Regioselective Syntheses of Substituted Thioxanthen- and Selenoxanthen-9-one Derivatives

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Various methoxy-substituted thioxanthen-9-one derivatives were regioselectively synthesized by a one-pot condensation of *S*-lithiated thiosalicylic ester or amides, obtained *via* directed lithiation of tertiary benzamides, with benzynes. Similarly, the synthesis of selenoxanthen-9-ones was achieved.

Keywords thioxanthen-9-one; selenoxanthen-9-one; lithiation; thiosalicylic ester; thiosalicylamide; selenosalicylamide; benzyne

Thioxanthen-9-one derivatives have been studied extensively owing to their medicinal properties such as antihistaminic,[1] antiparasitic,[2] neuroleptic,[3] and antitumor[4] activities. Although selenoxanthen-9-ones[5] have been less investigated than the corresponding thio-analogues, selenoxanthene and other selenium-containing compounds have attracted interest in the fields of radiation[6] and dye chemistry.[7] Thioxanthen-9-ones are generally synthesized[8] by acid-mediated cyclizations of *o*-(phenylthio)benzoic acids or of thiosalicylic acid derivatives with appropriate benzenes. For the preparation of unsymmetrically and highly substituted thioxanthen-9-ones, these methods lack regiochemical control in the ring closure steps.

Recently, we have developed a regioselective one-pot synthesis of acridone derivatives (**3**) by coupling of *N*-lithiated anthranilates (**1**) with benzynes (**2**) derived *in situ* from halobenzenes by the action of strong bases (Chart 1).[9] This method seems to have general utility, and may be applied to the construction of other fused ring systems.[10] In connection with our continuing studies on aromatic lithiation reactions,[11] we report here convenient and regioselective syntheses of thioxanthen-9-ones (**7**) and selenoxanthen-9-ones (**8**) using a similar coupling reaction of benzynes (**2**) with the *S*-lithiated thiosalicylic ester (**4**) or

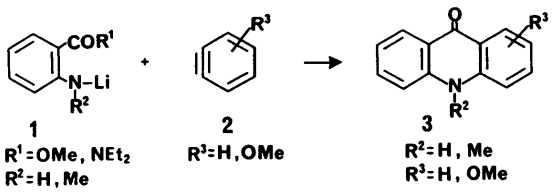


Chart 1

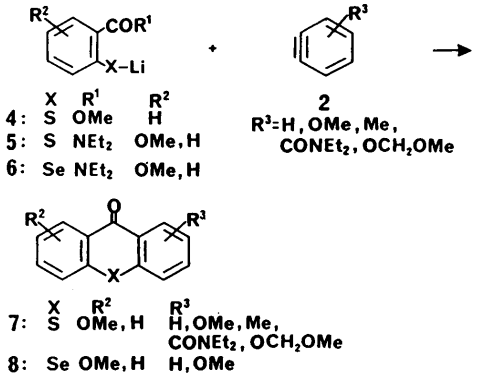
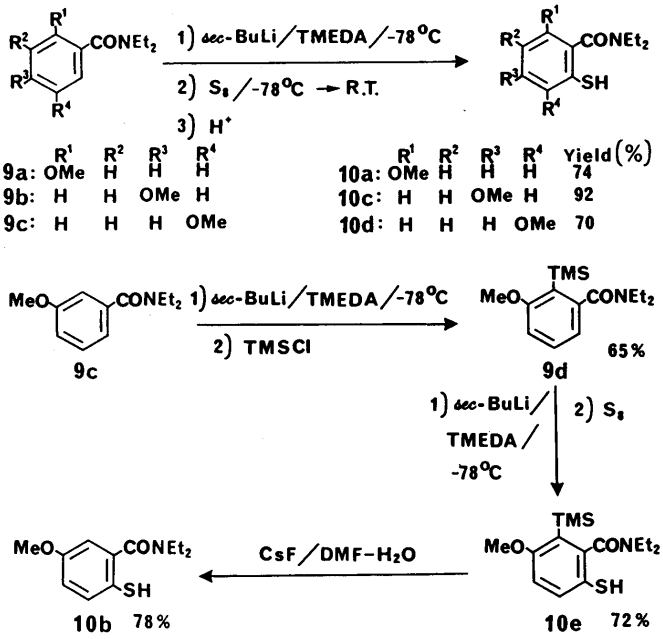


Chart 2



R.T. = room temperature

Chart 3

amides (**5**) and *Se*-lithiated selenosalicylamides (**6**), respectively (Chart 2).

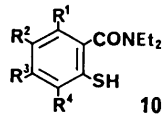
In general, the synthesis of substituted thiosalicylic[12] and selenosalicylic[13] acid derivatives is difficult and requires harsh reaction conditions. Therefore, we first attempted to develop a new, efficient synthesis of substituted thiosalicylic and selenosalicylic acids. The directed metalation reaction of tertiary benzamides[14] is becoming recognized as a significant method for the regioselective synthesis of poly-functionalized aromatics. C–S and C–Se bond formation[14a] by reaction of elemental sulfur and selenium with organolithium compounds has been reported. We therefore expected that the directed lithiation strategy would be applicable for the syntheses of substituted thiosalicyl- and selenosalicylamide derivatives.

