Bromination of Sydnones. I. Reaction with 3-Arylsydnones Containing Electron-Donors on the Aryl Ring

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Bromination has been examined for a series of 3-arylsydnones (**1**) with electron donors (dimethyl to dimethoxy) on the aryl ring. In no example was exclusive aryl ring bromination observed, however, exclusive sydnone ring bromination could be realized in every case. For two dimethoxyphenyl examples both aryl and sydnone ring bromination occurred.

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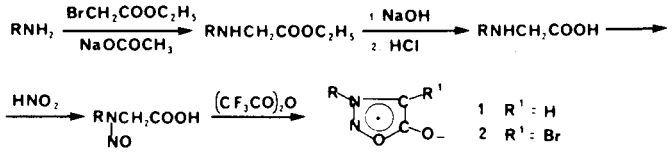
Sydnones (*cf.* **1**) undergo electrophilic aromatic substitution reactions with an ease apparently similar to that of furan [1]. Bromination occurs, with various brominating mixtures and with a large variety of 3-alkyl or aryl substituents, exclusively at the sydnone 4-position (when R^1 = H). In the case of 3-arylsydnones, where one could conceive of a competition between bromination on the aryl or sydnone rings, the exclusivity of sydnone ring bromination is attributable to the deactivation of the aryl substituent by the electron-withdrawing sydnone (a partial positive charge resides on the sydnone 3-position) [2]. It is surprising that the parameters affecting concomitant or exclusive bromination on the aryl ring (**1**, R = aryl) are unknown although competition has been observed on nitration of some aryl sydnones unsubstituted at the 4-position [3].

Our present interest in sydnone bromination stems from a desire to prepare 4-bromo-3-(2-aminophenyl)sydnone (**2**, R = 2-$NH_2C_6H_4$) and our observation that bromination of 3-(2-aminophenyl)sydnone (**1**, R = 2-$NH_2C_6H_4$) does not provide this compound but products derived from sydnone and aryl ring bromination and exclusive aryl ring bromination (dependent on reaction conditions) [4]. Accordingly, in order to probe the parameters affecting the site of bromination, we have undertaken the synthesis of a series of 3-aryl sydnones with electron donors on the aryl ring and subjected these to bromination under standard conditions.

The compounds chosen for study were all six of the possible 3-(dimethylphenyl)sydnones **1a-f**, three of which are known compounds (*viz.* 2,4-, 3,4- and 2,5-) [5], 3-(2,4,6-trimethylphenyl)sydnone **1g**, 3-(2-methyl-4-methoxyphenyl)-sydnone **1h**, and the 3-(2,4-, 3,4- and 3,5-dimethoxyphenyl)sydnones **1i-k** (Table 1).

All of the required sydnones were prepared from the appropriately substituted anilines by treatment with ethyl bromoacetate [5], hydrolysis to the *N*-arylglycine [5], nitrosation [5] and cyclization with trifluoroacetic anhydride [6] (Scheme 1). The glycine esters were not isolated or purified but were directly hydrolyzed to the corresponding glycines. Similarly, no attempt was made to purify any of the intermediate glycines or *N*-nitrosoglycines. While yields were not optimized, satisfactory quantities of pure sydnones could be obtained.

Scheme 1



a) R = 2,4-$Me_2C_6H_3$ b) R = 3,4-$Me_2C_6H_3$ c) R = 2,5-$Me_2C_6H_3$ d) R = 2,3-$Me_2C_6H_3$
e) R = 2,6-$Me_2C_6H_3$ f) R = 3,5-$Me_2C_6H_3$ g) R = 2,4,6-$Me_3C_6H_2$
h) R = 2-Me-4-$MeOC_6H_3$ i) R = 2,4-$(MeO)_2C_6H_3$ j) R = 3,4-$(MeO)_2C_6H_3$
k) R = 3,5-$(MeO)_2C_6H_3$

Bromination of the sydnones was effected by treatment with four equivalents of bromine in the presence of sodium bicarbonate [7]. For all of the studied sydnones, except the dimethoxy examples, bromination under these conditions gave the 4-bromo products **2a-h**. The corresponding 4-bromo compounds **2i-k** could also be prepared from the dimethoxyphenyl sydnones **1i-k** by treatment with 1.1 equivalents of bromine (Table 2). The identities of the 4-bromo sydnones were established *via* satisfactory elemental analyses 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 6.3-6.9 in the parent compounds).

