SHORT PAPER

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An efficient microwave-assisted one-pot conversion of carboxylic acids into hydrazides†

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A microwave-assisted protocol was developed to prepare hydrazides from corresponding carboxylic acids in good yields through transacylation with acethydrazide.

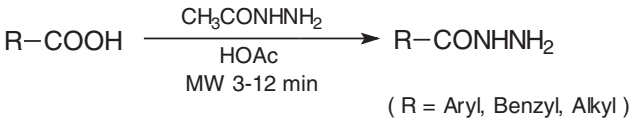
Keywords: microwave, carboxylic acid, hydrazides, transacylation, one-pot synthesis.

The conversion of carboxylic acids into the corresponding hydrazides constitutes an important functional group transformation. Hydrazides are very useful starting materials for the synthesis of various bioactive molecules, especially in the preparation of pharmaceuticals[1] and agrochemicals.[2]

To date, a variety of methods have been developed to carry out this conversion. The most widely used method is the hydrazinolysis of corresponding esters.[3] Esters seldom produce significant amounts of diacylhydrazine, but less reactive esters may require long reaction times or undesirably severe conditions. Recently, we have reported the dramatically accelerated hydrazinolysis of esters under combined microwave and ultrasound irradiation.[4] Acyl anhydrides, acid chlorides,[5] acid azides, and acyl imidazoles[6] all react with hydrazine to give hydrazides faster then esters do. However, acid chlorides are so reactive that it is difficult to stop the reaction short of diacylation. In general, this group of acylating agents is a second choice when the ester is unavailable or unreactive. Amides can be converted into hydrazides by reaction with hydrazine, but the reaction is somewhat slow.[7] It should be noted that all procedures mentioned above needed the preparation of carboxylic acid derivatives beforehand.

Direct conversion of carboxylic acids into corresponding hydrazides is attractive from the practical standpoint. However, these protocols generally need long reaction times, labour-expensive work-up, and harsh reaction conditions.[8] As an example,[8a] carboxylic acids were heated with hydrazine hydrate in the presence of activated alumina. The water formed was removed by azeotropic distillation using *n*-butanol as an entrainer. The yields were satisfactory. However, the process was very tedious. Therefore, it is desirable to develop a simpler and more efficient method for one-pot conversion of carboxylic acids into the corresponding hydrazides.

In many cases reactions that normally require a long time under classic heating conditions can be completed within several minute or even seconds in a microwave oven, at comparable reaction temperatures.[9] In connection with our interests in microwave-enhanced organic synthesis,[10] we report herein a microwave-assisted one-pot conversion of carboxylic acids into hydrazides (Scheme 1).



Scheme 1

It has been reported that primary amides could be prepared by transacylation of carboxylic acids with amides such as urea[11] and formamide,[12] Up to now, however, there is no report about the transacylation between carboxylic acids and hydrazides, whether under conventional conditions or microwave irradiation. As shown in Table 1, a number of carboxylic acids have been converted into the desired hydrazides by treated with acethydrazide in good yields under microwave irradiation, indicating a broader scope of application of our procedure.

Not only benzoic acids (Entries **1–7**), but also heterocyclic (Entries **8**, **9**), α, β- unsaturated (Entry **10**), and aliphatic acids (Entries **11–12**) work well to give hydrazides in good to excellent yields.

