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Studies on the Synthesis of Sydnone Derivatives and Their Properties. XV. Synthesis of 4-Sydnonylmethyl Acetates

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Synopsis. The convenient methods for the synthesis of 4-sydnonylmethyl acetates from *N*-(4-sydnonylmethyl)morpholines, 4-sydnonylmethanols, or bis(4-sydnonylmethyl) ethers are described.

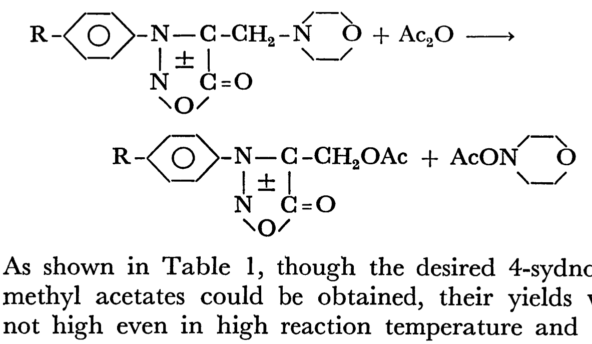
Sydnones are typical mesoionic compounds and their chemical, physical, and biological properties are peculiar.[1)] Generally, a sydnone ring is unstable to acid, alkali, and heat. Therefore, reaction conditions for the synthesis of sydnone compounds are considerably limited. For instance, no method to introduce electron-releasing groups, such as amino, hydroxyl, and alkoxy groups, into the 4-position of the sydnone ring has been found. It seems to be possible to substitute the 4-position by these groups in interposition of a methylene group. Imashiro and Masuda[2)] synthesized many kinds of 4-sydnonylmethylamines and found that some of them have a biological activity. We also found the synthetic method of 4-sydnonylmethanols and bis(4-sydnonylmethyl) ethers.[3)] Screening tests of some biological activities of these 4-sydnonylmethyl compounds are in progress.

We aim at synthesizing new derivatives of 4-sydnonylmethyl compounds, especially 4-sydnonylmethyl acetates in this work. The 4-sydnonylmethyl acetates may have a characteristic biological activity different from those of the previously synthesized 4-sydnonylmethyl compounds. The expectation of such a biological activity and an interest in reactivities of the 4-sydnonylmethyl compounds inspired us to develop the synthetic method of 4-sydnonylmethyl acetates.

For this purpose, three kinds of 4-sydnonylmethyl compounds, of which preparative methods had been reported,[2,3)] were examined as starting compounds for the 4-sydnonylmethyl acetates.

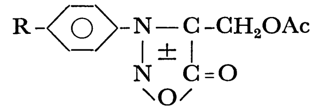
The first attempt to synthesize the 4-sydnonylmethyl acetates was led by the reaction of *N*-(4-sydnonylmethyl)morpholines, which were prepared by the modified method of Imashiro and Masuda,[2)] with acetic anhydride(Method A).

Method A:



As shown in Table 1, though the desired 4-sydnonylmethyl acetates could be obtained, their yields were not high even in high reaction temperature and long reaction time. Since a sydnone ring is generally unstable as described above, mild conditions should be desirable in the synthesis of sydnone compounds.

Table 1. Synthesis of 4-sydnonylmethyl acetates

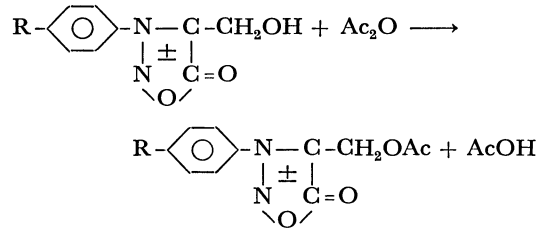


R	Method	Temp/°C	Time/min	Yield[a)]/%
H	A	90—100	480	48
CH_3	A	90—100	480	42
Br	A	90—100	480	47
H	B	30	4	76
CH_3	B	30	4	81
Br	B	30	4	84
H	C	30	5	71
CH_3	C	30	5	80
Br	C	30	5	81

a) After purification.

