A rapid and high-yield synthesis of aryloxyacetyl hydrazides under microwave irradiation and with phase transfer catalysis

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A series of aryloxyacetyl hydrazides **4a–l** were synthesised under microwave irradiation and phase transfer catalysis conditions. By the optimisation of the reaction conditions, a rapid, high-yield and efficient method for the preparation of aryloxyacetyl hydrazide was given.

Keywords: phase transfer catalyst, aryloxyacetyl hydrazide

Aryloxyacetyl hydrazide derivatives have a wide range of biological effects. Some are found to show antituberculotic activities.[1] Some are used as a post-emergence, selective herbicide[2] to control terrestrial and aquatic broad-leaved weeds in some plants. They have been also investigated as chemotherapeutic agents for lowering triglycerides and serum cholesterols and for possessing favorable hyper-lipidaemic activity in rats.[3] In addition, they are important intermediates in many reactions.[4,5] To date, many methods have been described for the preparation of aryloxyacetyl hydrazides.[6] We have previously reported reactions using aryloxyacetyl hydrazides, which were prepared by a method similar to Husain's classical method,[6c] to obtain aryloxyacetyl thiosemicarbazide and aryloxyacetyl hydrazone.[7,8] However, traditional methods of synthesis of aryloxyacetyl hydrazides suffer from disadvantages, such as long reaction time, low yield and inconvenience of handling.

In recent years, the use of microwave technology in organic synthesis has received considerable attention. This technology can increase the purity of products, enhance the chemical yield and shorten the reaction time.[9] Moreover, phase transfer catalyst, with the advantages of simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents, has established its significance in organic synthesis as one of the most useful methods for the acceleration of heterogeneous reactions.[10] In our previous work, we have had an interest in the microwave and phase transfer catalyst promotion of organic synthesis.[11,12]

In view of these facts and as a part of our work on the synthesis and biological activity of aryloxyaceic acid derivatives, we now report a rapid, efficient and high-yield method for the synthesis of aryloxacetyl hydrazides (Scheme 1).

In searching for the best reaction conditions for the reaction, we carried out a series of experiments. When we first started our work, we followed the Husain's classical method,[6c] which used *p*-nitrophenol and methyl chloroacetate to reflux in acetone with potassium carbonate for 15 h to produce methyl *p*-nitrophenoxyacetate which then without purification reacted with hydrazine hydrate for 12 h to produce *p*-nitroaryloxyacetyl hydrazide. However, it gave a low yield of 32%. In the report of Hamida *et al*.,[6b] *p*-nitroaryloxyacetyl hydrazide was obtained under microwave irradiation condition in three steps and the total yield was only 45%. In order to shorten reaction time and to increase the yield of aryloxacetyl hydrazide, we carried out the reaction under microwave irradiation and with phase transfer catalysis, and a satisfactory result was obtained. The reaction time was reduced to 4 min in the first step and 1 min in the second step. Moreover, a good yield of 83% was obtained.

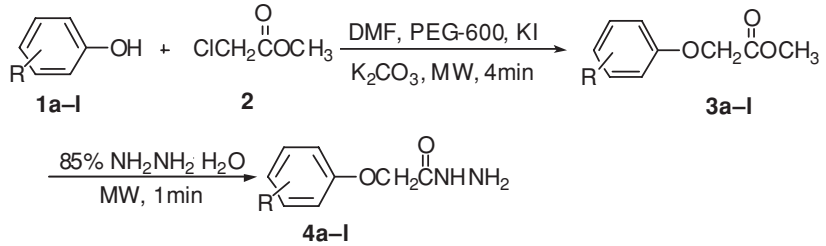
We investigated the significant solvent effect on the reaction. As different solvents were employed under otherwise similar reaction conditions, different results were obtained as shown in Table 1. There was almost no reaction at all in the polar protonic solvents H_2O and C_2H_5OH (entries 1 and 2). In contrast, good to excellent yields were achieved in the strongly polar non-protonic solvents CH_3CN, DMF and DMSO (entries 4, 5 and 6). From these data, we conclude that DMF is the best solvent for this reaction.

