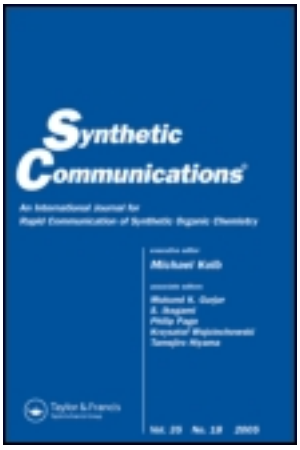

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Acylation of Sydnones with Acetic Anhydride in the Presence of Montmorillonite K-10

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ACYLATION OF SYDNONES WITH ACETIC ANHYDRIDE IN THE PRESENCE OF MONTMORILLONITE K-10

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ABSTRACT: Various 4-acetyl sydnones **2** can be prepared in good yield by reaction of the corresponding 3-arylsydnones (*cf.* **1**) with acetic anhydride at ~110°C catalyzed by Montmorillonite K-10. The reaction fails where an *ortho*-keto moiety is present; therein sydnone ring cleavage occurs to form the corresponding indazole **3**.

Sydnones *cf.* **1** are archetypal members of the class of compounds known as mesoionic.[1] They undergo a variety of transformations including electrophilic aromatic substitution (at the 4-position, if R' = H),[2] cleavage with HCl to form hydrazines[3] or heterocycles[4] and 1,3-dipolar cycloadditions to form pyrazoles or related species.[5] Perhaps the greatest interest in sydnones, however, stems from their biological activity; *inter alia* sydnones have shown efficacy as antibacterial,[6] antitumour,[7] antimalarial,[8] anti-inflammatory,[9] and antihypertensive[10] agents. Activity as MAO (monoamine oxidase) inhibitors has also been reported.[11]

In this vein, recently, we have become interested in the possibility that fused ring sydnones might be effective hypotensive agents due to a facilitated release of nitric oxide[12] and a likely avenue to such species would involve 4-

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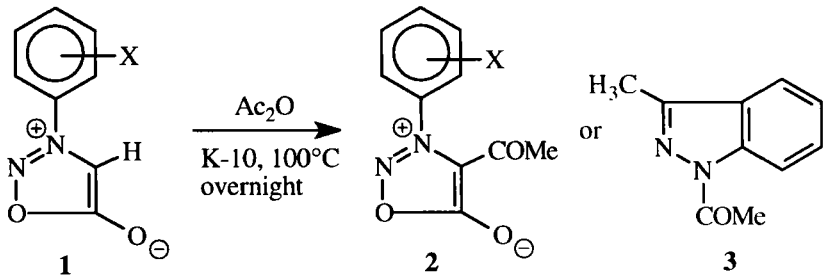
acetylsydnones (*cf.* **2**). Surprisingly, even though brominations, nitrations and similar processes can be effected readily,[2] Friedel-Crafts' type routes to 4-acyl (*cf.* **2**) or 4-aroyl sydnones (*cf.* **2**, COMe = COAr) are more capricious and, hitherto, only the former have been prepared using such methods. The difficulties stem from the fact that using the standard Friedel-Crafts' conditions (acid chloride / aluminum chloride) the sydnones do not react,[13] presumably due to coordination of the Lewis acid with the exocyclic oxygen atom in the sydnone. Successful acylation has relied on the use of alkyl anhydrides and acids such as perchloric,[14] phosphoric[15] or boron trifluoride[13] or alkyl carboxylic acids and phosphorus pentoxide.[16] However, for our purposes, all of the above approaches suffered from the disadvantage that messy, low yield product mixtures were obtained. More recently, Tien et al.[17] have prepared 4-acetylsydnones using acetic anhydride in the presence of a catalytic amount of perchloric acid under ultrasonication. This appears to be a substantial improvement, however, it does employ hazardous $HClO_4$ and the use of a high-powered ultrasonic bath, which may not be readily available. Accordingly, from recent reports,[18] we were drawn to the possibility that a solid clay catalyst might catalyze sydnone acylations. If successful, advantages would accrue from the easy removal (simple filtration) and inherent safety of the catalyst.

