A Novel and Green Method for N-acylation of Amines and Sulfonamides under Ultrasound Irradiation

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ABSTRACT

A facile and versatile method for acylation of structurally diverse amines and sulfonamides under focused ultrasonic irradiation in catalyst-free and solvent-free conditions is reported. There are several advantages to this approach such as simple and easier workup conditions, small amount of time and high yielding. The acylation reaction was carried out with acetic anhydride. All structures of synthesized products have been identified by NMR and mass spectroscopy.

Keywords: N-acylation, sulfonamide, ultrasonic irradiation, green chemistry.

INTRODUCTION

The N-acyl sulfonamide moiety is a common feature in several important bio molecules and has emerged as an important class drug synthesis¹-⁴. A large number of novel N-acylated-sulfonamides-sulfonamides molecules have been investigated for antibacterial activity⁴. They are also known as therapeutic agents for Alzheimer's disease⁵ and anti-proliferative agents⁶.

In the literature, several reaction pathways for the preparation of N-acyl sulfonamides have been developed, most of them were carried out by the condensation of the various sulfonamides with acyl chloride or anhydride under basic conditions⁷. Acylation of sulfonamides can also be achieved with concentrated H₂SO₄⁸, Lewis acids⁹ or heterogeneous solid acid¹⁰ in acetonitrile under acidic conditions. Another attractive method based on using of palladium-catalyzed acylation of aryl with sulfonamides under microwave irradiation¹¹.

Recently, an efficient method for acylation of sulfonamides in acetonitrile with H₃P₂W₁⁶O₆² as acidic solid catalyst is described by Boughelem et al.¹². Synthetic methods should be developed, to produce molecules that are no toxic to human health.
and the environment, because we are all inhabitants on Earth, everyone is a stakeholder, and every person aims contributing to environmental protection locally, nationwide and worldwide.

Chemists have focused on maximizing yield, reducing energy and minimizing the number of steps by application of the green chemistry principle of atom economy to chemical reactions.

Chemical synthesis usually requires an energy source; there are several types of traditional energy such as: light, heat and ionizing radiation. Sonication chemistry can be replaced the traditional energy used for the chemical reaction by irradiation ultrasonic.

In this protocol, ultrasound provides strange mechanism for supplying high energy chemistry, based on acoustic cavitation. It was suggested that sonication also assists in the breakdown of intermediates and desorption of the products from the surface. The use of ultrasound in chemical reactions provides specific activation based on a physical-chemical phenomena which are currently a matter of advanced research. In recent years, ultrasound irradiation has been considered as a successful method in organic synthesis, because it has several advantages such as: shorter reaction time, higher yield and milder conditions.

Herein, we describe a practical procedure for the acylation of various amines and sulfonamides with acetic anhydride at room temperature and without a solvent using ultrasonic irradiation.

**EXPERIMENTAL**

**General**

The sulfonamide derivatives were prepared according to the literature. All reactions were monitored by thin layer chromatography using Merck TLC Silicagel 60 F254, using the solvents indicated. Silica gel column chromatography was performed over. Sonication was performed in a FUNGILAB ultrasonic bath at a frequency of 40 kHz and nominal power 260 W. Melting points were measured in open capillary tubes on an electro thermal-apparatus.

$^1$H-NMR and $^{13}$C-NMR spectra were recorded on Bruker spectrometer (400 and 100MHz) using (CDCl$_3$) as solvent and (TMS) as an internal standard. IR spectra were recorded on a Perkin-Elmer FT-600 spectrophotometer. Mass spectra were performed on a Shimadzu QP operating at an IP of 30 or 70 eV.

**Typical experimental procedure for N-acylation of amines and sulfonamides**

In a glass tube was placed a mixture of amine or sulfonamide derivatives (1 equiv) and acetic anhydride (1 equiv) at room temperature. The mixture was immersed in the water of the sonicator bath for an appropriate time at room temperature. Reaction was monitored by TLC.

After completion of the reaction, the reaction mixture was diluted with the water, and extracted with ethyl acetate, the organic layer was dried over anhydrous sodium sulfate and the resulting residue was purified by silica gel chromatography using dichloromethane-petroleum ether (9:1), to give the N-acylamines or N-acylsulfonamides in good yields.

