Bromination of Sydnones. III [1]. Bromination of 3-(2-Substituted-phenyl)sydnones and Subsequent Side Chain Modification

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Bromination of the sydnone ring of several *ortho*-substituted *N*-arylsydnones is reported. Subsequent side-chain modification generally can be achieved without concomitant removal of the 4-bromo protective group.

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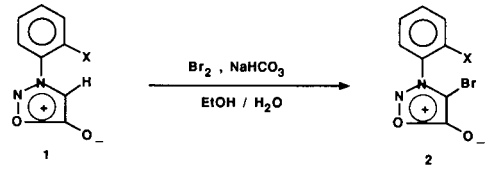
Sydnones (*cf.* **1**, R = alkyl, aryl, R^1 = H) readily undergo electrophilic aromatic substitution at the 4-position [2]. Recently, we have employed this reactivity for the bromination of 3-arylsydnones (**1**, R = aryl) bearing electron-donating groups on the aryl ring, with a view to probing the parameters affecting selective aryl ring substitution [1,3]. This, coupled with our findings that debromination can be effected smoothly, under mild conditions, with sodium borohydride [4], sodium dithionite [5] or sodium sulfite [6], led to consideration of the bromine atom as a protective functionality for the sydnone ring. Accordingly, the present study was undertaken to explore both the variety of *o*-substituted arylsydnones which could be brominated directly and the transformations possible in the presence of the 4-bromo moiety.

A series of 3-(2-substituted)phenyl sydnones **1a-k** was prepared, wherein the substituents were mainly electron-withdrawing and, in several cases, potentially susceptible to reaction with bromine (Table 1).

Direct bromination (bromine, sodium bicarbonate, ethanol-water [11]) of these species **1a-k** gave the corresponding 4-bromo compounds **2a-k** in fair to excellent yield (Table 2). The outcome of the reaction was apparently unaffected by the nature of the *ortho* substituent and in all cases (except **2f**) the derived bromo compounds were quite stable at room temperature [12]. The identities of the 4-bromo sydnones were established *via* satisfactory elemental analyses (except for **2f**) and the absence of both sydnone C-H stretch absorption in the infrared spectra (approximately 3120 cm^{-1} in the parent compounds) and sydnone ring proton absorption in the nuclear magnetic resonance spectra (approximately δ 6.5-6.9 in the parent compounds).



1 2

Table 1 Preparation of 3-Arylsydnones 1

Product 1	X	Starting Material	Route	Reference
a	CH_2OH	**1e**	sodium borohydride / t-butanol	[7]
b	CN	anthranilonitrile	a) bromoacetic acid b) nitrous acid c) trifluoroacetic anhydride	[7]
c	CH_2Cl	**1a**	mesyl chloride / triethylamine	[8]
d	CO_2H	anthranilic acid	a) chloroacetic acid b) nitrous acid c) trifluoroacetic anhydride	[9]
e	CO_2CH_3	methyl anthranilate	a) bromoacetic acid b) nitrous acid c) trifluoroacetic anhydride	[10]
f	CHO	**1a**	pyridinium dichromate	[7]
g	$CH(OH)CH_3$	**1f**	methyl magnesium bromide	—
h	$COCH_3$	o-aminoacetophenone	a) bromoacetic acid b) nitrous acid c) trifluoroacetic anhydride	[7]
i	$CONHCH_3$	**1e**	methylamine	—
j	CH_2N_3	**1c**	sodium azide / dimethyl sulfoxide	—
k	N_3	**2k**	sodium sulfite	[6]

