48(s,1H,ArH, p- to NO_2),8.56(s,1H,ArH,o- to NO_2)	-15.3
4b	1170(C-F) 1320(NO_2) 1450(C=N)	1.08(t,3H,J=7.2,CH_3), 1.96(hex.2H,J=7.2, $MeCH_2$), 3.16(t,2H, J=7.2,$SCCH_2$), 8.46(s,1H, ArH,p- to NO_2), 8.54(s,1H, ArH,o- to NO_2)	-15.3
4c	1160(C-F) 1330(NO_2) 1475(C=N)	1.52(d,6H,J=7.2, CH_3), 3.48(hep.1H,J=7.2,CH),8.48(s,1H,ArH, p- to NO_2),8.56(s,1H,ArH,o- to NO_2)	-15.5
4d	1130(C-F) 1330(NO_2) 1450(C=N)	0.98(t,3H,J_1=7.2,CH_3), 1.24-1.60(m,2H,J_1=7.2,J_2=5.4,$MeCH_2$), 1.68-2.04(m,2H,J_3=8.1,J_4=5.6,CH_2), 3.20(t,2H,J_3=8.1,$SCCH_2$), 8.48(s, 1H, ArH, p- to NO_2), 8.56(s, 1H, ArH, o- to NO_2)	-15.0
4e	1140(C-F) 1320(NO_2) 1460(C=N)	0.85(t,3H,J_1=5.4, CH_3), 1.36(m,6H,3xCH_2), 1.94(t,2H,J_2=7.2, $SCCCH_2$), 3.20(t,2H,J_2=7.2,$SCCH_2$), 8.48(s,1H,ArH,p- to NO_2), 8.56(s,1H,ArH, o- to NO_2)	-15.5
4f	1120(C-F) 1320(NO_2) 1440(C=N)	7.56(s,1H, p- Ar^1H), 7.64(m,2H, m- Ar^1H), 8.06-8.20(m, 2H, J=5.4Hz), o- Ar^1H), 8.58(s,1H, Ar^2H,p- to NO_2), 8.86(s,1H, Ar^2H, o- to NO_2)	-15.5
4g	1160(C-F) 1320(NO_2) 1450(C=N)	2.08(s,3H,CH_3),7.40(d,2H,J=8.1,Ar^1H o- to CH_3),8.06-8.16(d, 2H,J=8.1, Ar^1H m- to CH_3),8.60(s,1H,Ar^2H,p- to NO_2),8.88(s, 1H, Ar^2H, o- to NO_2)	-16.5
4h	1175(C-F) 1320(NO_2) 1480(C=N)	3.88(s, 3H, OCH_3), 7.08-7.20(d,2H, J=9.0, Ar^1H, m- to OCH_3), 8.06-8.20(d,2H,J=9.0, Ar^1H,o- to OCH_3),8.52(s,1H,Ar^2H,p- to NO_2), 8.82(s,1H,Ar^2H,o- to NO_2)	-17.5

a Recorded on Shimadzu IR-440 spectrophotometer.

b Measured on FX-90Q spectrometer.

c **4f-h** measured in DMSO-d_6.

d Obtained on Varian EM-360L spectrometer.

EXPERIMENTAL

DDQ, aldehydes and ketones are commercially available. Dry benzene and THF are prepared according to the literature procedure. Flash chromatography used silica gel H (10–40 μ).

2-Substitutent-5-trifluoromethyl-7-nitrobenzothiazolines. General Procedure. To a solution of 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**1**) (5.4 g, 20 mmole) in 1,4-dioxane (10 mL) was added dropwise, at r.t. aqueous ammonium sulfide containing 8% of sulfur (32.0 g, 80 mmole). The temperature was resulted in a raise up to 60°C. The reaction mixture was stirred at this temperature for 15 minutes and then the corresponding aldehyde or ketone (30 mmole) was added (see the text). It was continued to stir at 60°C for 45 minutes and was left to stand overnight. The crude product precipitated was collected by filtration and the sulfur powder formed was removed by a flash chromatography (silica gel, ethyl acetate as eluant). Sample for analyses was recrystallized from ethanol and the relevant data were listed in Tables I and II.

2-Substituent-5-trifluoromethyl-7-nitrobenzothiazoles. General Procedure. To a solution of **3** in dry benzene-THF (1 : 2) was added one equivalent of DDQ. The reaction mixture was stirred under refluxing for 1 hr and the solvent was removed to give a crude solid. For **4a-e**, the crude products were isolated chromatographically with benzene as solvent. Removal of the solvent and addition of water (0°C) gave comparatively pure products. For the isolation of **4f-h**, ethanol was added to the crude solids and followed by filtration. The residues were dried and the mother liquors were subjected to chromatography (with benzene or ethyl acetate as eluant), affording further **4f-h**. Sample for analyses were recrystallized from ethanol and the data obtained were listed in Tables I and II.

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