Fast Synthesis of *N*-Acylhydrazones Employing a Microwave Assisted Neat Protocol

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A variety of *N*-acylhydrazones were synthesized under microwave irradiation within 2.5−10 min, starting from benzo, salicyloyl, and isonicotinic hydrazides. The protocol developed employs microwave irradiation in the absence of solvents and catalysts, leading to high yields. The results are reproducible in a 500 mg to 5 g scale.

N-acylhydrazones have been widely employed in organic and analytical chemistry, mainly in terms of metal ligands.[1] They coordinate strongly with a variety of transition metal ions, forming complexes of varied biological and pharmaceutical activities.[2−8] The *N*-acyl group often plays important roles in controlling stereochemistry for metal calalysis.[9]

In the field of organic chemistry, their use as electrophiles in reactions with nucleophiles has recently made some important advances as they act as stable imine surrogates.[10,11] The hydrazide products can be transformed into various nitrogen containing compounds by cleavage of the N−N bond. It is expected that new stereoselective reactions that take advantage of *N*-acylhydrazones will be developed and that the use of *N*-acylhydrazones as imine equivalents will be expanded to the chemical and pharmaceutical industries.[9,12]

N-acylhydrazones are usually obtained by condensation of aldehydes or ketones with acylhydrazines, in the presence of an acid catalyst, in reaction times varying from 30 min to several hours.[9,13,14] Their purification can be accomplished by simple recrystallization, and they are stable at ambient temperature.

We have developed a friendly method for the synthesis of a library of *N*-acylhydrazones, based on microwave radiation. With this protocol, one can avoid the use of solvents and catalysts, and the products are obtained in short reaction times and in very good yields.

Both hydrazides and hydrazones are well-known for their pharmacological activities, such as antitubercular, antimalarial, and antibacterial agents, fungicides, and also anticonvulsant properties, among other applications.[15,16] In the present study, benzhydrazide (**1a**), salicyloylhydrazide (**1b**), and isonicotinic hydrazide (**1c**) were used to react with a wide range of ketones and aldehydes (Figure 1). The method is simple and economical since all the compounds are cheap and readily available.

To investigate the generalization of the method, we have tested the protocol with several types of ketones: cyclic aliphatic ketones (cyclohexanone, **2**; cyclopentanone, **3**), linear aliphatic ketones (butan-2-one, **4**; pentan-3-one, **5**, 4-methylpentan-2-one, **6**), aromatic ketones (acetophenone, **7**; isobutyrophenone, **8**) and heteroaromatic ketones (2-acetylfurane, **9**; 2-acetylthiophene, **10**; 2-acetylpyridine, **11**).

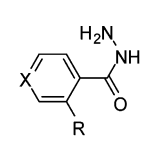
The protocol employed consists in placing equivalent amounts of hydrazide and ketone in a quartz tube, which was then subjected to microwave irradiation (Figure 2)with the power and times indicated in Table 1. After completion, the reaction mixture was allowed to cool down to room temperature, and the product was washed with ethyl ether. In most cases, purification was not needed since the hydrazone was pure enough for possible subsequent reaction steps, although recrystallization can be easily performed with ethanol for most cases. In this context, the synthesis was carried out minimizing the use of organic solvents and unnecessary purification steps.

The results shown in Table 1 demonstrate that the protocol developed by us provides *N*-acylhydrazones in 90% to quantitative yields (with exception to the moderate yield obtained in entries 7 and 22).

In general, reactions with salicyloyl hydrazide were faster than those with benzo or isonicotinic hydrazides, because of the better stability of the resulting hydrazone, owing to an OH group in *ortho* position, which can form intramolecular hydrogen bonding with the nitrogen (Figure 3).[17]

This fact is also visible in the IR spectra of salyciloylhydrazones, showing a characteristic low-frequency shift of the C═O band (see Supporting Information).

Reaction times were much faster than for similar reactions under conventional heating. For example, synthesis of



1a: R = H, X = CH
1b: R = OH, X = CH
1c: R = H, X = N

Figure 1. Structures of benzhydrazide (**1a**), salicyloylhydrazide (**1b**), and isonicotinic hydrazide (**1c**).