N,*N*-Diethyl *o*-anisamide (**9a**) was lithiated with *sec*-BuLi in tetrahydrofuran (THF) at −78 °C[15] in the presence of tetramethylethylenediamine (TMEDA) to generate the corresponding *ortho*-lithio species, which was subsequently treated with powdered sulfur at −78 °C. After usual work-up and chromatographic purification, *N*,*N*-diethyl-6-methoxythiosalicylamide (**10a**) was obtained in 74% yield as a pale yellow viscous oil (Chart 3). Similarly, 4-methoxy- (**10c**) and 3-methoxythiosalicylamide (**10d**) were regioselec-

tively prepared in 92% and 70% yields starting from *p*-anisamide (**9b**) and *m*-anisamide (**9c**), respectively. In the case of preparation of *N*,*N*-diethyl-5-methoxythiosalicylamide (**10b**), *m*-anisamide (**9c**) was also employed as a starting amide. *ortho*-Lithiated **9c** was quenched with chlorotrimethylsilane (TMSCl) to give *N*,*N*-diethyl-2-trimethylsilyl-3-methoxybenzamide (**9d**) in 65% yield. The conversion of **9d** into **10e** was carried out under similar conditions to those described above. Desilylation of **10e** with cesium fluoride[16] in a refluxing mixture of dimethylformamide (DMF) and water gave the desired **10b** in 78% yield. Previously, substituted thiosalicylic acid derivatives have been obtained by multi-step synthesis,[12] involving diazotization of appropriately substituted anthranilic acids followed by reaction of the diazonium salt with sodium polysulfide and then reduction. Our synthetic method developed herein using the directed lithiation strategy provided an alternative and more effective procedure for the preparation of substituted thiosalicylic acid derivatives. The structures of thiosalicylamides (**10a—d**) thus obtained were mainly confirmed by their nuclear magnetic resonance (^{1}H-NMR) spectra and mass spectra (MS) and those of their 2,4-dinitrophenyl derivatives (**11**) (see Tables I and II).

For the synthesis of thioxanthen-9-ones, we initially examined the reaction of methyl thiosalicylate (**12**) with halobenzenes (**13**) (Chart 4) under the conditions summarized in Table III. Thus, methyl thiosalicylate (**12**) was treated with an excess of lithium diisopropylamide (LDA) at −78 °C in THF in order to generate the *S*-lithiated thiosalicylate (**4**). It has been reported[9,11,17] that benzynes (**2**) may be generated from the corresponding halobenzenes by treatment with lithium amides, such as LDA, between −40 °C and −20 °C. Therefore, 2.0 eq of bromobenzene (**13a**) was added to the yellow solution of **4** at −20 °C, and the mixture was allowed to warm to room temperature. The solution turned black during this operation. After standard work-up, thioxanthen-9-one (**7a**) was obtained in 73% yield (Table III; run 1). The use of lithium *N*-isopropylcyclohexylamide (LCI) as a base instead of LDA led to the formation of **7a** in 98% yield (Table III; run 2). The use of 2.0 eq of halobenzenes (**13**) and 3.5 eq of base for **12** generally improved the yields of thioxanthen-9-ones in comparison with the case where 1.0 eq of **13** and 2.0 eq of base were used (Table III; runs 2 and 3). When *o*-bromoanisole (**13b**) was employed as the benzyne precursor and LDA as the base, 1-methoxythioxanthen-9-one (**7b**) was isolated as a single regioisomer in 79% yield (Table III; run 4). By the use of other bases such as LCI and lithium 2,2,6,6-tetramethylpiperidide (LTMP), similar yields of **7b** were obtained (Table III; runs 5 and 6). Compound **7b** was also obtained from *m*-bromoanisole (**13c**) and **12** in a lower yield (44%) (Table III; run 7). Therefore *o*-bromoanisole (**13b**) is a better precursor for 3-methoxybenzyne than *m*-bromoanisole (**13c**). Similar regiochemical behavior was observed in the reaction of 2,3-dimethoxybromobenzene (**13d**) or 2,4-dimethoxybromobenzene (**13e**) with **12** affording 1,2-dimethoxythioxanthen-9-one (**7c**)[8g] or 1,3-di-

TABLE I. ^{1}H-NMR Data of Thiosalicylamides (**10**)



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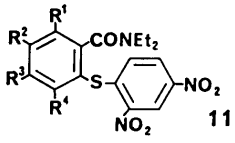
Compd. No.	^{1}H-NMR ($CDCl_3$)[a] δ
10a	1.10 (t, 3H, J=7.0), 1.30 (t, 3H, J=7.0), 3.12 (q, 2H, J=7.0), 3.51 (q, 2H, J=7.0), 3.60 (s, 1H), 3.74 (s, 3H), 6.56—7.27 (m, 3H)
10b	1.05 (t, 3H, J=7.0), 1.25 (t, 3H, J=7.5), 2.98 (s, 1H), 3.11 (q, 2H, J=7.5), 3.54 (q, 2H, J=7.0), 6.68 (s, 1H), 6.76 (dd, 1H, J=2.5, 8.4), 7.45 (d, 1H, J=8.4)
10c	1.15 (t, 6H, J=7.0), 3.33 (m, 4H), 3.70 (s, 3H), 3.73 (s, 1H), 6.60—7.80 (m, 3H)
10d	1.07 (t, 3H, J=7.2), 1.28 (t, 3H, J=6.6), 3.18 (q, 2H, J=6.6), 3.59 (q, 2H, J=7.2), 3.89 (s, 3H), 3.50—3.90 (br s, 1H), 6.61—7.08 (m, 3H)
10e	0.17 (s, 9H), 0.97 (t, 3H, J=7.0), 1.18 (t, 3H, J=7.0), 3.03 (q, 2H, J=7.0), 3.06 (q, 2H, J=7.0), 3.10 (s, 1H), 3.63 (s, 3H), 6.61 (d, 1H, J=8.4), 7.21 (d, 1H, J=8.4)

a) Listed as chemical shifts (multiplicity, number of protons, coupling constant in Hz).