We now wish to report that, in general, acylation of 3-arylsydnones **1** to the corresponding 4-acetyl derivatives **2** can be effected in moderate to excellent yield (25-86%) by heating the sydnone at 110°C overnight in the presence of Montmorillonite K-10 (6 g equivalents) using acetic anhydride as solvent. The reaction is successful in the presence of a variety of functional groups including alkyl (with **1b**), alkoxy (with **1c**), halo (with **1d** and **1e**), ester (with **1f**), nitro (with **1g**) and cyano (with **1h**) moieties. In general, *ortho*-substituents on the aryl ring apparently slow down the reaction considerably (with **1e**,**1g** or **1h**) and, when strongly electron-withdrawing groups are present (*e.g.* nitro, with **1g**, or cyano, with **1h**), complete conversion to **2** is not possible (even after extended heating) and the products were obtained by column chromatography. In this regard, it is surprising that the electron-withdrawing ester moiety (in **1f**) does not inhibit the reaction completion. Interestingly, when a keto (with **1**, X = COMe) functionality is present at the *ortho*-position, sydnone ring cleavage to

form an acylated indazole **3** results. This latter result is unusual but correlates well with the results of our previous studies on acid-induced reactions of *ortho*-substituted arylsydnones, wherein initial protonation of the carbonyl moiety triggers attack by the N-2 position of the sydnone ring, followed by hydrolysis and expulsion of carbon dioxide.[4,19] Strangely, the sydnone ester **1f** did not undergo degradation to an indazole under these conditions; apparently, therein, protonation of the less nucleophilic carbonyl oxygen atom does not occur.

The identities of the 4-acetylsydnones **2** followed from their spectral data, satisfactory microanalysis figures or comparison with authentic samples (for **2a-d**). For the new compounds (*viz.* **2e-h**) their IR spectra showed the absence of



1 **2** **3**

Table. Reaction of 3-arylsydnones with Ac_2O

Product	Group	Yield [%]	m.p.[°C]	lit.m.p.[°C]
2 a	X = H	61	143-4	144[21]
b	4-Me	86	116-17	117-9[21]
c	3-MeO	77	84-6	85.5-6[22]
d	4-Cl	83	130-1	129-30[21]
e	2-Br	63.5	127-9	-
f	2-MeO_2C	86	118-19	-
g	2-NO_2	38[a]	151-2	-
h	2-CN	25[a]	129-30	-
3	from **1**, X = 2-COMe	84	71-73	72[23]

[a]Unreacted starting material was present but was not isolated

the signature sydnone C-H stretch at ~3150cm^{-1} and the presence of the acetyl C=O stretch at ~1680 cm^{-1}; indicating that acylation had occurred. In their ^{1}H-NMR spectra, the absence of the sydnone ring proton (usually ~6.5-7 δ) was apparent and the acyl methyl signal was present at ~2 δ while in the ^{13}C-NMR spectra the acyl carbonyl signal appeared at ~184 ppm and a shift of the sydnone C-4 signal to ~110 ppm (from ~95 ppm in **1**) was observed. The latter is in line with the value (107.2 ppm) reported[20] for 4-acetyl-3-phenylsydnone **2a**.

No obvious trend in product yield was apparent in the effects of electron-donating or electron-withdrawing groups on the aryl ring, although especially low yields were obtained with the strongly electron withdrawing nitro and cyano groups.

Overall, we have shown that 4-acetylsydnones can be prepared in good to excellent yield using Montmorillonite K-10 as catalyst. The advantages to this method over those previously employed are that the catalyst is safer and readily removed from the reaction mixture. We plan to study this approach further in order to assess its scope and limitations.

EXPERIMENTAL

Preparation of 4-Acetyl-3-Arylsydnones (2); General Procedure.