For the dimethoxyphenyl sydnones, treatment with four equivalents of bromine gave different results. Thus, the 2,4- and 3,5-dimethoxyphenylsydnones **1i,k** gave dibromosydnones **3** and **4**, respectively. In contrast, the 3,4-dimethoxyphenyl analogue **1j** afforded **2j** in 60% yield, identical to the product formed with one equivalent of bromine. No other products could be isolated from the reaction mixture although thin layer chromatography indicated their presence.

Table 1

Non-brominated Sydnones **1**

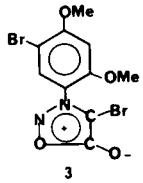
1		Mp °C	IR ν cm^{-1} (Potassium Bromide)	NMR δ [10]	Formula	Analysis % Calcd./Found C	H	N
a		[5]						
b		[5]						
c		[5]						
d	[8]	143-145	3106, 2910, 1740, 1452, 1180, 785	7.32 (m, 3H), 6.46 (s, 1H), 2.43 (s, 3H), 2.18 (s, 3H)	$C_{10}H_{10}N_2O_2$	63.16 63.29	5.26 5.45	14.74 14.51
e	[8]	130-132	3111, 2908, 1735, 1445, 1166, 928, 780	7.32 (m, 3H), 6.40 (s, 1H), 2.23 (s, 6H)	$C_{10}H_{10}N_2O_2$	63.16 62.96	5.26 5.08	14.74 14.43
f	[8]	135-137	3125, 3030, 2900, 1474, 1089, 773	7.35 (s, 3H), 6.75 (s, 1H), 2.47 (s, 6H)	$C_{10}H_{10}N_2O_2$	63.16 62.88	5.26 5.17	14.74 14.50
g	[8]	152-154	3102, 2902, 1720, 1450, 1083, 835, 740	7.06 (s, 2H), 6.36 (s, 1H), 2.39 (s, 3H), 2.17 (s, 6H)	$C_{11}H_{12}N_2O_2$	64.71 64.44	5.88 5.76	13.73 13.60
h	[8]	135-137	3100, 2957, 1748, 1445, 1080, 843, 798	7.40 (d, 1H), 6.90 (m, 2H), 6.47 (s, 1H), 3.90 (s, 3H), 2.33 (s, 3H)	$C_{10}H_{10}N_2O_3$	58.25 57.94	4.85 4.71	13.59 13.88
i	[9]	162-163	3163, 3075, 2952, 1775, 1744, 1455, 1015, 832	7.58 (d, 1H, J = 10 Hz), 6.69 (m, 3H), 3.93 (s, 6H)	$C_{10}H_{10}N_2O_4$	54.05 53.87	4.50 4.45	12.61 12.84
j	[9]	159-161	3101, 2907, 1735, 1448, 1011, 815, 720	7.10 (m, 3H), 6.75 (s, 1H) 3.97 (s, 6H)	$C_{10}H_{10}N_2O_4$	54.05 53.76	4.50 4.39	12.61 12.40
k	[9]	161-163	3121, 3100, 2957, 1743, 1503, 1061, 787	7.61 (s, 1H),7.04 (d, 2H), 6.72 (t, 1H), 3.82 (s, 6H)	$C_{10}H_{10}N_2O_4$	54.05 54.25	4.50 4.54	12.61 12.37

