Microwave Synthesis of some Substituted Hydrazones under Solvent - Free Conditions

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Abstract

Hydrazide of oxobenzotriazine (4) was synthesized from its corresponding esters. This hydrazide was then allowed to irradiate with various substituted benzaldehydes under solvent-free conditions forming new hydrazone compounds (5-10). The advantage of this work is to develop new synthetic route of hydrazones which is environmentally and economically desirable. The formation of all compounds were confirmed by analytical and spectral (^{1}H NMR, ^{13}C NMR, mass & IR) methods.

1 Introduction

In organic chemistry hydrazones and their derivatives constitute versatile class of compounds. The presence of hydrazone moiety in these compounds influence these compounds a variety of biological activities such as analgesic[1], antitumor[2], anticonvulsant[3], anti-inflammatory[4], antituberculous[5] anti-HIV[6,7] and anti-prion activities[8]. As it was known that the structure of hydrazone compounds consist of two connected nitrogen atoms of different nature and C-N double bond which is conjugated with a lone electron pair of the terminal nitrogen atom. This structure enable the compound to have both electrophilic and nuclophilic characters as shown in figure (1).[9]

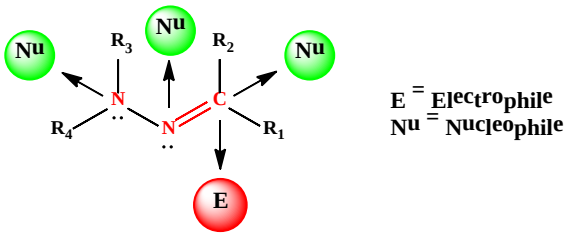


Figure 1: hydrazone structure.

There are numerous methods in the literature for the synthesis of hydrazides. The most popular method is acylation of hydrazine.[10] Generally, Hydrazides can be reacted with benzaldehyde or lactones in organic solvents forming the corresponding hydrazones.[11-13] These methods have several disadvantages such as the solvents used (mostly carcinogenic solvents)[14]. The long reaction time and low yield product are also undesirable and inconvenient for organic synthesis. In our earlier paper we reported the synthesis of hydrazone derivatives using the conventional method which involve long reaction time and lower yield.[15] Therefore, we report here a new synthetic method for the synthesis of some substituted hydrazone derivatives using microwave irradiation under solvent free conditions in order to achieve the product within shorter reaction time and higher product yield. In our next work is to study these hydrazones biologically, screened as anti-prion agents investigation.

2 Experimental

All reagents were purchased from commercial sources and used as supplied without further purification. Microwave reactions were carried out via Smith Creator™ Optimiser EXP reaction (Personal Chemistry, Inc.). Reactions were performed in Smith Process Vials ™. Melting points were recorded on a Gallenkamp machine. $^{1}H/^{13}C$ NMR spectra were recorded at 250 or 400 MHz on a Bruker AV-1400 model or a Bruker AV-1250 model NMR instrument. Accurate masses were obtained using a Water-Micromass LCT electrospray mass spectrometer. All reactions and measurement were performed at the chemistry department, university of Sheffield, United kingdom. Compound (1) was synthesized according to the well-known procedure[16]. Compound (3) was synthesized following the elsewhere published procedure.[17] Hydrazide (4) was synthesized following an earlier published procedure[15]. The structure of all compounds were confirmed using analytical and spectral NMR, mass & IR instrument.

2.1 Microwave synthesis of hydrazones 5-10

In a 20 mL microwave vial, equimolar quantities of hydrazide (4) and substituted benzaldehyde were heated to 40 ^{o}C (16 bar) via microwave irradiation for 5 minutes. The mixture was then allowed to cool to room temperature and then an ice cold water was added. The

precipitate was then collected and purified by recrystallization from ethanol affording the pure product as a white crystal compound. The physical and spectral data were presented in the following article.

