Oxidation of 3-Aryl-4-(1-hydroxyethyl)sydnones using DMSO-Ac_2O as Oxidant

Shaw-Tao Lin,*[a] Hsien-Ju Tien[b] and Jinn-Tsair Chen[b]

[a]*Department of Applied Chemistry, Providence University, Sha-Lu, Taichung Hsien, 433, Taiwan, ROC*
[b]*Department of Chemistry, National Cheng Kung University, Tainan, 701, Taiwan, ROC*

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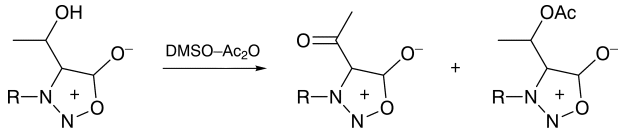
Treatment of 3-aryl-4-(1-hydroxyethyl)sydnones with DMSO-Ac_2O yielded esters and ketones, depending on the amount of Ac_2O used; application of a limited amount of Ac_2O with DMSO as an oxidant has been found to be the only method to convert the title compounds to the ketones.

Transformation of functional groups is a very important topic in organic chemistry.[1] The reactivity of any specific functional group is strongly dependent on the nature of its environment, *i.e.*, electron density, steric factors *etc*. The sydnone ring is a non-benzenoid heterocyclic aromatic five-membered ring and possesses some unusual characteristics. It can be regarded as a mesoionic system with positive and negative charges distributed around the ring depending on their resonance forms.[2] In general it is believed that C(4) possesses negative character and N(2) is positive, based on their orientation and calculations. Reduction and oxidation (redox) reactions involve electron transfer from one reactant to another. The feasibility of a redox process therefore strongly depends on the electron density of a functional group. Although, reduction of the carbonyl group of ketones or aldehydes by using sodium tetrahydroborate is a very feasible process,[3] only the carbonyl group at the C(4) position in the sydnone ring can be reduced by $NaBH_4$ in methanol media, because of the electron-donating character of the C(4) position.[4] On the other hand, a number of attempts to oxidize C(4) of 1-hydroxyethylsydnone to form an acetyl group have consistently failed. These attempts mainly involved use of dichromate–sulfuric acid in acetone or manganese dioxide in acetic acid with ultrasonic agitation[4] as the oxidation conditions. Strong oxidants (former) are hence likely to decompose the sydnone ring, while weaker oxidant (latter) does not cause any reaction. In the present work, a combination of dimethyl sulfoxide (DMSO) and acetic anhydride (Ac_2O) is used as an oxidant to convert the hydroxyl group to a carbonyl group. Esterification can be achieved along with this reaction in the presence of an excess of anhydride.

Results and Discussion

DMSO is known as a mild oxidant and is able to convert primary or secondary alcohols to the corresponding aldehydes or ketones without formation of acid or other oxidation products.[6] The oxidation is often activated by the presence of electrophilic reagents, such as thionyl chloride, oxalyl chloride, halogens, sulfuric trioxide/pyridine or acetic anhydride. Among these electrophilic agents, acetic anhydride is the most convenient.

In this study, a solution of 4-(1-hydroxyethyl)sydnone, DMSO and acetic anhydride was heated at 100 °C for 10 min to achieve oxidation. After the work-up process, ketones and/or esters were obtained from 3-aryl-4-(1-hydroxyethyl)sydnones, which contained various substituents on the phenyl ring. The relative fractions of ester and ketone thus produced have been found to depend on the amount of acetic anhydride used (Table 1). When a limiting amount of acetic anhydride was used as a catalyst, the reaction led to formation of ketones as the only product (condition A) while large amounts of acetic anhydride in the mixture yielded more ester products (conditions B and C).



1 R = Ph
2 R = 4-EtOC(O)C_6H_4
3 R = 4-MeC_6H_4
4 R = 4-BrC_6H_4
5 R = c-C_6H_{11}
6 R = 4-$EtOC_6H_4$
7 R = 4-$NO_2C_6H_4$
8 R = 3-$NO_2C_6H_4$
9 R = 3-$NO_2C_6H_4$

The esterification can be directed between the alcohol and acetic anhydride or acetyl group. This process is enhanced by the addition of acetate ions from either sodium acetate or triethylamine in the mixture of DMSO and acetic anhydride (entries 6, 7). To bring about oxidation of the hydroxy group, DMSO first reacts with an electrophilic reagent (*i.e.*, acetic anhydride) to form an intermediate *a* with a positive charge on the sulfur atom (Scheme 1). Thus sulfur facilitates a nucleophilic attack by the oxygen atom of the hydroxy group that separates from the acetic acid to

Table 1 Product distributions from the reaction of 4-(2-hydroxyethyl)sydnones by using DMSO–Ac_2O oxidant

