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AN EXPEDIENT METHOD FOR THE SYNTHESIS OF BIS(ACYLHYDRAZONES) UNDER MICROWAVE IRRADIATION IN SOLVENT-FREE MEDIUM

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Abstract - A simple, efficient and eco-friendly method for the synthesis of bis(acylhydrazones) from hexanediohydrazide and aldehydes under microwave irradiation without the use of solvent and catalyst is reported. The technique of microwave irradiation under solvent-free condition proved to be quite a valuable method in organic synthesis.

Keywords: Bis(acylhydrazones); Hexanediohydrazide; Adehydes; Microwave; Solvent-free.

INTRODUCTION

Acylhydrazones have been extensively investigated in recent years as they were found to be associated with various biological activities have promising analytical properties and can be used as catalysts (Patrica et al. 2006, Silva et al. 2004 and Holla et al. 2000). Their metal complexes usually have more active pharmacological properties, as described by Carcelli et al. (1995), Paolo et al. (1999) and Baldini et al. (2003). The cyclic products of acylhydrazones are an important class of heterocyclic compounds with a wide range of pharmaceutical and biological activities, as depicted by Hamid et al. (2004) and Kidwai et al. (2000). Bis(acylhydrazones), a category of them also have been extensively investigated in recent years (Alessia et al. 2006).

Usually, the synthetic method to produce acylhydrazones involves a reaction between acylhydrazides and aldehydes in ethanol at reflux temperature for about 2-3 hours. Then the solvent is concentrated and the solid is filtered and recrystallized, giving yields of about 70-80%.

Microwave-assisted heating has been shown to be an invaluable technology in synthesis, since it can often dramatically reduce reaction times, typically from days or hours to minutes or even seconds. It can also provide pure products in quantitative yield and selectivity. Some reports describe the synthesis of acylhydrazones and their derivcatives under microwave irradiation, as described by Rostamizadeh and Housaini (2004), Bose et al. (2000), Xia and Pan (2004); however, this was carried out either on solid supports or using solvent in a teflon vessel. Though the reaction time was shortened (10-20min), the procedure was even more tedious when using a solid support. When solvent is used, the reaction condition must be carefully controlled or a special apparatus should be used, due to the danger of using organic solvents in microwave irradiation because of their low boiling points and high vapor pressure. Since acylhydrazones are

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*To whom correspondence should be addressed partially soluble in aldehyde or aldehyde is absorbed onto the surface of the solid with a reaction occurring at the interphase, the reaction can in principle be performed without an additional solvent. The presence of a solvent could also be deleterious due to dilution of the reactant.

Solvent-free reaction techniques were successfully coupled with microwave (Loupy et al., 1998) synthesis because they avoid the use of low boiling points and high vapor pressure solvents, which may produce potentially dangerous conditions, such as an explosion. Additionally, a solvent-free process is less expensive and environmentally friendly. With the rapid development of combinatorial libraries, in which a systematic system of initial screening of potential activities of compounds is possible, a fast and solvent-free method could be very attractive.

RESULTS AND DISCUSSION

In this paper, we introduce a microwave-assisted solvent-free method for the synthesis of bis(acylhydrazones), which allows for a more rapid and easier procedure. Self-made hexanediohydrazide reacted with twelve aldehydes to produce twelve corresponding bis(acylhydrazones) (see Figure 1). **4f** is new compound. Several experiments were carried out at various reaction times, power levels and different reactant ratios to establish the optimum reaction conditions. The inside temperature of the MW reaction was also studied. The products were analyzed using IR, ^{1}H NMR and elemental analysis. The ^{1}H NMR spectra of most compounds display two sets of methylene, imine and amide proton signals, indicating that both *cis* and *trans* amide conformers were formed. It is known from conventional synthesis that the *cis* isomer is formed in excess (Palla et al., 1986). It is expected that the *cis* isomers of **4a** should be due to the formation of an intramolecular hydrogen bond (Cordier et al., 2004).

It was found that there was no inevitable relationship between the yields and the electron-withdrawing and -donating groups in the substrates of the benzene ring of the aldehydes. However, the substrates containing electron-withdrawing groups can make the reaction time shorter.

