SYNTHESIS OF 1-ARYL-3-PHENYLSULFONYL-1,2,4-TRIAZOLES FROM 1,5-DIARYL-3-PHENYLSULFONYLFORMAZANS

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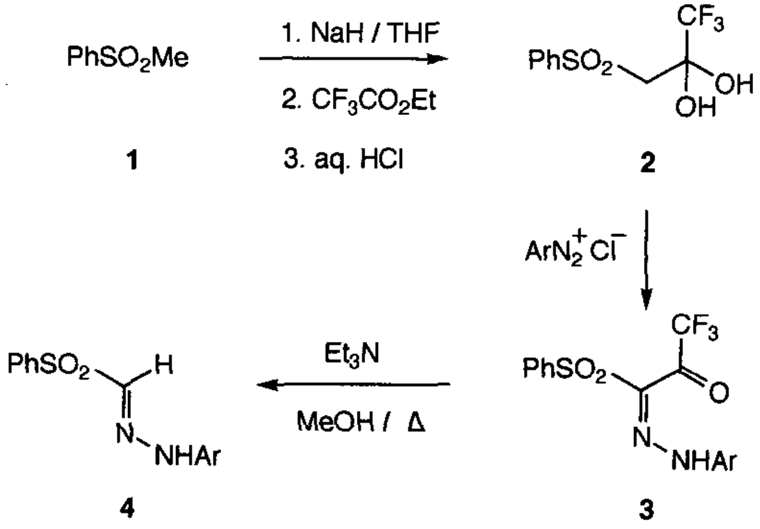
Abstract - 1,5-Diaryl-3-phenylsulfonylformazans (**5**) were prepared through phenylsulfonylmethanal arylhydrazones (**4**) starting from methyl phenyl sulfone. Treatment of these formazans (**5**) with formalin and potassium hydrogen sulfate in DMF gave 1-aryl-3-phenylsulfonyl-1,2,4-triazoles (**9**) instead of the expected 1,5-diaryl-3-phenylsulfonylverdazyls (**8**).

In our previous paper, we have shown that 1,1,1-trifluoro-3-phenylsulfonyl-2-propanone hydrate (**2**) or its ammonia adduct is a useful building block for the synthesis of 3-trifluoromethylpyrazoles[1] and 3-trifluoromethylpyrazines.[2] During the course of our further studies on the synthesis of CF_3-containing heterocycles using this building block, we found that 1,5-diaryl-3-phenylsulfonylformazans (**5**) were prepared from **2**, and the treatment of **5** with formalin and potassium hydrogen sulfate gave 1-aryl-3-phenylsulfonyl-1,2,4-triazoles (**9**) in moderate to good yields instead of the expected verdazyls (**8**). These findings will be described in this paper.

Since the synthesis of many 1,2,4-triazine derivatives from α-hydrazono ketones[3] and, more recently, 5-trifluoromethyl-1,2,4-triazines from 1,1,1-trifluoro-3-hydrazonoalkan-2-ones[4] has been known, 1-arylhydrazono-3,3,3-trifluoro-1-(phenylsulfonyl)propan-2-ones (**3**) now have a chance to serve as good starting materials for the synthesis of 1,2,4-triazine derivatives bearing a trifluoromethyl and a sulfonyl group. They were obtained on the treatment of **2** with arenediazonium chlorides in the usual manner

(Scheme 1). However, because the purification of the starting **2** was sometimes troublesome, **3** were directly obtained from **1** without isolation of **2** in 26-34% yields (Tables 1 and 2).



