Microwave Supported Solvent Free Reaction of EMME in the Synthesis of Pyrazolopyrimidopyrimidines

D. Shah Rina¹*, M. Shah Nirmal¹ and C. Ramani Vivek¹

¹Department of Chemistry, M. G. Science Institute, Navrangpura, Ahmedabad 380 009, India.

Authors’ contributions

This work was carried out in collaboration between all authors. Author MSN performed the experimental work and collected the data. Author CRV managed the literature searches. Author DSR designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. All authors managed the analyses of the entire study and organized orderly to finalized the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Diethyl ethoxy-methylenemalonate the versatile reagent used to synthesize pyrazolopyrimidopyrimidines (3) as antimicrobial agents from the reaction between EMME and 1-substituted 3-(methylthio) 3H-pyrazolo [3,4-d]pyrimidine-4-amines (1) using Gould Jacob reaction. A comparison of conventional and microwave supported solvent-free reaction has been studied.

Keywords: EMME; pyrazolopyrimidopyrimidines; Gould-Jacob reaction; microwave heating.

ABBREVIATIONS

EMME: diethyl ethoxymethylenemalonate,
DPO: diphenyl oxide,
MW: microwave

1. INTRODUCTION

Various pyrazolopyrimidopyrimidines have been synthesized in order to establish their synthetic and biological importance.
Pyrazolopyrimidopyrimidines found to relate number of biological activities such as analgesic, antipyretic, anti-inflammatory along with gastro protective effect in rats, antimicrobial and anticancer activity [1–8]. Different pyrimidopyrazolopyrimidines were synthesized as useful inhibitors of phosphodiesterase(PDE1) in the treatment of diseases like Parkinson's disease, depression, narcolepsy and damage to cognitive function [9–11].

Diethyl ethoxymethylenemalonate (EMME) has been reported as versatile synthon in the field of organic synthesis. Applications of EMME can be summarized as follows. The reagent can be used in Diels-Alder reaction [12], in Michael reaction [13] in [3+2] cycloadditions [14], in push-pull alkane [15], in 1,4-addition reaction [16], in 1,4- addition elimination reactions [17], in synthesis of quinolone derivatives by Gould-Jacob reaction [18], in preparation of 1,8-naphthyridines, 2H-pyrido[1,2-d]pyrimidin-4-ones, pyrazolones, pyrons, xanthrones, guanidine derivatives, 1,2,4-triazoles, 3-oxo-1,2,6-thiadiazines, 8-oxoimidazo[1,2-a]pyrimidines, 3H-pyrorolo[1,2-ajindol-3-ones, 1H-1,4-benzodiazepines and pyrid[3,2-e]pyrimido [1,2-c]pyrimdines [19,20]. Moreover microwave supported synthesis was given attention during the last four decades as it has be found to provide rapid, cleaner, high yielding and purity improving synthesis [21–24]. Sometimes found to avoid the use of solvent [21–23, 25–29]. The solvent free organic synthesis became remedy to resolve environmental issues [30]. Therefore, microwave assisted solvent-free reaction condition [21–23, 28, 30, 31], was found to be economic and environmentally benign system. Microwave assisted solvent-free synthesis of thieno[3,2-e]pyrimido[1,2-c]pyrimidines, pyrrolo[3,2-e]pyrimido[1,2-c]pyrimidines and furo[3,2-e]pyrimido[1,2-c]pyrimidines have also been reported [21–23]. In addition synthesis of pyrazolopyrimidopyrimidines have rarely been attended [1–8]. All these facts steered us to study Gould-Jacob reaction to synthesize pyrazolopyrimidopyrimidines from pyrazolo[3,4-d]pyrimidine-4-amines using EMME as synthon.