All products were obtained in excellent yields (85-93%) and within minutes (between 2 and 5 minutes). The optimum conditions, yields and inside temperature of the MW reaction are presented in Table 1.

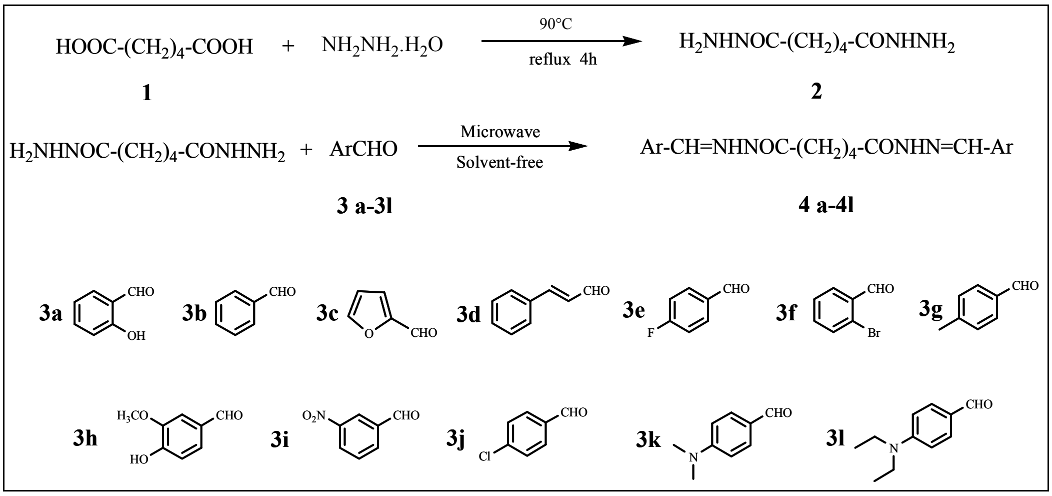

Figure 1: Synthesis of bis(acylhydrazones) (4a-4l)

EXPERIMENTAL

Melting points were determined with an XRC-1 micromelting point apparatus and were uncorrected. Infrared spectra were recorded on a FTS-40 spectrophotometer using KBr pellets. ^{1}H NMR spectra were measured on a Bruker DPX-400 spectrometer at 400 MHz using TMS as internal standard and DMSO-d$_6$ as solvent. Chemical shifts (δ) were expressed in ppm downfield from internal standard TMS and coupling constants *J* were given in Hz. Elemental analyses were performed on a PE-2400 elemental analyzer. The experiment was carried out in a domestic microwave oven (Galanz Cambi-Grill 750W).

Table 1: The optimum reaction condition and yields

Comp.	Power /W	Reaction time/min	Yields/%	Inside temperature/℃
4a	300	2	91	83
4b	300	2	91	83
4c	300	2	92	83
4d	300	3	88	110
4e	300	2.5	89	99
4f	300	4	93	123
4g	300	3	93	110
4h	495	5	85	143
4i	495	3	87	124
4j	495	3	92	124
4k	495	5	90	143
4l	495	5	89	143

Synthesis of Hexanediohydrazide (2)

One-tenth mol of hexanedioic acid **(1)** was dissolved in 0.8mol 85% hydrazine hydrate and the mixture was heated at 90℃ for 4h; upon cooling, a white crystal was separated out and recrystallized with ethanol-DMF to get the pure hexanediohydrazide **(2)**.

Synthesis of Bis(acylhydrazones) (4a-4l)

a) Thermal Conditions: General Procedure

Hexanediohydrazide and aldehydes at a ratio of 2:1 were mixed in ethanol and refluxed for about 2-4h; then the solvent was concentrated and the solid was filtered and recrystallized with ethanol-DMF to get the pure product.

b) Microwave Conditons

General procedure for **4a-4g**: 1 mmol of hexanediohydrazide **(2)** was put in a test tube and then 2.4 mmol liquid aldehydes **(3a-3g)** were added, The test tube was subjected to mechanical vibration to ensure maximum dissolution of the solid in the aldehydes. The reaction tubes were then subjected to microwave irradiation (300W) for the specified time. After the reaction had been completed, the solid was filtered and washed with cool ethanol to get pure products. No further purification was required.

