Debromination of 3-Aryl-4-bromosydnones with Sodium Borohydride

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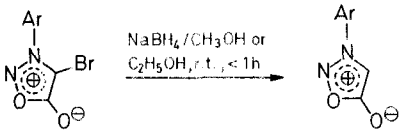
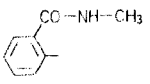
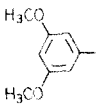
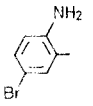
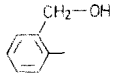
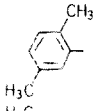
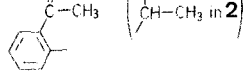
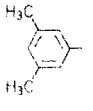
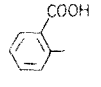
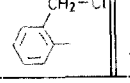
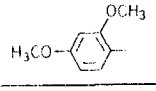
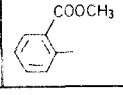
Debromination of 4-bromo-3-(2-substituted aryl) sydnones **1** with sodium borohydride in methanol occurs readily to give good yields of the corresponding parent sydnones **2**, except in those cases where the aryl substituent also reacts. The utility of the process for both sydnone purification and the preparation of novel sydnones has been examined briefly.

Sydnones **2** undergo electrophilic aromatic substitution with an ease apparently similar to that of furan[1]. In this regard, we have recently prepared 4-bromo-3-(2-substituted phenyl)-sydnones **1** with a view to protecting the sydnone 4-position from further reaction while allowing modification of the *o*-aryl substituents[2]. A crucial factor in the use of a bromine atom as a protective group is that it should be removable under mild conditions. While a few reagents (e.g. hydrazine[3], sodium hydrosulfide, sodium sulfide, and sodium *p*-thiocresylate[4]) have been utilized for debromination of 4-bromo-3-phenylsydnone, no systematic study of this process has been reported. Additionally, all of the above reagents have disadvantages, e.g. use of high temperature (c. ~ 100 °C with hydrazine), long reaction times (with NaSH, Na_2S, or *p*-thiocresylate) or susceptibility to reaction with other functional groups.

Serendipitously, on attempting to reduce 4-bromo-3-(2-acetylphenyl)-sydnone (**1m**) to the corresponding alcohol, with sodium borohydride in methanol at room temperature, we discovered that the major product was the debrominated alcohol **2m**. Clearly, aside from conventional carbonyl reduction, more unusual heteroaryl debromination had occurred. The facility of this process suggested its use as a general method for 4-bromosydnone debromination and, accordingly, the reduction of various 4-bromo-3-arylsyd-



1a-o **2a-o**

1,2	Ar	1,2	Ar	1,2	Ar
a		f		k	
b		g		l	
c		h		m	
d		i		n	
e		j		o	

Scheme A

nones **1** (see Table) was examined. In all cases complete reaction occurred in less than one hour at room temperature and in general the debrominated products **2** were isolated in excellent yield.

Table. Debromination of 4-Bromosydnones **1** with Sodium Borohydride

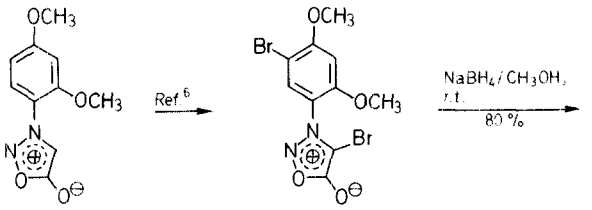
Product	Yield [%]	m.p. [°C]	Lit. m.p. [°C]
2a	82	134–136°	135°[7]
2b	88	120–122°	121–122°[2]
2c	86	135–136°	136–137°[9]
2d	79	144–146°	147.5°[10]
2e	92	113–115°	115–116°[11]
2f	70	189–191°	190–191°[2]
2g	80	172–173°	173–174°[8]
2h	87	88–90°	75–76°[12]
2i	89	135–136°	135–137°[6]
2j	87	163–164°	162–163°[6]
2k	84	162–163°	161–163°[6]
2l	45	71–73°	73–75°[2]
2m	55	94–96°	94–96°[2]
2n	35	207–208°	204°[13]
2o	14[a]	102–104°	104–106°[14]

[a] Together with a 40% yield of **2l**.