2. MATERIALS AND METHODS

2.1 Experimental

The chemicals were Laboratory grade and purchased from Adrich Chemicals and S D Fine chemicals. Melting points were determined by electro thermal method in open capillary tube and are uncorrected. The IR spectra were recorded in cm⁻¹ for KBr pellets on FT-IR Buck scientific spectrophotometer. The ¹H NMR spectra were recorded on Bruker 400 MHz spectrophotometer in DMSO-d⁶ using TMS as internal standard and the chemical shifts are expressed in ppm. MS spectra were recorded on LKB 9000 mass spectrophotometer. Microwave irradiation was carried out in CEM Discover microwave, Model No 90801 (2455 MHz, 700 watts). The purity of the newly synthesized compounds was routinely checked by TLC using silica gel G and spots were exposed in iodine vapour and or UV light.

2.1.1 General Procedure for the synthesis of 1-substituted 3-(methylthio) 3H-pyrazolo[3,4-d]pyrimidine-4-amines 1a-j [32-34]

Ethyl 5-amino-3-(methylthio)-1-substituted 1H-pyrazole-4-carbonitriles(1, 10 mmol) were refluxed with formamide (25 mL) for 8-10 h, then the cold reaction mixture was poured on to the crushed ice, the solid obtained was filtered washed with water and recrystallized from DMF to give titled compounds 2 a-j.

2.1.2 General Procedure for the synthesis of ethyl 10-S-methyl 4-oxo-8-substituted pyrazolo[3,4-e]pyrimido[1,2-c]pyrimidine-3-carboxylates 3a-j

2.1.2.1 Step 1: General Procedure for the synthesis of diethyl 2-[3-(methylthio)-1-substituted 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonates 2a-j

A mixture of 1-substituted 3-(methylthio) 3H-pyrazolo[3,4-d]pyrimidine-4-amines [32-34] (1, 5mmol) and EMME (5 mmol, 1.08 g) was taken in a 25 mL round bottomed flask and heated at 130-90°C for 3-3.5 h. It was allowed to cool, treated with n-hexane and the obtained solid was filtered, washed with n-hexane dried and recrystallized from ethanol to give required compound 2.

Diethyl 2-[3-(methylthio)-1-phenyl 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonate (2a): Yield: 79%, mp: 192-193°C, IR(KBr): 3356(NH), 1710, 1670(C=O), 1608, 1533(C=C, C=N) cm⁻¹. ¹H NMRDMSO): δ 11.36-39 (d, J=12 Hz, 1H, NH), δ 9.14-9.17(d, J=12 Hz, 1H, vinyl-H), δ 8.63(s, 1H, ArH at C2), 4.26-4.39(q, J=5.59, 2H, CH₂-ester), 3.11-3.14(t, J=5.91 Hz, 2H, 1H, CH₂-ester), 1.39-1.43(m, 2H, CH₂-ester), 1.03-1.07(m, 3H, CH₂-ester), 0.21-0.26(m, 3H, CH₂-ester).
Diethyl 2-[3-(methylthio)-1-(2-methylphenyl)] 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonate (2b) : Yield: 76 %, mp: 283-285°C, IR(KBr): 3366(NH), 1705, 1676(C=O), 1610, 1532(C=C, C=N) cm⁻¹. ¹H NMR(DMSO): δ 10.5-10.54(d, J=11.89 Hz, 1H, NH), δ 9.3-9.32(d, J=12.04 Hz, 1H, vinyl-H), δ 8.65(s, 1H, ArH at C2); 4.03-4.29(qx2, J=6.05 Hz, 4H, CH₂-ester), 2.4(s, 3H, CH₃), 1.98 (s, 3H, CH₃), 1.22-1.35(tx2, J=7.26 Hz, 6H, CH₂-ester). MS: 303 (M⁺), Anal. Calcd. for C₂₃H₂₅N₂O₄S: C, 57.13; H, 5.25; N, 15.86; Found: C, 57.19; H, 5.35; N, 15.89.

