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LETTER

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Open Vessel and Cooling while Heating Microwave-Assisted Synthesis of Pyridinyl *N*-Aryl Hydrazones

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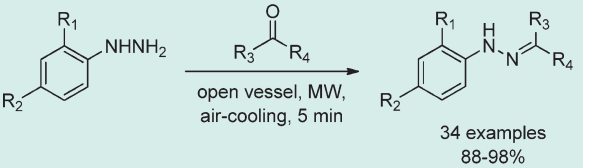
Supporting Information

ABSTRACT: We reported the first example of open vessel and cooling while heating microwave-assisted synthesis of pyridinyl *N*-aryl hydrazones. Compounds were prepared in excellent isolated yields (88−98%) in only 5 min, by reacting 4- and 2,4-(di)substituted phenylhydrazines, bearing both electron-donating (4-CH_3, 4-OCH_3) and -withdrawing (4-Cl, 4-Br, 4-CF_3, 4-NO_2, 2,4-Cl_2) groups with 2-, 3-, and 4-acetylpyridine. The method was successfully extended to other carbonyl compounds.

KEYWORDS: hydrazones, microwave synthesis, cooling while heating, open vessel



R_1 = H, Cl; R_2 = H, CH_3, OCH_3, Cl, Br, CF_3, NO_2, R_3 = H, CH_3; R_4 = phenyl, naphthalen-2-yl, pyrrol-2-yl, furan-2-yl, thiophen-2-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl

Aryl hydrazones (e.g., **1**, **3**, and **5**) are key building blocks for the synthesis of some heterocyclic compounds, such as indole and pyrazole. Our experience in this field led to the identification of new anti-HIV-1 agents (e.g., **2**),[1] inhibitors of tubulin polymerization (e.g., **4**),[2] and partial agonist/antagonist cannabinoid ligands (e.g., **6**)[3] (Chart 1). The biological importance of aryl hydrazones was reviewed by Rollas and Küçükgüzel, showing their antidepressant, analgesic, antiinflammatory, antiplatelet, antimalarial, antimicrobial, antimycobacterial, antitumoral, vasodilator, and antiviral activities.[4]

The synthesis of aryl hydrazones is well-known and generally involves the reaction of aryl hydrazines or aryl diazonium salts with carbonyl compounds.[5−7] Recent innovations in microwave-assisted organic synthesis prompted to apply this new energy source also to hydrazone preparation.[8] For example, Polshettiwar and Varma developed an efficient and general microwave protocol for the synthesis of cyclic, bicyclic and heterocyclic hydrazones using polystyrene sulfonic acid as catalyst in aqueous medium.[9] Furthermore, *N*-acylhydrazones were prepared in high yields under microwave irradiation, starting from benzo, salicyloyl, and isonicotinic hydrazides in the absence of solvents and catalysts.[10]

Our medicinal chemistry projects required a fast and efficient route to pyridinyl *N*-aryl hydrazones. Preliminary experiments suggested that this class of compounds does not tolerate prolonged heating and high temperatures, which lead to product decomposition. These results were supported by our observation that some pyridinyl *N*-aryl hydrazones decompose spontaneously at room temperature and must be stored at −20 °C.

Here, we wish to report the microwave-assisted synthesis of a focused library of *N*-aryl hydrazones prepared under cooling while heating open vessel mode. Compounds **18**−**41** were synthesized in excellent yields in only 5 min, by reacting 4- and 2,4-(di)substituted phenylhydrazines (**7**−**14**), bearing both electron-donating (4-CH_3, 4-OCH_3) and -withdrawing (4-Cl, 4-Br, 4-CF_3, 4-NO_2, 2,4-Cl_2) groups, with 2- (**15**), 3- (**16**), and 4-acetylpyridine (**17**) (Scheme 1). To the best of our knowledge, methods involving the use of cooling while heating approach in open vessel mode for the synthesis of aryl hydrazones have not been reported.