TABLE II. Physical Properties and Spectral Data of 2,4-Dinitrophenyl Thiosalicylamide Derivatives (**11**)



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Compd. No.	R^1	R^2	R^3	R^4	Formula (MS, m/z, M^+)	mp (°C) (Recrystal. sol.)	Analysis (%) Calcd (Found) C	H	N	S	UV λ_{max}^{EtOH} (log ε)	IR $\nu_{cm^{-1}}^{KBr}$
11a	OMe	H	H	H	$C_{18}H_{19}N_3O_6S$ (405)	114—115 (EtOH/ether)	53.33 (53.46)	4.72 (4.72)	10.37 (10.38)	7.90 (8.02)	274 (4.01), 298 (s) (3.97), 330 (4.09)	ν_{CO} 1615
11b	H	OMe	H	H	$C_{18}H_{19}N_3O_6S$ (405)	108—109 (EtOH/ether)	53.33 (53.34)	4.72 (4.70)	10.37 (10.36)	7.90 (7.92)	236 (4.07), 272 (s) (3.71), 330 (3.76)	ν_{CO} 1620
11c	H	H	OMe	H	$C_{18}H_{19}N_3O_6S$ (405)	118—120 (EtOH/ether)	53.33 (53.22)	4.72 (4.77)	10.37 (10.44)	7.90 (8.02)	238 (s) (3.74), 274 (3.42), 328 (3.51)	ν_{CO} 1610
11d	H	H	H	OMe	$C_{18}H_{19}N_3O_6S$ (405)	175—176 (EtOH/ether)	53.33 (53.35)	4.72 (4.73)	10.37 (10.44)	7.90 (8.01)	273 (3.41), 335 (3.50)	ν_{CO} 1613
11e	$Si(Me)_3$	OMe	H	H	$C_{21}H_{27}N_3O_6S_1Si$ (477)	92—93 (Ether/*n*-hexane)	52.82 (52.45)	5.70 (5.80)	8.80 (8.58)		243 (s) (4.34), 274 (s) (4.03), 337 (4.08)	ν_{CO} 1599

TABLE III. Synthesis of Thioxanthen-9-ones (7)

Run	Halobenzene (13)							Base	Molar ratio 12:13:base	Thioxanthen-9-one (7)					Yield (%)
		R^1	R^2	R^3	R^4	R^5	R^6				R^1	R^2	R^3	R^4	
1	**13a**	H	H	H	H	H	Br	LDA	1:2:3.5	**7a**	H	H	H	H	73
2	**13a**	H	H	H	H	H	Br	LCI	1:2:3.5	**7a**	H	H	H	H	98
3	**13a**	H	H	H	H	H	Br	LCI	1:1:2.2	**7a**	H	H	H	H	66
4	**13b**	OMe	H	H	H	H	Br	LDA	1:2:3.5	**7b**	OMe	H	H	H	79
5	**13b**	OMe	H	H	H	H	Br	LCI	1:2:3.5	**7b**	OMe	H	H	H	80
6	**13b**	OMe	H	H	H	H	Br	LTMP	1:2:3.5	**7b**	OMe	H	H	H	80
7	**13c**	OMe	H	H	H	Br	H	LCI	1:2:3.5	**7b**	OMe	H	H	H	44
8	**13d**	OMe	OMe	H	H	Br	H	LCI	1:2:3.5	**7c**	OMe	OMe	H	H	67
9	**13e**	OMe	H	OMe	H	H	Cl	LCI	1:2:3.5	**7d**	OMe	H	OMe	H	77
10	**13f**	OMe	H	H	OMe	H	Cl	LCI	1:2:3.5	**7e**	OMe	H	H	OMe	54
11	**13g**	OCH_2OMe	H	H	H	H	Cl	LCI	1:2:3.5	**7f**	OCH_2OMe	H	H	H	52
12	**13h**	$CONEt_2$	H	H	H	H	Br	LCI	1:2:3.5	**7g**	$CONEt_2$	H	H	H	22
13	**13i**	OMe	H	Me	H	H	Cl	LCI	1:2:3.5	**7h**	OMe	H	Me	H	76

