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SYNTHESIS AND CRYSTAL STRUCTURE OF 4-TRIFLUOROACETYL-3-PHENYLSYDNONE

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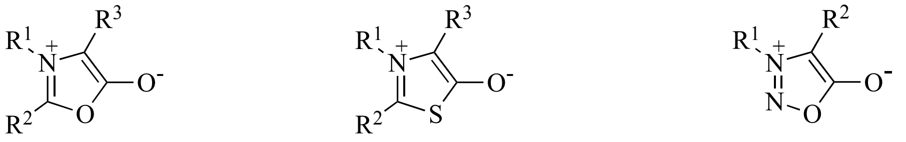
Abstract – 4-Trifluoroacetyl-3-phenylsydnone was first synthesized by trifluoromethylation of 4-formyl-3-phenylsydnone followed by oxidation of the corresponding trifluoromethyl alcohol. The structure of the product was determined by single-crystal X-ray analysis.

Mesoionic compounds are five-membered heterocycles with a sextet of electrons and can be represented as hybrids of a number of mesoionic/ionic forms (polar structures).[1] Amongst the many possible members of this family of compounds, 1,3-oxazolium-5-olates (münchnones, **1**), 1,3-thiazolium-5-olates (thiomünchnones, **2**) and 1,2,3-oxadiazolium-5-olates (sydnones, **3**) have long attracted significant attention from a wide variety of research areas due to its interesting structure and physicochemical properties (Figure 1).[2]



1

a: R^3=H
b: R^3=$COCF_3$

2

a: R^3=H
b: R^3=$COCF_3$

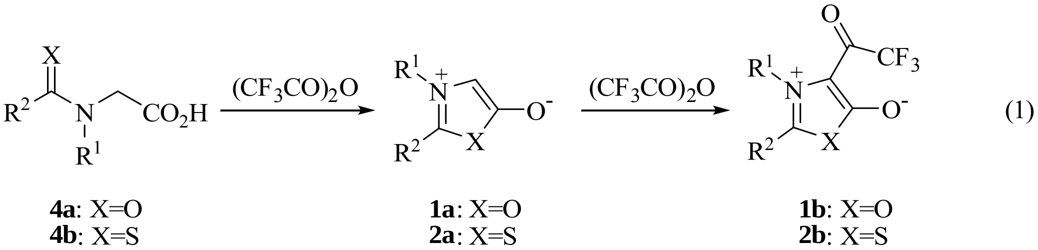
3

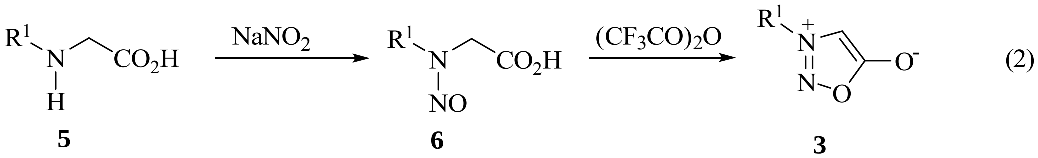
a: R^1=Ph, R^2=H
b: R^1=Ph, R^2=$COCF_3$
c: R^1=Ph, R^2=CHO
d: R^1=Ph, R^2=COMe
e: R^1=Ph, R^2=COPh

Figure 1. Mesoionic compounds

During our studies on the chemistry of trifluoroacetylated mesoionic compounds, we have focused on 4-trifluoroacetylated münchnones **1b** as useful synthons for trifluoromethyl-substituted heterocycles[3] and novel tetravalent phosphorus zwitterions.[4] In addition, we have recently studied on the reactivities of the structurally related 4-trifluoroacetylated thiomünchnones **2b**.[5]

Both **1b** and **2b** are easily prepared from *N*-acyl **4a** or *N*-thioacyl-*N*-alkyl(aryl)glycines **4b** in a one step through the cyclodehydration by trifluoroacetic anhydride (TFAA) followed by trifluoroacetylation at C-4 position of an intermediary münchnones **1a** or thiomünchnones **2a**, respectively (Eq. 1).[5]