In order to evaluate the catalytic effects on this reaction, another series of experiments were carried out. Using *p*-nitrophenol as an example and under the same reaction conditions shown in Scheme 1, we first examined the effect of the presence of the phase transfer catalyst. With the

Table 1 The effect of solvent on the yield of compound **4**

Entry	Solvent	Yield of **4a**[a](%)	Yield of **4g**[a](%)	Yield of **4k**[a](%)
1	H_2O	—	—	—
2	C_2H_5OH	—	—	—
3	CH_3COCH_3	11	24	12
4	CH_3CN	30	73	31
5	DMF	81	83	79
6	DMSO	54	70	77

[a]Isolated yields



Scheme 1

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Table 2 The effect of phase transfer catalysts on the yield of compound **4g**

Entry	Phase transfer catalysts	Yield [a]/%
1	None	59
2	PEG-400	78
3	PEG-600	83
4	Tetrabutylammonium Iodide	74

[a]Isolated yields.

Table 3 Aryoxyacetyl hydrazides prepared

Entry	R	Product	Yield[a]/%	M.p./°C	Lit M.p./°C
1	H	**4a**	81	104–106	108[6a]
2	2-Cl	**4b**	81	110–112	114[6a]
3	4-Cl	**4c**	83	156–158	158[6a]
4	2,4-diCl	**4d**	79	150–152	155[13]
5	2-NO_2	**4e**	86	128–130	132[14]
6	3-NO_2	**4f**	82	164–166	167[14]
7	4-NO_2	**4g**	83	188–190	190[15]
8	2-CH_3	**4h**	79	116–118	121[16]
9	3-CH_3	**4i**	77	106–108	110[16]
10	4-CH_3	**4j**	82	132–134	136[16]
11	4-OCH_3	**4k**	79	134–136	138–139[17]
12	Hydroquinone	**4l**	84b	234–236	238[1]

[a]Isolated yields. [b]Yield of 1,4-phenylenedioxyacetyl hydrazide.

enhancement of the ion exchange between the inorganic salt and the organic solution, phase transfer catalysts efficiently catalysed this solid-liquid diphase reaction and the results are shown in Table 2. It was found that PEG-600 was the best catalyst for this reaction. Next, we evaluated the catalytic effect of the added KI. The experiment results indicated that when KI was added 4g was produced in 83% yield. However, the yield of 4g was only 61% without addition of KI.

In conclusion, this is a good method for the preparation of aryloxyacetyl hydrazides under the conditions of microwave irradiation and phase transfer catalysis, and possesses the advantages of speed, a high yield, cleanliness, easy work-up over the reported methods. The catalyst PEG-600 is inexpensive, relatively nontoxic, highly stable and easily available.

Experimental

Melting points were determined in open capillaries and are uncorrected. Microwave irradiation was carried out with a WP 750B commercial microwave oven at 2450MHz.

General procedure for preparation of aryloxyacetyl hydrazides (**4a–4l**): Phenol (5 mmol), methyl chloroacetate (5 mmol), K_2CO_3 (5 mmol), KI (1 mmol), DMF (1 ml) and PEG-600 (0.5 mmol) were place in a dried round–bottomed flask and the mixture was irradiated by microwaves (200W) for 4 min. On completion of the reaction, the mixture was cooled to room temperature and then added to ethanol (10 ml) with constant stirring. After filtering off the inorganic salts, the reaction mixture was added to 85% hydrazine hydrate (5 mmol) and subjected to microwave irradiation (500W) for an additional 1 min. Then, it was cooled to room temperature, allowed to settle for 1 h, and the precipitates were filtered off and recrystallised from ethanol to afford the pure product **4**. The yields of **4** are shown in Table 3.

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