To a solution of the 3-arylsydnone **1** in acetic anhydride (1.5 mL / 100 mg) was added Montmorillonite K-10 (6 g equivalents) and the mixture was refluxed overnight at ~110°C. If TLC analysis showed that the reaction was not complete then the reflux was maintained until either complete or maximum conversion occurred, whereupon the insoluble clay was removed by filtration. The solid was washed with dichloromethane, acetone then dichloromethane again and the combined organics were removed *in vacuo* to yield the crude products which were recrystallized from warm ethanol or separated by column chromatography (dichloromethane as eluent).

Preparation of 4-Acetyl-3-phenylsydnone (2a).

Using 3-phenylsydnone **1a** (0.252 g, 1.56 mmol) in the general procedure gave the title compound **2a** as colourless needles, 0.193 g (61%);

m.p. 142-43°C (lit. m.p.[21] 144°C); IR (KBr) ν 3060 (aromatic CH str.), 1793 (sydnone C=O str.), 1665 (acetyl C=O str.), 1426, 1053, 770 cm^{-1} (lit.[16] 1789, 1667 cm^{-1}).

Preparation of 4-Acetyl-3-(4-methylphenyl)sydnone (2b).

Using 3-(4-methylphenyl)sydnone (0.107 g, 0.607 mmol) in the general procedure gave the title compound **2b** as colourless needles, 0.121 g (86%); m.p. 116-17°C (lit.[21] m.p. 117-19°C); IR (KBr) ν 2933 (alkyl CH str.), 1783 (sydnone C=O str.), 1678 (acetyl C=O str.), 1509, 1316, 1050, 827 cm^{-1}.

Preparation of 4-Acetyl-3-(3-methoxyphenyl)sydnone (2c)

Using 3-(3-methoxyphenyl)sydnone (0.254 g, 1.32 mmol) in the general procedure gave the title compound **2c** as colourless needles, 0.237 g (77%); m.p. 84-6°C (lit.[22] m.p. 85.5-6°C); IR (KBr) ν 3086 (aromatic CH str.), 1788 (sydnone C=O str.), 1686 (acetyl C=O str.), 1489, 1431, 1038, 782 cm^{-1} (lit.[22] 1790, 1690 cm^{-1}).

Preparation of 4-Acetyl-3-(4-chlorophenyl)sydnone (2d)

Using 3-(4-chlorophenyl)sydnone (0.152 g, 0.77 mmol) in the general procedure gave the title compound **2d** as colourless needles, 0.153 g (83%); m.p. 130-1°C (lit.[21] m.p. 129-30°C); IR (KBr) ν 3100 (aromatic CH str.), 1786 (sydnone C=O str.), 1663 (acetyl C=O str.), 1438, 1090, 838 cm^{-1} (lit.[21] 1794, 1662 cm^{-1}).

Preparation of 4-Acetyl-3-(2-bromophenyl)sydnone (2e)

Using 3-(2-bromophenyl)sydnone[24] (0.256 g, 1.06 mmol) in the general procedure, after 30 h, gave the title compound **2e** as light tan crystals, 0.16 g (63.5%); m.p. 125-7°C; IR (KBr) ν 1775 (sydnone C=O str.), 1670 (acetyl C=O str.), 1428, 1039, 770, 615 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.51 (s, 3H), 7.44 (m, 1H), 7.56 (m, 2H), 7.79 (m, 1H); ^{13}C-NMR ($CDCl_3$) 27.5 ($CO\underline{C}H_3$), 106.8 (sydnone <u>C</u>-COMe), 126.9, 128.5, 133.2, 133.8 (aromatic CH's), 118.9, 134.8 (aromatic C's), 165.9 (sydnone C=O), 184.0 (<u>C</u>OMe) ppm; analysis: calculated for $C_{10}H_7BrN_2O_3$: C, 42.42; H, 2.47; N, 9.90. Found: C, 42.43; H, 2.61; N, 9.49.

