HETEROCYCLES, Vol. 75, No. 2, 2008, pp. 391 - 395. © The Japan Institute of Heterocyclic Chemistry
Received, 26th July, 2007, Accepted, 17th October, 2007, Published online, 23rd October, 2007. COM-07-11185

N-BROMOSUCCINIMIDE (NBS) AS PROMOTER FOR ACYLATION OF SYDNONES IN THE PRESENCE OF ACETIC ANHYDRIDE UNDER NEUTRAL CONDITIONS

Hassan Ghasemnejad-Bosra,* Mina Haghdadi, and Issa Gholampour-Azizi

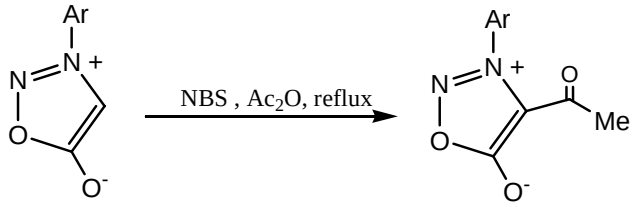
Islamic Azad University-Babol Branch, School of Science, P.O. Box 755, Babol. Iran *Corresponding author; Email: h_ghasem2000@yahoo.it

Abstract – Various 4 – acetyl sydnones (**2**) can be prepared by reaction of the corresponding 3–aryl sydnones (**1**) with acetic anhydride at ~110 ^{o}C promoted by *N*-Bromosuccinimide (NBS) as an effective reagent for acylation of sydnones under neutral conditions in satisfactory yields.

Sydnones (**1**) are archetypal members of the class of compounds known as mesoionic which were first prepared by Earl and his co-workers in 1935.[1]

They undergo a variety of transformations including electrophilic aromatic substitution (at the 4–position),[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 biological activity: *inter alia* sydnone; have been used efficaciously as antibacterial,[6] antitumor,[7] antimalarial,[8] anti-inflammatory,[9] and antihyhypertensive agents.[10] Their activity as MAO (monoamine oxidase) inhibitors has also been reported.[11]

Acylation occurs, with various acylation mixtures and with a large variety of 3-aryl substituents, exclusively at the sydnone 4-position.[12-16] It had been reported[17] that it was not possible to acetyl-3-aryl-sydnone with either acetic anhydride or benzoyl chloride in the presence of a lewis acid catalyst and Friedel-Craftes conditions to obtain the 4-acetylsydnone because the difficulties stem from the fact that using the standard Friedel-Craftes conditions (acid chloride/aluminum chloride) the sydnones do not react, presumably due to coordination of the lewis acid with the exocyclic oxygen atom in the sydnone.[18] Successful acylation has relied on the use of alkyl anhydrides and acids such as perchloric,[19] phosphoric[20] or boron trifluoride or alkyl carboxylicacids and phosphorus pentoxide.[21] More recently, Montmorillonite K-10[22] and $HClO_4$ under high powered ultrasonic bath[23] have been reported as efficient catalysts for acylation of 3- substituted sydnones in the presence acetic anhydride.



1a-j **2a-j**

Ar: (a) C_6H_5 , (b) 2-MeC_6H_4 , (s) 4-MeC_6H_4 ,(d) 2-$MeOC_6H_4$, (e) 4-$MeOC_6H_4$
(f) 2-$NO_2C_6H_4$, (g) 4-$NO_2C_6H_4$, (h) 4-ClC_6H_4 , (i) 2,4-$Cl_2C_6H_3$, (j) 4-Br-C_6H_4

Scheme 1

In this work, we have observed that NBS can efficiently enhance the conversion of the 3-arylsydnones **(1a-j)** to their 4-acetyl congeners **(2a-j)** in the presence of acetic anhydride under reflux (Table **1**).

Table **1**: Acetylation of the 3-arylsydnones **1a-j** to the corresponding 4-acetyl-sydnones **2a-j** by NBS in Ac_2O under reflux

Entry	Product [a]	Yield (%) [b]	Mp(°C)
1	**2a**	95	143-145
2	**2b**	90	105-107
3	**2c**	91	119-120
4	**2d**	90	104-105
5	**2e**	93	97-98
6	**2f**	90	151-152
7	**2g**	92	208-210
8	**2h**	93	129-131
9	**2i**	90	98-99
10	**2j**	94	169-170

[a]All the isolated products were characterized on the basis of their physical and ^{1}H-NMR, ^{13}C-NMR, IR spectral analysis and by direct comparison with literature data.[17, 19, 24, 25]

[b]Purified Yields.