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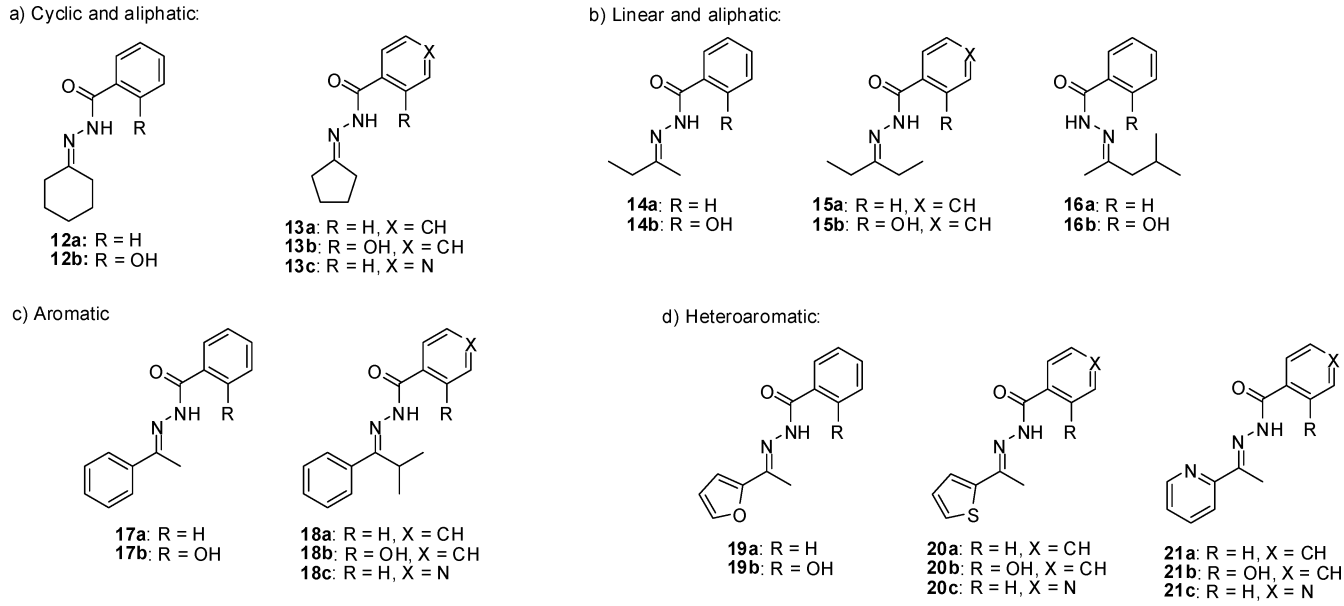

Figure 2. Library of *N*-acylhydrazones synthesized under neat microwave irradiation.

Table 1. Microwave Promoted Synthesis of *N*-acylhydrazones, Starting from Ketones

entry	hydrazide	ketone	product	power (W)	time (min)	*T* final (°C)	*P* final (bar)	yield (%)
1		2	12a	200	5	152	5.0	quantitative
2		3	13a	200	3	143	2.8	quantitative
3		4	14a	200	4	202	12.8	quantitative
4		5	15a	200	5	210	9.6	90
5		6	16a	200	2.5	159	3.9	93
6	1a	7	17a	200	10	262	11.8	92
7		8	18a	300	4	258	4.0	70
8		9	19a	100	10	175	4.7	90
9		10	20a	200	5	231	6.4	93
10		11	21a	200	4	216	7.0	90
11		2	12b	200	4	137	2.5	quantitative
12		3	13b	200	5	114	1.9	quantitative
13		4	14b	200	3	95	2.1	98
14		5	15b	200	5	208	11.2	91
15	1b	6	16b	200	2.5	161	4.5	90
16		7	17b	200	4	218	6.8	96
17		8	18b	200	5	229	6.1	90
18		9	19b	200	2.5	194	6.2	quantitative
19		10	20b	200	3	211	4.3	96
20		11	21b	200	5	?	?	90
21	1c	3	13c	200	6	182	5.3	94
22		8	18c	300	4	262	7.1	68
23		10	20c	200	4.5	247	8.0	quantitative
24		11	21c	200	5	208	5.5	97

hydrazone **12a** is accomplished in 6 h using refluxing methanol and acetic acid as catalyst,[18] while under MW irradiation the same product can now be obtained in only 5 min with quantitative yield (entry 1); hydrazone **17a** was previously obtained in 4 to 12 h using refluxing methanol

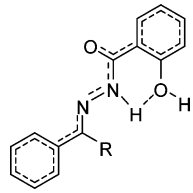

Figure 3. Electronic delocalization and intramolecular hydrogen bonding observed for salicyloyl hydrazides.