Diethyl 2-[3-(methylthio)-1-(2-ethylphenyl)] 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonate (2c) : Yield: 76 %, mp: 298-300°C, IR(KBr): 3360(NH), 1699, 1674(C=O), 1611, 1530(C=C, C=N) cm⁻¹. ¹H NMR(DMSO): δ 10.5-10.54(d, J=11.89 Hz, 1H, NH), δ 9.22-9.27(d, J=12.12 Hz, 1H, vinyl-H), δ 8.78(s, 1H, ArH at C2); δ 7.7-7.36(m, 10H, ArH), 4.02-4.29(qx2, J=6.05 Hz, 4H, CH₂-ester), 1.23-1.35(tx2, J=7.29 Hz, 6H, CH₂-ester). MS: 457(M⁺), Anal. Calcd. for C₂₃H₂₅N₂O₄S: C 58.01, H 5.53, N 15.37; Found: C 58.09, H 5.58, N 15.43.

Diethyl 2-[3-(methylthio)-1-(4-methylphenyl)] 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonate (2d) : Yield: 84 %, mp: 279-281°C, IR(KBr): 3365(NH), 1702, 1680(C=O), 1610, 1520(C=C, C=N) cm⁻¹. ¹H NMR(DMSO): δ 10.5-10.54(d, J=11.89 Hz, 1H, NH), δ 9.3-9.32(d, J=12.04 Hz, 1H, vinyl-H), δ 8.65(s, 1H, ArH at C2); 4.03-4.29(qx2, J=6.05 Hz, 4H, CH₂-ester), 2.4(s, 3H, CH₃), 1.98 (s, 3H, CH₃), 1.22-1.35(tx2, J=7.26 Hz, 6H, CH₂-ester). MS: 303 (M⁺), Anal. Calcd. for C₂₃H₂₅N₂O₄S: C, 57.13; H, 5.25; N, 15.86; Found: C, 57.19; H, 5.35; N, 15.89.

Diethyl 2-[3-(methylthio)-1-(4-chlorophenyl)] 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonate (2e) : Yield: 78 %, mp: 187-188°C, IR(KBr): 3366(NH), 1709, 1677(C=O), 1625, 1533(C=C, C=N) cm⁻¹. ¹H NMR(DMSO): δ 10.5-10.54(d, J=11.89 Hz, 1H, NH), δ 9.3-9.32(d, J=12.04 Hz, 1H, vinyl-H), δ 8.65(s, 1H, ArH at C2); 4.03-4.29(qx2, J=6.05 Hz, 4H, CH₂-ester), 2.4(s, 3H, CH₃), 1.98 (s, 3H, CH₃), 1.22-1.35(tx2, J=7.26 Hz, 6H, CH₂-ester). MS: 303 (M⁺), Anal. Calcd. for C₂₃H₂₅N₂O₄S: C, 52.9; H, 4.36; N, 15.16; Found: C, 51.88; H, 4.26; N, 15.29.
CH₃), 1.22-1.35 (t, J = 7.26 Hz, 6H, CH₂-ester). MS: 303 (M⁺), Anal. Calcd. for C₁₅H₁₅N₂O₅S: C, 48.20; H, 4.04; N, 20.71; Found: C, 48.32; H, 4.21; N, 20.62.

4-(4-(2,2-dioxyxycarbonyl) vinylamino)-3-(methyliothio) 1H-pyrazolo[3,4-d]pyrimidin-1-yl)pyridine-2-carboxylic acid (2j): Yield: 74%, mp: 183-184°C, IR(KBr): 2953-3000(b, OH), 1735, 1720, 1715, 1680(C=O), 1620, 1530(C=C, C=N) cm⁻¹. ¹H NMR(DMSO): δ 10.5-10.54(d, J = 11.89 Hz, 1H, CH₂ester), δ 9.3-9.32(d, J = 12.04 Hz, 1H, vinyl-H), δ 8.65(s, 1H, ArH at C2); 4.03-4.29(qx2, J = 6.05 Hz, 4H, CH₂-ester), 2.4 (s, 3H, CH₃), 1.98 (s, 3H, CH₃), 1.22-1.35 (t, J = 7.26 Hz, 6H, CH₂-ester). MS: 303 (M⁺), Anal. Calcd. for C₁₅H₁₅N₂O₅S: C, 50.84; H, 4.27; N, 17.79; Found: C, 50.68; H, 4.12; N, 17.88.