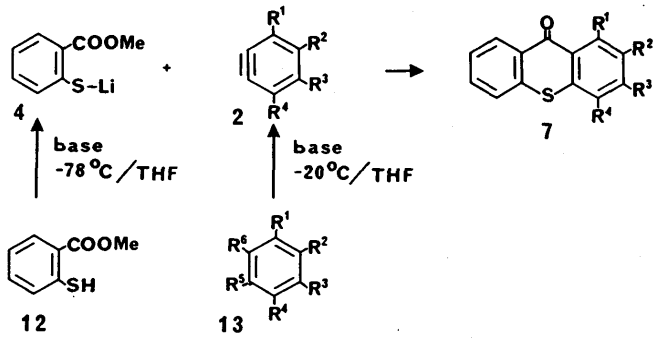


Chart 4

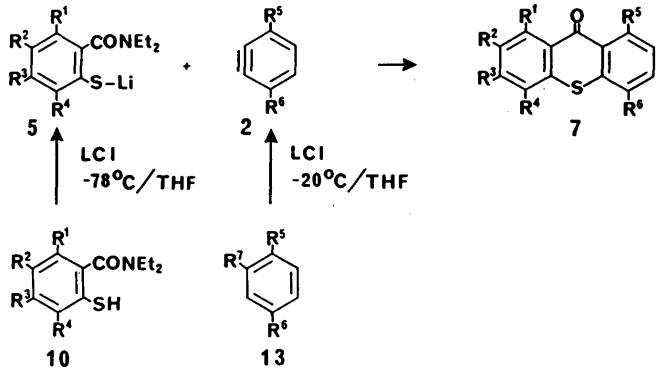


Chart 5

methoxythioxanthen-9-one (**7d**) in 67% or 77% yield, respectively (Table III; runs 8 and 9). The regiochemical control in these reactions may be rationalized in terms of the polarization effect of the alkoxy group in the corresponding benzyne intermediates.[9,11,17] This method is applicable to the preparation of not only methoxy-substituted thioxanthen-9-ones but also other functionalized thioxanthen-9-ones such as **7f** or **7g** (Table III; runs 11 and 12).

As shown above, the benzyne-based coupling reaction starting with **12** and **13** constitutes a convenient method for the preparation of methoxy-substituted thioxanthen-9-ones such as the 1-methoxy (**7b**) and 1,2- (**7c**), 1,3- (**7d**), 1,4-dimethoxy (**7e**)[8g,h,v] derivatives. However, regioisomers, 2-, 3-, and 4-methoxy-substituted thioxanthen-9-ones, could not be synthesized in this manner because of the opposite

TABLE IV. Synthesis of Thioxanthen-9-ones (7)

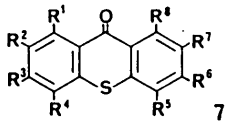
Run	10	13		Thioxanthen-9-one (7)						Yield (%)
				R^1	R^2	R^3	R^4	R^5	R^6	
1	**10a**	**13a**	**7b**	OMe	H	H	H	H	H	65
2	**10a**	**13b**	**7i**	OMe	H	H	H	OMe	H	61
3	**10a**	**13f**	**7j**	OMe	H	H	H	OMe	OMe	65
4	**10b**	**13a**	**7k**	H	OMe	H	H	H	H	50
5	**10b**	**13b**	**7l**	H	OMe	H	H	OMe	H	38
6	**10c**	**13a**	**7m**	H	H	OMe	H	H	H	90
7	**10c**	**13b**	**7n**	H	H	OMe	H	OMe	H	45
8	**10d**	**13a**	**7o**	H	H	H	OMe	H	H	60
9	**10d**	**13b**	**7p**	H	H	H	OMe	OMe	H	37

10: thiosalicylamide. **13**: halobenzene.

polarization effect of the alkoxy group on the benzynes for nucleophilic attack involving the thiolate anion (**4**). For the preparation of these compounds, we examined the reaction of methoxy-substituted thiosalycylamides (**10**) with **13** (Chart 5). The reaction between the amide (**10d**) and bromobenzene (**13a**) in the presence of LCI afforded 4-methoxythioxanthen-9-one (**7o**) in 60% yield (Table IV; run 8). In a similar manner, 2-methoxy- (**7k**)[8b,g] and 3-methoxy- (**7m**) thioxanthen-9-ones were obtained in 50% and 91% yields, respectively. As shown in Table IV (runs 2, 5, 7, and 9), highly substituted thioxanthen-9-ones such as 1,8- (**7i**), 1,7- (**7l**),[8i] 1,6- (**7n**), and 1,5-dimethoxy- (**7p**) thioxanthen-9-ones, which are difficult to obtain by classical methods, were regioselectively synthesized. These structures were established by infrared (IR), ^{1}H-NMR, and mass spectral evidence (see Table V).

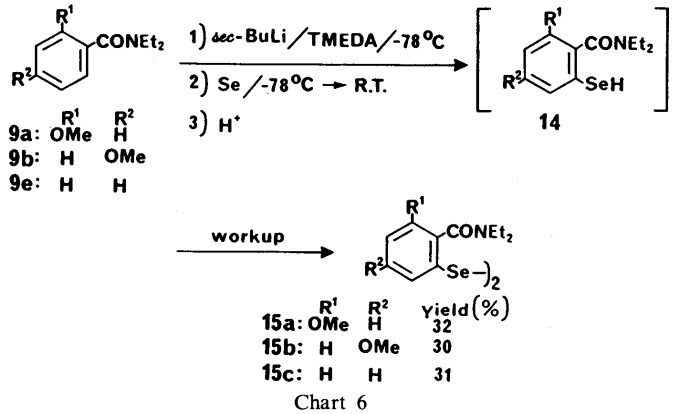
The method developed above was extended to the synthesis of selenoxanthen-9-ones.[5] Thus, lithiation of **9a**, **9b**, and *N*,*N*-diethylbenzamide (**9e**) under the standard conditions followed by treatment with powdered selenium afforded the corresponding *N*,*N*-diethylselenosalicylamides (**14a—c**), respectively (Chart 6). Selenols are generally more sensitive to air than thiols, and are oxidized to the corresponding diselenides.[18] Therefore, not surprisingly, during the acidic work-up and purification by column chromatography, the corresponding diselenides (**15a—c**) were isolated in moderate yields (see Table VI). The target selenoxanthen-9-ones (**8a—c**) were synthesized by the