**N-Phenylacetamide**

Oil; 88 % yield; $^1$H NMR (CDCl$_3$): 7.2-7.5 (m, 5H, Ar), 2.2 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$): 168.9, 138.5, 128.9, 128.0, 121.6, 24.0; LCMS (+) m/z, 136.07 [M+H]$^+$, C$_8$H$_9$NO.

**N-(4-Methoxyphenyl)acetamide**

Oil; 89 % yield; $^1$H NMR (CDCl$_3$): 6.9-7.4 (m, 4H, Ar), 2.2 (s, 3H, CH$_3$), 3.6 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$): 168.9, 158.9, 130.8, 122.6, 114.5, 55.8, 24.2; LCMS (+) m/z, 166 [M+H]$^+$, C$_9$H$_{11}$NO$_2$.

**N-(3,4-Dihydroisoquinolin-2(1H)-yl)acetamide**

Powder; 70 % yield; mp 110-111 °C; IR (KBr): 1660 (CO); $^1$H NMR (CDCl$_3$): 7.2–7.0 (m, 4H, Ar), 4.4 (s, 2H, CH$_2$), 3.4 (t, 2H, J=5.5 Hz, CH$_2$), 2.6 (t, 2H, J=5.8 Hz, CH$_2$), 2.1 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$): 169.2, 134.1, 127.7, 127.5, 126.9, 126.3, 49, 47, 28.6, 21.1; LCMS (+) m/z, 176.10 [M+H]$^+$, C$_{11}$H$_{13}$NO.

**N-(3,4-Dihydroisoquinolin-2(1H)-yl)acetamide**

Powder; 70 % yield; mp 110-111 °C; IR (KBr): 1660 (CO); $^1$H NMR (CDCl$_3$): 7.2–7.0 (m, 4H, Ar), 4.4 (s, 2H, CH$_2$), 3.4 (t, 2H, J=5.5 Hz, CH$_2$), 2.6 (t, 2H, J=5.8 Hz, CH$_2$), 2.1 (s, 3H, CH$_3$); $^{13}$C NMR (CDCl$_3$): 169.2, 134.1, 127.7, 127.5, 126.9, 126.3, 49, 47, 28.6, 21.1; LCMS (+) m/z, 176.10 [M+H]$^+$, C$_{11}$H$_{13}$NO.

**N-(4-Phenylpiperazin-1-yl)acetamide**

Powder; 74 % yield; mp 113-114 °C; IR (KBr): 1752 (CO); $^1$H NMR (CDCl$_3$): 7.45-6.95 (m, 5H, Ar), 3.62 (t, 4H, J=5.2, 4.8 Hz, CH$_2$), 3.25
N-(N-Cyclohexylsulfonyl) acetamide
Powder; 94 % yield; mp 198-199 °C; IR (KBr): 3371 and 3268 (NH), 1738 (CO), 1363 (SO
(KBr): 3374 and 3267 (NH), 1735 (CO), 1362 and 1154 (SO
Powder; 90 % yield; mp 168-169 °C; IR (KBr): 3370 and 3265 (NH), 1730(CO), 1360 and 1153 (SO); ¹H NMR (CDCl₃): 6.2-1.1 (m, 10H, CH₂), 3.2 (d, 1H, J7.35 Hz, CH), 2.0 (s, 3H, CH₃); ¹³C NMR (CDCl₃): 171.0, 43.9, 32.6, 25.7, 24.8, 21.6; LCMS (+) m/z, 222.09 [M+H]+, C₈H₆N₂O₄.

N-(N-(3-Fluorophenyl)sulfonyl) acetamide
Powder; 93 % yield; mp 147-148 °C; IR (KBr): 3260 and 3068 (NH), 1694 (CO), 1368 and 1162 (SO); ¹H NMR (CDCl₃): 6.9 (m, 1H, Ar), 7.06 (m, 2H, Ar), 7.3 (m, 1H, Ar); ¹³C NMR (DMSO-d₆): 22.9, 44.2, 125.8, 126.2, 126.7, 127.9, 128.6, 142.3; MS (+) m/z, 246.06 [M+NH₄]+, C₈H₆N₂O₄SF.

