November, 1983] © *1983 The Chemical Society of Japan* NOTES *Bull. Chem. Soc. Jpn.*, ***56***, *3535—3536 (1983)* 3535

Preparation of Sydnone-4-carboxamide Oximes and Their Conversion into 4-(1,2,4-Oxadiazol-3-yl)sydnones

Mou-Yung Yeh,*,† Tsutomu Nonaka,* Takushi Goto, Ming-Ching Hsu,†
Toshio Fuchigami, and Hsien-Ju Tien†
Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, 4259, Midori-ku, Yokohama 227
† *Department of Chemistry, National Cheng Kung University, Tainan, Taiwan, 700, Republic of China*

(Received May 26, 1983)

Synopsis. 3-Arylsydnone-4-carboxamide oximes (**2**) were prepared from the corresponding 3-arylsydnone-4-carbonitriles and hydroxylamine in high yields. The amide oximes **2** reacted with orthoesters to give 3-aryl-4-(1,2,4-oxadiazol-3-yl)sydnones.

Many sydnone compounds have been found to have biological and pharmacological activities.[1—3)] Some heterocyclic compounds are also well known to show such activities. It therefore must be interesting to synthesize sydnones having heterocyclic groups, but sydnones substituted directly by such groups (4-thiazolyl[3,4)] and 4-sydnonyl[5,6)] groups) at their 4-positions have been rarely reported. In this work, the preparation of sydnone compounds **2** with amidino-type groups, which are good precursors of heterocyclic groups, and the conversion of **2** into 4-(1,2,4-oxadiazol-3-yl)sydnones (**3**) were attempted.

Sydnone is a typical mesoionic compound and its chemical and physical properties are very unique.[1,7)] Sydnone compounds seem to be fairly different from others in both reactivity and stability: Although a sydnone ring has a somewhat aromatic nature, the synthesis of sydnone compounds substituted by electron-releasing groups at the 4-position was unsuccessfully tried using some common reactions.[8—12)] Therefore, both methods and conditions for the synthesis of sydnone compounds may often be restricted.

Results and Discussion

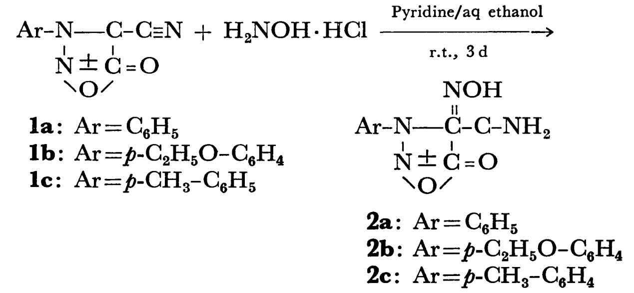
Nitriles are useful starting compounds for the preparation of amidines and imidic esters. However, the reaction of 3-phenylsydnone-4-carbonitrile (**1a**) with some nucleopliles did not give the corresponding addition products under conditions where common nitriles can react. The reaction of **1a** with free hydrazine at room temperature resulted in decomposition of **1a**, while hydrochlorides of hydrazine and aniline did not react in the presence of pyridine even at higher temperatures. The reaction with methanol in the presence of hydrogen chloride, so-called the Pinner reaction, also did not occur. These unsuccessful results may be due to the decrease of reactivity of the cyano group of **1a** by the electron-releasing nature[12)] of the 4-position and/or instability of the desired products under the reaction conditions.

Only hydroxylamine hydrochloride could react with **1a**—**c** at room temperature in the presence of pyridine to give the corresponding 3-arylsydnone-4-carboxamide oximes (**2a**—**c**) in their free states in high yields, as shown in Table 1. This successful synthesis may be caused by such adequate basicities of hydroxylamine and **2** that the former can react with the cyano group and the latter can be present in the free state without decomposition. It is interesting to note that the electrophilic reaction of **1** might be sensitive to the basicity of neucleophile, product, and reaction medium.

Table 1. 3-Arylsydnone-4-carboxamide oximes (**1a**—**c**)

Compd	Yield[a)]	Mp	IR(KBr)		
	%	θ_m/°C	ν_{OH}	ν_{NH}	$\nu_{C=O}$
			cm^{-1}	cm^{-1}	cm^{-1}
2a	86	183—185	3460	3330 3170	1735
2b	95	182—183	3450	3330 3180	1735
2c	96	170—171	3530	3375 3260	1755

a) Obtained pure without recrystallization.