Table 2

Brominated Sydnones

1	Yield % [8]	Mp °C	IR ν cm^{-1} (Potassium Bromide)	NMR δ [10]	Formula	Analysis % Calcd./Found C	H	N
a	78	139-141	3020, 2940, 1750, 1435, 1196, 700	7.27 (s, 3H), 2.47 (s, 3H), 2.21 (s, 3H)	$C_{10}H_9BrN_2O_2$	44.61 44.70	3.35 3.33	10.41 10.24
b	73	138-139	3040, 2970, 1750, 1440, 1200, 702	7.40 (s, 3H), 2.37 (s, 6H)	$C_{10}H_9BrN_2O_2$	44.61 44.32	3.35 3.28	10.41 10.31
c	96	116-117	3032, 2905, 1770, 1445, 1206, 830	7.27 (m, 3H), 2.45 (s, 3H), 2.25 (s, 3H)	$C_{10}H_9BrN_2O_2$	44.61 44.38	3.35 3.26	10.41 10.12
d	75	144-146	3062, 2910, 1762, 1426, 1205, 783	7.30 (m, 3H), 2.12 (s, 3H), 2.44 (s, 3H)	$C_{10}H_9BrN_2O_2$	44.61 44.85	3.35 3.29	10.41 10.29
e	75	158-160	3070, 2905, 1752, 1440, 1207, 788	7.32 (m, 3H), 2.18 (s, 6H),	$C_{10}H_9BrN_2O_2$	44.61 44.36	3.35 3.24	10.41 10.53
f	71	116-118	3017, 2910, 1755, 1205, 856, 782	7.33 (m, 3H), 2.50 (s, 6H),	$C_{10}H_9BrN_2O_2$	44.61 44.33	3.35 3.41	10.41 10.28
g	92	121-122	2903, 1740, 1436, 1208, 851, 710	7.13 (s, 2H), 2.43 (s, 3H), 2.15 (s, 6H)	$C_{11}H_{11}BrN_2O_2$	46.64 46.36	3.89 3.83	9.89 9.76
h	72	104-106	3040, 2920, 1750, 1440, 1285, 810	7.12 (m, 3H), 3.93 (s, 3H), 2.24 (s, 3H)	$C_{10}H_9BrN_2O_3$	42.11 42.42	3.16 3.05	9.82 9.65
i	79	95-97	3057, 2984, 1762, 1212, 1023, 810	7.30 (d, 1H, J = 10 Hz), 6.64 (m, 2H), 3.90 (s, 3H), 3.86 (s, 3H)	$C_{10}H_9BrN_2O_4$	39.87 39.67	2.99 3.12	9.30 9.42
j	60	154-156	3060, 2965, 1753, 1265, 1019, 810	7.44 (m, 3H), 4.02 (s, 3H) 3.97 (s, 3H)	$C_{10}H_9BrN_2O_4$	39.87 39.96	2.99 3.04	9.30 9.24
k	74	120-121	3093, 2980, 1764, 1462, 1209, 787	6.85 (m, 3H), 3.82 (s, 6H)	$C_{10}H_9BrN_2O_4$	39.87 39.56	2.99 2.81	9.30 9.09
3	91	161-163	3053, 2965, 1777, 1758, 1215, 820	7.53 (s, 1H), 6.67 (s, 1H), 4.02 (s, 3H), 3.94 (s, 3H)	$C_{10}H_8Br_2N_2O_4$	31.58 31.91	2.11 2.11	7.37 7.49
4	74	195-197	3090, 2969, 1765, 1456, 1200, 792	7.18 (dd, 2H), 4.00 (s, 3H), 3.88 (s, 3H)	$C_{10}H_8Br_2N_2O_4$	31.58 31.71	2.11 2.10	7.37 7.55

These results suggest that sydnone ring bromination precedes aryl ring bromination and the latter occurs only if the activating groups enhance the same positions, a situation precluded for the 3,4-dimethoxyphenyl case. Apparently, with excess bromine, tri- or tetrabromination does not occur, even where the two methoxy groups activate all aryl ring positions (as in **1k**). Seemingly, one bromine atom on the aryl ring is sufficiently electron-withdrawing and/or sterically perturbing to inhibit further bromination.