As a model study, we investigated the reaction of phenylhydrazine hydrochloride (**7**) with 2-acetylpyridine (**15**) in the presence of sodium acetate in 96° ethanol to furnish 2-(1-(2-phenylhydrazono)ethyl)pyridine (**18**) (Table 1). The best molar ratio phenylhydrazine hydrochloride/2-acetylpyridine/sodium acetate was found to be 1.5/1/1.5 (data not shown). Ethanol was the solvent of choice mainly due to its high loss tangent value (tan δ = 0.041),[11] allowing a rapid microwave heating of the reaction mixture. By comparison, oil bath heating required a time of 5 h at reflux temperature to furnish compound **18** in high yields (entry 1, Table 1), as reported by Lemster and co-workers.[12]

Attempts to synthesize **18** in closed vessel mode showed very low yields. In fact, when we heated the reaction mixture at 80 °C for 2 min by applying a microwave irradiation of 50 W with or without in situ cooling, derivative **18** was isolated in 15% and 23% yields, respectively (entries 2 and 3, Table 1). Raising the temperature up to 130 °C caused a decrease of the yield (entries 4 and 5, Table 1), probably because of the dielectric overheating of the starting materials or the reaction products. On the contrary, compound **18** was isolated in 50% yield, by heating the reaction mixture at 80 °C for 5 min in open vessel mode with a power of 250 W (entry 6, Table 1). Thus, the best yield (98%) was reached when the mixture was in situ cooled during microwave irradiation under the same reaction conditions (entry 7, Table 1). This result could be explained by taking into

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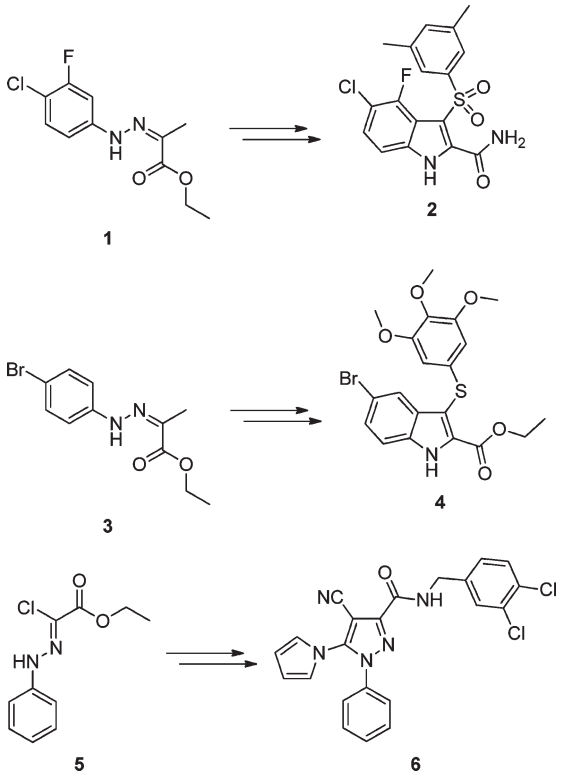
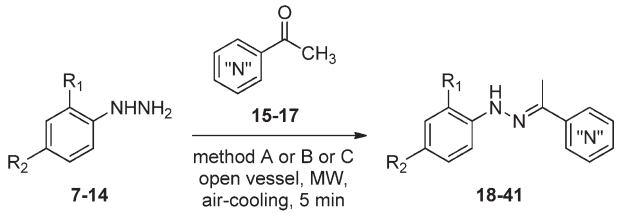
Chart 1. Examples of Aryl Hydrazones (1, 3, and 5) Involved in the Synthesis of Biologically Active Compounds 2, 4, and 6



Scheme 1. Synthesis of Pyridinyl *N*-Aryl Hydrazones 18−41



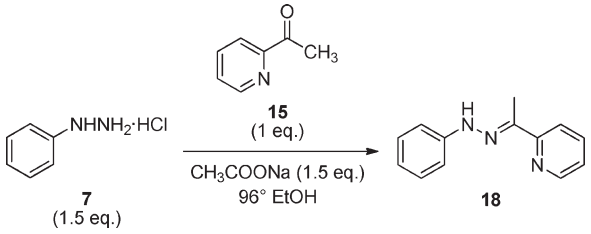
account that the external cooling prevents microwave overheating by continuously removing latent heat of the reaction, allowing a higher level of microwave output power to be directly transferred to the reaction mixture.[13]

Encouraged by these very promising results, we examined the scope and limits of the present method, by reacting 2- (**15**), 3- (**16**), and 4-acetylpyridine (**17**) with a wide range of 4- and 2,4-(di)substituted phenylhydrazines (**7**−**14**), bearing both electron-donating (4-CH_3, 4-OCH_3) and -withdrawing (4-Cl, 4-Br, 4-CF_3, 4-NO_2, 2,4-Cl_2) groups (Table 2).