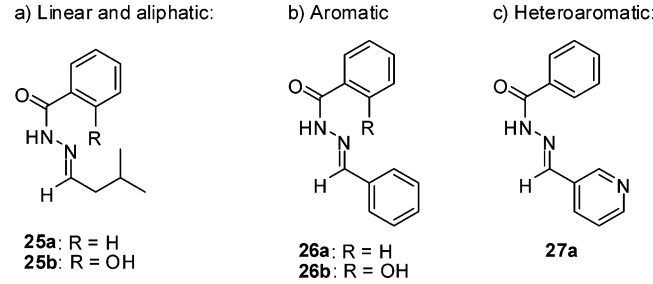

Figure 4. *N*-acylhydrazones synthesized by reaction with aldehydes under neat microwave irradiation.

or hexane (with acetic acid as catalyst), whereas under MW irradiation the same product is achieved in 10 min (entry 6).[19,20]

The intramolecular hydrogen bonding mentioned before is more pronounced for salyciloylhydrazones with a high degree of electron delocalization,[17] explaining the shorter reaction times observed with aromatic and heteroaromatic hydrazones when changing from benzo or isonicotinic to salyciloyl hydrazide (entries 6, 8, 9 compared with entries 16, 18, 19, 23).

Reaction between benzhydrazide (**1a**) or isonicotinic hydrazide (**1c**) and isobutyrophenone (**8**) (entries 7 and 22) were more difficult than all the others because of the bulkiness of the starting ketone. Different powers were tested, and the best result was obtained at 300W, leading to 70% of hydrazone **18a** and 67% of hydrazone **18c**, recovering 20% and 15% of starting hydrazides, respectively. Nevertheless, the here described protocol for the synthesis of **18a** represents an improvement to the procedure described in the literature that required 12 h in refluxing methanol in the presence of acetic acid to afford **18a** in 68% yield.[20]

To broaden the scope of the protocol, some examples of reactions between hydrazides and representative aldehydes (3-methyl-butanal, **22**; benzaldehyde, **23**, and 2-pyrideinecarboxaldehyde, **24**), were tested (Figure 4). The results obtained are shown in Table 2 and demonstrate that the methodology is valid also for aldehydes.

Table 2. Microwave Promoted Synthesis of *N*-acylhydrazones, Starting from Aldehydes[a]

entry	hydrazide	aldehyde	product	power (W)	time (min)	*T* final (°C)	*P* final (bar)	yield (%)
1	1a	22	25a	200	4	180	5.6	93
2	1b	22	25b	200	4	176	7.0	95
3	1a	23	26a	200	5	194	6.1	quantitative
4	1b	23	26b	200	7	201	4.1	89
5	1a	24	27a	200	4	205	5.8	quantitative

[a] *N*-acylhydrazones **15b**, **17b**, **18b**, **20b**, **21b**, **25a**, and **25b** are here reported for the first time and are fully characterized.

In conclusion, a protocol for microwave neat synthesis of *N*-acylhydrazones is here reported for the first time. According to our results, microwave irradiation enhanced yields and reaction times, avoiding the use of solvents and catalyst. The reactions were reproducible from 500 mg to 5 g scale and could be applied to a large number of ketones and aldehydes. The described method could be a useful synthetic path to obtain *N*-acylhydrazones at industrial scale. Although a specific reactor was used to monitor temperature and pressure, a standard glass tube with Teflon cap can be used as well.

Experimental Section

General Procedure for Microwave Synthesis. Five grams of hydrazide and 1 equiv of ketone or aldehyde (and a magnetic stirring bar) were placed in a quartz tube, which was introduced in the microwave oven inside the reactor equipped with temperature and pressure probes. Reaction times and power were applied according to Tables 1 and 2. After completion, the system was allowed to cool down to room temperature, resulting in crystallization of the hydrazones obtained. Ethyl ether was added to the quartz tube and the product was filtrated under reduced pressure and washed with ethyl ether.

Supporting Information Available. Characterization data, microwave output graphics and spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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