According to the results shown in the Table **1**, the reactions proceed within few hours at 100 °C in satisfactory yields. Numerous repetitions of the reactions under different molar conditions indicated that, the most effective conversions occur when equimolar amounts of 3-arylsydnones and NBS are used in the reactions. Longer reaction times are required when lesser amounts of NBS are employed. It is also important to note that, no acetylated products were afforded when the reactions were carried out in the absence of NBS. This substantiates the vitality of *N*-bromosuccinimide in promoting the reactions probably by converting acetic anhydride into a more reactive acetylating reagent. The advantages or the characteristic aspects of the described method in this paper in comparison with other previously reported are the following: The yields of acylated products are better than the pervious reported yields. In addition, the catalyst NBS is inexpensive, no moisture sensitivity, no large amount of NBS required, and no special efforts are required for the reaction.

Table **2**: IR, ^{1}H-NMR and ^{13}C-NMR spectral data of the 4-acetyl sydnones **2a-j**

Product [a]	IR (KBr) (cm^{-1})	^{1}H-NMR ($CDCl_3$) (ppm)	^{13}C-NMR ($CDCl_3$) (ppm)
2a	3060,1763,1665,1426 1053,770	2.39 (s, Me, 3H), 8.01-8.39 (m, 5H)	28.14 (CO*Me*), 108.3 (C4), 126.21, 131.25, 136.72, 144.63 (Ar), 166.7 (C5), 183.80 (CO)
2b	3053,1780,1660,1425 1250,795	2.36 (s, Me, 3H), 2.69 (s, 3H), 7.93 – 8.30 (m, 3H), 8.69-8.73 (m, 1H)	16.30 (Me), 28.32 (CO*Me*), 108.40 (C4), 115.19, 132.46, 134.57, 138.30, 138.60, 143.30 (Ar), 165.40 (C5), 184.30 (CO)
2c	3058,2933,1783,1678 1509,1316,1050,827	2.38 (s, Me, 3H), 2.61 (s, 3H), 7.50 - 7.55 (dd, 2H), 7.85 -7.90 (dd, 2H)	21.30 (Me), 28.32 (CO*Me*), 107.40 (C4), 124.97, 128.59, 140.27 (Ar), 165.80 (C5), 184.10 (CO)
2d	3080,1780,1680,1489 1431,1038,770	2.58 (s, Me, 3H), 3.84 (s, 3H), 7.80-7.86 (m, 2H),8.45-8.56 (m, 2H)	28.23 (CO*Me*), 56.50 (OMe), 108.74 (C4), 118.07, 124.78, 132.11, 132.32, 149.10 (Ar), 166.70 (C5), 184.42 (CO)
2e	3085,1786,1675,1491 1442,1055,485	2.63 (s, Me, 3H), 3.94 (s, 3H), 7.22-7.26(dd, 2H),7.82-7.86 (dd, 2H)	28.41 (CO*Me*), 55.72 (OMe), 107.30 (C4), 126.57, 129.50, 139.69, 158.32 (Ar), 166.20 (C5), 184.20 (CO)
2f	3098,1788,1672,1537 1359,1052,848,788	2.47 (s, Me, 3H), 7.56 (m, 1H), 7.92(m, 2H), 8.44 (m, 1H)	27.50 (CO*Me*), 106.90 (C4), 126.10, 128.20, 128.80, 133.40, 133.90, 143.30 (Ar), 165.10 (C5), 184.80 (CO)
2g	3100,1795,1670,1530 1350,1055,850,792	2.58 (s, Me, 3H), 8.26-8.29 (dd, 2H) 8.80-8.85 (dd, 2H)	28.20 (CO*Me*), 106.70 (C4), 126.87, 130.80, 139.29, 148.26 (Ar), 165.80 (C5), 184.30 (CO)
2h	3100,1786,1663,1438 1090,838	2.60 (s, Me,3H),7.92-7.95 (m, 2H) 8.52-8.56 (m, 2H)	27.90 (CO*Me*), 106.60 (C4), 127.01, 137.80, 140.27, 148.86 (Ar), 165.80 (C5), 184.10 (CO)
2i	3110,1790,1660,1440 1100,840	2.40 (s, Me, 3H),7.86-.88 (q, 1H), 8.48 -8.50 (q, 1H),8.98 (q, 1H)	27.20 (CO*Me*), 107.50 (C4), 123.98, 127.43, 132.96, 141.56, 142.42, 145.33 (Ar), 165.60 (C5), 184.80 (CO)
2j	3095,1770,1675,1428 1035,1039,770	2.58 (s, Me, 3H), 7.81-7.86 (dd, 2H) , 8.61-8.66 (dd, 2H)	27.50 (CO*Me*), 106.80 (C4), 126.90, 128.50, 133.20, 134.80 (Ar), 165.90 (C5), 184.00 (CO)

[a]All the isolated products were characterized on the basis of their physical and ^{1}H-NMR, ^{13}C-NMR, IR spectral analysis and by direct comparison with literature data.[17, 19, 24, 25]

EXPERIMENTAL

Chemicals were obtained from Merck and Fluka chemical companies. IR spectra were recorded using a Shimadzu 435-U-04 spectrophotometer (KBr pellets) and NMR spectra were obtained in $CDCl_3$ using a 90 MHz JEOL FT NMR spectrometer. All melting points were determined on Büchi 530 melting point apparatus, and reported uncorrected.