Preparation of 4-Acetyl-3-(2-methoxycarbonylphenyl)sydnone (2f)

Using 3-(2-methoxycarbonylphenyl)sydnone[24] (1.01 g, 4.56 mmol) in the general procedure gave the title compound **2f** as light tan crystals, 1.026 g (85%); m.p. 118-9°C; IR (KBr) ν 2953, 1770 (sydnone C=O str.), 1717 (ester C=O str.), 1679 (acetyl C=O str.), 1429, 1292 and 774 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.48 (s, 3H), 3.83 (s, 3H), 7.41 (m, 1H), 7.78 (m, 2H), 8.25 (m, 1H); ^{13}C-NMR ($CDCl_3$) 27.4 ($CO\underline{C}H_3$), 52.7 ($CO_2\underline{C}H_3$), 107.5 (sydnone C-COMe), 126.7, 131.7, 132.1, 133.4 (aromatic CH's), 126.3, 134.8 (aromatic C's), 163.1 (ester C=O), 165.8 (sydnone C=O), 184.5 (COMe) ppm; analysis: calculated for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.82; N, 10.69. Found: C, 55.06; H, 3.92; N, 10.31.

Preparation of 4-Acetyl-3-(2-nitrophenyl)sydnone (2g)

Using 3-(2-nitrophenyl)sydnone[24] (1.006 g, 4.83 mmol) in the general procedure, after 36h, followed by column chromatography (SiO_2, CH_2Cl_2 as eluent) afforded the title compound **2g** as light yellow crystals, 0.463 g (38%); m.p. 151-2°C; IR (KBr) ν 3098, 1788 (sydnone C=O str.), 1672 (acetyl C=O str.), 1537 & 1354 (nitro str.), 1052, 848 and 788 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.47 (s, 3H), 7.56 (m, 1H), 7.92 (m, 2H), 8.44 (m, 1H); ^{13}C-NMR ($CDCl_3$) 27.3 ($CO\underline{C}H_3$), 106.9 (sydnone C-COMe), 126.1, 128.2, 133.4, 134.9 (aromatic CH's), 128.8, 143.3 (aromatic C's), 165.1 (sydnone C=O), 184.8 (COMe); analysis: calculated for $C_{10}H_7N_3O_5$: C, 48.19; H, 2.81; N, 16.87. Found: C, 47.94; H, 2.93; N, 16.68.

Preparation of 4-Acetyl-3-(2-cyanophenyl)sydnone (2h)

Using 3-(2-cyanophenyl)sydnone[24] (0.152 g, 0.81 mmol) in the general procedure, after 36h, followed by column chromatography (SiO_2, CH_2Cl_2 as eluent) afforded the title compound **2h** as light tan crystals, 0.046 g (25%); m.p. 129-30°C; IR (KBr) ν 2235 (nitrile str), 1803 (sydnone C=O str.), 1665 (acetyl C=O str.), 1458, 1425, 777 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.54 (s, 3H), 7.63 (d, 1H), 7.88 (m, 3H); ^{13}C-NMR ($CDCl_3$) 27.5 ($CO\underline{C}H_3$), 106.9 (sydnone C-COMe), 110.3 (C-CN), 113.4 (CN), 126.5, 132.5, 133.8, 134.0 (aromatic CH's), 136.4 (aromatic C), 165.1 (sydnone C=O), 184.4 (COMe);

analysis: calculated for $C_{11}H_7N_3O_3$: C, 57,59; H, 3.05; N, 18.33. Found: C, 57.65; H, 3.10; N, 18.10.

Preparation of 1-Acetyl (1H)-3-Methylindazole (3)

Using 3-(2-acetylphenyl)sydnone[24] (**1**, X = 2-COMe) [0.50 g, 2.45 mmol] in the general procedure yielded the title compound **3** as light tan crystals, 0.36 g (84%); m.p. 71-3°C (lit. m.p.[23] 72°C); IR (KBr) ν 1702, 1447 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 2.57 (s, 3H), 2.75 (s, 3H), 7.35 (t, 1H), 7.54 (t, 1H), 7.63 (d, 1H), 8.41 (d, 1H); ^{13}C-NMR ($CDCl_3$) 12.2 ($\underline{C}H_3$), 23.1 ($CO\underline{C}H_3$), 115.7, 120.0, 124.1, 129.3 (aromatic CH's), 126.5, 139.7, 148.7 (aromatic C), 170.7 ($\underline{C}OMe$); analysis: calculated for $C_{10}H_{10}N_2O$: C, 68.97; H, 5.75; N, 16.09. Found: C, 68.68; H, 5.66; N, 15.85.