			Yield (%)	
Entry	Reactant	Condition[a]	Ketone (**K**)	Ester (**E**)
1	**1**	A	84	—
2	**1**	B	46	38
3	**1**	C	31	53
4	**1**	D	—	—
5	**1**	E	—	40
6	**1**	F	—	75
7	**1**	G	—	63
8	**2**	A	70	—
9	**2**	C	35	40
10	**3**	A	83	—
11	**3**	C	15	70
12	**4**	A	76	—
13	**4**	C	—	70
14	**5**	A	65	—
15	**5**	C	20	40
16	**6**	A	80	—
17	**6**	C	8	80
18	**7**[b]	A	63	—
19	**7**[b]	C	20	47
20	**8**	A	50	—
21	**8**	C	15	42
22	**9**	A	54	—
23	**9**	C	16	46

[a]Isolated yields. The mixtures containing sydnone (2.4 mmol) were heated at 100 °C for 10 min. A, DMSO–Ac_2O [10.0 ml: 0.5 ml (2.0 equiv)]; B, DMSO–Ac_2O (5.0 ml: 5.0 ml); C, DMSO–Ac_2O [0.2 ml (1.0 equiv.)/10.0 ml]; D, AcOH (10.0 ml) used only; E, Ac_2O (10.0 ml) used only; F, NaOAc (1.0 g, 12.2 mmol) was added to solution B; G, Et_3N (1.0 ml, 7.2 mmol) was added to solution B. [b]Reaction time was 20 min instead of 10 min.

*To receive any correspondence.

Table 2 Physical properties and spectral data of new 4-acetyl- (**A**) and 4-acetoxy- (**B**) sydnones

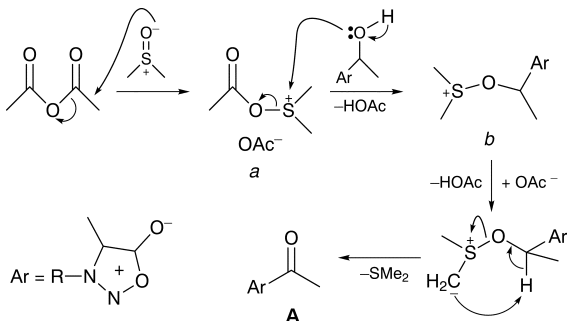
Product	Mp/°C (colour)	IR (ν/cm^{-1})[a]	δ_H ($CDCl_3$) (J/Hz)	m/z[b]
2	102–104 red flakes	1713	1.38 (t, 3 H, *J* 7.2), 1.57 (d, 3 H, *J* 7.5), 4.38 (q, 1 H, *J* 7.2), 4.63 (q, 1 H, *J* 7.5), 7.81 (d, 2 H, *J* 8.5), 8.25 (d, 2 H, *J* 8.5)	278, 176
7	112–114 yellow powder	1731	1.59 (d, 3 H, *J* 7.2), 4.65 (q, 1 H, *J* 7.2), 7.81 (d, 2 H, *J* 8.7), 8.14 (d, 2 H, *J* 8.7)	251, 148
8	121–123 yellow crystals	1737	1.59 (t, 3 H, *J* 7.3), 4.65 (q, 1 H, *J* 7.3), 7.81 (t, 1 H, *J* 8.7), 8.14 (d, 1 H, *J* 8.7), 8.70 (d, 1 H, *J* 8.7), 8.73 (s, 1 H)	251, 148
9	124–126 yellow powder	1719	1.53 (d, 3 H, *J* 7.3), 4.60 (q, 1 H, *J* 7.3), 7.80 (d, 1 H, *J* 8.5), 7.91–7.96 (m, 2 H), 8.35 (t, 1 H, *J* 8.6)	251, 148
2A	132–134 light yellow flakes	1783, 1769	1.24 (t, 3 H, *J* 7.2), 2.54 (s, 3 H), 4.30 (q, 2 H, *J* 7.2), 7.88 (d, 2 H, *J* 8.7), 8.25 (d, 2 H, *J* 8.7)	251, 176
9A	142–144 light yellow flakes	1731, 1530,[c] 1350[c]	2.47 (s, 3 H), 7.55 (d, 1 H, *J* 8.5), 7.89–7.94 (m, 2 H), 8.44 (d, 1 H, *J* 8.5)	249, 148
1B	58–60 white flakes	1737	1.59 (d, 3 H, *J* 8.6), 1.92 (s, 3 H), 5.52 (q, 1 H, *J* 8.6), 7.47 (m, 5 H)	248, 104
2B	89–91 red granules	1731	1.25 (t, 3 H, *J* 7.3), 1.61 (d, 3 H), 1.95 (s, 3 H), 4.39 (q, 2 H, *J* 7.3), 5.50 (q, 1 H, *J* 8.5), 7.60 (d, 2 H, *J* 8.7), 8.25 (d, 2 H, *J* 8.7)	320, 176
3B	51–52 white granules	1746	1.60 (d, 3 H, *J* 8.5), 1.95 (s, 3 H), 2.46 (s, 3 H), 5.53 (q, 1 H, *J* 8.5), 7.39 (m, 4 H)	262, 118
4B	— red liquid	1743	1.58 (d, 3 H, *J* 8.5), 2.20 (s, 3 H), 4.63 (q, 1 H, *J* 8.5), 7.26 (d, 2 H, *J* 9.0), 7.55 (d, 2 H, *J* 90)	326, 182
5B	68–70 white granules	1743	1.31–2.08 (m, 10 H), 1.66 (d, 3 H, *J* 8.5), 2.02 (s, 3 H), 4.62 (m, 1 H), 5.75 (q, 1 H, *J* 8.5)	254, 84
6B	85–86 white granules	1746	1.32 (t, 3 H, *J* 7.5), 1.54 (d, 3 H, *J* 8.5), 1.94 (s, 3 H), 4.01 (q, 2 H, *J* 7.5), 5.47 (q, 1 H, *J* 8.5), 6.93 (d, 2 H, *J* 8.5), 7.32 (d, 2 H, *J* 8.5)	292, 148
7B	130–131 light yellow powder	1734, 1545,[c] 1360[c]	1.65 (d, 3 H, *J* 8.5), 1.98 (s, 3 H), 5.47 (q, 1 H, *J* 8.5), 7.79 (d, 2 H, *J* 9.0), 8.46 (d, 2 H, *J* 9.0)	293, 267
8B	107–109 light yellow needles	1737, 1550,[c] 1350[c]	1.65 (d, 3 H, *J* 8.5), 1.95 (s, 3 H), 5.48 (q, 1 H, *J* 8.5), 7.81 (t, 1 H, *J* 9.0), 8.64 (d, 1 H, *J* 9.0), 8.78 (m, 2 H)	293, 148
9B	104–106 yellow needles	1740, 1560,[c] 1355[c]	1.65 (d, 3 H, *J* 8.5), 1.96 (s, 3 H), 5.45 (q, 1 H, *J* 8.5), 7.50 (d, 1 H, *J* 9.0), 7.68 (t, 1 H, *J* 9.0), 7.93 (t, 1 H, *J* 9.0), 8.34 (d, 1 H, *J* 9.0)	293, 148