3 Results and discussion

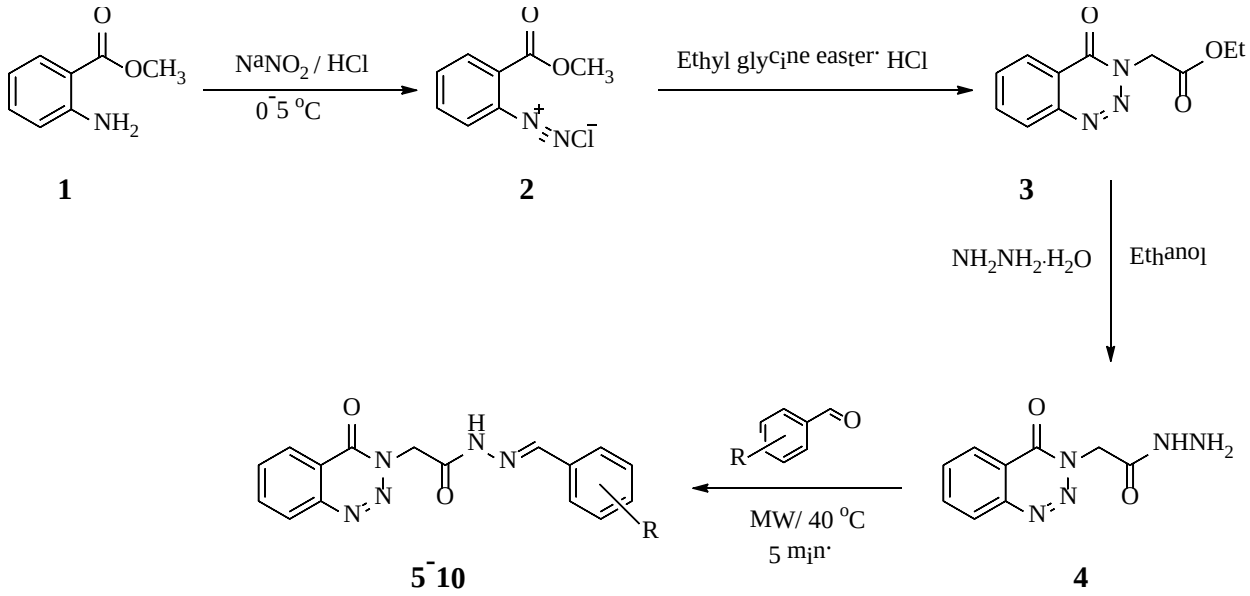
In our pervious batch protocol, we reported that the synthesis of hydrazones were obtained within three hours at room temperature in good percentage yield using absolute ethanol as a solvent. Continuation of our interest in the development of green organic synthesis, a microwave protocol was used as a simple and efficient protocol to achieve this new series of hydrazones in shorter reaction time and excellent percentage yield.

The reaction was irradiated for five minutes at 40 ^{o}C (16 bar) under solvent-free conditions. The progress of the reaction was followed by TLC check. The product was obtained in an excellent yield within only 5 minutes as shown in Table 1, Scheme 1.

Table 1: Batch and microwave conditions for hydrazones **5-10**

Comp. No.	Batch yield %	Batch time/h.	Microwave yield %	Microwave time/ min.
5	61	3	93	5
6	57	3	91	5
7	63	3	94	5
8	69	3	93	5
9	69	3	90	5
10	68	3	96	5

It is obvious from the results that performing the reaction under batch conditions using ethanol as a solvent provide 57-69 % of the pure products while under solvent-free conditions 90-96 % of the pure products were obtained when the reaction accomplished using microwave irradiation. Furthermore, it was noticeable that only five minutes was sufficient to obtain the products in high yield under microwave irradiation which was much better than the conventional batch conditions.



Scheme 1

(*E*)-*N'*-(2,6-dichlorobenzylidene)-2-(4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl)acetohydrazide (5).

Yellow solid, mp: 137-138 °C. 93% yield. ^{1}H NMR (DMSO-d$_6$, 400MHz): δ 12.1 (bs, 1H, NH), 8.4-7.4 (m, 7 Ar-H), (s, 1H, CH), 5.5, 5.2 (s, 2H, CH$_2$ in and out of the plane). ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 168.4, 155.3, 144.2, 140.0, 136.1, 134.4, 134.3, 133.6, 131.7, 129.8, 129.4, 128.6, 119.5, 51.1. υ_{max} (ATR) cm^{-1} 3230 (NH), 1710, 1663 (C=O), 1603 (C=N), 1337 (C-N). High resolution mass spectrum m/z % (ES): found 376.0368 requires for ($C_{16}H_{12}N_5O_2Cl_2$ $[M + H]^+$) 376.0368.

(*E*)-*N'*-(4-methoxy-3-nitrobenzylidene)-2-(4-oxobenzo[*d*][1,2,3]triazin-3(4*H*)-yl)acetohydrazide (6).