General procedure for **4h-4l**: 1 mmol of hexanediohydrazide **(2)** and 2 mmol of solid aldehydes **(3h-3l)** were mixed thoroughly in an agate mortar and then the mixture was put into the microwave oven (495W) and irradiated for a specified time to produce the crude solid, which recrystallized with ethanol-DMF to give pure products.

Hexanedioic Acid, Bis[[(2-hydroxyphenyl)methylene]hydrazide] (4a)

White solid; m.p.: 294-296℃; IR(KBr) υ (cm^{-1}): 3440(OH), 3203(NH), 3069(=CH), 1681(C=O), 1491(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.57,11.16(2s, 2H, NH), 10.08(s, 2H, OH), 8.32,8.23(2s, 2H, CH=N), 7.60-6.80(m, 8H, Ar-H), 2.60-1.60(m, 8H, CH$_2$); Elemental analysis: Calcd.(%) for $C_{20}H_{22}N_4O_4$(382.4): C 62.82, H 5.80, N 14.65; Found: C 62.78, H 5.63, N 14.69.

Hexanedioic Acid, Bis[(phenylmethylene)hydrazide] (4b)

White solid; m.p.: 216-218℃; IR(KBr) υ (cm^{-1}): 3185(NH), 3094(=CH), 1670(C=O), 1486(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.31,11.18(2s, 2H, NH), 8.14,7.95(2s, 2H, CH=N), 7.90-7.34(m, 10H, Ar-H), 2.65-1.59(m, 8H, CH$_2$); Elemental analysis: Calcd.(%) for $C_{20}H_{22}N_4O_2$(350.4): C 68.55, H 6.33, N 15.99; Found: C 68.68, H 6.42, N 15.85.

Hexanedioic Acid, Bis[(2-furanylmethylene)hydrazide] (4c)

White solid; m.p.: 250-252℃; IR(KBr) υ (cm^{-1}): 3180(NH), 3093(H-C=N), 1662(C=O), 1473(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.24,11.12(2s, 2H, NH), 8.03,7.83(2s, 2H, CH=N), 7.78-6.55(m, 6H, Ar-H), 2.55-1.56(m, 8H, CH$_2$); Elemental analysis: Calcd.(%) for $C_{16}H_{18}N_4O_4$(330.3): C 58.17, H 5.49, N

16.96; Found: C 58.08, H 5.60, N 16.85.

Hexanedioic Acid, Bis[(3-phenyl-2-propenylidene)hydrazide] (4d)

White solid; m.p.: 262-264 ℃ ; IR(KBr) υ (cm^{-1}): 3238(NH), 3063(=CH), 1666(C=O), 1448(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.19,11.08(2s, 2H, NH), 7.90,7.77(2d, 2H, CH=N, *J*=5.6Hz), 7.57-6.92(m, 10H, Ar-H), 2.54-1.56(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{24}H_{26}N_4O_2$(402.5): C 71.62, H 6.51,, N 13.92; Found: C 71.78, H 6.60, N 13.85.

Hexanedioic Acid, Bis[[(4-fluorophenyl)methylene]hydrazide] (4e)

White solid; m.p.: 236-238℃; IR(KBr) υ (cm^{-1}): 3235(NH), 3057(=CH), 1661(C=O), 1461(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.32,11.19(2s, 2H, NH), 8.13,7.94(2s, 2H, CH=N), 7.71-7.16(m, 8H, Ar-H), 2.63-1.57(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{20}H_{20}F_2N_4O_2$(386.4): C 62.17, H 5.22, N 14.50; Found: C 62.38, H 5.15, N 14.41.

Hexanedioic acid, bis[[(2-bromophenyl)methylene]hydrazide] (4f)

White solid; m.p.: 272-274℃; IR(KBr) υ (cm^{-1}): 3191(NH), 3052(=CH), 1674(C=O), 1463(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.58,11.41(2s, 2H, NH), 8.48,8.29(2d, 2H, CH=N, *J*=2.8), 7.90-7.27(m, 8H, Ar-H), 2.65-1.62(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{20}H_{20}Br_2N_4O_2$(508.2): C 47.27, H 3.97, N 11.02; Found: C 47.08, H 3.80, N 11.11.