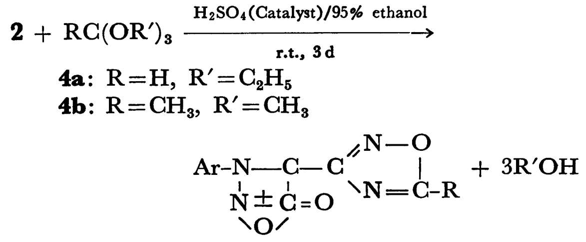
$$\text{Ar-N—C-C}\equiv\text{N} + \text{H}_2\text{NOH}\cdot\text{HCl} \xrightarrow[\text{r.t., 3 d}]{\text{Pyridine/aq ethanol}} \text{Ar-N—}\overset{\text{NOH}}{\overset{\|}{\text{C}}}\text{-C-NH}_2$$

1a: Ar$=$C$_6$H$_5$
1b: Ar$=$*p*-C$_2$H$_5$O-C$_6$H$_4$
1c: Ar$=$*p*-CH$_3$-C$_6$H$_5$

2a: Ar$=$C$_6$H$_5$
2b: Ar$=$*p*-C$_2$H$_5$O-C$_6$H$_4$
2c: Ar$=$*p*-CH$_3$-C$_6$H$_4$

The conversion of **2** prepared thus into 3-aryl-4-(1,2,4-oxadiazol-3-yl)sydnones (**3a**—**f**) was successfully carried out using the acid-catalyzed reaction with orthoesters (**4a**—**b**).[13)] The reaction proceeded at room temperature (for 3 d) in the presence of sulfuric acid as a catalyst and **3** could be obtained in high yields, as shown in Table 2. Similar results could be obtained by using boron trifluoride etherate, instead of sulfuric acid, at higher temperature(90—100 °C) for shorter time(5 min).

The preparation of **2** in this work seems to be the



$$\textbf{2} + \text{RC(OR}')_3 \xrightarrow[\text{r.t., 3 d}]{\text{H}_2\text{SO}_4\text{(Catalyst)/95\% ethanol}} \text{Ar-N—C—C}\overset{\text{N—O}}{\underset{\text{N=C-R}}{}} + 3\text{R}'\text{OH}$$

4a: R$=$H, R$'=$C$_2$H$_5$
4b: R$=$CH$_3$, R$'=$CH$_3$

3a: Ar$=$C$_6$H$_5$, R$=$H
3b: Ar$=$C$_6$H$_5$, R$=$CH$_3$
3c: Ar$=$*p*-CH$_3$-C$_6$H$_4$, R$=$H
3d: Ar$=$*p*-CH$_3$-C$_6$H$_4$, R$=$CH$_3$
3e: Ar$=$*p*-C$_2$H$_5$O-C$_6$H$_4$, R$=$H
3f: Ar$=$*p*-C$_2$H$_2$O-C$_6$H$_4$, R$=$CH$_3$

TABLE 2. 3-ARYL-4-(1,2,4-OXADIAZOL)SYDNONES (**3a**—**f**)

Compd	Yield[a)] %	Mp θ_m/°C	IR(KBr) ν_{OH}[b)] cm^{-1}	$\nu_{C=O}$ cm^{-1}	$\nu_{C=N}$ cm^{-1}
3a	87	173—174	3140 3070	1779	1573
3b	82	148—150	—	1779	1565
3c	86	198—200	3140 3075	1779	1569
3d	81	151—152	—	1778	1568
3e	84	153—154	3150 3067	1780	1570
3f	83	135—137	—	1782	1575

a) Aftera recrystallization from 95% ethanol. b) 1,2,4-Oxadiazole ring.

first report of the synthesis of sydnones substituted by an amidino-type group which may be a good precursor of longer carbon-nitrogen alternate and heterocyclic groups in addition to a 1,2,4-oxadiazol-3-yl group. The new type of sydnone compounds such as **2** and **3** is also expected to be biologically or pharmacologically active.

