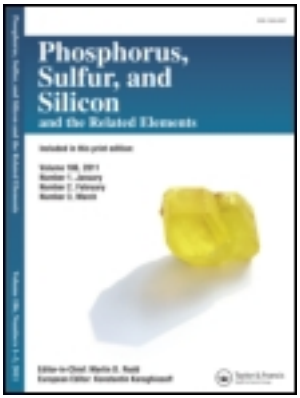

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One-Pot Synthesis of Some Nitrogen and Sulfur Heterocycles Using Thiosemicarbazide Under Microwave Irradiation in a Solventless System

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One-Pot Synthesis of Some Nitrogen and Sulfur Heterocycles Using Thiosemicarbazide Under Microwave Irradiation in a Solventless System

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A thiazolon, triazines, and triazinones were synthesized under microwave irradiation in a solventless system in a very short time and in excellent yields.

Keywords α-chloroacetic acid; benzil; diethyl acetylendicarboxylate; diketone; dimethyl acetylendicarboxylate; thiosemicarbazide; triazine

1,2,4-triazines, 1,2,4-triazinones, and thiazolones are an important class of heterocyclic compounds with a particularly wide range of biological properties.[1] There has been considerable attention in the creation and development of evergreen and solventless methods in organic methodology,[2] dictated by stringent environmental protection laws.[3] Organic solvents are not only expensive, but are often flammable, toxic, and environmentally hazardous.

Microwave irradiation in organic synthesis is a useful technique today.[4–7] Dry media using microwave thermolysis have attracted much attention because it omits the use of hazardous and relatively expensive organic solvents, and the reaction can be conducted in open vessels.[8]

Solvent-free organic reactions or dry-media techniques under microwave irradiation are one of the main topics of research in our laboratory.[9] We have reported recently the synthesis of heterocyclic systems under microwave irradiation in a solventless system.[10] In view of the current trust on solventless systems, there is merit in developing

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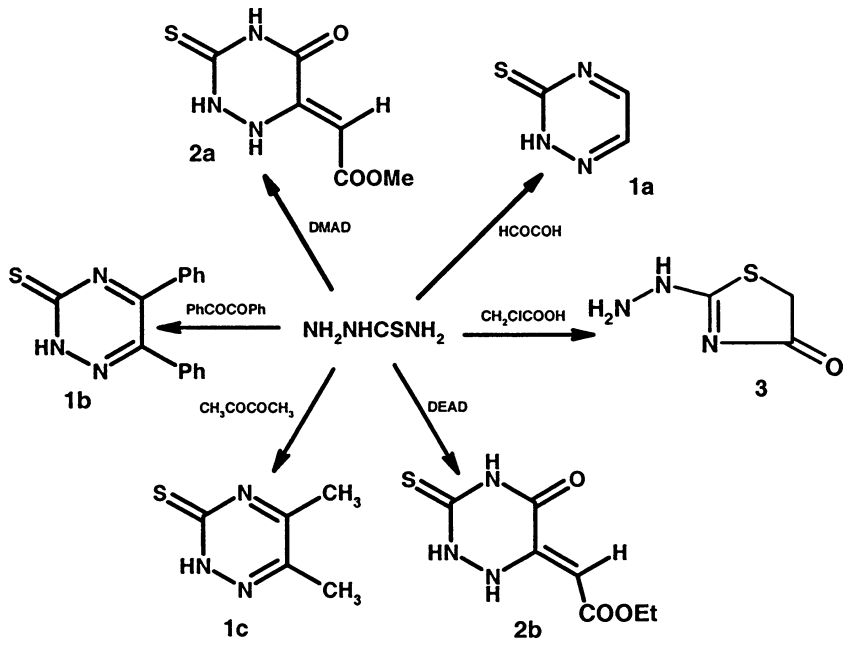
a truly solvent-free condition for the synthesis of heterocyclic systems. Herein we wish to report our results for the synthesis of some useful basic heterocyclic systems, which are interesting from the biological point of view as well as for the use as precursors for the synthesis of fused bicyclic heterocycles.

1,2,4-triazines (**1a–c**) were prepared from the condensation of thiosemicarbazide with diketons (RCOCOR, R=H, Ph, CH_3) under microwave irradiation in a solventless system (Scheme 1). These compounds have been synthesized under conventional heating in solvents.[11]

Reaction of thiosemicarbazide with Dimethyl Acetylendicarboxylate (DMAD) and Diethyl Acetylendicarboxylate (DEAD) in either hot methanol or in a solventless system under microwave irradiation gave 3-mercapto-6-(methoxycarbonylmethylen) 1,2,4-triazine-5(4)-one(**2a**) and 3-mercapto-6-(ethoxycarbonylmethylen)1,2,4-triazine-5(4) -one(**2b**), respectively.

2-hydrazinothiazolon-5-one (**3**) was prepared from the condensation reaction of thiosemicarbazide with chloroacetic acid under microwave irradiation in a solventless system. This reaction needs a long reaction time and a solvent under conventional heating.[12]



SCHEME 1

In conclusion, these procedures for the synthesis of the previously mentioned heterocycles have some advantages over the existing methods and will make a useful and important addition to the present methods. The main advantages of these new methods are a mild reaction condition, reduced reaction times, high yields, and a minimum requirement for expensive and hazardous solvents.