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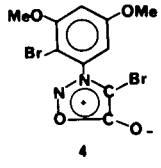

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The dibromo compounds **3** and **4** were identified by elemental analysis, absence of sydnone C-H stretch in the infrared spectra and, principally, from their nuclear magnetic resonance (nmr) spectra. Structure **3** was assigned from the nmr spectrum, *viz.*, two singlets (1H each) at δ 7.53 and δ 6.67 and two singlets (3H each) at δ 4.02 and δ 3.94. Assuming sydnone ring bromination (apparent from the lack of sydnone C-H stretch in the infrared spectrum) subsequent bromination should occur to give **3** or between the methoxy groups. If the latter had occurred the anticipated nmr spectrum would be two doublets in the aromatic region for the two ortho protons. However, the spectrum for the former would be identical to that obtained, with a singlet for the proton shielded by the methoxy groups (δ 6.67) and another for the proton deshielded by the electron-withdrawing sydnone ring (δ 7.53). The preference for structure **3** is undoubtedly due to the greater steric hindrance at the aryl ring 3-position.

Assignment of structure **4** also followed from the nmr spectrum. Again bromination on the sydnone ring was apparent and consequently the additional bromine atom could be in only one of two places on the aryl ring, *viz.* as shown in **4** or between the methoxy groups. In the latter, due to symmetry, one would expect a simple nmr spectrum of two singlets, one for the two aryl protons and one for the two methoxy groups. However, the obtained spectrum displayed a double doublet (δ 7.18, J_{AB} = 2 Hz) in the aromatic region and two singlets for the methoxy groups, exactly as expected for **4** where *meta* coupling (J = 2-3 Hz) would occur between the dissimilar aryl ring protons and the methoxy groups would reside in different environments. That bromination would not occur between the methoxy groups, was at first surprising since the sydnone would seem to be at least as bulky as a methoxy group. However, examination of molecular models suggests that the planar sydnone ring does indeed offer less hindrance to the incoming electrophile.

An interesting sidelight to this study was the unusual deshielding of the sydnone ring proton (δ 7.61) observed in the nmr spectrum of 3-(3,5-dimethoxyphenyl)sydnone **1k**. "Normal" sydnone ring protons (including those of the apparent congeners **1i** and **1j**) appear in the range δ 6.3-6.9. There is little doubt that the peak at δ 7.61 is due to the sydnone ring proton since this absorption disappears on mono- or dibromination and the remaining splitting pattern in the aryl region, *viz.* a doublet (J = 2 Hz, 2H, δ 7.04) and a triplet (J = 2 Hz, 1H, δ 6.72), fits that expected for the three protons on the aryl ring. It is probable that this phenomenon is due to solvent effects since large, solvent induced, shifts in the position of sydnone ring proton absorption have been previously observed [3a].

Overall, we have shown that, surprisingly, aryl attached electron donors, ranging from dimethyl to dimethoxy, are not sufficiently activating to overcome the electron-withdrawing effect (upon the aryl ring) and activated nature of the sydnone ring. Aryl ring bromination did occur in two cases but therein subsequent to sydnone ring bromination and only with the strongest activating groups (*i.e.* methoxy) situated so as to enhance the same aryl ring positions. These results are at variance with previous observations regarding nitration of some sydnones, wherein nitration occurred either on the aryl or sydnone ring depending on structure and reaction conditions [3], and presumably reflect the different media in which the reactions were performed. Under the acidic conditions employed for nitration the polar sydnone ring may be deactivated by proton association, leaving a reasonably activated aryl ring the opportunity to compete effectively for the electrophile. This situation is precluded for bromination under the present conditions. More puzzling are our data regarding bromination of 3-(2-aminophenyl)sydnone (see Introduction) [4]. One would not expect the lone amino group to be more activating than two methoxy groups, yet that is what the results suggest. A possible explanation is that, in the amino case, initial *N*-bromination occurs and subsequent bromination takes place intermolecularly from the *N*-bromo intermediate. A similar pathway is negated for the sydnones examined in the present study.

We plan to extend this study to other electrophiles to assess the generality of the present findings.

EXPERIMENTAL

General Synthesis of Non-Brominated Sydnones **1a-k**.

All of the sydnones used in this study were prepared by a modification of Puranik's method [5].

a) Glycines.