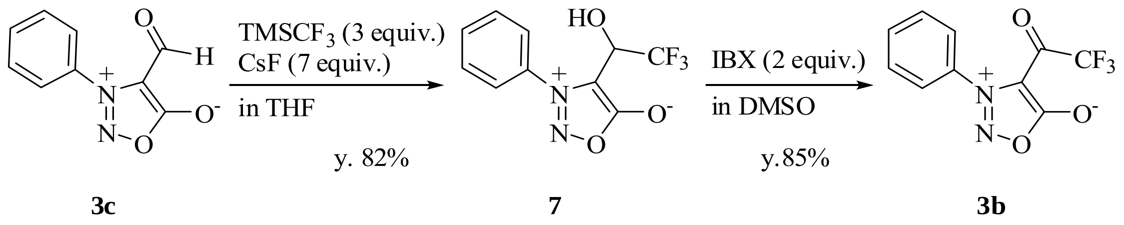




Sydnones **3** are typically prepared in two steps by *N*-nitrosation of *N*-substituted α-amino acids **5** followed by cyclodehydration of the resulting nitrosamines **6** (Eq. 2).[2e,6] Acylation has been extensively studied and a number of methods have been developed for the preparation of the 4-formyl (**3c**),[7] 4-acetyl (**3d**)[8] and 4-benzoyl-3-phenylsydnone (**3e**)[9] from their 4-unsubstituted 3-phenylsydnone (**3a**). However, 3-phenylsydnone (**3a**) is reported not to undergo direct trifluoroacetylation using TFAA as similar to münchnones **1** and thiomünchnones **2**.[10] Indeed, the sydnones have been known not to react with acid chloride using the standard Friedel-Crafts' conditions, presumably due to coordination of the Lewis acid with the exocyclic oxygen atom of the sydnone.[9,10] Our attempted introduction of the trifluoroacetyl group at 4-positon of the sydnone (**3a**) was unsuccessful: (1) direct trifluoroacetylation of 3-phenylsydone (**3a**) with TFAA (2) lithiation of 3-phenylsydnone (**3a**) with LDA followed by trifluoroacetylation (3) metalation of 4-bromo-[11] and 4-iodo-3-phenylsydnone[12] followed by trifluoroacetylation with CF_3CO_2Et or TFAA. To the best of our knowledge there are no procedure known so far for the synthesis of 4-trifluoroacetylated sydnones **3**.

In the present study, we report a facile synthesis of 4-trifluoroacetyl-3-phenylsydnone (**3b**) and its X-ray structure.

4-Formyl-3-phenylsydnone (**3c**) was prepared in moderate yield (43%) by the formylation of 3-phenylsydnone (**3a**)[13] according to the reported procedure.[7a]



(3)

Here, **3c** was found to react smoothly with trifluoromethyltrimethylsilane[14] at 0 °C in THF in the presence of CsF to give the trifluoromethyl alcohol **7** in 82% yield (Eq. 3).

As a trifluoromethyl group is strong electron-withdrawing substituent, the oxidation of the trifluoromethyl alcohols to the corresponding ketones has been proved exceptionally difficult.[15] Among various oxidizing reagents, *o*-iodoxybenzoic acid (IBX) is reported to be more efficient and practical oxidant for the synthesis of ary and heteroaryl trifluoromethyl ketones than the Dess-Martin periodinane reagent and others.[16] The compound **7** was then oxidized to the trifluoromethyl ketone **3b** by IBX in 85% yield.[17]

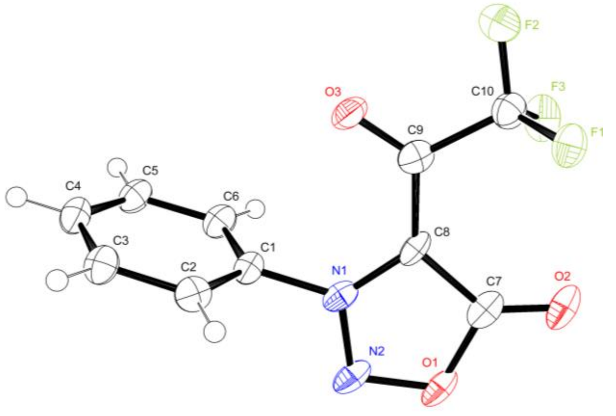
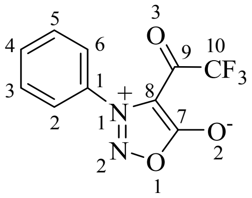