EXPERIMENTAL

The melting points were obtained on Electrotermal IA 9100 Digital Melting Point apparatus. The IR spectra were recorded on a 4300 Shimadzu spectrometer. ^{1}HNMR spectra were recorded on a 300 MHZ spectrometer using TMS as internal standard. The microwave oven used was an LG MOD MC-838 WR.

General Procedure

Two reactants were mixed in a beaker thoroughly using a spatula. The beaker was placed in a microwave oven for the specified time. The progress of the reaction was indicated by TLC using n-hexan:ethyl acetate (1:3). The crude product was crystallized from an appropriate solvent. The selected physical and spectroscopic data are given below.

Selected Data for 3-Mercapto-1,2,4-triazine 1a

m.p. $> 300^\circ$C, yellow brownish powder from E_tOH (Lit.[11] decom. 310°C), Yield 93%. Irradiation time: 7 min (900 W). IR (KBr) (ν_{max}, cm^{-1}): 3161(NH str), 3010(=CH str), 1606(C=C), 1519(C=C), 1470, 1308, 1274, 1088, 1053, 915, 836, 717, 669, 623.

Selected Data for 5,6-Diphenyl-3-mercapto-1,2,4-triazine 1b

m.p. = 224°C, yellow orange powder from AcOH, (Lit.[11] 225–822°C), Yield 90%, Irradiation time: 6 min (900W). IR (KBr) (ν_{max}, cm^{-1}) 3121(NH str), 3050 (=CH str), 1559(C=C), 1535(C=C), 1444, 1367, 1333, 1179, 1053, 1026, 766, 695. ^{1}HNMR: δ (d_6-DMSO), 7.55(m, 10H, Ph), 7.70(br, 1H, NH).

Selected Data for 5, 6-Dimethyl-3-mercapto-1,2,4-triazine 1c

m.p. = 233°C, yellow brownish powder from AcOH, (Lit.[11] 233–723°C), Yield 89%, Irradiation time: 7 min (900 W). IR (KBr) (ν_{max} cm^{-1}): 3125(NH str), 2864(RH, str), 1533(C=C), 1446, 1366, 1329, 1223, 1181,

1040, 1024, 879, 761, 695. MS, m/z; M^+, 141(100), 113(12), 91(65), 72(7), 54(46).

3-Mercapto-6-(methoxycarbonylmethylene)1,2,4-triazin-5(4)-One 2a

Method a

m.p. = 168°C, yellow powder from MeOH, Yield 85%, Irradiation time: 9 min (720 W). IR (KBr) (ν_{max}, cm^{-1}): 3339(NH str), 3316(NH str), 3266(NH str), 3060(=CH), 1740(CO ster), 1688(CO amid), 1608(C=C), 1441, 1398, 1338, 1212, 1137, 1011, 905, 815, 756, 712, 651, 606. ^{1}HNMR: δ (d_6-DMSO), 10.10(br, 1H, NH amid), 8.82(br, 1H, NH), 6.74(s, 1H, =CH), 3.73(s, 3H, OMe). MS, m/z; M^+, 201(100), 174(74), 142(41), 117(30), 85(52), 69(7), 57(26).

Method b

An equimolar mixture of thiosemicarbazide (1 mmol) and DMAD (1 mmol) was refluxed in MeOH (10 mL) for 20 min. After cooling, the precipitated solid was filtered and dried to afford **2a** (80%).

3-Mercapto-6-(ethoxycarbonylmethylen) 1,2,4-triazin-5(4)-One 2b

Method a

m.p. = 135°C, yellow microneedles from EtOH, Yield 89%, Irradiation time: 9 min (720 W). IR (KBr) (ν_{max}, cm^{-1}): 3339(NH str), 3282(NH str), 3241(NH str), 3032(=CH), 2981(RH, str), 1740(CO ster), 1684(CO amid), 1630(C=C str), 1608(C=C str), 1409, 1373, 1202, 955, 903, 858. ^{1}HNMR: δ (d_6-DMSO), 10.08(br, 1H, NH amid), 8.51(br, 1H, NH), 6.53(s, 1H, =CH), 4.51(q, J = 7, 2H, CH_2), 1.45(t, J = 7, 3H, CH_3).

Method b

An equimolar mixture of thiosemicarbazide (1 mmol) and DEAD (1 mmol) was refluxed in EtOH (10 mL) for 30 min. After cooling, the precipitated solid was filtered and dried to afford **2b** (76%).

Selected Data for 2-Hydrazinothiazol-5-One 3

m.p. = 230°C decom, brown powder from EtOH, (Lit.[12] 230°C), Yield 89%, Irradiation time: 7 min (900 W). IR (KBr) (ν_{max}, cm^{-1}) 3324(NH str), 3196(NH_2 str), 2989(HC–H), 1721(CO str), 1613(C=N str), 1388, 1326, 1224, 891, 722, 697.

Caution

Although we did not have any accident using a microwave oven, an efficient hood is highly recommended.

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