N-(N-(3-Fluorophenyl)sulfonyl) acetamide
Cristal; 90%  yield; mp 173-174 °C; IR (KBr): 3261 (NH), 1695 (CO), 1361 and 1155 (SO); ¹H NMR (CDCl₃): 8.1 (s, 1H, NH), 7.2-7.0 (m, 4H, Ar), 4.5 (s, 2H, CH₂), 3.7 (t, 2H, J5.7 Hz, CH₂), 2.9 (t, 2H, J5.8 Hz, CH₂), 2.1 (s, 3H, CH₃); ¹³C NMR (CDCl₃): 173, 134.1, 127.5, 126.9, 126.3, 125.7, 48.1, 47.2, 25.3, 21.6; MS (+) m/z, 255.07 [M+NH₄]+, C₁₅H₁₄N₂O₄S.

Table 1: Synthesis of N-acylamines

| Entry | Substrate | Product | Time (min) | Yield (%) |
|-------|-----------|---------|------------|-----------|
| 1     | ![Image](https://example.com/1.png) | ![Image](https://example.com/2.png) | 15         | 88        |
| 2     | ![Image](https://example.com/3.png) | ![Image](https://example.com/4.png) | 15         | 89        |
| 3     | ![Image](https://example.com/5.png) | ![Image](https://example.com/6.png) | 30         | 70        |
| 4     | ![Image](https://example.com/7.png) | ![Image](https://example.com/8.png) | 30         | 74        |
Table 2: Synthesis of N-acyl sulfonamides

| Entry | Substrate | Product | Time (min) | Yield (%) |
|-------|-----------|---------|------------|-----------|
| 5     | ![Substrate 5](image1) | ![Product 5](image2) | 30         | 94        |
| 6     | ![Substrate 6](image1) | ![Product 6](image2) | 15         | 90        |
| 7     | ![Substrate 7](image1) | ![Product 7](image2) | 15         | 95        |
| 8     | ![Substrate 8](image1) | ![Product 8](image2) | 30         | 96        |
| 9     | ![Substrate 9](image1) | ![Product 9](image2) | 30         | 93        |
| 10    | ![Substrate 10](image1) | ![Product 10](image2) | 40         | 90        |
| 11    | ![Substrate 11](image1) | ![Product 11](image2) | 60         | 60        |
| 12    | ![Substrate 12](image1) | ![Product 12](image2) | 35         | 80        |
| 13    | ![Substrate 13](image1) | ![Product 13](image2) | 20         | 85        |
| 14    | ![Substrate 14](image1) | ![Product 14](image2) | 30         | 83        |

(R)-N-(N-(1-Phenylethyl)sulfamoyl) acetamide
Powder; 85 % yield; mp 171-172 °C; IR (KBr): 3370 and 3265 (NH), 1698 (CO), 1361 and 1152 (SO₂); ¹H NMR (CDCl₃): 8.1 (s, 1H, NH), 7.5-7.2 (m, 5H, Ar), 5.9 (s, 1H, NH), 5.15 (m, 1H, "CH,"
2.00 (s, 3H, CH₃), 1.50 (d, 3H, J 6.9 Hz, CH₃);¹³C NMR (CDCl₃): 171.3; 145.1; 128.2; 126.8; 126.4; 47.2; 21.0; 20.6 ppm; LCMS (+) m/z, 243.07 [M+H]+, C₁₀H₁₄N₂O₃S.

**Ethyl-1-(N-acetysulfamoyl)pyrrolidine-2-carboxylate**

Powder; 83 % yield; mp 199-200°C; IR (KBr): 3254 (NH), 1733 (CO), 1692 (CO), 1369 and 1166 (SO₂);¹HNMR (CDCl₃): 8.7 (s, 1H, NH), 4.7 (m, 1H, *CH*₂), 4.3 (q, 2 H, J 2.4 Hz, CH₂), 3.4-3.7 (m, 6H, CH₂), 2.1 (s, 3H, CH₃), 1.3 (t, 3H, J 2.4 Hz, 3H, CH₃);¹³CNMR (CDCl₃): 171.1, 171.0, 61.3, 60.6, 55.2, 27.7, 21.4, 21.6, 14.1; LCMS (+) m/z, 265.08 [M+H]+, C₉H₁₆N₂O₅S.