Figure 2. Ortep drawing of **3b** (50% probability)

Single crystals of **3b** were prepared at room temperature by the vapor diffusion method using two solvents, $CHCl_3$ and hexane.[18] The molecular structure of **3b** was unequivocally confirmed by X-ray diffraction study of single crystals (Figure 2).[19] Its selected bond lengths and angles are reported in Table 1. These results revealed that the two C7-C8 (1.448 (7) Å) and C8-C9 (1.441 (7) Å) bonds have the double-bond characteristic, compared to normal values for C=C (1.34 Å), benzene double bond (1.39 Å) and C-C (1.54 Å), and the two C-O bonds C7-O2 (1.189 (6) Å) and C9-O3 (1.210 (6) Å) are lightly shorter than a normal carbonyl bond length (1.23 Å). The bond distances and angles were within reported values of 4-acetylsydnone derivatives.[20] The sydnone ring is almost planar, with a maximum deviation from the mean plane of 0.013 Å, but is not coplanar with phenyl ring, having a dihedral angle of 71.2 (6)°. The trifluoroacetyl group is slightly twisted relative to the sydnone ring, forming a C7-C8-C9-O3 dihedral angle of -172.6 (5)°.

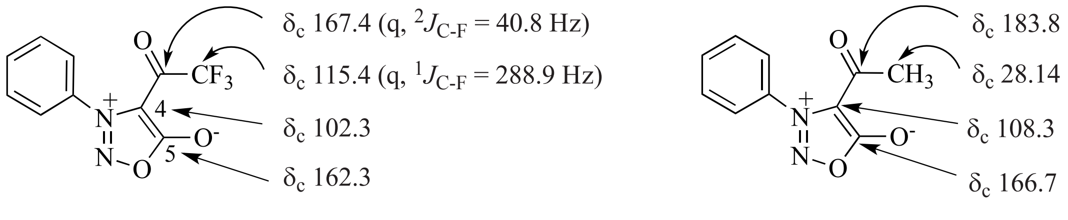
Table 1. Selected bond lengths and angles of compound **3b**



3b

Bond length (Å)		Bond angle (°)		Dihedral angle (°)	
O1-N2	1.354 (5)	N2-O1-C7	111.9 (4)	N2-N1-C1-C2	71.2 (6)
O1-C7	1.415 (6)	N2-N1-C8	115.6 (4)	N2-N1-C8-C7	1.5 (6)
N2-N1	1.287 (7)	O1-N2-N1	105.3 (4)	O1-C7-C8-N1	-2.2 (5)
N1-C8	1.356 (6)	N1-C8-C7	104.8 (4)	O1-C7-C8-C9	171.2 (5)
C8-C7	1.448 (7)	O1-C7-C8	102.4 (4)	N1-C8-C9-O3	-0.3 (8)
C8-C9	1.441 (7)	O1-C7-O2	121.1 (5)	O2-C7-C8-C9	-6 (1)
N1-C1	1.459 (9)	N2-N1-C1	115.4 (4)	C7-C8-C9-O3	-172.6 (5)
C7-O2	1.189 (6)	O2-C7-C8	136.4 (5)	N2-O1-C7-O2	-180.0 (5)
C9-O3	1.210 (6)	C1-N1-C8	129.0 (4)	N2-O1-C7-C8	2.4 (5)
C9-C10	1.551 (6)	C7-C8-C9	131.5 (5)	C7-C8-C9-C10	7.9 (8)

The ^{13}C NMR spectrum of **3b** exhibited the carbon signal of C-4 at 102.3 ppm and C-5 at 162.3 ppm (Figure 3). These signals are comparable to those previously observed for 4-acetyl-3-phenylsydnone (**3d**), in which the carbons of C-4 and C-5 appeared at 108.3 and 166.7 ppm, respectively.[8a]



3b **3d**[8a]

Figure 3

In summary, we developed the first synthesis of 4-trifluoroacetyl-3-phenylsydnone (**3b**) from 4-formyl-3-phenylsydnone (**3c**) *via* a two-step process. Although the direct trifluoroacetylation of the sydnone C4 position was unsuccessful, our method makes novel compound **3b** readily accessible for further study as building blocks for the synthesis of fluorine-containing compounds in view of the chemistry of the 4-trifluoroacetylated münchnones **1b**.[3-5] A current limitation is the low yields in the preparation of 4-formylsydnones and work is underway to develop an efficient preparation of 4-formylsydnones.

