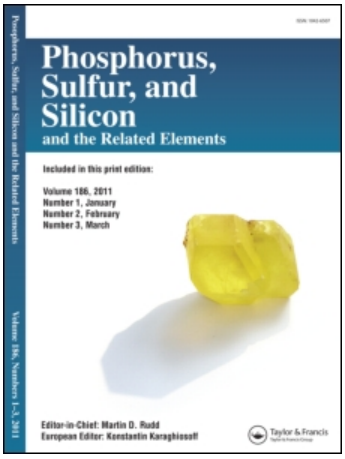

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Microwave-Assisted Synthesis of Substituted Pyrazoles and Pyrazolo [3, 4-*d*]thiopyrimidines

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Microwave-Assisted Synthesis of Substituted Pyrazoles and Pyrazolo [3,4-*d*]thiopyrimidines

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Ethyl(ethoxymethylene)cyanoacetate and ethoxymethylene malononitrile were synthesized from the reaction of malononitrile or ethylcyanoacetate with triethyl orthoformate or orthoacetate in N, N-dimethylacetamide under microwave irradiation. In a similar manner, substituted pyrazoles were synthesized from the reaction of ethyl (ethoxymethylene)cyanoacetate and ethoxymethylene malononitrile with phenylhydrazine. These pyrazoles were converted to pyrazolo[3,4-d]thiopyrimidines upon treatment with arylisothiocyanate and thiourea under microwave irradiation.

Keywords Ethylcyanoacetate; malononitrile; pyrazolo[3,4-d]thiopyrimidine; triethyl orthoacetate; triethyl orthoformate

Pyrazoles are a class of heterocyclic compounds that have many derivatives with a wide range of interesting properties, such as antihyperglycemic, analgestic, anti-inflammatory, anti-pyretic, anti-bacterial, hypoglycemic, and sedative-hypnotic activity. In particular, aryl pyrazoles are important in medicinal and pesticide chemistry.[2] Recently, some arylpyrazole derivatives were reported to have nonnucleoside HIV-1 reverse transcriptase inhibitory activity.[3] The pyrazole moiety is a core structure in a number of biologically active compounds, such as pyrazolo[3,4-d]pyrimidine.[4] The antitumor activty.[5,6] of several derivatives of the pyrazolo[3,4-d]pyrimidine system has prompted investigation of these compounds. The antitumor activity,[5–6] of several derivatives of the pyrazolo[3,4-d]pyrimidine system has prompted investigation of these compounds.

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Organic synthesis under microwave irradiation is presently under extensive examinations.[7–10] The relatively low cost of modern domestic microwave ovens makes them readily available to academic and industrial chemists, and the use of such unconventional reaction conditions reveals several features such as a short reaction time compared to conventional heating, reduction of the usual thermal degradation, and better selectivity.[1–13] An attractive synthetic methodology is the possibility of performing reactions in solvent-free conditions or on solid inorganic supports.

Indeed, in several cases, a solid-state organic reaction occurs more efficiently and more selectively than does its solution counterpart, because molecules in a crystal are arranged tightly and regularly.[14–18] Mineral oxides are very efficient MW absorbents.[17]

This results in a very rapid and homogeneous heating and consequently, reactions in solid supports under microwaves show strange MW effects.[18]

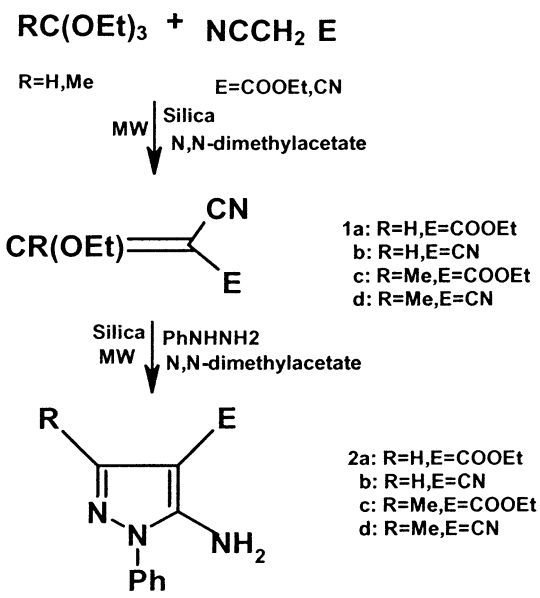
In continuation of our interest to perform organic reactions under microwave irradiation[19] and the synthesis of heterocyclic systems,[20] here we wish to report the synthesis of pyrazoles and pyrazolo[3,4-d]thiopyrimidines.