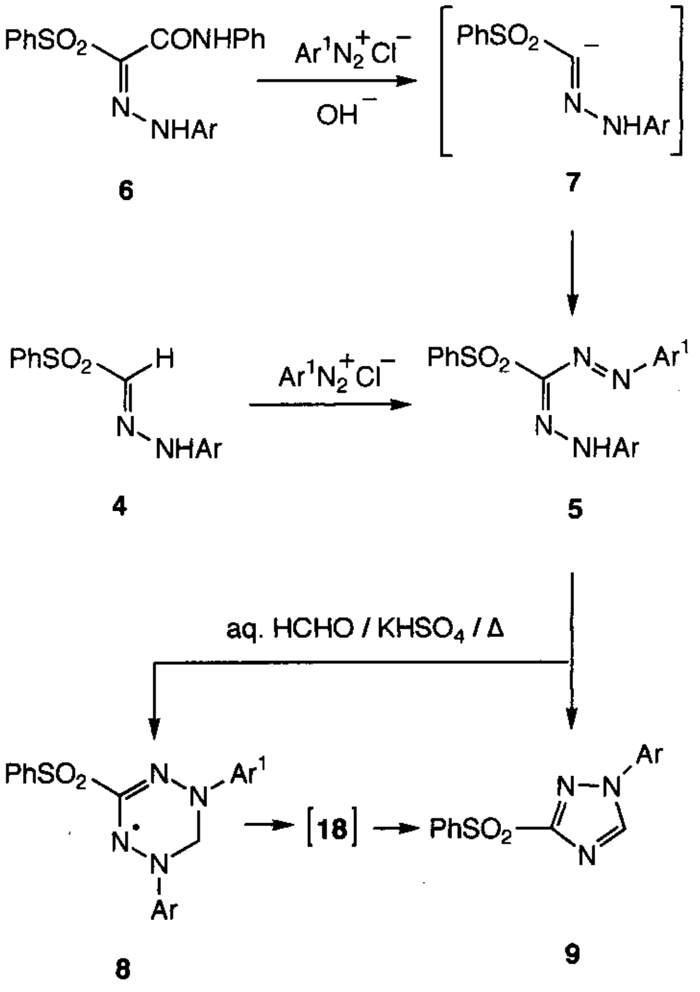
3 , 4	Ar
a	Ph
b	4-MeC_6H_4
c	4-$MeOC_6H_4$
d	4-ClC_6H_4

Scheme 1

Cyclization of hydrazone (**3a**) to 1,2,4-triazine derivatives was then attempted using guanidine hydrochloride, benzamidine hydrochloride, or urea in the presence of bases in methanol. However, instead of the expected 1,2,4-triazines, in all cases a small amount of the same product was obtained. It was identified as phenylsulfonylmethanal phenylhydrazone (**4a**), suggesting that it was formed by the base-catalyzed methanolysis of **3a**. When a mixture of **3a** and triethylamine in methanol was refluxed, it was obtained in 89% yield. Other hydrazones (**4b-d**) were similarly obtained in moderate to good yields (Tables 1 and 2). It is noteworthy that the new compounds (**4**) can be regarded as arylhydrazones of an unknown aldehyde, phenylsulfonylmethanal, and would be important in the chemistry of hydrazone derivatives, such as formazans, hydrazidoyl halides,[5] amidrazones,[6] and diazo compounds.[7]

The anion (**7**) of **4** has been reported to be the intermediate in the formation of formazans (**5**) from 2-phenylsulfonylglyoxalamide aryhydrazones (**6**)[8] (Scheme 2). The same formazan (**5a**) was obtained in 86% yield by reacting **4a** with benzenediazonium chloride. Other formazans (**5b**-**g**) were similarly prepared in 63 - 88% yields from **4**; the physical and spectral properties are summarized in Tables 1 and 2.

1,2,4,5-Tetrazin-1(2*H*)yls, a class of compounds of stable heterocyclic radicals, are called verdazyls,[9] and a typical synthetic procedure is the treatment of formazans with formaldehyde in the presence of potassium hydrogen sulfate.[10]

