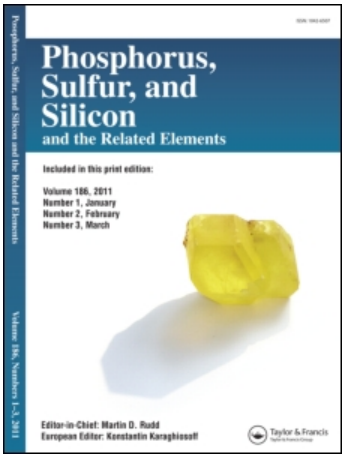


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Syntheses of 4,5-Diaryl-1,2,3-thiadiazoles[1]

Lila Karimi[a]; Latifeh Navidpour[a]; Mohsen Amini[a]; Abbas Shafiee[a]
[a] Deapartment of Chemistry, Tehran University of Medical Sciences, Tehran, Iran

To cite this Article Karimi, Lila , Navidpour, Latifeh , Amini, Mohsen and Shafiee, Abbas(2005) 'Syntheses of 4,5-Diaryl-1,2,3-thiadiazoles[1]', Phosphorus, Sulfur, and Silicon and the Related Elements, 180: 7, 1593 — 1600
To link to this Article: DOI: 10.1080/104265090884283
URL: http://dx.doi.org/10.1080/104265090884283

Phosphorus, Sulfur, and Silicon, 180:1593–1600, 2005

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/104265090884283

Taylor & Francis
Taylor & Francis Group

Syntheses of 4,5-Diaryl-1,2,3-thiadiazoles[1]

Lila Karimi
Latifeh Navidpour
Mohsen Amini
Abbas Shafiee
Deapartment of Chemistry, Tehran University of Medical Sciences, Tehran, Iran

Reaction of thionyl chloride with semicarbazones of 1-(4-methylsulfonylphenyl)-2-(4-substituted pheny)lethanone gave 4-(4-methylsulfonylphenyl)-5-(4-substituted) pheny-1,2,3-thiadiazoles ***5****. Compounds 5-phenyl-4-(substitutedphenyl)-1,2,3-thiadiazoles* ***14*** *were similarly prepared. Chlorosulfonation of the latter followed by ammonia gave the desired compounds 5-(4-aminosulfonylphenyl)-4-(substituted) phenyl-1,2,3-thiadiazoles* ***6****.*

Keywords 1,2,3-Thiadiazole; 4,5-diaryl-1,2,3-thiadiazole; sulfonamide

INTRODUCTION

Highly selective cyclooxygenase (COX-2) inhibitor currently provide effective treatment of inflammatory diseases such as rheumatoid arthritis and osetoarthritis, with improved therapeutics and fewer side effects.[2] Recent studies have shown that selective COX-2 inhibitors can induce apotosis in colon, stomach, prostate, and breast cancer cell lines.[3–6] Selective COX-2 inhibitors offer potential for the prophylactic prevention of inflammatory neurodegerative disorders such as Alzheimer's disease.[7]

Diarylheterocycles (such as Celecoxibe, Refecoxib, and Valdecoxib) constitute a major class of selective COX-2 inhibitor drugs that possess a central five-membered heterocycles ring. Diarylthiadiazoles, **4** (Figure 1) showed only moderate COX-2 inhibition activity.[8] We now report synthesis of a series of 1,2,3-thiadiazoles with a suitably disposed sulfonamide or methylsulfonyl pharmacophore.