TABLE V. Physical Properties and Spectral Data of Thioxanthen-9-ones (7)



Compd. No.[a]	Formula (MS, m/z, M^+)	mp (°C) (Recrystal. sol.)	UV λ_{max}^{EtOH} (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	NMR ($CDCl_3$)[b] δ
7a	$C_{13}H_8OS$ (212)	213 ($CHCl_3$/*n*-hexane)	258 (4.37), 289 (s) (3.45), 300 (s) (3.29), 381 (3.53)	ν_{CO} 1640	7.33—7.83 (m, 6H), 8.43—8.88 (m, 2H)
7b	$C_{14}H_{10}O_2S$ (242)	135 (MeOH)	258 (4.65), 300 (4.07), 309 (4.16), 382 (3.88)	ν_{CO} 1638	3.97 (s, 3H), 6.73—7.50 (m, 6H), 8.26—8.52 (m, 1H)
7c	$C_{15}H_{12}O_3S$ (272)	135—136[c] (MeOH)	258 (4.28), 314 (3.34), 392 (3.44)	ν_{CO} 1645	3.86 (s, 3H), 3.98 (s, 3H), 7.10—7.46 (m, 5H), 8.23—8.46 (m, 1H)
7d	$C_{15}H_{12}O_3S$ (272)	145 (*n*-Hexane/ether)	261 (4.66), 299 (4.29), 313 (s) (4.08)	ν_{CO} 1630	3.79 (s, 3H), 3.92 (s, 3H), 6.33—6.56 (m, 2H), 7.26—7.59 (m, 3H), 8.30—8.59 (m, 1H)
7e	$C_{15}H_{12}O_3S$ (272)	194[d] (*n*-Hexane/MeOH)	256 (4.59), 268 (s) (4.34), 321 (4.10), 389 (3.82)	ν_{CO} 1640	3.89 (s, 6H), 6.37 (d, 1H, J=9.0), 6.97 (d, 1H, J=9.0), 7.16—7.50 (m, 3H), 8.23—8.46 (m, 1H)
7f	$C_{15}H_{12}O_3S$ (272)	90 (*n*-Hexane/MeOH)	258 (4.63), 298 (s) (3.92), 307 (4.06), 382 (3.80)	ν_{CO} 1642	3.52 (s, 3H), 5.33 (s, 2H), 6.97—7.46 (m, 6H), 8.26—8.50 (m, 1H)
7g	$C_{18}H_{17}NO_2S$ (311)	160 (*n*-Hexane/ether)	259 (4.64), 271 (s) (3.78), 303 (3.69), 374 (s) (3.79), 382 (3.87)	ν_{CO} 1630	1.00 (t, 3H, J=8.0), 1.40 (t, 3H, J=8.0), 3.10 (q, 2H, J=8.0), 3.66 (q, 2H, J=8.0), 7.13—7.62 (m, 6H), 8.36—8.59 (m, 1H)
7h	$C_{15}H_{12}O_2S$ (256)	112—113 (*n*-Hexane/ether)	261 (4.29), 300 (s) (3.99), 309 (4.13), 381 (3.76)	ν_{CO} 1635	2.36 (s, 3H), 3.92 (s, 3H), 6.63 (s, 1H), 6.83 (s, 1H), 7.26—7.50 (m, 3H), 8.30—8.52 (m, 1H)
7i	$C_{15}H_{12}O_3S$ (272)	193—194 ($CHCl_3$/*n*-hexane)	257 (3.89), 316 (3.52), 370 (3.12)	ν_{CO} 1657	3.93 (s, 6H), 6.77—7.50 (m, 6H)
7j	$C_{16}H_{14}O_4S$ (302)	217—218[e] ($CHCl_3$/*n*-hexane)	238 (s) (3.10), 245 (3.91), 323 (3.51), 385 (3.10)	ν_{CO} 1655	3.85 (s, 3H), 3.91 (s, 6H), 6.82—7.57 (m, 5H)
7k	$C_{14}H_{10}O_2S$ (242)	127—128[f] (MeOH)	253 (4.52), 272 (4.50), 302 (3.15), 390 (3.74)	ν_{CO} 1640	3.88 (s, 3H), 7.13—7.50 (m, 5H), 7.96 (d, 1H, J=3.0), 8.43—8.63 (m, 1H)
7l	$C_{15}H_{12}O_3S$ (272)	137—138[g] (MeOH)	256 (s) (3.83), 265 (s) (3.90), 271 (3.92), 310 (s) (3.21), 320 (3.34), 405 (3.20)	ν_{CO} 1613	[h]
7m	$C_{14}H_{10}O_2S$ (242)	129 ($CHCl_3$/*n*-hexane)	232 (4.13), 250 (4.43), 260 (4.51), 267 (4.53), 273 (4.50), 282 (4.28), 312 (3.79), 373 (3.74)	ν_{CO} 1640	3.53 (s, 3H), 6.83 (s, 1H), 7.00—7.53 (m, 4H), 8.33—8.56 (m, 2H)
7n	$C_{15}H_{12}O_3S$ (272)	146—147 (MeOH)	235 (s) (3.95), 252 (4.41), 269 (4.42), 279 (s) (4.10), 296 (3.86), 378 (3.61)	ν_{CO} 1630	3.82 (s, 3H), 3.97(s, 3H), 6.70—7.55 (m, 5H), 8.38 (d, 1H, J=9.0)
7o	$C_{14}H_{10}O_2S$ (242)	165 (MeOH/ether)	259 (4.63), 298 (3.85), 308 (4.00), 385 (3.81)	ν_{CO} 1630	3.96 (s, 3H), 6.97—7.66 (m, 5H), 8.13—8.26 (m, 1H), 8.43—8.63 (m, 1H)
7p	$C_{15}H_{12}O_3S$ (272)	234—235 ($CHCl_3$/*n*-hexane)	250 (s) (4.22), 259 (4.33), 317 (3.99), 390 (3.53)	ν_{CO} 1638	4.02 (s, 6H), 7.00—7.52 (m, 5H), 8.06—8.18 (m, 1H)