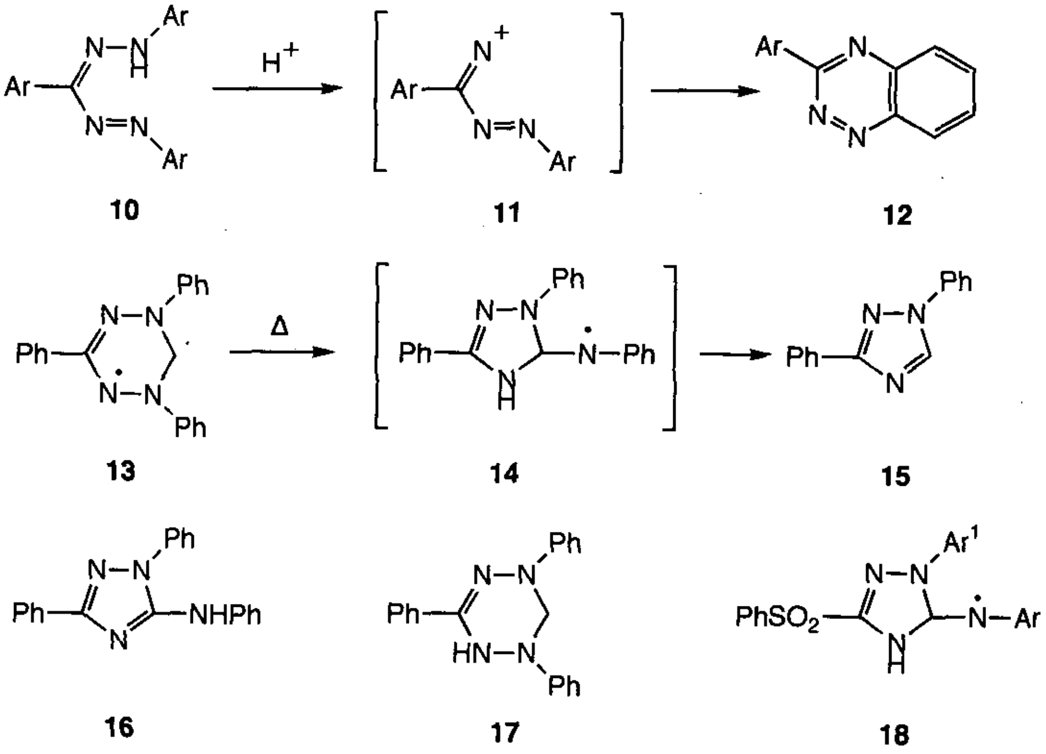


5	Ar	Ar^1
a	Ph	Ph
b	4-MeC_6H_4	4-MeC_6H_4
c	4-$MeOC_6H_4$	4-$MeOC_6H_4$
d	4-ClC_6H_4	4-ClC_6H_4
e	4-$MeOC_6H_4$	Ph
f	4-$MeOC_6H_4$	4-MeC_6H_4
g	4-$MeOC_6H_4$	4-ClC_6H_4

9	Ar
a	Ph
b	4-MeC_6H_4
c	4-$MeOC_6H_4$
d	4-ClC_6H_4

Scheme 2

Accordingly, the treatment of formazans (**5**) under similar conditions is expected to give the new derivatives of verdazyls (**8**)[11] which have a phenylsulfonyl substituent at the C-3 position. Thus, a mixture of formazan (**5a**), formalin, and potassium hydrogen sulfate in DMF was heated at 80 - 100 °C to produce a yellowish green crystal in 75% yield. However, the structural elucidation of the product showed it to be 1-phenyl-3-phenylsulfonyl-1,2,4-triazole (**9a**) instead of the expected verdazyl (**8a**) ($Ar=Ar^1=Ph$). Mass spectral and analytical data confirmed the molecular formula $C_{14}H_{11}N_3O_2S$ for **9a**, indicating the loss of PhNH from **8a**. In the ^{1}H-nmr spectrum, no methylene hydrogens at the C-6 position of **8** were detected, while a singlet resonance at δ 8.58 was assigned to the C-5 hydrogen of the 1,2,4-triazole ring.[12]



Scheme 3

Other 1,2,4-triazoles (**9b**-**d**) were obtained in the same manner in 60 - 70% yields as shown in Tables 1 and 2. Because formazan can exist in the tautomer, two kinds of 1,2,4-triazoles would be produced when formazan bearing two different substituents at the N-1 and N-5 positions is subjected to reaction. For example, formazan (**5f**) gave a mixture of 1,2,4-triazoles (**9b**) and (**9c**) in the ratio of 47:53 as determined by the ^{1}H-nmr.