Table 2 4-Bromo-3-Arylsydnones 2 by Direct Bromination of 1

2	Yield %	Mp °C	IR ν cm^{-1} (potassium bromide)	NMR δ [14]	Formula	Analysis % Calcd. / Found C	H	N
a	81	114-116	3450, 3060, 2950, 1765, 1738, 1440, 1220, 1025, 768	7.50 (m, 4H), 5.72 (s, 1H), 4.52 (s, 2H)	$C_9H_7BrN_2O_3$	39.85 39.91	2.58 2.45	10.33 9.98
b	79	122-124	3095, 2250, 1670, 1632, 1430, 1210, 1041, 785	7.85 (m)	$C_9H_4BrN_3O_2$	40.60 40.97	1.50 1.45	15.79 16.04
c	78	116-117	3036, 2965, 1764, 1725, 1205, 1027, 776	7.67 (m, 4H), 4.53 (s, 2H)	$C_9H_6BrClN_2O_2$	37.31 37.38	2.07 2.05	9.67 9.71
d	76	120-122	3300-2650, 1715 (brd), 1400, 1255, 1225, 1040, 765	7.90 (m) [CO_2H not observed]	$C_9H_5BrN_2O_4$	37.89 38.29	1.75 1.80	9.82 9.75
e	87	131-132	2950, 1775, 1720, 1295, 1028, 774	7.66 (m, 4H), 3.83 (s, 3H)	$C_{10}H_7BrN_2O_4$	40.13 40.26	2.34 2.43	9.36 9.16
f	30	105-106	2990, 2910, 1773, 1715, 1687, 1203, 1025, 785	9.90 (s, 1H), 7.98 (m, 4H)	$C_9H_5BrN_2O_3$	—		
g	41	132-134	3410, 2970, 1735, 1432, 1205, 1025, 770, 615	7.82, 7.48 (m, 4H), 5.26 (brd. s, 1H), 4.70 (q, 1H), 1.37 (d, 3H)	$C_{10}H_9BrN_2O_3$	42.11 42.40	3.16 3.01	9.82 9.58
h	76	114-116	1761, 1718, 1692, 1216, 1026, 777	8.03 (m, 4H), 2.60 (s, 3H)	$C_{10}H_7BrN_2O_3$	42.40 42.64	2.47 2.57	9.89 9.89
i	78	150-152	3341, 3069, 1771, 1737, 1542, 1201, 1025, 765	8.75 (brd. s, 1H), 7.86 (s, 4H), 2.70 (d, 3H)	$C_{10}H_8BrN_3O_3$	40.27 40.22	2.68 2.67	14.09 13.95
j	29	59-60	3060, 2930, 2855, 2105, 1760, 1495, 1210, 1025, 770	7.61 (m, 4H), 4.42 (s, 2H)	$C_9H_6BrN_5O_2$	36.49 36.24	2.03 1.84	23.65 23.50
k	44	134-136	3040, 2138, 2110, 1774, 1505, 1305, 1212, 1028, 774	7.33 (m)	$C_8H_4BrN_5O_2$	34.04 34.36	1.42 1.61	24.82 24.39

The bromoaldehyde **2f** could be isolated as a colourless, crystalline solid with a sharp melting point and satisfactory infrared and nmr spectra, however, rapid degradation was apparent and satisfactory microanalytical results were not obtained. The identity of **2f** is reasonably secure, however, on account of its spectra and the fact that a compound of identical melting point and R_f (thin layer chromatography) could be obtained by oxidation of the bromoalcohol **2a** (*vide infra*). Aldehydes are often subject to air oxidation and it is likely that this is the case with **2f**; however, no attempt was made to identify the products arising from its decomposition.

With various 4-bromosydnones in hand, the next step was to explore interconversions of these compounds *via* side-chain modification in the presence of the 4-bromo moiety. The transformations examined are shown in Table 3. It can be seen that the 4-bromo functionality remains intact through oxidation (entries 1 and 2), nucleophilic substitution (entries 4 and 5) and reaction with electrophiles (entries 3 and 7) but is susceptible to removal with sodium borohydride (entry 6). This surprising, latter result was the stimulus for our examination of the generality in sydnones of bromine removal by sodium borohydride [4].

Thus, oxidation of a primary or secondary alcohol to the corresponding aldehyde or ketone, respectively, [entries 1 & 2] could be performed in the presence of the 4-bromo substituent using pyridinium dichromate in dichloromethane at room temperature. The *o*-acetyl product **2h** was identical in all respects to an authentic sample prepared by direct bromination. While, as alluded to previously, the *o*-formylsydnone **2f** could not be fully characterized on account of its instability, the sample obtained was identical (infrared, melting point, thin layer chromatography) to that from direct bromination.

Displacement reactions were also successful in the presence of the bromine moiety. Thus, 4-bromo-3-(2-azidomethylphenyl)sydnone **2j** could be prepared from 4-bromo-3-(2-chloromethylphenyl)sydnone **2c** by nucleophilic displacement with azide ion in dimethylsulfoxide at about 40° (entry 4). Similarly, conversion of 4-bromo-3-(2-carbomethoxyphenyl)sydnone **2e** to the corresponding *N*-methylcarboxamide **2i** could be effected using methylamine in methanol in a pressure vessel at 60° (entry 5). Both products were identical to the products obtained by direct bromination of the appropriate non-brominated sydnones **1j** and **1i**. It was gratifying that no debromination occurred under these conditions since it has been shown previously that 4-bromosydnones can be converted to their debrominated congeners by the action of nucleophiles [4 and *loc. cit.*].

Successful side chain modification was also apparent using electrophilic conditions. Thus, the 4-bromo hydroxymethyl sydnone **2a** was converted to the known [*vide infra*] 4-bromo chloromethyl sydnone **2c** using para tolenesulfonyl chloride/triethylamine and the known [*vide infra*] 4-bromo azido sydnone **2k** could be prepared from 4-bromo-3-(2-aminophenyl)sydnone **2** (X = NH_2) by a diazotization/azidation process.