Hexanedioic Acid, Bis[[(4-methylphenyl)methylene]hydrazide] (4g)

White solid; m.p.: 244-246℃; IR(KBr) υ (cm^{-1}): 3247(NH), 3055(=CH), 1666(C=O), 1462(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.23,11.10(2s, 2H, NH), 8.09,7.91(2s, 2H, CH=N), 7.54-7.14(m, 8H, Ar-H), 2.63-1.57(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{22}H_{26}N_4O_2$(378.5): C 69.82, H 6.92, N 14.80; Found: C 69.78, H 6.80, N 14.97.

Hexanedioic Acid, Bis[[(3-methoxy-4-hydroxyphenyl)methylene] hydrazide] (4h)

White solid; m.p.: 213-216℃; IR(KBr) υ (cm^{-1}): 3489(OH), 3240(NH), 3059(=CH), 1662(C=O), 1461(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.11,11.00(2s, 2H, NH), 9.43,9.39(s, 2H, OH), 8.01,8.00(2s, 2H, CH=N), 7.21-6.74(m, 6H, Ar-H), 3.76(s, 6H, CH_3), 2.62-1.56(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{22}H_{26}N_4O_6$(442.5): C 59.72, H 5.92, N 12.66; Found: C 59.78, H 5.70, N 12.51.

Hexanedioic Acid, Bis[[(3-nitrophenyl)methylene]hydrazide] (4i)

White solid; m.p.: 256-258℃; IR(KBr) υ (cm^{-1}): 3194(NH), 3086(=CH), 1667(C=O), 1454(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.57,11.43(2s, 2H, NH), 8.45,8.38(2s, 2H, CH=N), 8.25-7.62(m, 8H, Ar-H), 2.70-1.60(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{20}H_{20}N_6O_6$(440.4): C 54.54, H 4.58, N 19.08; Found: C 54.71, H 4.60, N 18.95.

Hexanedioic Acid, Bis[[(4-chlorophenyl)methylene]hydrazide] (4j)

White solid; m.p.: 265-268℃; IR(KBr) υ (cm^{-1}): 3207(NH), 3066(=CH), 1666(C=O), 1489(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 11.38,11.25(2s, 2H, NH), 8.12,7.93(2s, 2H, CH=N), 7.67-7.39(m, 8H, Ar-H), 2.63-1.61(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{20}H_{20}Cl_2N_4O_2$(419.3): C 57.29, H 4.81, N 13.36; Found: C 57.38, H 4.71, N 13.25.

Hexanedioic Acid, Bis[[[4-(dimethylamino)phenyl]methylene] hydrazide] (4k)

Yellow solid; m.p.: 302-304 ℃ ; IR(KBr) υ (cm^{-1}): 3188(NH), 3078(=CH), 1671(C=O), 1463(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 10.99,11.88(2s, 2H, NH), 7.98,7.81(2s, 2H, CH=N), 7.45-6.63(m, 8H, Ar-H), 2.93-2.88(m, 12H, CH_3), 2.60-1.55(m, 8H, CH_2); Elemental analysis: Calcd.(%) for $C_{24}H_{32}N_6O_2$(436.6): C 66.03, H 7.39, N 19.25; Found: C 66.17, H 7.51, N 19.21.

Hexanedioic Acid, Bis[[[4-(diethylamino)phenyl]methylene] hydrazide] (4l)

Yellow solid; m.p.: 224-225℃; IR(KBr) υ (cm^{-1}): 3193(NH), 3091(=CH), 1668(C=O), 1471(C=N); ^{1}H NMR(400MHz,DMSO-d_6): δ 10.95,10.84(2s, 2H, NH), 7.95,7.79(2s, 2H, CH=N), 7.42-6.57(m, 8H, Ar-H), 3.37-3.32(m, 8H, N-CH_2), 2.62-1.55(m, 8H, CH_2), 1.09-1.02(m, 12H, CH_3); Elemental analysis: Calcd.(%) for $C_{28}H_{40}N_6O_2$(496.7): C 68.26, H 8.18, N

17.06; Found: C 68.13, H 8.11, N 17.23.

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