White solid, mp: 142 °C. 91% yield. ^{1}H NMR (DMSO-d$_6$, 400MHz): δ 12.0 (bs, 1H, NH), 8.3-7.4 (m, 7 Ar-H), (s, 1H, CH), 5.6, 5.2 (s, 2H, CH$_2$ in and out of the plane), 3.9 (s, 3H, OCH$_3$). ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 168.2, 163.4, 155.3, 153.2, 145.6, 144.2, 142.6, 140.1, 136.1, 133.6, 133.0, 128.6, 127.1, 125.0, 124.0, 57.45, 51.2. υ_{max} (ATR) cm^{-1} 3231 (NH), 1738, 1655

(C=O), 1614 (C=N), 1347 (C-N). High resolution mass spectrum m/z % (ES): found 383.1104 requires for ($C_{17}H_{15}N_6O_5$ $[M + H]^+$) 383.1104.

(*E*)-*N'*-(3,4-dimethoxybenzylidene)-2-(4-oxobenzo[d][1,2,3]triazin-3(4*H*)-yl)acetohydrazide (7).

Pale yellow solid, mp: 146 °C. 94% yield. ^{1}H NMR (DMSO-d_6, 400MHz): δ 11.9 (bs, 1H, NH), 8.4-7.0 (m, 7 Ar-H), (s, 1H, CH), 5.6, 5.2 (s, 2H, CH_2 in and out of the plane), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.8, 163.0, 155.3, 151.1, 149.5, 148.1, 145.0, 144.3, 136.1, 133.6, 128.6, 127.0, 125.0, 122.3, 121.9, 56.0, 55.9, 51.2. υ_{max} (ATR) cm^{-1} 3182 (NH), 1695, 1672 (C=O), 1520 (C=N), 1388 (C-N). High resolution mass spectrum m/z % (ES): found 368.1376 requires for ($C_{18}H_{18}N_5O_4$ $[M + H]^+$) 368.1359.

(*E*)-*N'*-(3,5-dimethoxybenzylidene)-2-(4-oxobenzo[d][1,2,3]triazin-3(4*H*)-yl)acetohydrazide (8).

Pale yellow solid, mp: 149-150 °C. 93% yield. ^{1}H NMR (DMSO-d_6, 400MHz): δ 11.9 (bs, 1H, NH), 8.3-6.6 (m, 7 Ar-H), (s, 1H, CH), 5.6, 5.2 (s, 2H, CH_2 in and out of the plane), 3.8 (s, 6H, $(OCH_3)_2$). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.2, 161.1, 155.3, 144.7, 144.3, 136.3, 136.2, 128.6, 125.0, 119.5, 105.3, 105.2, 102.7, 55.8, 51.2. υ_{max} (ATR) cm^{-1} 3189 (NH), 1698, 1619 (C=O), 1591 (C=N), 1356 (C-N). High resolution mass spectrum m/z % (ES): found 368.1354 requires for ($C_{18}H_{18}N_5O_4$ $[M + H]^+$) 368.1359.

(*E*)-*N'*-(2-chloro-6-fluorobenzylidene)-2-(4-oxobenzo[d][1,2,3]triazin-3(4*H*)-yl)acetohydrazide (9).

White solid, mp: 138 °C. 90% yield. ^{1}H NMR (DMSO-d_6, 400MHz): δ 12.1 (bs, 1H, NH), 8.5-7.3 (m, 7 Ar-H), (s, 1H, CH), 5.5, 5.2 (s, 2H, CH_2 in and out of the plane). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.3, 162.2, 159.6, 155.3, 144.3, 137.9, 136.1, 134.0, 133.6, 132.2, 132.1, 128.6, 126.8, 125.0, 120.5, 51.0. υ_{max} (ATR) cm^{-1} 3205 (NH), 1698, 1665 (C=O), 1600 (C=N), 1355 (C-N). High resolution mass spectrum m/z % (ES): found 360.0667 requires for ($C_{16}H_{11}N_5O_2Cl$ $[M + H]^+$) 360.0652.

(*E*)-*N'*-(2,6-dimethylbenzylidene)-2-(4-oxobenzo[d][1,2,3]triazin-3(4*H*)-yl)acetohydrazide (10)

White solid, mp: 138 ^{o}C. 96% yield. ^{1}H NMR (DMSO-d_6, 400MHz): δ 11.9 (bs, 1H, NH), 8.6-7.1 (m, 7 Ar-H), (s, 1H, CH), 5.5, 5.2 (s, 2H, CH_2 in and out of the plane), 2.4 (s, 6H, $(CH_3)_2$). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.9, 155.3, 144.3, 137.8, 136.1, 133.6, 130.8, 129.4, 129.3, 129.1, 128.6, 125.0, 119.5, 51.1, 21.7. υ_{max} (ATR) cm^{-1} 3121 (NH), 1683, 1602 (C=O), 1578 (C=N), 1337 (C-N). High resolution mass spectrum m/z % (ES): found 336.1468 requires for ($C_{18}H_{18}N_5O_2$ $[M + H]^+$) 336.1461.