**RESULTS AND DISCUSSION**

Following our efforts to develop novel methods for acylation²⁴-²⁷,¹² and in continuation of our investigation on the use of ultrasound irradiation to accelerate reactions²⁸-³⁰, we describe a novel method for acylation the different amines and sulfonamides with acetic anhydride under ultrasonic irradiation, in absence of solvent and catalyst.

The main mechanism of sonochemical was the formation of cavitation bubbles³¹, under certain conditions, some bubbles implode, generating very high temperatures and pressures, these transient, localized hot spots drive high-energy chemical reactions³²-³⁴.

In order to carry out the acylation of the amine function under ultrasonic irradiation, the amine was chosen as a model substrate, the reaction of amine with acetic anhydride using ultrasonic irradiation as shown in scheme 1, the reaction was completed at 15-30 min, the acylated products were isolated in good yields (Scheme 1).

The N-acylation of amines was successfully achieved using acetic anhydride under ultrasound irradiation. The reactions proceed smoothly in high yields (70-89 %) and in short reaction time (table 1). The structures of all compounds were unambiguously confirmed by spectroscopic methods. Proton nuclear magnetic resonance spectra showed singlets at 2.20-2.25 ppm corresponding to the proton of CH₃ acetyl. Infrared spectra showed bands at 1650-1700 cm⁻¹ of functional group C=O.

Encouraged by this result, we extended the reaction to sulfonamides derivatives using ultrasonic irradiation (Scheme 2). The results are reported in (Table 2, entry 5-14). In all cases, we obtained the corresponding products N-acyl sulfonamides in good to excellent yields.

**Scheme 2: Catalyst-free synthesis of N-acylsulfonamides under ultrasonic irradiation**

For the resulting products, Infrared spectra showed band at 1650-1700 cm⁻¹ of functional group (C=O) of acetyl moiety and band at 1170-1395 cm⁻¹ of sulfonyl group. In Proton nuclear magnetic resonance spectra, the structure of N-acyl sulfonamides was confirmed by a singlet at 2.27 ppm corresponding to CH₃ group.

The structures of all molecules synthesized were confirmed by usual spectroscopic methods, IR,¹HNMR,¹³CNMR and mass spectrometry.

**CONCLUSION**

In summary, the acylation of amines or sulfonamides was successfully achieved using acetic anhydride under ultrasound irradiation. This methodology provides a green and much improved approach over the classic methods. Ultrasound can be an effective technology for process intensification in with cavitation collapse can affect chemical transformations. The use of
ultrasound is expected to enhance the rate of reaction by various mechanisms.

The non-conventional method offers advantages over conventional processes, short time span to complete reaction, easy work procedure and excellent yields.