The appropriate aniline (0.05 mole), ethyl bromoacetate (0.05 mole), sodium acetate (0.075 mole) and ethanol (13 ml) were heated at 125° overnight. The mixture was cooled, poured into water and extracted with dichloromethane (2 × 50 ml). The solvent was removed *in vacuo* and the residual oil was heated under reflux with 10% aqueous sodium hydroxide

(0.05 mole) and ethanol (2 ml) for 10 minutes after complete dissolution (usually about 30 minutes). The mixture was cooled, acidified (*p*H 5-6) with concentrated hydrochloric acid and extracted with dichloromethane (2 × 20 ml). The combined organics were dried (drierite) and the solvent removed *in vacuo* to afford heavy oils or solids which were used without further purification.

b) Nitrosation.

The glycines (0.03 mole) were suspended or dissolved in 12% hydrochloric acid (50 ml), the mixture cooled to 0-5° and 10 ml of an aqueous solution of sodium nitrite (0.035 mole) added dropwise with stirring. After 4 hours dichloromethane (50 ml) was added and stirring was continued for a further 30 minutes, whereupon the organic layer was separated. Further extraction with dichloromethane (25 ml), combining the organic layers, drying (drierite) and evaporation *in vacuo* gave oils or solids which were used without further purification.

c) Cyclization.

The *N*-nitrosoglycines were redissolved in dichloromethane (10 ml/g). With stirring at 0°, trifluoroacetic anhydride (1 ml/g) was added over 5 minutes. After 1 hour the mixture was poured into water (10 ml/g) and solid sodium bicarbonate added cautiously, with stirring, to remove glycine contaminants and neutralize trifluoroacetic acid. The dichloromethane layer was separated, dried (drierite) and evaporated *in vacuo* to yield solids which were purified by recrystallization or column chromatography.

General Synthesis of Brominated Sydnones **2a-h**, **3** and **4** Using Excess Bromine.

To the sydnones (1.35 mmoles) in ethanol (12 ml) was added sodium bicarbonate (6.55 mmoles) in water (9 ml). With stirring a solution of bromine (5.5 mmoles) in ethanol (9 ml) was added dropwise over 5 minutes. After a further 30 minutes the mixture was poured into water (40 ml). When complete crystallization had occurred, the solid was removed by filtration, dried and recrystallized from ethanol.

General Synthesis of Brominated Sydnones **2i-k** Using One Equivalent of Bromine.

The general procedure as outlined above was followed with the exception that 1.1 equivalents of bromine were employed. Work-up and subsequent purification of the bromo sydnones were the same as previously described.

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REFERENCES AND NOTES

[1] M. Ohta and H. Kato, in "Nonbenzenoid Aromatics", Vol 1, J. P. Snyder, ed, Academic Press, Inc, New York, NY, 1969, p 146.

[2] C. Tin-Lok, J. Miller and F. Stansfield, *J. Chem. Soc.*, 1213 (1964).

[3] P. M. Weintraub and R. E. Bambury, *Tetrahedron Letters*, 579 (1969); H. J. Tien, T. Nonaka, T. Fuchigami, T. Sekine and M. Ohta, *Nippon Kagaku Kaishi*, 1310 (1978); *Chem. Abstr.*, **90**, 72115 (1979).

[4] S. J. Hodson and K. Turnbull, unpublished results.

[5] B. G. Ugarkar, B. V. Badami, G. S. Puranik and K. G. S. Bhat, *Arch. Pharm. (Weinheim)*, **311**, 109 (1978).

[6] W. Baker, W. D. Ollis and V. D. Poole, *J. Chem. Soc.*, 1542 (1950).

[7] C. V. Greco, M. Pesce and J. M. Franco, *J. Heterocyclic Chem.*, **3**, 391 (1966).

[8] Recrysallization from ethanol.

[9] Column chromatography on silica gel.

[10] All nmr spectra were run in deuteriochloroform except for those for compounds **1k**, **2j-k** and **4** which were run in hexadeuteriodimethyl sulfoxide/deuteriochloroform (2:1) mixtures.