EXPERIMENTAL

All melting points were determined using a Yanagimoto hot-stage melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on Bruker AVANCE500 spectrometer with tetramethylsilane (Me_4Si) as an internal reference. ^{13}C-NMR spectra were obtained on a Bruker AVANCE500 spectrometer (at 126 MHz). Both ^{1}H- and ^{13}C-NMR spectral data are reported in parts per million (δ) relative to Me_4Si. Infrared (IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer. Low- and high-resolution MS were obtained with a JEOL JMS-GC mate II spectrometer with a direct inlet system at 70 eV and a Bruker micrOTOF-Q mass spectrometer with methanol as the solvent. Elemental analyses were carried out on a Yanaco CHN Corder MT-5, and X-ray crystallographic data were recorded on a Rigaku VariMax SaturnCCD724/α diffractometer using graphite monochromated Mo-Kα radiation at the Advanced Research Support Center, Ehime University. Standard work-up means that the organic layers were finally dried over Na_2SO_4, filtered, and concentrated *in vacuo* below 37 °C using a rotary evaporator.

Materials: The following compounds were prepared by employing the reported method.

2-(*N*-Nitroso-*N*-phenylamino)acetic acid (6): Pale brown crystals, 92% yield. mp 101–102 °C ($CHCl_3$/hexane) (mp[13] 103–104 °C). IR (KBr) ν_{max} 3001, 2873, 2783, 2666, 2576, 1731, 1466, 1436, 1263, 1238, 1149, 962, 763 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 4.69 (s, 2H, NC*H*$_2$), 7.40–7.42 (m, 1H, Ar*H*), 7.49–7.52 (m, 4H, Ar*H*) ppm.

3-Phenylsydnone (3a): Pale orange crystals, 85% yield. mp 143–144 °C ($CHCl_3$/hexane) (mp[13] 136–137 °C). IR (KBr) ν_{max} 3127, 3080, 3062, 2361, 2343, 1760, 1472, 1441, 1088, 948, 756, 726, 683 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 6.70 (s, 1H, *H*-4), 7.63 (t, *J* = 8.0 Hz, 2H, Ar*H*), 7.68 (t, *J* = 7.8 Hz, 1H, Ar*H*), 7.72 (d, *J* = 8.4 Hz, 2H, Ar*H*) ppm.

4-Formyl-3-phenylsydnone (3c): Yellow crystals, 43% yield. mp 112–113 °C ($CHCl_3$/hexane) (mp[7e] 115–117 °C). IR (KBr) ν_{max} 3104, 3061, 2359, 1787, 1647, 1471, 764 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.61–7.67 (m, 4H, Ar*H*), 7.75 (tt, *J* = 7.3, 1.4 Hz, 1H, Ar*H*), 9.59 (s, 1H, C*H*O) ppm.

4-(2,2,2-Trifluoro-1-hydroxyethyl)-3-phenylsydnone (7): A mixture of **3c** (500 mg, 2.63 mmol) and (trifluoromethyl)trimethylsilane (0.5 M in THF, 15 mL, 7.50 mmol) was stirred at 0 °C for 15 min under atmosphere of argon. To the mixture was added portionwise cesium fluoride (2.80 g, 18.4 mmol), and the whole was stirred for an additional 3 h. The reaction mixture was quenched by adding 10% HCl (15 mL), and stirred for 15 min. After adding water (150 mL), the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane: EtOAc = 6:1 to 1:1) to give **7** as yellow crystals (560 mg, 82% yield). Mp 123–124 °C ($CHCl_3$/hexane). IR (KBr) ν_{max} 3369, 1739, 1275, 1186, 1169, 1156, 1126, 859, 769, 691, 667 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) $\delta = 4.28$ (d, $J = 10.6$ Hz, 1H, O*H*), 4.82 (dq, $J = 10.6$, 6.4 Hz, 1H, C*H*), 7.58 (d, $J = 8.1$ Hz, 2H, Ar*H*), 7.68 (t, $J = 8.2$ Hz, 2H, Ar*H*), 7.76 (t, $J = 7.4$ Hz, 1H, Ar*H*) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$) $\delta = 64.7$ (q, $^2J_{C\text{-}F} = 35.9$ Hz, *C*CF_3), 102.7 (*C*-4), 123.3 (q, $^1J_{C\text{-}F} = 283.9$ Hz, *C*F_3), 125.1 (*C*H), 130.3 (*C*H), 133.0 (*C*H), 133.2 (*C*), 167.3 (*C*-5) ppm. MS *m/z*: 260 (M^+, 2.0), 59 (100). *Anal.* Calcd for $C_{10}H_7F_3N_2O_3$: C, 46.16; H, 2.71; N, 10.77. Found: C, 46.18; H, 2.87; N, 10.95.