Thus, 4-H- (**7**), 4-CH_3- (**8**), 4-OCH_3- (**9**), 4-Cl- (**10**), 4-Br- (**11**), and 2,4-Cl_2-phenylhydrazine (**14**) hydrochlorides rapidly reacted with 2- (**15**), 3- (**16**), and 4-acetylpyridine (**17**) in the presence of sodium acetate to furnish the corresponding hydrazones **19**−**32** (entries 2−15, Table 2), **39** (entry 22, Table 2), and **41** (entry 24, Table 2), under the optimized reaction conditions for derivative **18** (method A). Similarly, reaction of (4-(trifluoromethyl)phenyl)hydrazine (**12**) with 2- (**15**), 3- (**16**), and 4-acetylpyridine (**17**), as well as that of (4-nitrophenyl)hydrazine (**13**) with 2-acetylpyridine (**15**) gave the corresponding derivatives **33**−**35** (entries 16−18, Table 2) and **36** (entry 19, Table 2), respectively (method B). All experiments proceeded expeditiously and delivered excellent isolated yields, ranging from 88% to 98%. The isolation procedure simply involved the filtration of the high purity precipitated pyridinyl *N*-aryl hydrazones, followed by washing with petroleum ether and drying. The method very well tolerated both electron-donating and -withdrawing substituents on the phenylhydrazines, as well as the different position of the acetyl group on the pyridine nucleus. Reaction time was considerably shorter compared to conventional thermal process (e.g., 60-fold time reduction for compound **18**).

However, when we applied these reaction conditions to the synthesis of derivatives **37** (entry 20, Table 2), **38** (entry 21, Table 2), and **40** (entry 23, Table 2), the desired compounds were not isolated in good yields, even prolonging the reaction time up to 20 min (data not shown). Our experiments showed that phenyl hydrazones **37**, **38**, and **40** can be successfully prepared with a microwave-assisted protocol by dissolving the appropriate starting materials in methanol in the presence of a catalytic amount of concentrated HCl (method C).

Table 1. Optimization of Reaction Conditions for Compound 18



entry	heating	mode	temp (°C)	ramp time	hold time	power (W)	maxpress[a] (PSI)	air-cooling	yield[b] (%)
1	oil bath		80		5 h				90[c]
2	MW[d]	CV[e]	80	1 min	2 min	50	250	off	15
3	MW	CV	80	1 min	2 min	100	250	on	23
4	MW	CV	110	1 min	2 min	125	250	off	10
5	MW	CV	130	1 min	4 min	150	250	off	3
6	MW	OV[f]	80	1 min	5 min	250		off	50
7	MW	OV	80	1 min	5 min	250		on	98

[a] maxpress: maximum pressure. [b] isolated yield. [c] From ref 12. [d] MW: microwave. [e] CV: closed vessel. [f] OV: open vessel.

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Table 2. Microwave Synthesis of Pyridinyl *N*-Aryl Hydrazones 18−41

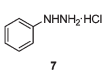
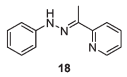
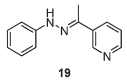
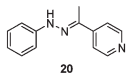
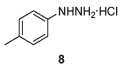
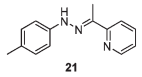
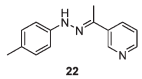
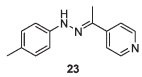
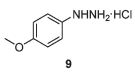
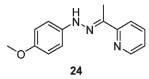
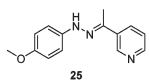
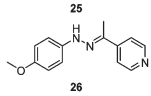
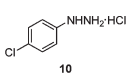
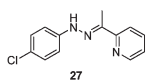
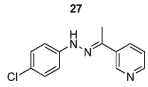
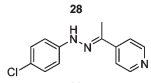
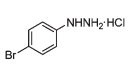
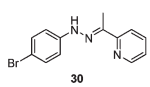
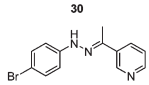
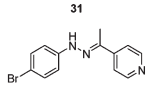
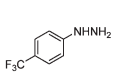
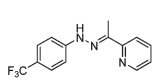
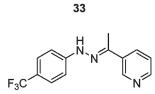
entry	hydrazine	acetylpyridine	product	yield[a] (%)	method
1	 7	 15	 18	98	A[b]
2		 16	 19	95	A
3		 17	 20	97	A
4	 8	 15	 21	94	A
5		 16	 22	94	A
6		 17	 23	90	A
7	 9	 15	 24	95	A
8		 16	 25	98	A
9		 17	 26	94	A
10	 10	 15	 27	92	A
11		 16	 28	90	A
12		 17	 29	96	A
13	 11	 15	 30	91	A
14		 16	 31	88	A
15		 17	 32	93	A
16	 12	 15	 33	96	B[c]
17		 16	 34	88	B
18		17	35	94	B
19	13	15	36	96	B
20		16	37	92	C[d]