There may exist two possible pathways from formazans (**5**) to 1,2,4-triazoles (**9**): (a) a cationic mechanism under acidic conditions and (b) the initial formation of the expected verdazyls (**8**) followed by the elimination of ArNH to give **9**. Heating of 1,3,5-triarylformazans (**10**) in an acidic solution is known to give 3-arylbenzo[*e*][1,2,4]triazines (**12**) through cationic intermediates (**11**),[13, 14] excluding the possibility of pathway (a) (Scheme 3). On the other hand, 1,2,4-triazole formation from verdazyls has been reported; thermal decomposition of 1,3,5-triphenylverdazyl (**13**) at 200 °C resulted in the formation of a mixture of aniline, 1,3-diphenyl-1,2,4-triazole (**15**), and 5-anilino-1,3-diphenyl-1,2,4-triazoles (**16**),[10] while thermal disproportionation of **13** at 80 °C in benzene for 4 days resulted in a mixture of **16** and leucoverdazyl (**17**).[15] In these reactions, the intermediary formation of the radical (**14**) is proposed.[13]

Table 1. Physical Properties of Compounds (**3**, **4**, **5**, and **9**)

	Yield (%)	mp (℃)	Molecular Formula	Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
3a	34	193 - 194	$C_{15}H_{11}N_2O_3F_3S$	50.56	3.11	7.86	50.60	3.22	7.69
3b	28	167 - 168	$C_{16}H_{13}N_2O_3F_3S$	51.89	3.54	7.56	51.79	3.60	7.35
3c	27	166 - 167	$C_{16}H_{13}N_2O_4F_3S$	49.74	3.39	7.25	49.80	3.44	7.00
3d	26	176 - 177	$C_{15}H_{10}N_2O_3ClF_3S$	46.11	2.58	7.17	45.93	2.64	7.33
4a	89	130 - 131	$C_{13}H_{12}N_2O_2S$	59.98	4.65	10.76	59.90	4.70	10.72
4b	72	105 - 106	$C_{14}H_{14}N_2O_2S$	61.29	5.14	10.21	61.35	5.14	10.19
4c	97	149 - 150	$C_{14}H_{14}N_2O_3S$	57.29	4.86	9.65	57.88	4.84	9.60
4d	83	146 - 147	$C_{13}H_{11}N_2O_2ClS$	52.97	3.76	9.50	52.99	3.78	9.48
5a	86	210 - 211	(lit.,[8] mp 148)						
5b	75	201 - 202	(lit.,[8] mp 201)						
5c	88	181 - 182	(lit.,[8] mp 176)						
5d	63	202 - 203	(lit.,[8] mp 203)						
5e	79	201 - 202	$C_{20}H_{18}N_4O_3S$	60.90	4.60	14.20	60.66	5.04	14.10
5f	85	197 - 198	$C_{21}H_{20}N_4O_3S$	61.75	4.94	13.72	61.70	5.11	13.60
5g	63	191 - 192	$C_{20}H_{17}N_4O_3ClS$	56.01	4.00	13.06	55.85	4.21	12.97
9a	75	143 - 144	$C_{14}H_{11}N_3O_2S$	58.93	3.89	14.73	58.84	3.98	14.72
9b	70	130 - 131	$C_{15}H_{13}N_3O_2S$	60.18	4.38	14.04	60.08	4.53	14.00
9c	60	121 - 122	$C_{15}H_{13}N_3O_3S$	57.13	4.16	13.33	56.99	4.22	13.31
9d	66	163 - 164	$C_{14}H_{10}N_3O_2ClS$	52.59	3.15	13.14	52.59	3.23	13.11

Moreover, a few examples of the direct formation of 1,2,4-triazoles from formazans under the conditions of verdazyl synthesis have been reported; treatment of 3-(4-nitrophenyl)-1,5-diphenylformazan with formalin and sodium hydroxide yielded 1-phenyl-3-(4-nitrophenyl)-1,2,4-triazole, but in a low yield (27%).[10] In the reaction of 1-(tetrazol-5-yl)-3,5-diphenylformazan with formalin, a mixture of 1,2,4-triazolo[3',4':5,1]imidazo[4,3-*c*]-1,2,4-triazole and 1,3-diphenyl-1,2,4-triazole was formed.[16] These