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REFERENCES AND NOTES

1. a) Ohta, M. and Kato, H., in *Nonbenzenoid Aromatics*, Vol.1, Snyder, J.P., ed., Academic Press, Inc., New York, NY, 1969, p 146. b) Stewart, F.H.C., *Chem. Rev.*, **64**, 129 (1964).
2. Turnbull, K. *J. Heterocycl. Chem.*, **22**, 965 (1985).
3. Earl, J.C. and Mackney, A.W. *J. Chem. Soc.*, 899 (1935).
4. Gelvin, C.R. and Turnbull, K. *Helv. Chim. Acta*, **75**, 1931 (1992).
5. Huisgen, R., Grashey, R., Gotthardt, H. and Schmidt, R. *Angew. Chem.*, **74**, 29 (1962).
6. a) Brookes, P. and Walker, J. *J. Chem. Soc.*, 4409 (1959). b) Ackermann, E. *Pharmazie*, **22**, 537 (1967), [*Chem. Abstr.*, **68**, 28171 (1968)].
7. Kier, L.B. and Roche, E.B. *J. Pharm. Sci.*, **56**, 149 (1967).
8. Mc Caustland, D.J., Burton, W.H and Cheng, C.C. *J. Heterocycl. Chem.*, **8**, 89 (1971).
9. a) Pala, G., Mantegani, A., Coppi, G. and Genova, R. *Chim. Ther.*, **4**, 31 (1969); [*Chem. Abstr.*, **71**, 3328 (1969)]. b) Kamiya, T., Saito, Y. and Teraji,

T. (Fujisawa Pharm. Co., Ltd.), Japan. 72 32,073, [*Chem. Abstr.*, **78**, 42592 (1973)].

10. Saito, Y. and Kamitani, T. (Takeda Chem. Ind., Ltd.), Japan. 70 10,510; [*Chem. Abstr.*, **73**, 14853 (1970)].

11. Cameron, D.P. and Wiseman, E.H. *J. Med. Chem.*, **11**, 820 (1968).

12. Preston, P.N. and Turnbull, K. *J. Chem. Soc., Perkin Trans. 1*, 1229 (1977); the sydnobenzotriazine reported therein may have released NO on treatment with acid, base or on heating.

13. Yashunskii, V.G. and Vasil'eva, V.F. *Dokl. Akad. Nauk SSSR*, **130**, 350 (1960) [*Chem. Abstr.*, **54**, 10999h].

14. Tien, H.-J. and Ohta, M. *Bull. Chem. Soc. Jpn.*, **45**, 2944 (1972).

15. Tien, H.-J. *Hua Hsueh*, 8 (1977) [*Chem. Abstr.*, **92**, 110930k (1980)].

16. Greco, C.V., Tobias, J. and Kier, L.B. *J. Heterocycl. Chem.*, **4**, 160 (1967).

17. Tien, H.-J., Yeh, J.-C. and Wu, S.-C. *J. Chin. Chem. Soc.*, **39**, 443 (1992).

18. Cornelis, A. and Laszlo, P. *Synlett*, 155 (1994); Laszlo, P. and Mathy, A. *Helv. Chim. Acta*, **70**, 577 (1987).

19. Saljoughian, M. and Turnbull, K. *J. Heterocycl. Chem.*, **25**, 1817 (1988).

20. Wang, S.P., Kuo, C.N., Ma, S. and Yeh, M.-Y. *Spec. Lett.*, **26**, 431 (1993).

21. Tien, H.-J., Fang, G.-M., Lin, S.-T. and Tien, L.-L. *J. Chin. Chem. Soc.*, **39**, 107 (1992).

22. Gotthardt, H. and Reiter, F. *Liebigs Ann. Chem.*, 63 (1979).

23. Auwers, K. and v. Meyenburg, F. *Chem. Ber.*, **24**, 2370 (1891).

24. Applegate, J. and Turnbull, K. *Synthesis*, 1011 (1988).

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