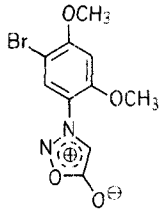
The reaction was successful in the presence of halides (aryl and alkyl), alkyl, alkoxy, amino, amido, cyano, and nitro groups. The process is limited in that keto and ester groups are concomitantly reduced. The latter is unusual under these conditions and may reflect the increased electrophilicity of the ester due to the strongly electron-withdrawing sydnone ring. Additionally, isolation of products containing alcohol or carboxylic acid groups (**2l–n**) was not as straightforward as for other substituents and yields were low. This is undoubtedly due to borohydride reaction with the hydroxy group, giving water soluble borates which remained incompletely hydrolyzed.

Overall, we have developed a mild and usually efficient route to debromination of sydnones. Reaction progress can be conveniently monitored by T.L.C. Extra borohydride may then be added as required. It should be noted that since sodium borohydride reacts vigorously with methanol it is necessary to use an excess. However, this does not alter the outcome of the reaction **1** → **2** (except where ester or keto groups are present, *vide infra*), no reduction of the sydnone ring occurring under these conditions. For large scale reactions, ethanol, with which sodium borohydride is less reactive, may be the solvent of choice. In general, at least twice as much sodium borohydride is necessary to reduce 4-bromosydnones containing groups capable of interaction with the borohydride.

We envisage use of the bromine as a protective group for reactions involving modification of aryl substituents with reagents known to react at the sydnone 4-position (e.g. thionyl chloride[5]). Additionally, since aryl bromines do not react, the process may be useful for the preparation of novel sydnones by debromination of multiply brominated species. We have briefly investigated this possibility by subjecting the dibromodimethoxyphenylsydnone (**3**; prepared by direct bromination of **2j**)[6] to the standard conditions. Debromination occurred to yield the aryl brominated species **4**; inaccessible by direct bromination of **2j**. We plan to further investigate the generality of this latter method.



2j **3**



Scheme **B** **4**

Lastly, we considered that the bromination/debromination process might be an alternative to recrystallization for the purification of sydnones **2**. Sydnones are generally prepared by *N*-nitrosation of *N*-arylglycines and subsequent cyclization with an acid anhydride[1]. Due to the toxic nature of the *N*-nitroso intermediates it is often desirable to effect their cyclization without purification[6]; impure sydnones often result and, consequently, several recrystallizations may be necessary to achieve satisfactory purity. We have noted that even relatively impure sydnones **2** can be brominated to give quite pure 4-bromo congeners **1**. In such cases, subsequent treatment with sodium borohydride may provide the parent sydnones cleanly, in reasonable yield. We attempted this two step purification procedure for two sydnones (**2h, j**) and we were able to achieve overall yields of 50–60% (**2** → **1** → **2**) in under 90 min. Thus, in some cases, the process may offer a viable alternative to recrystallization.

Debromination of 4-Bromosydnones 1 with Sodium Borohydride; General Procedure:

To a stirred solution (or suspension) of the bromosydnone **1** (0.2 g) in methanol (or ethanol) [5 ml] is added sodium borohydride (0.2 g) in portions with stirring. After 15 min the mixture is examined by T.L.C. and, dependent on the results, more sodium borohydride is added or the mixture is worked-up. When all of the starting material has been consumed the solvent is removed under a stream of air and water (20 ml) is added. In all cases, except those involving alcohol or carboxylic acid products, the insoluble products are removed by filtration and dried to afford the debrominated sydnones **2** of near analytical purity in the yields shown in the Table.

For product mixtures involving alcohols or carboxylic acids, the aqueous solutions are briefly heated, evaporated to dryness under a stream of air, and extracted several times with dichloromethane. Subsequent column chromatography on silica provided the alcohols **2l, m** (dichloromethane as eluant) and the carboxylic acid **2n** (acetone/methanol 15/1 as eluant) is low yield (see Table).

3-(5-Bromo-2,4-dimethoxyphenyl)-sydnone (4):

Prepared from **3** (0.30 g, 0.79 mmol) as described above; yield: 0.20 g (84%); m.p. 187–188°C.

$C_{10}H_9BrN_2O_4$	calc.	C 39.89	H 3.01	N 9.30
(301.09)	found	39.82	3.16	9.06

I.R. (KBr): ν_{max} = 3122, 1760, 1593, 1455, 1213, 1015 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/DMSO-d_6 2/3): δ = 7.88 (s, 1H); 7.12 (s, 1H); 6.98 (s, 1H); 4.03 ppm (s, 6H).

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