Table 2. Spectral Data of Compounds (**3**, **4**, **5**, and **9**)

	Ms, m/z (%)	Ir (KBr), cm^{-1}	^1H-Nmr, δ ppm
3a	356 (M^+, 26), 214 (12) 126 (23), 91 (100)	3210, 1685, 1530 1460, 1430, 1300	($CDCl_3$) 7.36 - 8.11 (m, 10H), 12.90 (br s, 1H)
3b	370 (M^+, 41), 245 (18) 228 (23), 105 (100)	3215, 1710, 1530, 1450, 1310, ,1200	($CDCl_3$) 2.39 (s, 3H), 7.26 - 8.12 (m, 9H), 12.74 (s, 1H)
3c	386 (M^+, 33), 261 (6) 244 (22), 121 (100)	3200, 1675, 1595 1530, 1435, 1290	($CDCl_3$) 3.84 (s, 3H), 6.94 - 8.12 (m, 9H), 12.79 (s, 1H)
3d	390 (M^+, 29), 265 (10) 248 (18), 125 (100)	3215, 1685, 1530 1440, 1290, 1165	($CDCl_3$) 7.33 - 8.12 (m, 9H), 12.73 (s, 1H)
4a	260 (M^+, 43), 118 (38) 115 (34), 92 (100)	3265, 1600, 1545 1515, 1490, 1445	($CDCl_3$) 6.91 - 7.95 (m, 10H), 7.89 (s, 1H), 11.36 (s, 1H)
4b	274 (M^+, 49), 132 (44) 119 (32), 105 (100)	3275, 1550, 1490 1440, 1300, 1275	(DMSO - d_6) 2.22 (s, 3H), 6.91 - 7.94 (m, 9H), 7.83 (s, 1H), 11.31 (s, 1H)
4c	290 (M^+, 47), 149 (49) 135 (83), 121 (100)	3275, 1550, 1500 1445, 1320, 1300	(DMSO - d_6) 3.72 (s, 3H), 6.88 - 7.93 (m, 9H), 7.78 (s, 1H), 11.27 (s, 1H)
4d	294 (M^+, 44), 152 (47) 139 (28), 125 (100)	3260, 1600, 1540 1480, 1440, 1310	(DMSO - d_6) 7.02 - 7.96 (m, 10H), 7.92 (s, 1H), 11.47 (s, 1H)
5e	394 (M^+, 35), 135 (61) 107 (62), 77 (100),	1595, 1500, 1410 1315, 1300, 1245	($CDCl_3$) 3.90 (s, 3H), 6.96 - 8.15 (m, 14H)
5f	408 (M^+, 49), 135 (74) 119 (85), 91 (100)	1590, 1500, 1445 1305, 1250, 1165	($CDCl_3$) 2.37 (s, 3H), 3.88 (s, 3H), 6.94 - 8.15 (m, 13H)
5g	428 (M^+, 32), 135 (86) 107 (93), 77 (100)	1595, 1500, 1420 1320, 1250, 1160	($CDCl_3$) 3.90 (s, 3H), 6.96 - 8.14 (m, 13H)
9a	285 (M^+, 19), 118 (96) 104 (80), 77 (100)	3140, 1590, 1505 1445, 1385, 1330	($CDCl_3$) 7.43 - 8.18 (m, 10H), 8.58 (s, 1H)
9b	299 (M^+, 56), 141 (3) 131 (5), 118 (100)	3120, 1520, 1445 1330, 1300, 1230	($CDCl_3$) 2.40 (s, 3H), 7.29 - 8.18 (m, 9H), 8.52 (s, 1H)
9c	315 (M^+, 100), 174 (16) 147 (34), 134 (58)	3090, 1590, 1615 1440, 1330, 1250	($CDCl_3$) 3.88 (s, 3H), 6.99 - 8.19 (m, 9H), 8.47 (s, 1H)
9d	319 (M^+, 25), 138 (36) 125 (24), 118 (100)	3125, 1500, 1445 1390, 1340, 1320	($CDCl_3$) 7.48 - 8.17 (m, 9H), 8.57 (s, 1H)

reactions suggest that verdazyls are the intermediates in the formation of 1,2,4-triazoles from formazans. Therefore, our cyclization of formazans (**5**) to 1,2,4-triazoles (**9**) would proceed through the initial formation of verdazyls (**8**) followed by rearrangement to the 1,2,4-triazole radical (**18**), pathway (b), although we could not isolate the corresponding verdazyls (**8**) under the various reaction conditions.