First we investigated the addition of ethylcyanoacetate to triethyl orthoformate or orthoacetate under microwave irradiation. The reactions were simply conducted by mixing ethylcyanoacetate with triethyl orthoformate or orthoacetate, silica gel, and N,N-dimethylacetamide in a beaker and placing the beaker in a microwave oven for a short period of time. The progress of the reaction was monitored by TLC using ethyl acetate and n-hexane (1:9). Ethyl(ethoxymethylene)cyanoacetate **1a**[21] and ethyl α-cyano-β-ethoxycrotonat **1c**[22] were prepared, respectively.

In a similar manner, the reaction of malononitrile with triethyl orthoformate or orthoacetate in N,N-dimethylacetamide on the surface of silica gel gave ethoxymethylene malononitrile **1b**[23] and ethoxyethylidene malononitrile **1d**,[24] respectively.

The reaction of **1a–d** with phenylhydrazine under microwave irradiation in a solventless system gave 3-amino-4-carbethoxy-2-phenylpyrazole **2a**,[21] 3-amino-4-cyano-5-methyl-2-phenylpyrazole **2b**,[25,26] 3-amino-4-carbethoxy-5-methyl-2-phenylpyrazole **2c**,[27] and 3-amino-4-cyano-5-methyl-2-phenylpyrazole **2d**,[25,26] respectively (Scheme 1).

The reaction of phenylisothiocyanate and 4-nitrophenylisothiocyanate with **2b** and **2d** under microwave irradiation gave 4-imino-1,5-diphenylpyrazolo[3,4-d]pyrimidine-6(7H)-thione **3a**,[28] 4-imino-3-methyl-1,5-diphenylpyrazolo[3,4-d]pyrimidine-6(7H)-thione **3b**, 4-imino-3-methyl-l-phenyl-5-(4-nitrophenyl) pyrazolo[3,4-d]pyrimidine-6(7H)-thione **3c**, and 4-imino-l-phenyl-5-(4-nitrophenyl) pyrazolo[3,



SCHEME 1

4-d]pyrimidine 6(7H)-thione **3d**. The reaction of **2a–2d** with thiourea under microwave irradiation gave 1- phenyl pyrazolo[3,4-d]pyrimidin-4(5H)-one-6(7H)-thione **4a**, 4-amino-l-phenyl pyrazolo[3,4-d]pyrimidin-6(7H)-thione **4b**, 3-methyl-l-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one-6(7H)-thione **4c**, and 4-amino-3-methyl-l-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one-6(7H)-thione **4d** respectively (Scheme 2).

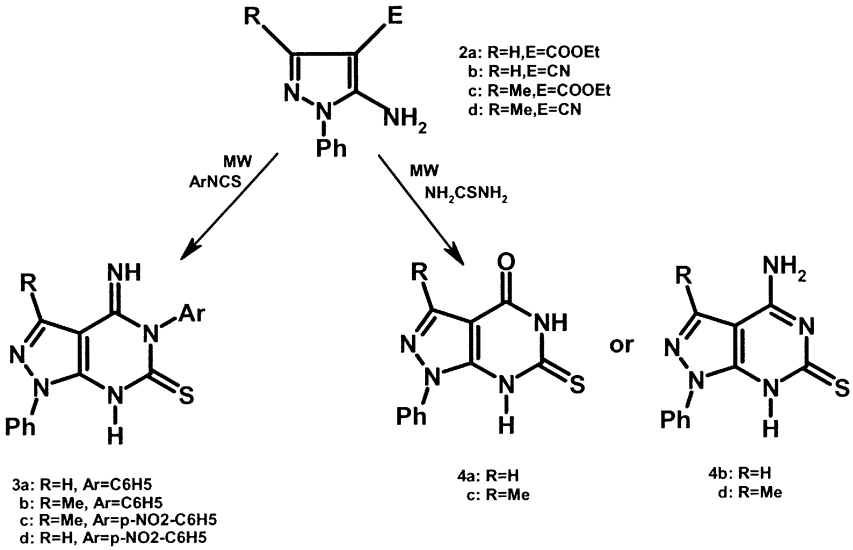
EXPERIMENTAL

The melting points were obtained using an electrothermal IA 9100 digital melting point apparatus. The IR spectra were recorded on a Bruker (400–4000 cm^{-1}) spectrometer. ^{1}HNMR spectra were recorded on a 300 MHz spectrometer using TMS as internal standard. Mass spectrometric measurements were made on an Agilent Technologies 6890 N Network GC system. The microwave oven used was LG MOD MC-838 WR.