[a] ν_{CO}; [b] Mass unit of the molecular ion and the base peak. [c] ν_{NO_2}.

form intermediate *b*. This pathway involves abstraction of hydrogen from a methyl group next to the sulfur atom in intermediate *b* to form *c*. Notably, the acidity of the hydrogens of the methyl group is enhanced by the positive charge on the sulfur atom. The methylene anion in *c* subsequently abstracts a hydrogen from the carbon attached at C(4) of the sydnone ring, followed by loss of dimethyl sulfide to form the ketone as the final product. Abstraction of a hydrogen from the carbon attached at C(4) of the sydnone ring followed by loss of a DMSO molecule might be an alternative pathway for the formation of ketones. In general, the presence of a nitro group lowered the yield of both ketones and esters. At least 20 min reaction time is required to yield comparable results for 4-(1-hydroxyethyl)-3-(4-nitrophenyl)sydnone (**7**, entries 18–23). The electron-withdrawing group on the phenyl ring decreases the electron density at the C(4) position on the sydnone ring which further destabilizes intermediate *b*, and consequently affords a lower yield. This mechanism shows the presence of a positive charge on intermediates *b*.

Experimental

3-Substituted 4-(1-hydroxyethyl)sydnones were prepared by the reactions of the corresponding 4-lithiosydnones with acetaldehyde according to the literature.[7]



Scheme 1

Typical Oxidation of 3-*Aryl*-4-(1-*hydroxyethyl*)*sydnone using DMSO–Ac$_2$O*.—After the mixture of DMSO–Ac_2O (10 ml, with ratios as given in Table 1), containing 3-aryl-4-(1-hydroxyethyl)-sydnone, was heated at 100 °C for 10 min, the solution was cooled and chloroform (30 ml) added. This mixture was then washed with water (50 ml × 5) to remove DMSO and acetic acid. The organic layer was dried ($MgSO_4$), evaporated, and then absorbed by silica gel for chromatographic separation by using ethyl acetate–*n*-hexane (1:2, v/v) as eluent. The product ester was washed out before the product ketone. Melting points of the known 4-acetyl derivatives were compared with those of the authentic compounds. All of the 4-(1-ethoxycarbonyl)sydnones are new compounds synthesized in this study and their properties are reported in Table 2 (CHN elemental analyses within ±0.05%).

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Techniques used: ^{1}H NMR, MS, IR, elemental analysis

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