Experimental

3-Arylsydnone-4-carbonitriles (**1a**—**c**) were prepared from the corresponding 4-formylsydnones by the Schmidt reaction.[14)]

Typical procedures for the preparation of **2** and **3** were as follows: To a suspension of **1a** (3.74 g, 0.02 mol) in 95% ethanol (50 ml)-pyridine (5 ml), hydroxylamine hydrochloride (2.10 g, 0.03 mol) in water (10 ml) was added with stirring. The stirring was continued for 3 days at room temperature. The resulting precipitates (**2a**) were collected by filtration, and concentration of the filtrate afforded additional **2a**. To a suspension of **2a** (0.44 g, 0.002 mol) in 95% ethanol (20 ml), **4a** (2 ml) and concentrated sulfuric acid (2 drops) were added. By a procedure similar to the preparation of **2a**, the crude product of **3a** was obtained and recrystallized from 95% ethanol. All the products, **2a**—**c** and **3a**—**f** were confirmed by spectral (IR, ^{1}H-NMR, and MS) and analytical data.

The compound, **2a**: ^{1}H NMR (DMSO-d_6) δ=9.92 (1H, s, OH), 7.73 (5H, s, aromatic), 5.91 (2H, s, NH$_2$); MS (70 eV), *m/e* 220 (M^+), 162 ($M^+-NO-CO$). Found: C, 49.34; H, 3.58; N, 25.34%. Calcd for $C_9H_8N_4O_3$: C, 49.10; H, 3.66; N, 25.45%.

The compound, **2b**: ^{1}H NMR (DMSO-d_6) δ=9.95 (1H, s, OH), 7.60 (2H, d, J=9 Hz, aromatic), 7.41 (2H, d, J=9 Hz, aromatic), 5.90 (2H, s, NH$_2$), 2.42 (3H, s, CH$_3$); MS (70 eV), *m/e* 234 (M^+), 176 ($M^+-NO-CO$). Found: C, 51.26; H, 4.13; N, 23.92%. Calcd for $C_{10}H_{10}N_4O_3$: C, 51.28; H, 4.30; N, 23.92%.

The compound, **2c**: ^{1}H NMR (DMSO-d_6) δ=9.93 (1H, s, OH), 7.65 (2H, d, J=9 Hz, aromatic), 7.14 (2H, d, J=9 Hz, aromatic), 5.89 (2H, s, NH$_2$), 4.12 (2H, q, J=7 Hz, CH$_2$), 1.40 (3H, t, J=7 Hz, CH$_3$); MS (70 eV), *m/e* 264 (M^+), 206 ($M^+-NO-CO$). Found: C, 50.09; H, 4.36; N, 21.15%. Calcd for $C_{11}H_{12}N_4O_4$: C, 50.00; H, 4.58; N, 21.20%.

The compound, **3a**: ^{1}H NMR (Acetone-d_6) δ=9.20 (1H, s, oxadiazolyl), 7.81 (5H, m, aromatic); MS (70 eV), *m/e* 230 (M^+), 172 ($M^+-NO-CO$). Found: C, 52.22; H, 2.31; N, 24.04%. Calcd for $C_{10}H_6N_4O_3$: C, 52.18; H, 2.63; N, 24.34%.

The compound, **3b**: ^{1}H NMR (Acetone-d_6) δ=7.73 (5H, m, aromatic), 2.50 (3H, s, CH$_3$); MS (70 eV), *m/e* 244 (M^+), 186 ($M^+-NO-CO$). Found: C, 54.41; H, 3.14; N, 22.91%. Calcd for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94%.

The compound, **3c**: ^{1}H NMR (Acetone-d_6) δ=9.22 (1H, s, oxadiazolyl), 7.70 (2H, d, J=9 Hz, aromatic), 7.47 (2H, d, J=9 Hz, aromatic), 2.48 (3H, s, CH$_3$); MS (70 eV), *m/e* 244 (M^+), 186 ($M^+-NO-CO$). Found: C, 54.18; H, 3.14; N, 22.72%. Calcd for $C_{11}H_8N_4O_3$: C, 54.10; H, 3.30; N, 22.94%.