Our method described here is the first preparative one for obtaining 1,2,4-triazoles from formazans in moderate to good yields, and the phenylsulfonyl substituent may play an important role in this reaction.

EXPERIMENTAL

Melting points were determined with a MRK MEL-TEMP II and are uncorrected. Ir spectra were recorded on a JASCO A-102 spectrophotometer. Mass and ^{1}H-nmr spectra were taken with a JEOL JMS DX-300 spectrometer and a JEOL GSX-400 spectrometer, respectively. Microanalyses were performed with a YANACO CHN-Coder MT-5.

1-Arylhydrazono-3,3,3-trifluoro-1-(phenylsulfonyl)propan-2-ones (3)

A general procedure: A solution of methyl phenyl sulfone (15.6 g, 100 mmol) in dry THF (80 ml) was added to sodium hydride, which was prepared by washing *ca.* 60% sodium hydride in oil (8.00 g, *ca.* 200 mmol) with hexane under nitrogen atmosphere. The mixture was stirred for 3 h at room temperature. Ethyl trifluoroacetate (13.1 ml, 110 mmol) was added dropwise during 4 h to the yellowish brown mixture of the carbanion of the methyl phenyl sulfone, and the stirring was continued for 16 h at room temperature. The reaction mixture was added dropwise to a vigorously stirred ice-water consisting of crushed ice (*ca.* 20 g) and 2 N hydrochloric acid (70 ml). To this mixture was added a solution of arenediazonium chloride prepared in the usual manner from arylamine (60 mmol), concentrated hydrochloric acid (12 ml), and sodium nitrite (4.70 g, 66 mmol), and the stirring was maintained for 3 h at 0 - 5 °C. The precipitates were collected by filtration to give the crude product. Removal of the solvent of the filtrate gave an oily residue, which crystallized after several days to yield an additional product. The combined product was recrystallized from MeOH to give the yellow **3**.

Phenylsulfonylmethanal arylhydrazones (4)

A general procedure: To a stirred mixture of **3** (10 mmol) in MeOH (50 ml) was added dropwise triethylamine (2.8 ml, 20 mmol). An exothermic reaction occurred with the color change to orange. After refluxing for 5 h, the solvent was removed *in vacuo*, and the oily residue was mixed with a small amount of MeOH to give precipitates. They were collected by filtration and recrystallized from MeOH to give the product (**4**) as orange crystals.

1,5-Diaryl-3-phenylsulfonylformazans (5)

A general procedure: To a cooled (0 - 5 °C) and stirred solution of **4** (5.0 mmol) in pyridine (5 ml) was added dropwise a solution of arenediazonium chloride prepared in the usual manner from arylamine (5.5 mmol), concentrated hydrochloric acid (1.4 ml), and sodium nitrite (430 mg, 6.1 mmol). After stirring for 15 min, a small amount of water was added, and the mixture was allowed to stand in a refrigerator to form precipitates, which were collected by filtration, washed with MeOH, and then recrystallized from $CHCl_3$-acetone to give the product (**5**) as red or brown crystals.

1-Aryl-3-phenylsulfonyl-1,2,4-triazoles (9)

A general procedure: To a stirred solution of **5** (1.0 mmol) in DMF (30 ml) was added potassium hydrogen sulfate (950 mg, 7.0 mmol) and then 35% formalin (8.6 g, *ca.* 100 mmol). The mixture was heated at 80 - 100 °C for 2.5 - 5 h. Water (30 ml) was added to the cooled mixture, which was made alkaline (pH 11-13) by the addition of 2 N sodium hydroxide. The mixture was poured into crushed ice (*ca.* 500 g), and then allowed to stand in a refrigerator for more than one day. The precipitates formed were collected by filtration and recrystallized from MeOH-$CHCl_3$ to give the product (**9**) as yellow or green crystals.

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