Overall, we have shown that the bromine atom is a valuable protective moiety for the sydnone ring since it can be added readily, removed under mild conditions and remains intact under a variety of reaction conditions.

EXPERIMENTAL

Preparation of 3-Arylsydnones **1**.

Table 3 Side Chain Modification of 4-Bromo-3-(2-Substituted Phenyl)sydnones 2

Product	Starting Material	Yield %	Route	Reference	Entry #
2f	**2a**	20	pyridinium dichromate	[7]	1
2h	**2g**	50	pyridinium dichromate	[7]	2
2c	**2a**	61	tosyl chloride / triethylamine	[8]	3
2j	**2c**	66	sodium azide / dimethyl sulfoxide	—	4
2i	**2e**	47	methylamine	—	5
2a, 1a, 1e	**2e**	—	sodium borohydride / t-butanol	[7]	6
2k	**2** (X = NH_2)	75	1. nitrous acid 2. sodium azide	[10]	7

3-(2-(1-Hydroxyethyl)phenyl)sydnone **1g**.

To the aldehyde (2.80 g, 14.70 mmoles) in dry tetrahydrofuran (47 ml) at 0° was added methyl magnesium bromide (9.97 ml, 24.92 mmoles, 3.1 *M*) dropwise under nitrogen. After one hour, a solution of ammonium chloride (1.34 g, 24.92 mmoles) in water (60 ml) was added and the mixture was extracted with dichloromethane (3 x 100 ml). The organic layers were separated, combined, dried (drierite), filtered and evaporated *in vacuo* to yield a dark oil. Column chromatography (silica gel) using gradation elution (dichloromethane to dichloromethane/methanol 30:1) followed by recrystallization from dichloromethane/petroleum ether gave **1g** (1.60 g, 53%) as an off-white solid, mp 94-96°, lit [4] mp 94-96°; ir: 3440 (OH str), 3105 (sydnone CH str), 1740, 1725 (sydnone C=O str) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (d, 3H), 3.22 (s, 1H), 4.85 (q, 1H), 6.62 (s, 1H), 7.57 (m, 4H).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.85; N, 13.59. Found: C, 58.51; H, 4.55; N, 13.82.

3-(2-(*N*-Methylcarboxamido)phenyl)sydnone **1i**.

To methanol (20 ml) and methylamine (10 ml, 4.0 g, 12.9 mmoles, 40% aqueous solution) was added 3-(2-carbomethoxyphenyl)sydnone **1e** (0.31 g, 1.41 mmoles) and the mixture was heated at 60° in a sealed vessel. After one hour, the solvent was removed under a stream of air and the resultant solid was recrystallized from methanol to afford **1i** (0.13 g, 44%) as colourless needles, mp 192.4°, lit [4] mp 190-191°; ir: 3341 (NH str), 3131 (sydnone CH str), 1744 (sydnone C=O str), 1650 (amide C=O str) cm^{-1}; ^1H nmr (deuteriochloroform/deuteriodimethyl sulfoxide 1:2): δ 2.76 (d, 3H), 7.20 (s, 1H), 7.72 (s, 4H), 8.55 (s, 1H).

Anal. Calcd. for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.11; N, 19.18. Found: C, 54.61; H, 4.23; N, 19.52.

3-(2-Azidomethylphenyl)sydnone **1j**.

To a warm, stirred solution of sodium azide (0.23 g, 3.54 mmoles) in dimethyl sulfoxide (8 ml) was added 3-(2-chloromethylphenyl)sydnone **1c** (0.45 g, 2.14 mmoles) slowly. After brief warming on the steam bath, the mixture was poured into water (15 ml). The precipitated solid was removed by filtration, dried and recrystallized from ethanol to afford **1j** (0.36 g, 78%) as colourless needles, mp 86-87°; ir: 3115 (sydnone CH str), 2105 (azide str), 1764 (sydnone C=O str) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (s, 2H); 6.65 (s, 1H); 7.65 (m, 4H).

Anal. Calcd. for $C_9H_7N_5O_2$: C, 49.77; H, 3.23; N, 32.26. Found: C, 49.86; H, 3.21; N, 32.20.

General Synthesis of Brominated Sydnones **2a-k**:

To the sydnone (1 mmole) in ethanol (14 ml) was added sodium bicarbonate (3 mmoles) in water (8 ml). With stirring, a solution of bromine (3 mmoles) in ethanol (8 ml) was added dropwise over 5 minutes. Removal of the ethanol under a stream of air (or nitrogen) gave the product as a crystalline solid which was removed by filtration, dried and recrystallized from dichloromethane/-petroleum ether.

Preparation of 4-Bromo-3-(2-formylphenyl)sydnone **2f** by Oxidation of **2a**.