Received July 2, 2004; accepted July 2, 2004.
Address correspondence to Abbas Shafiee, Faculty of Pharmacy, Tehran University of Medical Sciences, PO Box. 14155-6451, Tehran, Iran. E-mail: ashafiee@ams.ac.ir

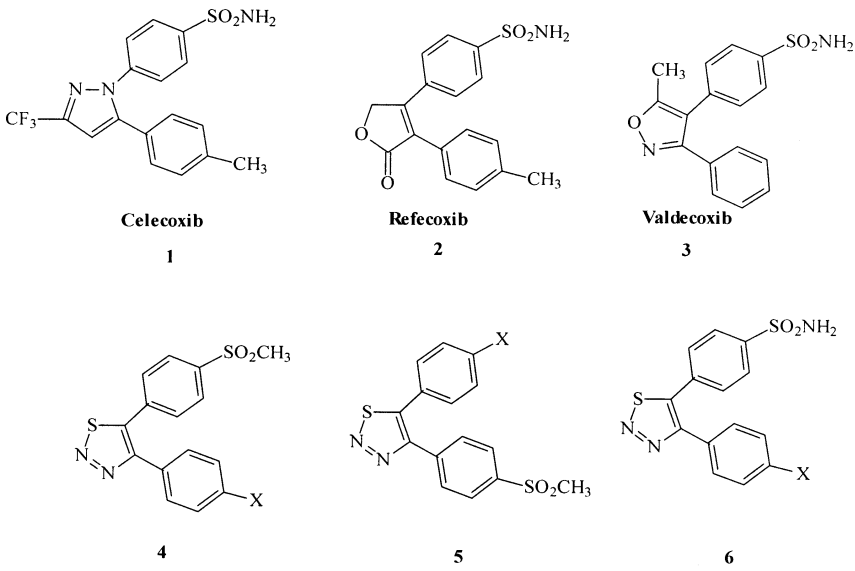
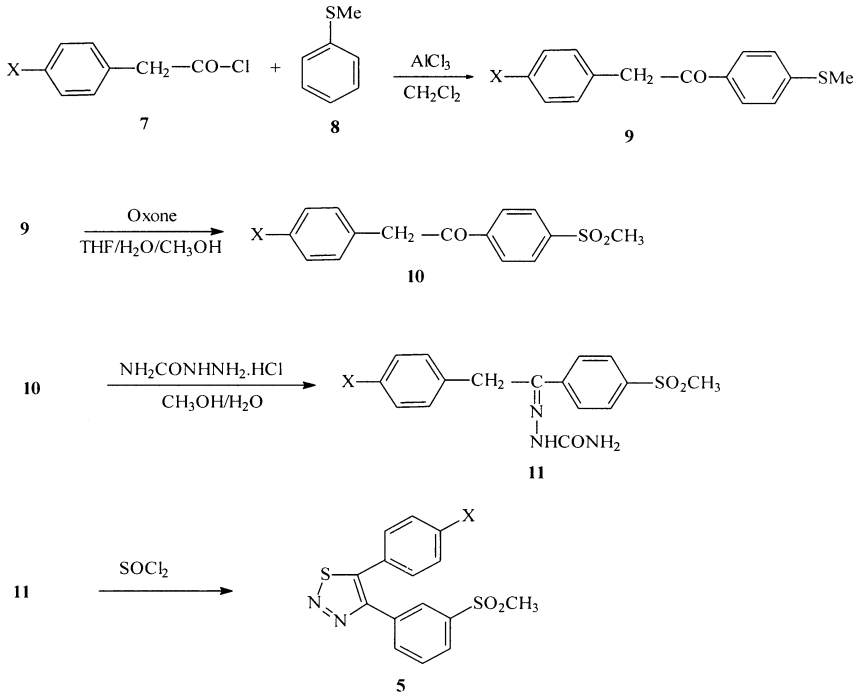


FIGURE 1 Structure of COX-2 inhibitors and 4,5-diaryl-1,2,3-thiazoles.