Synthesis of 1a–d

General Procedure

Malononitrile or ethylcyanoacetate (0.1 mmol) and triethyl orthoformate or orthoacetate (0.1 mmol), silica gel (1 g), and N,N-dimethylacetamide (1 mL) were thoroughly mixed in a beaker using



SCHEME 2

a spatula. The beaker was placed in a microwave oven for a specified time. The progress of the reaction was monitored by TLC using ethyl acetate and n-hexane (1:9). The mixture was extracted with ethanol. The solvent was evaporated and the crude product was passed through a columm of silica gel using ethyl acetate and n-hexane (1:9), giving **1a–d**.

Ethyl(ethoxymethylene)cyanoacetate 1a

Irradiation time was 10 min (900 W), m.p. = 52°C (Lit.[21]52–53°C), yield 55%.

Ethoxymethylene Malononitrile 1b

Irradiation time was 5 min (720 W), m.p. = 66–67°C (Lit.[23] 65–68°C), yield 95%.

Ethyl α-Cyano-β-ethoxycrotonate 1c

Irradiation time was 10 min (900 W), m.p. = 74°C (Lit.[27]C), yield 60%.

Ethoxyethylidene Malononitrile 1d

Irradiation time was 4 min (900 W), m.p. = 87°C (Lit,[24] 90°C), yield 89%.

Synthesis of Pyrazoles

General Procedure

la–d (0.1 mmol), phenylhydrazine (0.1 mmol), silica gel (1 g), and N, N-dimethylacetamide(1 mL) were a thoroughly mixed in a beaker using a spatula. The beaker was placed in a microwave oven for a specified time. The progress of the reaction was monitored by TLC using ethyl acetate and n-hexane (1:9). The mixture was extracted with ethanol. The solvent was evaporated and the crude product was purified by re-crystallization from an appropriate solvent, giving **2a–d**.

3-Amino-4-carbethoxy-2-phenylpyrazole 2a

Irradiation time was 9 min (900 W), m.p. = 99°C from ethanol/water (50:50), (Lit.[21] 99–101°C), yield 60%.

3-Amino-4-cyano-2-phenylpyrazole 2b

Irradiation time was 9 min (900 W), m.p. = 130°C from ethanol/water (50:50), (Lit.[25,26] 130°C), yield 92%.

3-Amino-4-carbethoxy-5-methyl-2-phenylpyrazole 2c

Irradiation time was 9 min (900 W), m.p. = 215°C from ethanol/water (50:50), (Lit.[27] 215°C), yield 62%.

3-Amino-4-cyano-5-methyl-2-phenylpyrazole 2d

Irradiation time was 9 min (900 W), m.p. = 125°C from ethanol/water (50:50), (Lit.[25,26] 125°C), yield 83%.

Synthesis of Pyrazolo[3,4-d]thiopyrimidines

General Procedure

An appropriate pyrazole (0.1 mmol) was thoroughly mixed with phenylisothiocyanate, 4-nitrophenyl isothiocyanate, or thiourea (0.1 mmol), in a beaker using a spatula. The beaker was placed in a microwave oven for a specified time. The progress of the reaction was monitored by TLC using ethyl acetate and n-hexane (1:9). The crude product was crystallized from an appropriate solvent.

4-Imino-1,5-diphenyl pyrazolo[3,4-d]pyrimidine-6(7H)-thione 3a

Irradiation time was 8 min (900 W), m.p. = 227°C from ethanol (Lit.[28] 227°C), yield 82%.

4-Imino-3-methyl-1,5-diphenyl Pyrazolo[3,4-d]pyrimidine-6(7H)-thione 3b

Irradiation time was 8 min (900 W), m.p. = 260°C from ethanol, yield 65%. ^{1}HNMR: δ (d_6-DMSO), 2.41 (s, 3H, CH_3), 7.13 (s, 1H, NH), 7.32 (m, 10H, Ar-H), 9.35 (br, 1H, NH). IR (KBr) (υ_{max}, cm^{-1}): 3362 (NH, str), 3246 (NH, str), 3062 (Ar-H, str), 2998 (alkyl-H, str), 1627 (C=S, str), 1584 (C=N, str), 1544 (C=C, str), 1436 (C=C, str), 1374, 1329, 1205, 1147, 1072, 750, 687. MS, m/z; M^+, 333.

4-Imino-3-methyl-1-phenyl-5-(4-nitrophenyl)pyrazolo[3,4-d]pyrimidine-6(7H)-thione 3c

Irradiation time was 7 min (2 × 5 min, 400 W), m.p. = 192°C from methanol, yield 75%. ^{1}HNMR: δ (d_6-DMSO), 2.46 (s, 3H, CH_3), 7.04 (s, 1H, NH), 7.22 (m, 5H, Ar-H), 8.14 (d, J = 7, 2H, Ar-H), 8.51 (d, J = 7, 2H, Ar-H), 10.21 (br, 1H, NH). IR (KBr) (υ_{max}, cm^{-1}): 3421 (NH, str), 3310 (NH, str), 3050 (Ar-H, str), 2980 (alkyl-H, str), 1617 (C=S, str), 1587 (C=N, str), 1553 (C=C, str), 1504 (C=C, str), 1462 (N=O, str), 1434, 1329, 1249, 1181, 1112, 1087, 962, 850, 750, 690. MS, m/z; M^+, 378.