The synthesis of 4-nitrobenzoyl hydrazine was chosen as the model for comparison of the microwave approach with the conventional heating method. With the conventional method, a mixture of 4-nitrobenzoic acid and acethydrazide in acetic acid was refluxed for 50 minutes. After recrystallisation, 88% yield of desired hydrazide was obtained as yellowish needles. In comparison, with the microwave protocol, 4-nitrobenzoic acid gave the hydrazide in 95% isolated yield within 3 min. Aromatic carboxylic acids bearing electron-withdrawing moieties are significantly more reactive than those bearing electron-donating groups. For example, unlike 4-nitrobenzoic acid, 4-methoxylbenzoic acid needed 9 minutes to reach 89% yield. Surprisingly, *ortho*-substituted benzoic acids, such as 2-nitro, 2-methoxyl, and 2-fluorobenzoic acid, produced no desired products after 15 min under the similar conditions. Lower yields were obtained in the absence of solvent due to the severe sublimation of aromatic carboxylic acids under microwave irradiation. Long chain aliphatic carboxylic acids, such as lauric acid and stearic acid (Entries **12** and **13**), gave desired hydrazides in satisfactory yields. However, in the cases of lower carboxylic acids such as butyric acid, no transacylation products were obtained under similar reaction conditions.

One of the requirements of green chemical technology is the use of less toxic reagents.[13] The acute toxicity and inhalation danger of hydrazine used in traditional methods make these procedures intrinsically unsafe. From environmental considerations, another advantage of our method is the use of acethydrazide ($CH_3CONHNH_2$), an easily available and inexpensive reagent, as an alternative to the acutely toxic hydrazine monohydrate for the preparation of hydrazides.

In summary, a straightforward and efficient procedure has been developed for the one-pot conversion of carboxylic acids into their corresponding hydrazides. The method has many advantages over previously reported processes, including simple experimental procedures, short reaction times, a green reagent system and safe handling.

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Table 1 Microwave-assisted one-pot conversion of carboxyl acids into hydrazides

Entry	Hydrazides	Time/min	Yield (%)	M.p./°C	
				Obs.	Lit. [14]
1	Benzoyl hydrazine	6	82	112	112.5
2	4-Nitrobenzoyl hydrazine	3	95	214	213–214
3	3-Nitrobenzoyl hydrazine	6	93	154	150–152
4	4-Chlorobenzoyl hydrazine	5	87	164	163
5	4-Fluorobenzoyl hydrazine	6	84	162	161.5–163
6	4-Methylbenzoyl hydrazine	6	85	118	117
7	4-Methoxybenzoyl hydrazine	10	89	137	139
8	α-Naphthoyl hydrazine	5	88	167	166
9	Furoyl hydrazine	8	80	80	78
10	Phenylacetyl hydrazine	11	72	115	116
11	Cinnamyl hydrazine	11	77	103	101
12	Lauroyl hydrazine	12	87	105	104.5
13	Stearyl hydrazine	12	89	112	114

All yields refer to isolated products characterised by mp data and spectral analysis (IR and ^{1}H NMR).

Experimental

Melting points are uncorrected and recorded on WRS capillary apparatus. IR spectra were obtained on Nicolet Nexus 470 infrared spectrometer in KBr discs and ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer with TMS as internal standard. All reactions were carried out at 200W in a MW-800 II multimode cavity refluxing system.

General procedure: Carboxylic acid (20 mmol), acethydrazide (3.0 g, 40 mmol) and HOAc (1 ml) were mixed together and subjected to microwave irradiation (200 W) for an optimal time. On completion of the reaction (monitored by TLC), acetic acid was removed *in vacuo* and then iced water (3 ml) was added to the residue. The crude product was collected by filtration and recrystallized from appropriate solvents. The products are all known compounds and were characterised by comparison their melting points, IR and ^{1}H NMR data with authentic samples.

Recrystallisation solvents: aqueous ethanol (Entries **3, 4, 6, 8, 11**); water (Entries **1, 7, 10**); ethanol (Entries **2, 9, 12, 13**); ethyl acetate (Entry **5**).

Selected spectral data of as-synthesized hydrazides: 4-nitrobenzoyl hydrazine (Entry **2**), IR (cm^{-1}, KBr): 3310, 3015, 1620, 1530, 1355, 1070, 840; ^{1}H NMR (ppm, DMSO-d_6): 4.63 (s, 2H, NH_2), 7.90–8.45 (m, 4H, aromatic), 10.05 (s, 1H, NH).

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