RESULTS AND DISCUSSION

Synthesis of thiadiazoles have been reported via several pathways. Reaction of aryl isothiocyanates with diazomethane gave the arylthiazole ring.[9] Diazotizing of α-amino ketones followed by ammonium hydrogen sulfide[10] or thionyl chloride with hydrazone gave 1,2,3-thiadiazole.[11] In the present work, reaction between semicarbazone of ketones and thionyl chloride that has been reported[12] was extended for the preparation of 4,5-diaryl thiadiazole. The synthetic reactions used for the synthesis of 5-(4-substituted phenyl)-4-(4-methylsulfonylphenyl)-1,2,3-thiadiazole **5** and sulfonamide derivatives **6** are outlined in Schemes 1 and 2, respectively. Friedel-Crafts acylation of thioanisole **8** with substituted phenylacetyl choride **7** afforded 1-(4-methylthiophenyl)-2-(4-substitutedphenyl)ethanone **9**. Oxidation of compound **9** with oxone at room temperature resulted in the Baeyer-Villiger rearrangement and the corresponding ester of **9** instead of the expected compound **10** was isolated. However, Reaction of the ketone **10** with semicarbazide hydrochloride in methanol-water yielded the corresponding semicarbazione **11**. Reaction of the latter with thionyl chloride gave the desired compounds **5** in moderate to good yield (69–80%) (Scheme 1).



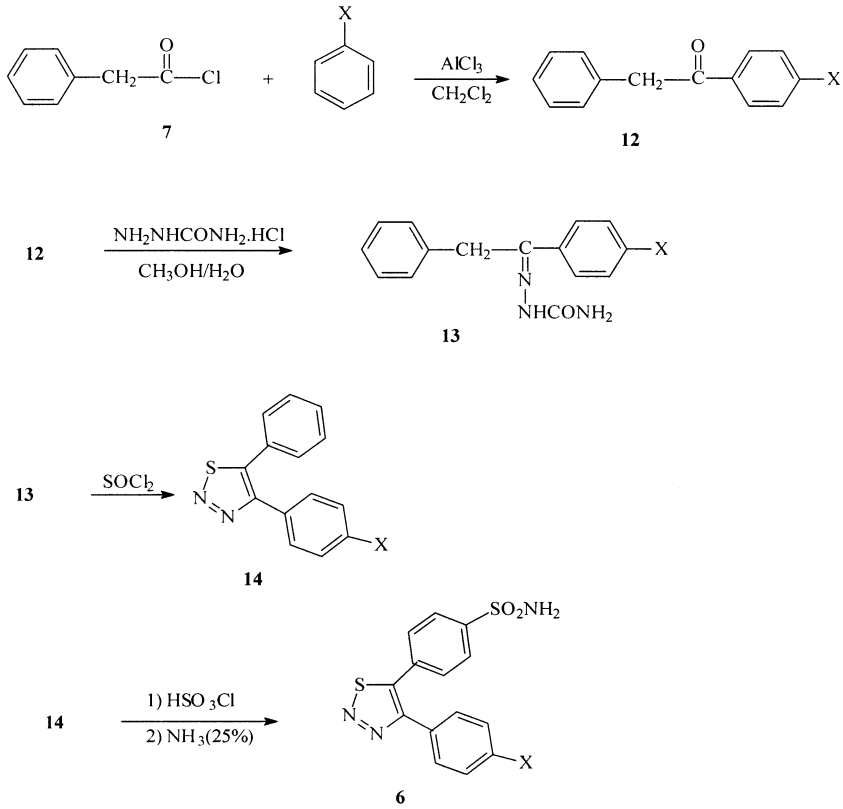
a) X = F
b) X = Cl
c) X = Br
d) X = H
e) X = OCH_3

SCHEME 1

Thiadiazoles **14** was prepared in a similar manner (Scheme 2). Chlorosulfonation of **14** at ice-bath temperature followed by aqueous ammonia gave the desired compounds **6**. The structures of all compounds were confirmed by IR, ^{1}H-NMR, and Mass spectra.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were obtained using a Nicolet FT-IR Magna 550 spectrographs; the ^{1}HNMR were obtained on a 400 Varian Unity plus spectrometer. Mass spectra were obtained on a Finnigan



a) X = F
b) X = Cl
c) X = Br

SCHEME 2

MAT TSQ 70 spectrometer at 70 eV. Column chromatography was carried out using silica gel (230–400 mesh).