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REFERENCES

1. Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. Curr. Med. Chem. 2003, 10, 925-953.
2. Rathish, I. G.; Kalim, J.; Shamim, A.; Sameena, B.; Alam, M. S.; Mymooana, A. Eur. J. Med. Chem. 2012, 49, 304-309.
3. Yildirim, A.; Atmaca, U.; Keskin, A.; Topa, M.; Celik, M.; Gulcin, I. Bioorg. Med. Chem. 2015, 23, 2598-2605.
4. Banwell, M. G.; Crasto, C. F.; Easton, C. J.; Forrest, A. K.; Karoli, T.; March, D. R.; Mensah, L.; O’Hanlon, P. J.; Oldham, M. D.; Yue, W. Bioorg. Med. Chem. Lett. 2000, 10, 2263-2267.
5. Hasegawa, T.; Yamamoto, H. Bull. Chem. Soc. Jpn. 2000, 73, 423-428.
6. McCuskey, A.; Keane, M. A.; Mudgee, L. M.; Sim, A. T.; Sakoff, J.; Quinn, R. Eur. J. Med. Chem. 2000, 35, 957-964.
7. Drummond, J.T.; Johnson, G.; Tetrahedron Lett. 1988, 29, 1653-1656.; Guzzo, P. R.; Teng, M.; Miller, M. J. Tetrahedron. 1994, 50, 8275-8292.
8. Massah, A.; R.; Asad, B.; Hoseinpour, M.; Molseghi, A.; Kalbasi, R. J.; Nahghash, H. J. Tetrahedron. 2009, 65, 7696-7705.
9. Raji Reddy, C.; Mahidal, B.; Yaragorla, S. R. Tetrahedron Lett. 2007, 48, 7528-7532.
10. Singh, D. U.; Singh, P. R.; Samant, S. D. Tetrahedron Lett. 2004, 45, 4805-4982; Massah, A.; Reza, Momeni, A.; Reza, Dabagh, M.; Aliyan, H. Synth. Commun. 2008, 38, 265-273.
11. Wu, X.; Rönn, R.; Gossas, T.; Larhed, M. J. Org. Chem. 2005, 70, 3094-3098.
12. Bougheloum, C.; Barbey, C.; Berredjem, M.; Messalhi, A.; Dupont, N. J. Mol. Struct. 2013, 1041, 6-15.
13. Safari, J.; Zarnegar, Z. Ultrason. Sonochem. 2014, 21, 1132-1139.
14. Banitabe, S. H.; Safari, J.; Dkhaili, S. Ultrason. Sonochem. 2013, 20, 401-407.
15. Dilbeck, G. A.; Field, L.; Gallo, A. A.; Gargiulo, R. J. J. Org. Chem. 1978, 43, 4593-4596.
16. Khaligh, N. G.; Shirin, F. Ultrason. Sonochem. 2013, 20, 26-31.
17. Cravotto, G.; Cintas, P. Chem. Soc. Rev. 2006, 35, 180-196.
18. Gholap, R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. Green Chem. 2004, 6, 147-150.
19. Driowya, M.; Puissant, A.; Robert, G.; Aubergier, P.; Benhida, R.; Bougrin, K. Ultrason. Sonochem. 2009, 12, 1132-1138.
20. Belhani, B.; Bouzina, A.; Aouf, N. E.; Berredjem, M. Monatsh. Chem. 2015, 146, 1871-1875.
21. Belhani, B.; Berredjem, M.; Le Borgne, M.; Bouaziz, Z.; Lebreton, J.; Aouf, N. E. RSC Adv. 2015, 5, 39324-39329.
22. Nasrollahzadeh, M.; Ehsani, A.; Rostami-Vartouni, A. Ultrason. Sonochem. 2014, 21, 275-282.
23. Bouzina, A.; Berredjem, M.; Bouacida, S.; Mrazig, H.; Aouf, N. E. RSC Adv. 2015, 5, 99775-99780.
24. Ouarna, S.; K'tir, H.; Lakrout, S.; Ghorab, H.; Amira, A.; Aouf, Z.; Berredjem, M.; Aouf, N. F.; Vartouni, A.
25. Bouchareb, F.; Boufas, W.; Cheloufi, H.; Berredjem, M.; Aouf, N. E. *Phosphorus, Sulfur Silicon Relat. Elem.* **2014**, *189*, 587-595.
26. Berredjem, M.; Bouchareb, F.; Ait Kaki, S.; Dekhil, M.; Aouf, N.E. *Arab. J. Chem.* **2013**, DOI: [10.1016/j.arabjc.2013.01.016](http://dx.doi.org/10.1016/j.arabjc.2013.01.016).
27. Bouasla, R.; Berredjem, M.; Hessainia, S.; Berredjem, H.; Aouf, N. E. *J. Chem. Chem. Eng.* **2011**, *5*, 1153-1159.
28. Grib, I.; Bouzina, A.; Aouf, N. E.; Berredjem, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2016**, *191*, 1086-1091.
29. Bouzina, A.; Aouf, N. E.; Berredjem, M. *Res. Chem. Intermed.* **2016**, *42*, 5993-6002.
30. Mansouri, R.; Aouf, Z.; Lakrout, S.; Berredjem, M.; Aouf, N. E. *J. Braz. Chem. Soc.* **2016**, *27*, 546-550.
31. Leighton, T. G. *The Acoustic Bubble.* Academic Press: London, 1994.
32. Flint, E. B.; Suslick, K. S. *Science.* **1991**, *253*, 1397-1399.
33. Suslick, K. S.; Didenko, Y.; Fang, M. M.; Hyeon, T.; Kolbeck, K. J. *Philos. Trans. R. Soc. London, Ser. A.* **1999**.
34. Mason, T. J.; Peters, D. *Practical Sonochemistry Power Ultrasound Uses and Applications*, 2nd ed.; Ellis Horwood: New York, 2002; Mason, T. J. *Ultrason. Sonochem.* **2007**, *14*, 476-483.