To the alcohol **2a** (0.40 g, 1.48 mmoles) of dichloromethane (30 ml) was added pyridinium dichromate (0.84 g, 2.24 mmoles) with stirring at room temperature. After 18 hours, the insoluble material was removed by filtration and the filtrate was evaporated *in vacuo* at room temperature. The residue was redissolved in dichloromethane (2 ml) and subjected to rapid column chromatography on silica using dichloromethane as eluant. Evaporation of the solvent and trituration with ether afforded **2f** as an off-white powder (0.08 g, 20%) identical (mp, infrared) to an authentic sample.

Preparation of 4-Bromo-3-(2-acetylphenyl)sydnone **2h** by Oxidation of **2g**.

The title compound **2h**, identical (mp infrared) to an authentic sample, was prepared in 50% yield by pyridinium dichromate oxidation of **2g** using the method employed for **2f**.

Preparation of 4-Bromo-3-(2-chloromethylphenyl)sydnone **2c** by Reaction of **2a** with Tosyl Chloride.

To the alcohol **2a** (0.20 g, 0.74 mmoles) in dichloromethane (4 ml) and triethylamine (0.20 g, 1.98 mmoles) was added *para*-toluenesulfonyl chloride (0.20 g, 1.05 mmoles). After stirring overnight the mixture was washed successively with hydrochloric acid (10%, 2 x 5 ml), water (10 ml), aqueous sodium carbonate (5%, 2 x 5 ml), water (5 ml) and saturated aqueous sodium chloride (10 ml). The organic layer was separated, dried (sodium sulfate) and evaporated *in vacuo* to yield an oil which crystallized on standing. Recrystallization from dichloromethane/petroleum ether afforded **2c** as off-white needles (0.13 g, 61%) identical (mp, infrared) to an authentic sample.

Preparation of 4-Bromo-3-(2-azidomethylphenyl)sydnone **2j** by Reaction of **2c** with Sodium Azide.

The product **2j**, identical (mp infrared) to an authentic sample, was prepared in 66% yield from **2c** using the method employed for the non-brominated analogue **1j**.

Preparation of 4-Bromo-3-(2-(*N*-methylcarboxamido)phenyl)sydnone **2i** from **2e** and Methylamine.

To methanol (10 ml) and methylamine (40% aqueous, 5 ml) was added the 4-bromosydnone ester **2i** (0.15 g, 0.51 mmoles) and the mixture was heated at 60° in a sealed vessel. After 3 hours, the solvent was removed under a stream of air and the resultant solid was recrystallized from methanol to afford **2i** (0.07 g, 47%) as pale tan needles identical (mp, infrared) to an authentic sample.

Attempted Reduction of 4-Bromo-3-(2-carbomethoxyphenyl)sydnone **2e** with Sodium Borohydride.

To a refluxing solution of the bromo sydnone ester **2e** (0.15 g, 0.50 mmoles) and sodium borohydride (0.048 g, 1.25 mmoles) in *t*-butyl alcohol (2 ml) was added methanol (0.4 ml) dropwise over one hour. After one hour more, the mixture was allowed to cool and water (2.5 ml) was added. The solvent was reduced to half volume under a stream of air and the mixture was extracted with dichloromethane (2 x 8 ml). The combined extracts were dried (magnesium sulfate) and evaporated *in vacuo* to yield a dark oil which contained, *inter alia*, starting material, the bromo alcohol **2a** and the debrominated alcohol **1a** (tlc evidence).

Preparation of 4-Bromo-3-(2-azidophenyl)sydnone **2k** by Diazotization/Azidation of 4-Bromo-3-(2-aminophenyl)sydnone **2** (X = NH_2).

To a suspension of 4-bromo-3-(2-aminophenyl)sydnone (0.50 g, 1.95 mmoles) in water (2.5 ml) at 0° was added concentrated hydrochloric acid (0.75 ml) dropwise with stirring. To this mixture was added sodium nitrite (0.22 g, 3.14 mmoles) in water (0.75 ml), followed, after 30 minutes, by sodium azide (0.21 g, 3.23

mmoles) in water (0.5 ml). After a further 30 minutes, the resultant solid was removed by filtration, washed with water (2 x 10 ml), dried and recrystallized from dichloromethane/petroleum ether to yield **2j** (0.40 g, 75%) as colourless needles, mp 133-135°; ir: 2135, 2105 (azide str), 1773 (sydnone C=O str) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.40 (m).

Anal. Calcd. for $C_8H_4BrN_5O_2$: C, 34.04; H, 1.42; N, 24.82. Found: C, 34.36; H, 1.61; N, 24.49.

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[12] It is our experience that the majority of 3-(2-substituted aryl)sydnones decompose over a period of days to weeks unles stored in the refrigerator. This instability has been noted previously [13].

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[14] Samples **2b,c,e,f,j,k** were run in deuteriochloroform and samples **2a,d,g,h,i** were run in deuteriochloroform/deuteriodimethyl sulfoxide.