a) *Anal.* Calcd (Found) for **7a**: C, 73.58 (73.68); H, 3.80 (3.83); S, 15.08 (14.94). **7b**: C, 69.42 (69.48); H, 4.16 (4.20); S, 13.21 (13.19). **7c**: C, 66.17 (65.88); H, 4.44 (4.33); S, 11.76 (11.48). **7d**: C, 66.17 (66.02); H, 4.44 (4.49); S, 11.76 (11.48). **7e**: C, 66.17 (66.18); H, 4.44 (4.51); S, 11.76 (11.39). **7f**: C, 66.17 (66.09); H, 4.44 (4.45); S, 11.76 (11.78). **7g**: C, 69.44 (69.36); H, 5.50 (5.47); N, 4.50 (4.45); S, 10.28 (10.17). **7h**: C, 70.30 (69.72); H, 4.72 (5.11); S, 12.49 (11.93). **7i**: C, 66.17 (66.13); H, 4.44 (4.42); S, 11.76 (11.74). **7j**: C, 63.57 (63.66); H, 4.67 (4.64); S, 10.59 (10.54). **7k**: C, 69.42 (69.46); H, 4.16 (4.33); S, 13.21 (13.15). **7l**: C, 66.17 (66.37); H, 4.44 (4.39); S, 11.76 (11.80). **7m**: C, 69.42 (69.53); H, 4.16 (4.17); S, 13.21 (13.15). **7n**: C, 66.17 (66.17); H, 4.44 (4.40); S, 11.76 (11.91). **7o**: C, 69.42 (69.52); H, 4.16 (4.23); S, 13.21 (13.05). **7p**: C, 66.17 (66.11); H, 4.44 (4.38); S, 11.76 (11.65). *b*) Listed as chemical shifts (multiplicity, number of protons, coupling constant in Hz. *c*) Lit.[8g] mp 143—144 °C. *d*) Lit.[8v] mp 194—196 °C. *e*) Lit.[8i] mp 208—209 °C. *f*) Lit.[8g] mp 129 °C. *g*) Lit.[8i] mp 136—138 °C. *h*) Not soluble enough in $CDCl_3$ or DMSO-d_6.

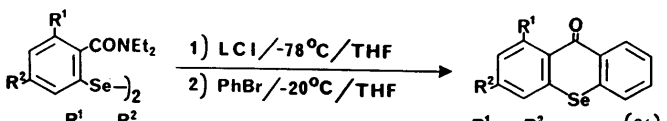


	R^1	R^2
9a	OMe	H
9b	H	OMe
9e	H	H

	R^1	R^2	Yield (%)
15a	OMe	H	32
15b	H	OMe	30
15c	H	H	31

Chart 6

coupling of benzyne intermediates with *Se*-lithiated selenosalicylamides (**6**) derived from the corresponding diselenides (**15**) with LCI as shown in Chart 7. Spectral data for these selenoxanthen-9-ones are summarized in Table VII. The parent seleonoxanthen-9-one, first synthesized in 1914,[13] and methyl- and chloro-substituted selenoxanthen-9-ones[19] have been prepared by Friedel–Crafts reactions of chloroselenyl benzoyl chlorides with benzenes, acid-catalyzed ring closure of *o*-(phenylseleno)benzoic acids, or photocyclization of selenobenzoate. However, our work constitutes the first preparation of methoxy-substituted selenoxanthen-9-ones (**8a, b**).[5]

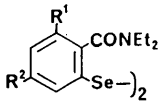


	R^1	R^2
15a	OMe	H
15b	H	OMe
15c	H	H

	R^1	R^2	Yield (%)
8a	OMe	H	42
8b	H	OMe	22
8c	H	H	40

Chart 7

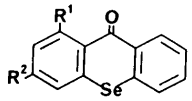
TABLE VI. Physical Properties and Spectral Data of Diselenides (**15**)