Preparation of 1-[4-methylthiophenyl]-2-(4-substituted Phenyl)ethanone 9

General Procedure

To a stirring mixture of aluminum chloride (0.9 mol) in methylen chloride (100 mL) at ice-bath temperature phenyl acetyl chloride (0.06 mole) was added. After 30 min thioanisole (0.06 mole) was slowely added

and stirred for 24 h. Cruched ice (100 g) was added and the mixture extracted with methylen chloride (3 × 100 mL). Organic phase was dried (sodium sulfate) and filtered. The solvent was evaporated under reduced pressure and the residue was crystallized from hexane. The yield was 50–80%.

Selected data for 2-(4-flurophenyl)-1-(4-methylthiophenyl)ethanone ***9a.*** White solid, m.p. 135–138°C, yield = 75%. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 4.19 (s, 2H, CH_2), 6.97–7.30 (m, 6H), 7.80 (d, 2H, J = 8.8 Hz); IR (KBr)(ν_{max}, cm^{-1}): 1676 (CO); MS, *m/z* (%): 260(M^+, 52), 213 (13), 151 (38), 137 (23), 109 (100).

Compounds **9b–9d** were prepared similarly (See Table I).

Using halobenzene instead of thioanisole compounds **12a–12c** were prepared similarly (see Table I).

Preparation of 1-(4-Methylsulfonyl)phenyl-2-(4-substituted Phenyl)ethanone 10

General Procedure

To a magnetically stirred solution of compound 9 (8 mmol) in a mixture of methanol (80 mL) and THF (80 mL) was added slowly oxone (10.60 g, 16 mmol) in water (40 mL) at ice-bath temperature. After 4 h the mixture was filtered and the volume was reduced to about 40 mL under reduced pressure. The mixture was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried (sodium sulfate) and the

TABLE I Data for Compounds 9(a–c) and 12(a–c)

Comp. No.	X	Yield (%)	m.p. °C	Formula	Calcd. (%) C	Calcd. (%) H	Found (%) C	Found (%) H
9a	F	75	135–138	$C_{15}H_{13}FOS$	69.21	5.03	69.37	4.93
9b	Cl	68	124–127	$C_{15}H_{13}ClOS$	65.09	4.73	65.19	4.46
9c	Br	51	170–172	$C_{15}H_{13}BrOS$	56.08	4.08	56.32	4.26
9d	H	60	97–98	$C_{15}H_{141}OS$	74.34	5.92	73.99	5.50
9e	OCH_3	55	110–114	$C_{16}H_{16}O_3S$	70.56	5.92	70.11	5.98
10a	F	82	150–153	$C_{15}H_{13}FO_2S$	61.63	4.48	61.19	4.73
10b	Cl	70	180–184	$C_{15}H_{13}ClO_3S$	58.35	4.24	58.60	4.39
10c	Br	52	188–191	$C_{14}H_{13}ClO_3S$	51.00	3.71	51.09	3.79
10d	H	45	175–178	$C_{15}H_{14}O_3S$	65.67	5.14	65.98	4.88
10e	H	46	163–165	$C_{16}H_{16}O_3S$	66.64	5.59	66.02	5.40
12a	F	42	71–74	$C_{14}H_{11}FO$	78.49	5.18	78.41	4.96
12b	Cl	54	95–98	$C_{14}H_{11}ClO$	72.89	4.83	72.51	4.61
12c	Br	54	95–98	$C_{14}H_{11}BrO$	61.11	4.05	60.89	3.86

solvent was removed under reduced pressure. The residue was crystallized from chloroform: hexane (1:1). The yield was 45–82%.

Selected data for 2-(4-fluorophenyl-1-(4-methylsulfonylphenyl)-ethanone ***10a.*** White solid, m.p. 150–153°C, yield = 82%. ^{1}H NMR ($CDCl_3$): δ 3.11 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.19–7.32 (m, 4H, aromatic), 8.06 (d, 2H, J = 8.8 Hz), 8.19 (d, 2H, J = 8.8 Hz), IR (KBr)(ν_{max}, cm^{-1}): 1691 (CO), 1314, 1153 (SO_2); MS, *m/z* (%): 292 (M^+, 17), 212 (15), 183 (100), 138 (12).