Conclusion:

In this work we reported solvent free ecofriendly synthesis of hydrazones under microwave condition. The advantage of this protocol is to avoid using of solvent and increase the percentage yield of the product. It is clear that synthesizing this series of hydrazones using microwave irradiation under solvent-free conditions was found to be the optimal or most suitable reaction method which produces a higher product yield with shorter reaction time compared with the conventional batch method in the presence of ethanol as a reaction media.

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Reference

1. Almasirad, A.; Tajik, M.; Bakhtiari D. *Journal of Pharmacy and Pharmaceutical Sciences.* 8(3), 419–425, **2005**.
2. Nasr, Tamer; Bondock, Samir; Youns, Mahmoud *European Journal of Medicinal Chemistry*. 76, 539-548, **2014.**
3. Sinha, R.; Sara, UVS; Khosa, R. L.; Stables, J.; Jain, *J. Medicinal Chemistry Research*. 20(9), 1499-1504, **2011**.
4. A. S. de Miranda, W. B. J'unior, Y. K. C. da Silva et al., "Design,synthesis, antinociceptive and anti-inflammatory activities ofnovel piroxicam analogues," in *Molecules*. vol. 17, no. 12, pp.14126–14145, **2012**.
5. Andreani, A.;Burnelli, S.; Granaiola, M.; Leoni, A.; Locatelli, A.; Morigi, R.; Rambaldi, M.; Varoli, L.;Calonghi, N.; Cappadone, C.; Farruggia, G.; Zini, M.; Stefanelli, C.; Masotti, L.; Radin, N.S.; Shoemaker, R. H. *J. Med. Chem*. *51*, 809, **2008**.
6. Noulsri, E.; Richardson, R.;Lerdwana, S.; Fucharoen, S.; Yamagishi, T.; Kalinowski, D. S.; Pattanapanyasat, K. *Am. J.Hematology*. *84*, 170, **2009**.
7. Chen K, Tan Z, He M, Li J, Tang S, Hewlett I, YuF, Jin Y, Yang M. Structure-Activity relationships(SAR) research of thiourea derivatives as dualinhibitors targeting both HIV-1 capsid and humancyclophilin A. *Chem Biol Drug Des*. 76(1):25-33, **2010**.
8. Duo Lu, Kurt Giles, Zhe Li, Satish Rao, Elena Dolghih, J. Pharmacol. Exp. Ther. 347:325–338, November **2013**.
9. (a) Kim, S.; Yoon, J.-Y. *Sci. Synth*. *27*, 671, **2004**. (b). Brehme, R.; Enders, D.; Fernandez,R.; Lassaletta, J. M. *Eur. J. Org. Chem*. 5629, **2007**.
10. H.Pausen and D.stoye "The chemistry of hydrazides" John Wiley and Songs , 515,**1970**.
11. M. Freifelder, *J. Org. Chem.*, 31, 3875, **1966**.
12. T. Govindasami, "Synthesis, Characterization and Antibacterial Activity of Biologically Important Vanillin Related Hydrazone Derivatives," Int. *J. Org. Chem.*, vol. 1, No. 9, . 71–77, **2011**.
13. A. Özdemir, G. Turan-Zitouni, Z. A. Kaplancikli, and M. D. Altintop, "The synthesis of some new hydrazone derivatives containing the benzothiazole moiety," *J. Serbian Chem. Soc.*, vol. 77, No. 2, pp. 141–146, **2012**.
14. J. Nawrot Modranka and E. Nawrot, *Acta Poloniae Pharmaceutica ñ Drug Research*, Vol. 63 No. 5 pp. 429ñ434, **2007.**
15. Mohammed S. Al-Ajely and Aymen N. Yaseen *International Journal of Scientific & Engineering Research*, Volume 7, Issue 4, April-**2016**.
16. P. Wiklund and J. Bergman, "The Chemistry of Anthranilic Acid," *Current Organic Synthesis*, vol. 3, No. 3.379–402, **2006**.
17. H. K. Krishnan, N. M. Muni, and N. S. Sahruna, *J. Adv. Chem.*,vol. 4, No. 1, pp. 266–275, **2014**.