Compd. No.	Formula (MS m/z, M^+)	mp (°C) (Recrystal. solv.)	Analysis (%) Calcd (Found) C	H	N	UV λ_{max}^{EtOH} (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	^{1}H-NMR ($CDCl_3$)[a] δ
15a	$C_{24}H_{32}N_2O_4Se_2$ (570)	111—112 (Ether)	50.53 (50.59)	5.65 (5.62)	4.91 (4.98)	250 (s) (3.91), 295 (3.41)	ν_{CO} 1615	1.00 (t, 6H, J=7.0), 1.26 (t, 6H, J=7.0), 3.10 (q, 4H, J=7.0), 3.50 (q, 4H, J=7.0), 3.79 (s, 6H), 6.66—7.43 (m, 6H)
15b	$C_{24}H_{32}N_2O_4Se_2$ (570)	95—96 (Ether)	50.53 (50.50)	5.65 (5.69)	4.91 (4.91)	292 (3.64)	ν_{CO} 1610	1.18 (t, 12H, J=7.3), 3.40 (q, 8H, J=7.3), 6.72 (dd, 2H, J=2.4, 8.3), 7.13 (d, 2H, J=8.3), 7.36 (d, 2H, J=2.4)
15c	$C_{22}H_{28}N_2O_2Se_2$ (510)	89—90 (Ether)	51.77 (51.79)	5.53 (5.54)	5.49 (5.50)	256 (s) (3.93)	ν_{CO} 1610	1.10 (t, 12H, J=7.3), 3.33 (q, 8H, J=7.3), 7.08—7.83 (m, 8H)

a) Listed as chemical shifts (multiplicity, number of protons, coupling constant in Hz).

TABLE VII. Physical Properties and Spectral Data of Selenoxanthen-9-ones (**8**)



Compd. No.	Formula (MS m/z, M^+)	mp (°C) (Recrystal. solv.)	Analysis (%) Calcd (Found) C	H	UV λ_{max}^{EtOH} (log ε)	IR $\nu_{cm^{-1}}^{KBr}$	^{1}H-NMR ($CDCl_3$)[a] δ
8a	$C_{14}H_{10}O_2Se$ (290)	113—114 (EtOH/*n*-hexane)	58.15 (57.88)	3.49 (3.57)	255 (4.47), 309 (3.98), 388 (3.77)	ν_{CO} 1640	3.98 (s, 3H), 6.87—7.56 (m, 6H), 8.30—8.40 (m, 1H)
8b	$C_{14}H_{10}O_2Se$ (290)	125—126 (EtOH/*n*-hexane)	58.15 (58.24)	3.49 (3.63)	254 (s) (4.12), 263 (4.16), 270 (4.16), 277 (4.16), 287 (s) (3.98), 312 (3.60), 376 (3.47)	ν_{CO} 1620	3.90 (s, 3H), 6.93—7.57 (m, 5H), 8.53—8.63 (m, 2H)
8e	$C_{13}H_8OSe$ (260)	182—185[b] (EtOH/*n*-hexane)	60.25 (59.81)	3.11 (3.35)	260 (4.18), 277 (s) (4.08), 288 (s) (3.79), 316 (s) (3.37), 384 (3.45)	ν_{CO} 1635	7.41—7.61 (m, 6H), 8.58—8.68 (m, 2H)

a) Listed as chemical shifts (multiplicity, number of protons). b) Lit.[13a] mp 191—192 °C.

In conclusion, we have demonstrated the utility of the directed lithiation reaction of tertiary benzamides for the regioselective synthesis of various thiosalicylamides and selenosalicylamides. The coupling reaction of *S*-lithiated thiosalicylamide or *Se*-lithiated selenosalicylamide with benzynes derived from the corresponding halobenzenes has been shown to be an effective, convenient and regioselective method for the syntheses of thioxanthen-9-ones and selenoxanthen-9-ones, respectively.

Experimental

All melting points are uncorrected. The IR spectra were determined on a JASCO 810 spectrophotometer, ultraviolet (UV) spectra on a Hitachi 323 spectrophotometer, ^{1}H-NMR spectra on JEOL 90Q, JEOL JNM-PMX 60 and Hitachi R-600 spectrometer using tetramethylsilane as an internal standard. The MS were determined on a JEOL JMX-DX 303 mass spectrometer. Elemental analyses were performed at the microanalytical laboratory of the Center for Instrumental Analysis in Nagasaki University. All solvents used for lithiation reactions were freshly distilled from sodium benzophenone ketyl before use. Chromatography was carried out by flash chromatography on a column of Kieselgel 60 (230—400 mesh).

Typical Procedure for the Synthesis of *N,N*-Diethylthiosalicylamides (10) The following procedure for the synthesis of thiosalicylamide **10a** is representative.

***N,N*-Diethyl-6-methoxythiosalicylamide (10a)** A solution of *sec*-BuLi (1.00 M in cyclohexane, 17.85 ml, 17.85 mmol) was injected into a stirred solution of *N,N*-diethyl *o*-anisamide (**9a**; 3 g, 15 mmol) and TMEDA (2.85 ml, 17.85 mmol) in THF (50 ml) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1 h, powdered sulfur was added, and then the dry ice-acetone bath was removed. After being stirred for a further 12 h, the reaction mixture was treated with saturated ammonium chloride solution, acidified with 10% HCl, and then evaporated. The residue was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to dryness to give crude **10a** as a viscous oil which was chromatographed over silica gel using $CHCl_3$ as an eluent to give pure **10a** (2.6 g, 74%) (see Tables I and II).