The compound, **3d**: ^{1}H NMR (Acetone-d_6) δ=7.66 (2H, d, J=9 Hz, aromatic), 7.48 (2H, d, J=9 Hz, aromatic), 2.52 (3H, s, CH$_3$-oxadiazolyl), 2.47 (3H, s, CH$_3$-phenylene); MS (70 eV), *m/e* 258 (M^+), 200 ($M^+-NO-CO$). Found; C, 55.61; H, 3.75; N, 21.40%. Calcd for $C_{12}H_{10}N_4O_3$: C, 55.81; H, 3.90; N, 21.70%.

The compound **3e**: ^{1}H NMR (Acetone-d_6) δ=9.22 (1H, s, oxadiazolyl), 7.68 (2H, d, J=9 Hz, aromatic), 7.13 (2H, d, J=9 Hz, aromatic), 4.18 (2H, q, J=7 Hz, CH$_2$), 1.43 (3H, t, J=7 Hz, CH$_3$); MS (70 eV), *m/e* 274 (M^+), 216 ($M^+-NO-CO$). Found: C, 52.67; H, 3.38; N, 20.10%. Calcd for $C_{12}H_{10}N_4O_4$; C, 52.56; H, 3.68; N, 20.43%.

The compound, **3f**: ^{1}H NMR (Acetone-d_6) δ=7.70 (2H, d, J=9 Hz, aromatic), 7.17 (2H, d, J=9 Hz, aromatic), 4.20 (2H, q, J=7 Hz, CH$_2$), 2.53 (3H, s, CH$_3$-oxadiazolyl), 1.44 (3H, t, J=7 Hz, $C\underline{H}_3$-CH$_2$); MS (70 eV), *m/e* 288 (M^+), 230 ($M^+-NO-CO$). Found: C, 54.20; H, 4.13; N, 19.52%. Calcd for $C_{13}H_{12}N_4O_4$: C, 54.17; H, 4.20; N, 19.44%.

The authors are grateful to the National Science Council, R. O. C. for making a possible partipation of Professor Yeh.

References

1) M. Ohta and H. Kato, "Non-benzenoid Aromatics," Academic Press, New York (1969), p. 117.

2) Y. Imashiro and K. Masuda, Japan Patent 6932411 (1969); *Chem. Abstr.* **72**, 111482q (1970): Y. Saito and T. Kamitani, *ibid.*, 7021710 (1970); *Chem. Abstr.*, **73**, 87926k (1970): K. Masuda and T. Okutani, *ibid.*, 7020903 (1970); *Chem. Abstr.*, **73**, 87928n (1970): I. S. Slyusarenko, Z. M. Kol'tova, V. I. Mamonov, and V. G. Yashunskii, *Khim. Farm. Zh.*, **5**, 12 (1971); *Chem. Abstr.*, **76**, 14441a (1972).

3) K. G. Upadhya, B. V. Badami, G. S. Puranik, V. N. Biradar, and S. Nanjappa, *Arch. Pharm. (Weiheim, Ger.)*, **313**, 684 (1980); *Chem. Abstr.*, **94**, 47195y (1981).

4) H.-J. Tien, K. Kanda, A. Chinone, and M. Ohta, *Bull. Chem. Soc. Jpn.*, **46**, 3304 (1973).

5) F. H. C. Stewart, *J. Chem. Soc.*, **1963**, 701.

6) H.-J. Tien and M.-Y. Yeh, *J. Chinese Chem. Soc. (Taipei)*, **24**, 123 (1977).

7) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

8) H. Kato and M. Ohta, *Bull. Chem. Soc. Jpn.*, **32**, 282 (1959).

9) M. Hashimoto, Dr. Sci. Dissertation, Tokyo Institute of Technology, Japan 1969.

10) H.-J. Tien, *Cheng Kung Ta Hsueh Pao*, **14**, 19 (1979); *Chem. Abstr.*, **92**, 181090x (1980).

11) M.-Y. Yeh, H.-J. Tien, and T. Nonaka, *J. Org. Chem.*, **48**, 1382 (1983).

12) H.-J. Tien, T. Nonaka, T. Fuchigami, T. Sekine, and M. Ohta, *Nippon Kagaku Kaishi*, **1978**, 1310.

13) G. I. Gregory, P. W. Seale, K. W. Warburton, and M. J. Wilson, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 47.

14) M.-Y. Yeh, H.-J. Tien, L.-Y. Huang, and M.-H. Chen, *J. Chinese Chem. Soc. (Taipei)*, **30**, 29 (1983).