Microwave-assisted synthesis of 1,4-disubstituted thiosemicarbazides and semicarbazides under solvent-free conditions in the absence of catalyst

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Thirty-two 1-aroyl/aryloxyacetyl-4-(2-furoyl)thiosemicarbazides and corresponding semicarbazides were synthesised in excellent yields under microwave irradiation and solvent-free conditions without using any catalyst.

Keywords: 1-aroyl/aryloxyacetyl-4-(2-furoyl)thiosemicarbazides, 1-aroyl/aryloxracetyl-4-(2-furoyl)semicarbazides, microwave irradiation, solvent-free synthesis

Microwave-promoted solvent-free heterogeneous reactions are well known as environmentally benign methods that also usually provide improved selectivity, enhanced reaction rates, cleaner products and manipulative simplicity.[1,2]

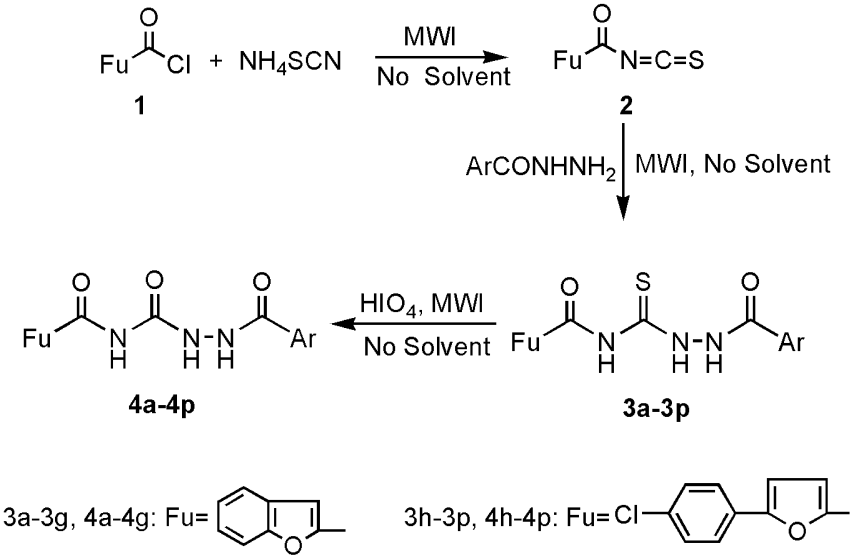
The chemistry of thiosemicarbazides and semicarbasides has attracted much attention in recent years due to their important biological activity and their utilisation in the preparation of the corresponding semicarbazides and of metal complexes and heterocyclic compounds.[3-6] Thiosemicarbazides can be readily prepared by the reaction of aroylchlorides with ammonium thiocyanate and acid hydrazides under reflux or phase transfer catalysis. The analogous species, 1,4-diaroylsemicarbazides, however, cannot be obtained using similar methods because of the instability of the intermediate, aroylisothiocyanates.

In continuation of our ongoing program to synthesise biologically active compounds[7-10] and develop benign and rapid strategies for organic transformations, we have explored an expeditious solvent-free route for the synthesis of 1-aroyl/aryloxyacetyl-4-(2-furoyl)thiosemicarbazides under microwave irradiation (MWI) in the absence of catalyst (Scheme 1).

2-Furoyl chloride (**1**) was treated with ammonium thiocyanate under MWI and solvent-free conditions to give 2-furoyl isothiocyanate (**2**). Compound **2** did not need to be isolated and further reacted immediately with aroyl or aryloxyacetyl hydrazines affording 1-benzoyl/aryloxyacetyl-4-(2-furoyl)thiosemicarbazides in excellent yields. It is confirmed from experiments that the phase transfer catalyst PEG-400 offered no advantage in this reaction compared with traditional methods (Table 1).[9,11]

According to our previous studies,[9,11] treatment of **3a–3p** with KIO_3 in a water suspension was an efficient method for the transformation forming semicarbazides **4a–4p.** The transformation of **3a–3p** to **4a–4p**, however, did not occur in the presence of KIO_3 under MWI and solvent-free conditions. It was interesting to note that $HIO_4{\cdot}2H_2O$ was quite an efficient reagent for this transformation under the same conditions to afford semicarbazides **4a–4p** in excellent yields.

In summary, we have described a facile and convenient method for the synthesis of 1,4-disubstituted thiosemicarbazides/semicarbazides, with the advantages of no pollution by escaping solvents, simple operation and short reaction time over the reported methods.



3a–3g, 4a–4g, Ar= C_6H_5 (**a**); 4-$CH_3OC_6H_4$ (**b**); 2-ClC_6H_4 (**c**); 4-ClC_6H_4 (**d**); 2-$NO_2C_6H_4$ (**e**); 4-$NO_2C_6H_4$ (**f**); 2-IC_6H_4 (**g**); **3h–3p, 4h–4p**, Ar= $C_6H_5OCH_2$ (**h**); 2-$CH_3C_6H_4OCH_2$ (**i**); 4-$CH_3C_6H_4OCH_2$ (**j**); 4-$CH_3OC_6H_4OCH_2$ (**k**); 2-$NO_2C_6H_4OCH_2$ (**l**); 3-$NO_2C_6H_4OCH_2$ (**m**); Ar= 4-$NO_2C_6H_4OCH_2$ (**n**); 1-NaphthylOCH$_2$ (**o**); 4-$ClC_6H_4OCH_2$ (**p**).