General Procedure for Acetylation of 3-Arylsydnones 1a-j to the corresponding 4-Acetyl Derivatives 2a-j

To a stirred solution of 3-arylsydnone **(1a-j)** (1 mmol) in acetic anhydride (1 mmol) was added NBS (0.018 g, 1 mmol), and the mixture was refluxed at ~110 ^{o}C for 4 h. After complete conversion of the substrates as indicated by TLC using EtOAc/hexane mixture (1:1), the resulting reaction mixture was

poured into ice water to destroy the excess acetic anhydride and neutralized with sodium carbonate. The resulting mixture was filtered, the filtrate was extracted with CH_2Cl_2 (2x25 mL), and then dried with anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure to leave a solid brown residue, which was recrystallized from warm EtOH (95%) to yield pure crystals of the products **(2a-j)** in 90-95% yield (Table **1**). The products were characterized on the basis of their physical and spectral analysis (Table **2**) and by direct comparison with literature data.[17, 19, 24, 25]

ACKNOWLEDGEMENTS

We wish to thank the Islamic Azad University-Babol Branch, Babol, Iran, for financial support to carry out this research.

REFERENCES

1. M. Ohta and H. Kato, In *Nonbenzeneoid Aromatics* Vol. 1, ed. by J. P. Snyder; Academic Press: New York, 1969, p. 146; F. H. C. Stewart, *Chem. Rev*., 1964, **64**, 129.
2. K. Turnbull, *J. Heterocycl. Chem*., 1985, **22**, 965.
3. J. C. Earl and A. W. Mackney, *J. Chem. Soc*., 1935, 899.
4. C. R. Gelvin and K. Turnbull, *Helv. Chim. Acta*, 1992, **75**, 1931.
5. R. Huisgen, R. Grashey, H. Gotthardt, and R. Schmidt, *Angew. Chem.*, 1962, **74**, 2.
6. P. Brooks and J. Walker, *J. Chem. Soc*., 1959, 4409; E. Ackermann, *Pharmazie*, 1967, **22**, 537 (*Chem. Abstr*., 1968, **68**, 28, 171).
7. L. B. Kier and E. B. Roche, *J. Pharm. Sci*., 1967, **56**, 149.
8. D. J. McCaustland, W. H. Burton and C. C. Cheng, *J. Heterocycl. Chem.*, 1971, **8**, 89.
9. G. Pala, A. Mantegani, G. Coppi and R. Genova, *Chim. Ther*., 1969, **4**, 31 (*Chem. Abstr*., 1969, **71**, 3328); T. Kamiya, Y. Saito, and T. Teraji, Fujisawa Pharm. Co., Ltd., Japanes Patent 7232073, 1972 (*Chem. Abstr*., 1973, **78**, 42592).
10. Y. Saito and T. Kamiya, Takeda Chem. Ind. Ltd., Japanese Patent 7010510, 1970 (*Chem. Abstr*., 1970, **73**, 14853).
11. D. P. Cameron and E. H. Wiseman, *J. Med. Chem*., 1968, **11**, 820.
12. A. Cornelis and P. Laszlo, *Synlett*, 1994, 155.
13. P. Laszlo and A. Mathy, *Helv. Chim. Acta*, 1987, **70**, 577.
14. D. Azarifar, H. Ghasemnejad-Bosra, M. A. Zolfigol, and M. Tajbaksh, *Heterocycles*, 2006, **68**, 175.
15. D. Azarifar and H. Ghasemnejad-Bosra, *Synthesis*, 2006, 1123.
16. D. Azarifar, H. Ghasemnejad-Bosra, R. Ghorbani-Vaghei, and M. Tajbaksh, *Heterocycles*, 2006, **68**, 2343.

17. V. F. Vasil'eva and V. G. Yashunski, *Khim. Nauk. Prom*., 1958, **3**, 282.
18. V. F. Vasil'eva and V. G. Yashunski, *Dokl. Akad. Nauk. SSSR*., 1960, **130**, 350.
19. H.-J. Tien and M. Ohta, *Bull. Chem. Soc. Jpn*., 1972, **45**, 2944.
20. H.-J. Tien, *Hua-Hsuel (Chemistry)*., 1977, 29.
21. C. V. Greco, J. Tobias, and L. B. Kier, *J. Heterocycl. Chem*., 1964, **4**, 160.
22. K. Turnbull and J. C. George, *Synth. Commun*., 1996, **26**, 2757.
23. H.-J. Tien, J.-C. Yeh, and S.-C. Wu, *J. Chin. Chem. Soc*., 1992, **39**, 443.
24. D. Azarifar, H. Ghasemnejad-Bosra, and M. Tajbaksh, *J. Heterocycl. Chem*., 2007, **44**, 467.
25. H.-J. Tien, G.-M. Fang, S.-T. Lin, and L.-L. Tien, *J. Chin. Chem. Soc*., 1991, **38**, 17.