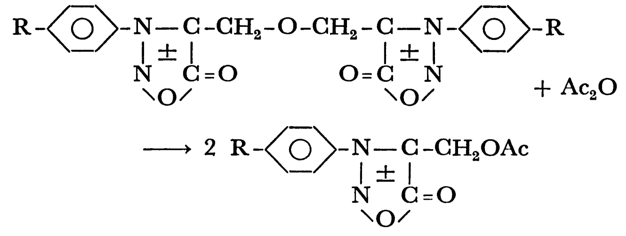
The second attempt was done by acetylating directly 4-sydnonylmethanols[3)] with acetic anhydride in the presence of a catalytic amount of sulfuric acid and was successful as expected. The acetylation was completed within a few minutes at room temperature (about 30 °C) and the 4-sydnonylmethyl acetates could be obtained in high yields as shown in Table 1 (Method B).

Method B:



In the synthesis of the 4-sydnonylmethanols, considerable amounts of bis(4-sydnonylmethyl) ethers were formed as a by-product under a reaction condition.[3)] The third attempt was the synthesis of the 4-sydnonylmethyl acetates from these ethers (Method C). The ethers also reacted with acetic anhydride in the presence of sulfuric acid to give the corresponding 4-sydnonylmethyl acetates in high yields comparable to those in Method B.

Method C:



The above fact may suggest that the 4-sydnonylmethyl acetates can be efficiently and conveniently obtained from a mixture of the 4-sydnonylmethanols and the bis(4-sydnonylmethyl) ethers, without separation of the each component from mixed products in their syntheses.

In all the methods, the yield of the 4-sydnonylmethyl acetates was not affected by both an electron-releasing group (*p*-CH_3) and an electron-withdrawing one (*p*-Br) attached to the benzene ring of the starting sydnone compounds. This fact may suggest a potentiality of the general application of these methods to the synthesis of a variety of 4-sydnonylmethyl acetates, though few examples were given in the present work.

Experimental

Starting Materials. N-*(4-Sydnonylmethyl)morpholines*: *N*-(3-Phenyl-4-sydnonylmethyl)morpholine was prepared by the method of Imashiro and Masuda.[2] *N*-[3-(*p*-methylphenyl)-4-sydnonylmethyl]morpholine and *N*-[3-(*p*-bromophenyl)-4-sydnonylmethyl]morpholine were newly synthesized according to a similar procedure. The former compound: yield, 72%; appearance, colorless needles; mp, 118—120 °C. IR (KBr): 2810, 1740, 1730, 1240, and 1110 cm^{-1}. MS (70 eV): *m/e* 275 (M$^+$). Found: C, 61.15; H, 6.24; N, 15.44%. Calcd for $C_{14}H_{17}N_3O_3$: C, 61.09; H, 6.22; N, 15.26%. The latter compound: yield, 77%; appearance, colorless needles: mp, 128—130 °C. IR (KBr): 2830, 1730, 1235, and 1110 cm^{-1}. MS (70 eV): *m/e* 339 (M$^+$) and 341 (M$^+$). Found: C, 45.85; H, 4.08; N, 12.54; Br, 23.61%. Calcd for $C_{13}H_{14}N_3BrO_3$: C, 45.90; H, 4.15; N, 12.35; Br, 23.49%.