4-Imino-1-phenyl-5-(4-nitrophenyl)pyrazolo[3,4-d]pyrimidine-6(7H)-thione 3d

Irradiation time was 10 min (900 W), m.p. = 189°C from methanol, yield 65%. ^{1}HNMR: δ (d_6-DMSO), 7.15 (s, 1H, NH), 7.31 (m, 5H, Ar-H), 8.11 (s, 1H, =CH), 8.22 (d, J = 7, 2H, Ar-H), 8.58 (d, J = 7, 2H, Ar-H), 10.48 (br, 1H, =NH). IR (KBr) (υ_{max}, cm^{-1}): 3391 (NH, str), 3230 (NH, str), 3035 (Ar-H st), 1622 (C=S, str), 1590 (C=N, str), 1509 (C=C, str), 1437 (N=O, str), 1315, 1111, 1010, 855, 764, 692. MS, m/z; M^+, 364.

1-Phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one-6(7H)-thione 4a

Irradiation time was 10 min (2 × 5 min, 300 W), m.p. = 200°C from methanol, yield 65%. ^{1}HNMR: δ ($CDCl_3$), 7.39(s, 1H, =CH), 7.52 (m, 3H, Ar-H), 8.15 (m, 2H, Ar-H), 8.22 (s, 1H, NH), 10.88 (s, 1H, NH), IR (KBr) (υ_{max}, cm^{-1}): 3430 (NH, str), 3321 (NH, str), 3052 (Ar-H, st), 1660

(C=O, str), 1618 (C=N, str), 1549 (C=C, str), 1461, 1372, 1279, 1200, 1128, 946, 913, 784, 753, 701, 603. MS, m/z; M^+, 244.

4-Amino-1-phenylpyrazolo[3,4-d]pyrimidine-6(7H)-thione 4b

Irradiation time was 7 min (900 W), m.p. = 215°C from methanol, yield 80%. ^{1}HNMR: δ (d_6-DMSO), 7.18(s, 1H, =CH), 7.47 (m, 3H, Ar-H), 7.99 (m, 2H, Ar-H), 8.63 (s, 2H, NH_2), 9.84 (s, 1H, NH), IR (KBr) (υ_{max}, cm^{-1}): 3408 (NH, str), 3312 (NH_2, str), 3035 (Ar-H, str), 1625 (C=N, str), 1588 (C=C, str), 1543 (C=C, str), 1498 (C=C, str), 1440, 1296, 1161, 1019, 936, 806, 760. MS, m/z; M^+, 243.

3-Methyl-1-phenylpyrazolo[3,4-d]pyrimidin-4(5H)-one-6(7H)-thione 4c

Irradiation time was 7 min (900 W), m.p. = 217°C from methanol, yield 53%. ^{1}HNMR: δ (d_6-DMSO), 2.23 (s, 3H, CH_3), 7.49 (m, 3H, Ar-H), 8.01 (m, 2H, Ar-H), 8.18 (br, 1H, NH), 12.61 (br, 1H, NH). IR (KBr) (υ_{max}, cm^{-1}): 3458 (NH, str), 3257 (NH, str), 3050 (Ar-H, =CH, str), 2981 (alkyl-H, str), 1656 (C=O, str), 1546 (C=N, str), 1461 (C=C, str), 1438, 1380, 1141, 1103, 1050, 1006, 659, 559, 446. MS, m/z; M^+, 258.

4-Amino-3-methyl-1-phenylpyrazolo[3,4-d]pyrimidine-6(7H)-thione 4d

Irradiation time was 7 min (900 W), m.p. > 300°C from methanol, yield 87%. ^{1}HNMR: δ (d_6-DMSO), 2.11 (s, 3H, CH_3), 7.52 (m, 3H, Ar-H), 7.98 (m, 2H, Ar-H), 8.05 (s, 2H, NH_2)_8.45 (br, 1H, NH). IR (KBr) (υ_{max}, cm^{-1}): 3352 (NH, str), 3127 (NH, str), 3045 (Ar-H, str), 2991 (alkyl-H, str), 1689 (C=O, str), 1636 (C=N, str), 1524 (C=C, str), 1473 (C=C, str), 1380, 1298, 1197, 943, 777, 690.

CAUTION

Although we did not have any accident, the use of a microwave oven in an efficient hood is highly recommended.

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