Compound **10b** to **10e** were prepared similarly (see Table I).

Preparation of 1-(4-Methylsufonylphenyl)-2-(4-substituted Phenyl)ethanone Semicarbazone 11

General Procedure

To a solution of compound **10** (6.5 mmol) in ethanol (50 mL) was added (1.76 g) by sodium acetate (13 mmol) and (1.6 g) semicarbazide hydrochloride (13 mmol) in water (15 mL) and the mixture refluxed for 24 h. The mixture was filtered and the volume was reduced to about 50 mL under reduced pressure. It was cooled and the precipitate was filtered. The solids were recrystallized from ethanol-water to give compound **11**. The yield was 60–85%.

Selected data for 2-(4-flurophenyl)-1-(4-methylsulfonylphenyl) ethanone semicarbazone ***11a.*** White solid m.p. 122–125°C, yield = 73%. ^{1}H NMR ($CDCl_3$): δ 3.11 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 7.15–7.28 (m, 2H), 7.38–7.48 (m, 2H), 8.01 (d, 2H, J = 8.8 Hz), 8.25 (d, 2H, J = 8.8 Hz).

Preparation of 5-(4-Substituted Phenyl)-4-(4-methylsulfonylphenyl)-1,2,3-thiadiazole 5

General Procedure

To compound **11** (1 g) was added thionyl chlorid (5 mL) and stirred at 0°C for 3 h. CH_2Cl_2 (20 mL) was added and filtered on the aqueous saturated solution of sodium bicarbonate. The organic phase was dried (sodium sulfate) and filtered and the solvet was removed under reduced pressure. Purificaction was carried out by column chromatography (silica gel) with the solvent system chloroform: ethylacetat (5:1) and the desired compound was crystallized from chloroform-petroleum ether.

Selected data for 5-(4-flurophenyl)-4-(4-methylsulfonylphenyl)-1,2,3-thiadiazole ***5a.*** White solid, m.p. 173–175°C, yield = 71%. ^{1}H

TABLE II Data for Compounds 5a–e, 6a–c, and 14a–c

Comp. no.	X	m.p. °C	Yield (%)	Formula	Calcd. (%) C	Calcd. (%) H	Calcd. (%) N	Found (%) C	Found (%) H	Found (%) N
5a	F	173–175	71	$C_{15}H_{11}FN_2O_2S_2$	53.88	3.32	8.38	53.67	3.63	8.65
5b	Cl	170–172	80	$C_{15}H_{11}ClN_2O_2S_2$	51.35	3.16	7.98	50.99	3.01	7.73
5c	Br	188–191	69	$C_{15}H_{11}BrN_2O_2S_2$	45.57	2.80	7.09	45.61	2.89	7.40
5d	H	153–154	71	$C_{15}H_{11}N_2O_2S_2$	56.94	3.82	8.85	57.03	3.45	8.61
5f	OCH_3	123–126	75	$C_{16}H_{14}N_2O_3S_2$	55.47	4.07	8.09	55.92	4.28	8.22
6a	F	157–161	37	$C_{14}H_{10}FN_3O_2S_2$	50.14	3.01	12.53	49.86	3.09	12.18
6b	Cl	166–168	29	$C_{14}H_{10}ClN_3O_2S_2$	47.78	2.87	11.94	47.42	2.55	11.65
6c	Br	145–147	46	$C_{14}H_{10}BrN_3O_2S_2$	42.43	2.54	10.60	42.03	2.51	10.96
14a	F	oil	62	$C_{14}H_9FN_2S_2$	65.61	3.54	10.93	65.47	3.79	10.61
14b	Cl	oil	60	$C_{14}H_9ClN_2S$	61.65	3.32	10.27	61.96	3.49	10.30
14c	Br	oil	33	$C_{14}H_9BrN_2S$	53.01	2.86	8.83	53.26	2.53	8.56

NMR ($CDCl_3$): δ 3.11 (s, 3H, CH_3), 7.09–7.23 (m, 2H), 7.28–7.45 (m, 2H), 7.82 (d, 2H, J = 8.8 Hz), 7.99 (d, 2H, J = 8.8 Hz), IR (KBr)(ν_{max}, cm^{-1}): 1310, 1150 (SO_2); MS, *m/z* (%): 334 (M^+, 10), 306 (100), 274 (17), 243 (85).