3-Phenyl-4-(trifluoroacetyl)sydnone (3b): To a stirred suspension of **7** (90 mg, 0.35 mmol) in DMSO (3 mL) was added IBX (194 mg, 0.70 mmol) at rt under atmosphere of argon, and the whole was stirred for 12 h. After adding water (30 mL), the mixture was extracted with EtOAc (x 3). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The residue was dissolved in Et_2O, and the resulting precipitate was filtered off, the filtrate was purified by column chromatography (silica gel, hexane:EtOAc = 6:1 to 3:1) to give **3b** as colorless crystals (76 mg, 85% yield). Mp 59–60 °C ($CHCl_3$/hexane). IR (KBr) ν_{max} 3067, 1830, 1678, 1433, 1348, 1262, 1226, 1170, 1150, 963, 771, 763 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) $\delta = 7.51$ (d, $J = 7.6$ Hz, 2H, Ar*H*), 7.65 (t, $J = 7.7$ Hz, 2H, Ar*H*), 7.75 (t, $J = 7.7$ Hz, 1H, Ar*H*) ppm. ^{13}C NMR (125.77 MHz, $CDCl_3$) $\delta = 102.3$ (*C*-4), 115.4 (q, $^1J_{C\text{-}F} = 288.9$ Hz, *C*F_3), 124.6 (*C*H), 129.9 (*C*H), 133.1 (*C*H), 134.5 (*C*), 162.3 (*C*-5), 167.4 (q, $^2J_{C\text{-}F} = 40.8$ Hz, *C*CF_3) ppm. MS *m/z*: 258 (M^+, 1.0), 200 (100). *Anal.* Calcd for $C_{10}H_5F_3N_2O_3$: C, 46.53; H, 1.95; N, 10.85. Found: C, 46.52; H, 2.11; N, 10.67.

Crystal Data and Structure Refinement for 3b:

Crystal Data

Empirical Formula	$C_{10}H_5F_3N_2O_3$
Formula Weight	258.16
Crystal Color, Habit	colorless, block
Crystal Dimensions	0.250 x 0.200 x 0.100 mm
Crystal System	monoclinic
Lattice Type	Primitive
a	8.8236(7) Å
b	5.4183(3) Å
c	10.8400(7) Å
α	90°
β	100.765(7)°
γ	90°
V	509.13(6) $Å^3$
Space Group	$P\ 2_1$

Z value	2
D_{calc}	1.684 $g \cdot cm^{-3}$
F_{000}	260.00
μ (MoKα)	0.161 mm^{-1}
Temperature	100 K
No. of Reflections Measured	Total: 9711 Unique: 2716 ($R_{int} = 0.1013$)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.753–0.984)

Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares on F^2
Function Minimized	$\Sigma\ w\ (Fo^2 - Fc^2)^2$
Least Squares Weights	$w = 1/[\sigma^2(Fo^2) + (0.1098 \cdot P)^2 + 0.1895 \cdot P]$ where $P = (\mathrm{Max}(Fo^2,0) + 2Fc^2)/3$
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (All reflections)	2716
No. Variables	163
Reflection/Parameter Ratio	16.66
Residuals: R1 ($I > 2.00\sigma(I)$)	0.0784
Residuals: R (All reflections)	0.1005
Residuals: wR2 (All reflections)	0.1977
Goodness of Fit Indicator (GOF)	1.046
Max Shift/Error in Final Cycle	0.000
Maximum peak in Final Diff. Map	0.63 $e^-/Å^3$
Minimum peak in Final Diff. Map	−0.34 $e^-/Å^3$

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19. The structure of **3b** was confirmed by X-ray analysis (CCDC 1567627).

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