***N,N*-Diethyl-2-trimethylsilyl-3-methoxybenzamide (9d)** A solution of *sec*-BuLi (1.00 M in cyclohexane, 52.17 ml, 52.17 mmol) was injected into a stirred solution of *N,N*-diethyl *m*-anisamide (**9c**; 9 g, 43.48 mmol) and TMEDA (9.85 ml, 65.22 mmol) in THF (200 ml) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1 h, a solution of TMSCl (5.67 g, 52.17 mmol) in THF (10 ml) was injected, and the dry ice-acetone bath was removed. The reaction mixture was stirred overnight at room temperature, quenched with saturated NaCl solution and evaporated. The residue was acidified with 10% HCl and extracted with ether. The ether layer was separated, dried (Na_2SO_4), and evaporated to dryness to give a crude oil. This oil was distilled to afford **9d** (7.89 g, 65%), bp 130—133 °C/0.4 mmHg (see Tables I and II).

***N,N*-Diethyl-5-methoxythiosalicylamide (10b)** A solution of *sec*-BuLi (1.00 M in cyclohexane, 4.73 ml, 4.73 mmol) was injected into a stirred solution of **9d** (1.2 g, 4.30 mmol) and TMEDA (0.89 ml, 5.59 mmol) in THF (150 ml) at −78 °C under nitrogen, and stirring was continued for 1 h. Powdered sulfur was added and then the dry ice-acetone bath was removed. The reaction mixture was stirred overnight at room temperature. Standard work-up in a similar manner to that described for **10a** gave **10e** (0.96 g, 72%) after chromatographic purification. A solution of **10e** (2.0 g, 6.43 mmol) and cesium fluoride (1.17 g, 7.72 mmol) in DMF and water (10 : 1, 50 ml) was refluxed for 15 h. DMF and water were removed under reduced pressure to give the residue, which was extracted with $CHCl_3$. The

organic layer was washed with water and dried (Na_2SO_4). The $CHCl_3$ layer was evaporated to give a crude oil which was purified by chromatography to afford pure **10b** (1.2 g, 78%) (see Tables I and II).

Typical Procedure for Thioxanthen-9-ones (7) The following procedure for synthesis of thioxanthen-9-one (**7a**) is representative.

Thioxanthen-9-one (7a) A solution of methyl thiosalicylate (**12**; 3.0 g, 17.85 mmol) in THF (30 ml) was added to a solution of LCI (64.2 mmol; prepared from a 1.25 M solution of *n*-BuLi in hexane, 51.36 ml, 64.20 mmol, and *N*-isopropylcyclohexylamine, 12.39 ml, 64.20 mmol) in THF (50 ml) at −78 °C under nitrogen. The solution was stirred at −78 °C for 1 h, then the cold bath was removed and the reaction mixture was allowed to warm to −20 °C over 10 min. A THF solution (20 ml) of bromobenzene (**13a**; 5.61 g, 35.70 mmol) was injected into the solution. The reaction mixture was stirred overnight at room temperature, quenched with saturated ammonium chloride solution and 10% HCl, and evaporated. The residue was extracted with $CHCl_3$. The extract was dried. (Na_2SO_4) and evaporated to give a residue. This residue was chromatographed ($CHCl_3$ eluent) and the product was recrystallized ($CHCl_3$/*n*-hexane) to give pure **7a** as orange needles (3.71 g, 98%), mp 213 °C (lit.[8b] mp 209 °C) (see Table V).

Typical Procedure for the Synthesis of Diselenides (15) The following procedure for the preparation of diselenide (**15c**) is representative.

Diselenide (15c) Powdered selenium (1.16 g, 14.68 mmol) was added to a stirred THF solution of the lithiated *N,N*-diethylbenzamide (**9e**; 1.3 g, 7.39 mmol), prepared under standard conditions as described for **10a**, and the mixture was stirred overnight at room temperature, quenched with saturated ammonium chloride solution and 10% HCl, and evaporated. The residue was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give a crude oil which was purified by chromatography ($CHCl_3$ eluent) and crystallized (ether) to give pure **15c** (1.2 g, 31%), mp 89—90 °C (see Table VI).

Typical Procedure for the Synthesis of Selenoxanthen-9-ones (8) The following procedure for synthesis of selenoxanthen-9-one (**8c**) is representative.

Selenoxanthen-9-one (8c) A solution of diselenide (**15c**; 1.18 g, 4.61 mmol) in THF (30 ml) was added to a solution of LCI (16.59 mmol) in THF (50 ml) at −78 °C under nitrogen. The mixture was stirred at −78 °C for 1 h and then the cold bath was removed. The reaction mixture was allowed to warm to −20 °C over 10 min. A THF solution (20 ml) of bromobenzene (**13a**; 1.45 g, 9.22 mmol) was then injected into the solution. The reaction mixture was stirred overnight at room temperature, quenched with saturated ammonium chloride solution and evaporated. The residue was extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed (benzene eluent) and the product was recrystallized (EtOH/*n*-hexane) to give **8c** (0.48 g, 40%), mp 182—185 °C (lit.[13a] mp 191—192 °C) (see Table VII).

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