Compounds 5b–5f were prepared similarly (Table II).

Preparation of 4-[4-(4-Substituted Phenyl)1,2,3-thiadiazole-5-yl]benzen-sulfonamide 6

General Procedure

To a magnetically stirred solution of compound **14** (1 mmol) at ice-bath temperature was slowly added to chlorosulfonic acid (5 mL). After 5 h crushed ice was added and the precipitate was filtered. It was dissolved in methanol and excess amounts of ammonia solution (25%) was added. The solution was stirred for 24 h. The solvent was removed at reduced pressure and the residue purified by preparative TLC with the solvent system chloroform: ethyl acetate and crystallized from $CHCl_3$-peteroleum ether.

*Selected data for 4-[4-(4-flurophenyl)-1,2,3-thiadiazole-5-yl]benzensulfonamide **6a**.* White solid, m.p. 157–161°C, yield = 37%. ^1H NMR ($CDCl_3$/DMSO-d_6): 7.15–7.58 (m, 2H), 7.22 (bs, 2H, NH_2), 7.49 (d, 2H, J = 8.8 Hz), 7.53–7.62 (m, 2H), 7.94–8.10 (m, 2H), IR (KBr)(ν_{max}, cm^{-1}): 3310 and 3380 (NH_2); MS, *m/z* (%): 335 (18), 309 (100), 275 (35), 255 (73), 155 (22), 95 (15).

REFERENCES

[1] A. Shafiee, M. Amini, and M. Salimi, *Partially Presented at ISOCS-XXI, 21st International Symposium Organic Chemistry of Sulfur*, July 4–9, (2004) Madrid, Spain.
[2] C. Hawkey, L. laine, T. Simon, A. Beaulieu, J. Maldona-Cocco, and E. Acevedo, *Arthritis Rheum*., **43,** 370 (2000).
[3] S. Arico, S. Pattirgre, C. Bauvy, P. Gane, A. Barbat, P. Codogno, and E. Ogier-Denis, *J. Biol. Chem*., **227,** 27613 (2002).
[4] G. Davies, L. A. Martin, N. Sacks, and M. Dowsett, *Ann. Oncol*., **13,** 669 (2002).
[5] H. Sawaoka, S. Kawano, S. Tsuji, M. Tsujii, and E. S. Gunawan, *Am. J. Physiol*., **274,** 1061 (1998).
[6] H. X. Liu, A. Kirschenbaum, S. Yao, R. Lee, J. F. Holland, and A. C. Levine, *J. Urol*., **164,** 820 (2000).
[7] G. M. Pasinetti, *Arch. Gerontol. Geriatr*., **33,** 13 (2001).
[8] J. Y. Gauthier, Y. Leblanc, W. C. Black, C. Chi-Chang, W. A. Cromlish, R. Gorden, B. Kennedy, K. L. Cheul, J. Mancini, D. Riendeau, P. Tagari, P. Vicker, E. Wong, X. Lijing, and P. Prasit, *Bioorg. Med. Chem. Lett*., **6,** 87 (1996).
[9] J. C. Sheehand and P. T. Izzo, *J. Am. Chem. Soc*., **71,** 4059 (1949).
[10] L. Wolff, *Ann. Chem*., **325,** 129 (1902).
[11] R. Eloy and C. Moussebois, *Bull. Soc. Chim. Belge*, **68,** 423 (1959).
[12] A. Shafiee, I. Lalezari, M. Mirshad, and D. Nercesian, *J. Het. Chem*., **14,** 567 (1977).