Scheme 1

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Table 1 Synthesis of **3a–3p** under MWI and solvent-free conditions

Compd	M.p./°C (lit.)	Yield/%[a]		
		I[b]	II[c]	Lit.[9,11]
3a	213–214(212–213[11])	87	86	89
3b	208–210(209–210[11])	83	83	84
3c	216–217(217–218[11])	88	90	87
3d	217–218(216–217[11])	82	85	85
3e	211–213(211–212[11])	84	85	85
3f	230–231(230–231[11])	89	92	90
3g	185–186(185–186[11])	83	84	86
3h	211–212(212–213[9])	85	91	94
3i	193–194(193–194[9])	81	86	90
3j	199–200(199–200[9])	85	90	96
3k	170–171(171–172[9])	80	79	88
3l	221–222(220–221[9])	78	82	86
3m	227–228(226–227[9])	79	85	89
3n	209–210(208–209[9])	79	82	87
3o	197–198(196–197[9])	86	87	93
3p	202–203(203–204[9])	88	85	92

[a]Based on aroylhydrazine;
[b]In the absence of catalyst;
[c]In the presence of PEG-400.

Table 2 Synthesis of **4a–4p** under MWI and solvent-free conditions

Compd.	M.p./°C (Lit)	Yield/%[d]	
		No solvent	Lit.
4a	236–237(236–237[11])	91	92
4b	236–237(235–236[11])	90	89
4c	207–208(208–209[11])	89	90
4d	242–243(243–244[11])	95	96
4e	214-215(214–215[11])	93	92
4f	244–245(243–244[11])	87	88
4g	170–172(171–172[11])	89	90
4h	182–185(183–184[9])	82	91
4i	201–204(203–204[9])	88	92
4j	191–192(190–191[9])	85	89
4k	177–178(178–179[9])	90	93
4l	192–195(193–194[9])	86	91
4m	200–201(200–201[9])	89	88
4n	182–183(181–182[9])	89	87
4o	191–194(192–193[9])	92	90
4p	195–196(196–197[9])	93	92

[d]Based on thiosemicarbazide.

Experimental

Acid hydrazides,[12] 2-benzofuroyl chloride[13] and 5-(2-chlorophenyl)-2-furoyl chloride[14] were prepared according to literature procedures.

Synthesis of 1-aroyl/aryloxyacetyl-4-(2-furoyl) thiosemicarbazides **3a–3p**. *General procedure*: 2-Furoyl chloride (**1**) (1 mmol) and ammonium thiocyanate (1.5 mmol) were mixed thoroughly in an agate mortar. The mixture was subsequently irradiated in a domestic microwave oven at 350W for 0.5 min periods up to a total irradiation time of 5 min**.** After cooling the mixture to room temperature, aroyl or aryloxyacetyl hydrazines (0.95 mmol) was added to the reaction mixture and mixed thoroughly. The mixture was subjected to microwave irradiation (490W) for 0.5 min periods up to a total irradiation time of 3 min. After the reaction was completed, the reaction mixture was washed with distilled water (3×10 ml) and the product was obtained as solid and recrystallised from DMF-EtOH-H_2O (6:3:1), giving the pure product **3a–3p**. The results are shown in Table 1.

Synthesis of 1-aroyl/aryloxyacetyl-4-(2-furoyl)semicarbazides **4a–4p**. *General procedure:* Thiosemicarbazides **3a–3p** (1 mmol) and $HIO_4{\cdot}2H_2O$ (1.5 mmol) were mixed thoroughly in an agate mortar. Then the mixture was subjected to microwave irradiation (490W) for 3 min. After the reaction completed, the reaction mixture was washed with distilled water (3×10 ml) and the product was obtained as a solid and recrystallised from DMF-EtOH-H_2O (6:4:1), giving the pure product **4a–4p**. The results are shown in Table 2.

The structures of all compounds were characterised by m.p., IR, ^{1}H NMR, TLC and elemental analyses and compared with the data obtained from our previous work.[9,11]

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References

1 S. Caddick, *Tetrahedron*, 1995, **51**, 10403.
2 S.A. Galema, *Chem. Soc. Rev*., 1997, **26**, 233.
3 S. Rollas, S. Karaku, B.B. Durgun, M. Kiraz and H. Erdeniz, *Il Farmaco*, 1996, **51**, 811.
4 X.M. Feng, R. Chen, G.Y. Huang and Z.Y. Zhang, *Yingyong Huaxue*, 1992, **9**, 89 (in Chinese); *CA,* 1992, **117**, 171286.
5 N. Takeuchi, T. Kasama, R. Ikeda, K. Shimizu and K. Hatakeyama., *Chem. Pharm. Bull.,* 1984, **32**, 2249.
6 E. Palaska, G. Sahin, P. Kelicen, N.T. Durlu and G. Altinok, *Farmaco*, 2002, **57**, 101.
7 T.B. Wei, J. C. Chen, X.C. Wang and Y.M. Zhang, *J. Chem. Res. (S),* 1995, 138.
8 X.C. Wang, Z. Li, Y.X. Da and J.C. Chen, *Synth. Commun.,* 1999, **29**, 4163.
9 Z. Li, X.C. Wang, Y.X. Da and J.C. Chen, *Synth. Commun.,* 2001, **31**, 1433.
10 X.C. Wang, Z. Li, Y.X. Da and J.C. Chen, *Synth. Commun.,* 2000, **30**, 3405.
11 Z. Li, Z.J. Quan and X.C. Wang, *Youji Huaxue*, 2003, **23**, 833 (in Chinese); *CA*. 2003, **140**, 4997.
12 M.I. Husain and M. Amir, *J. Ind. Chem. Soc*. 1986, **63**, 317.
13 G.Y. Jin, M.Y. Xie and G.F. Zhao, *Yingyong Huaxue,* 1995, **12**, 99 (in Chinese); *CA*. 1995, **123**, 186182r.
14 A. Krutosikova and J. Kovac, *Collect. Czech. Chem. Commun*., 1976, **41**, 2577.