4-Sydnonylmethanols and Bis(4-sydnonylmethyl) Ethers: 3-Phenyl-4-sydnonylmethanol, 3-(*p*-methylphenyl)-4-sydnonylmethanol, bis(3-phenyl-4-sydnonylmethyl) ether, and bis[3-(*p*-methylphenyl)-4-sydnonylmethyl] ether were prepared by the method of the previous work.[3] 3-(*p*-Bromophenyl)-4-sydnonylmethanol and bis[3-(*p*-bromophenyl)-4-sydnonylmethyl] ether were newly synthesized by a similar method. The former compound: yield, 67%; appearance, colorless powder; mp 161—163 °C. IR (KBr): 3395, 1710, 1245, and 1010 cm^{-1}. MS (70 eV): *m/e* 270 (M$^+$) and 272 (M$^+$). Found: C, 39.74; H, 2.62; N, 10.14%. Calcd for $C_9H_7N_2BrO_3$: C, 39.87; H, 2.60; N, 10.34%. The latter compound: yield, 23%, appearance, pale yellow needles; mp, 175—176 °C. IR (KBr): 3080, 1735, 1260, 1250, 1040, and 1000 cm^{-1}. MS (70 eV): *m/e* 253 [1/2(M$^+$−16)] and 255 [1/2(M$^+$−16)]. Found: C, 41.19; H, 2.10; N, 10,65%. Calcd for $C_{18}H_{12}N_4Br_2O_5$: C, 41.25; H, 2.31; N, 10.69%.

Synthesis of 4-Sydnonylmethyl Acetates. Typical procedures for the synthesis of the titled compounds are shown below. *Method A*: One gram (3.6 mmol) of *N*-[3-(p-methylphneyl)-4-sydnonylmethyl]morpholine was added into 3 ml of acetic anhydride and the reaction mixture was heated at 90—100 °C in a water bath. After 8 h, the reaction mixture was poured into crushed ice. Recrystallization of the resulting solid from ethanol afforded 0.38 g (1.5 mmol, 42%) of pure 3-(*p*-methylphenyl)-4-sydnonylmethyl acetate as colorless needles. Mp, 129—131 °C. IR (KBr): 3050, 1740, 1230, and 1030 cm^{-1}. MS (70 eV): *m/e* 248 (M$^+$). NMR (chloroform-*d*): δ 2.06 (s, 3H), 2.52 (s, 3H), 4.91 (s, 2H), and 7.42 (s, 4H) ppm. Found: C, 58.35; H, 4.97; N, 11.30%. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29%.

Method B: One gram (5.3 mmol) of 3-phenyl-4-sydnonylmethanol was added into 3 ml of acetic anhydride containing one drop of sulfuric acid. After 4 min at room temperature, the reaction mixture was poured into crushed ice. Recrystallization of the resulting pale yellow solid from ethanol afforded 0.92 g (4.0 mmol, 76%) of pure 3-phenyl-4-sydnonylmethyl acetate as colorless needles. Mp, 97—98 °C. IR (KBr): 3060, 1750, 1220, and 1020 cm^{-1}. MS (70 eV): *m/e* 234 (M$^+$). NMR (chloroform-*d*): δ 2.08 (s, 3H), 4.95 (s, 2H), and 7.65 (m, 5H) ppm. Found: C, 56.29; H, 4.19; N, 11.69%. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96%.

Method C: One gram (1.9 mmol) of bis[3-(*p*-bromophenyl)-4-sydnonylmethyl] ether was added into 3 ml of acetic anhydride containing one drop of sulfuric acid. After 5 min at room temperature, the reaction mixture was poured into crushed ice. Recrystallization of the resulting solid from ethanol afforded 0.97 g (3.1 mmol, 81%) of pure 3-(*p*-bromophenyl)-4-sydnonylmethyl acetate as colorless needles. Mp. 88—91 °C. IR (KBr): 3060, 1750, 1215, and 1010 cm^{-1}. MS (70 eV): *m/e* 312 (M$^+$) and 314 (M$^+$). NMR (chloroform-*d*): δ 2.10 (s, 3H), 4.95 (s, 2H), and 7.66 (m, 4H) ppm. Found: C, 42.21; H, 2.28; N, 8.84; Br, 25.43%. Calcd for $C_{11}H_9N_2BrO_4$: C, 42.19; H, 2.90; N, 8.95; Br, 25.52%.

References

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3) M. -Y. Yeh and H. -J. Tien, *Bull. Cheng Kung Univ. Sci. and Eng. Sec.*, **14**, 23 (1979).