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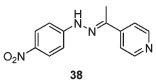
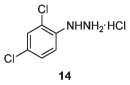
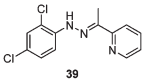
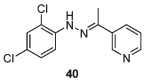
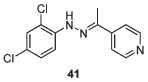
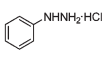
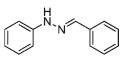
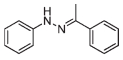
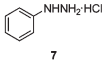
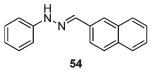
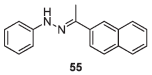
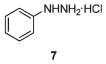
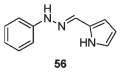
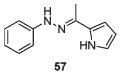
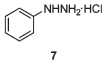
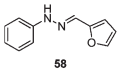
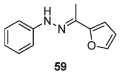
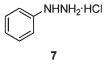
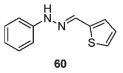
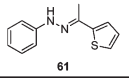
Table 2. Continued

entry	hydrazine	acetylpyridine	product	yield[a] (%)	method
21		 17	 38	95	C
22	 14	 15	 39	97	A
23		 16	 40	93	C
24		 17	 41	90	A

[a] Isolated yield. [b] A: Hydrazine (1.5 equiv), acetylpyridine (1 equiv), CH_3COONa (1.5 equiv), 96° ethanol, open vessel, 250 W, air-cooling, 80 °C, 5 min. [c] B: Hydrazine (1.5 equiv), acetylpyridine (1 equiv), 96° ethanol, open vessel, 250 W, air-cooling, 80 °C, 5 min. [d] C: Hydrazine (1.5 equiv), acetylpyridine (1 equiv), catalytic 37% HCl, methanol, open vessel, 250 W, air-cooling, 65 °C, 5 min.

Table 3. Microwave Synthesis of Hydrazones 52−61

entry	hydrazine	carbonyl compound	product	yield[a] (%)	method
1	 7	 42	 52	98	A[b]
2		 43	 53	95	A
3	 7	 44	 54	97	A
4		 45	 55	94	A
5	 7	 46	 56	98	A
6		 47	 57	96	A
7	 7	 48	 58	94	A
8		 49	 59	96	A
9	 7	 50	 60	95	A
10		 51	 61	98	A

[a] Isolated yield. [b] Hydrazine (1.5 equiv), carbonyl compound (1 equiv), CH_3COONa (1.5 equiv), 96° ethanol, open vessel, 250 W, air-cooling, 80 °C, 5 min.

To further validate the present method, we decided to explore the reaction of phenylhydrazine hydrochloride (**7**) with other carbonyl compounds **42**−**51** (Table 3).

Thus, benzaldehyde (**42**), acetophenone (**43**), 2-naphthaldehyde (**44**), 1-(naphthalen-2-yl)ethanone (**45**), 1*H*-pyrrole-2-carbaldehyde (**46**), 1-(1*H*-pyrrol-2-yl)ethanone (**47**), furan-2-carbaldehyde (**48**), 1-(furan-2-yl)ethanone (**49**), thiophene-2-carbaldehyde (**50**), and 1-(thiophen-2-yl)ethanone (**51**) were converted, according to the method A, to the corresponding phenylhydrazones **52**−**61** in excellent yields (entries 1−10, Table 3). Experiments confirmed that the method is useful to prepare not only *N*-pyridinyl- but also *N*-(hetero)aryl hydrazones.

In conclusion, we have developed a new microwave-assisted protocol for a very fast synthesis of pyridinyl *N*-aryl hydrazones in open vessel mode, under cooling while heating conditions.

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Hydrazones were prepared in excellent isolated yields in only 5 min, by reacting a wide range of phenylhydrazines with 2-, 3-, and 4-acetylpyridine. The method was successfully extended to other carbonyl compounds. High power microwave heating allowed us to slash the time of the reaction. At the same time, the external cooling precluded the decomposition of both starting materials and reaction products. Finally, the open vessel mode could lead to a rapid scale up of the reaction to multigram level.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterization data of all synthesized compounds, example of microwave output graphics, and copies of ^{1}H NMR spectra of compounds **20**−**23**, **25**, **26**, **31**−**35**, **37**−**41**, and **55**−**59**. This information is available free of charge via the Internet at http://pubs.acs.org/.

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