2.1.2.2 Step 2: General method for synthesis of ethyl 10-S-methyl 4-oxo-8-substituted pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylates 3a-j:

Diethyl 2-[3-(methyliothio) 1-substituted 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonates (2, 2 mmol) was dissolved in boiling DPO (5 mL) and heated at 250°C for 1.5-2 h. The excess of solvent distilled in vacuo and chilled methanol (15 mL) was added to the cold reaction mixture, the solid obtained was collected by filtration and crystallized from DMF: ethanol (6:4 v/v).

Method II:

A mixture of 1-substituted 3-(methyliothio) 3H-pyrazolo[3,4-d]pyrimidin-4-amine (1, 2 mmol) and EMME (2 mmol, 0.44 g) was taken in a Pyrex tube and subjected to microwave irradiation in a microwave oven at an output of 700 watts at 150°C for 17-20 min. Progress of reaction was monitored through TLC at an interval of 45 seconds. On completion, the reaction mixture was allowed to cool at room temperature, treated with chilled methanol and the solid obtained was crystallized from DMF.

Ethyl 10-S-methyl-4-oxo-8-phenylpyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3a): Overall yield: 62% (Method I), 85% (Method II), mp: 263-265°C, IR(KBr) cm⁻¹: 1730, 1697(C=O), 1610, 1512(C=C, C=N). ¹H NMR(DMSO): δ 9.18(s, 1H, ArH at C6), 7.4-8.81(m, 6H, ArH), 4.13-4.24 (q, 2H, CH₂CH₃ of ester), 2.81(s, 3H, SCH₃), 1.4-1.45(t, 3H, CH₃CH₂ of ester). MS: 381(M⁺), Anal. Calcd. for C₁₅H₁₃N₂O₅S: C 56.68, H 3.96, N 18.41; Found: C 56.54, H 3.72, N 18.35.

Ethyl 10-S-methyl-4-oxo-8-(2-methylphenyl) pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3b): Overall yield: 60% (Method I), 83% (Method II), mp: >300°C, IR(KBr) cm⁻¹: 1724, 1690(C=O), 1604, 1506(C=C, C=N). ¹H NMR(DMSO): δ 9.15(s, 1H, ArH at C6), δ 7.39-8.8(m, 1H, ArH), 4.14(q, 2H, CH₂CH₃ of ester), 2.79(s, 3H, CH₃), 2.1(s, 3H, SCH₃), 1.8(s, 3H, Ar-CH₃), 1.18(t, 3H, CH₂CH₃ of ester). MS: 395(M⁺), Anal. Calcd. for C₁₅H₁₇N₂O₅S: C 57.71, H 4.33, N 17.32, Found: C 57.63, H 4.23, N 17.44.

Ethyl 10-S-methyl-4-oxo-8-(2-ethylphenyl) pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3c):

Overall yield: 61% (Method I), 84% (Method II), mp: >300°C, IR(KBr) cm⁻¹: 1723, 1692(C=O), 1605, 1516(C=C, C=N). ¹H NMR(DMSO): δ 9.13(s, 1H, ArH at C6), δ 7.38-8.79(m, 5H, ArH), 4.29(q, 2H, CH₂CH₃), 4.15(q, 2H, CH₂CH₃ of ester), 2.8(s, 3H, SCH₃), 1.37-1.41(t, 3H, Ar-CH₂CH₃), 1.2(t, 3H, CH₂CH₃ of ester). MS: 409(M⁺), Anal. Calcd. for C₁₅H₁₇N₂O₅S: C, 58.67; H, 4.68; N, 17.10; Found: C, 58.59; H, 4.72; N, 17.18.

Ethyl 10-S-methyl-4-oxo-8-(4-methylphenyl) pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3d):

Overall yield: 56% (Method I), 83% (Method II), mp: >300°C, IR(KBr) cm⁻¹: 1724, 1694(C=O), 1615, 1519(C=C, C=N). ¹H NMR(DMSO): δ 9.15(s, 1H, ArH at C6), 7.4-8.8(m, 5H, ArH), 4.13-4.24 (q, 2H, CH₂CH₃ of ester), 2.79(s, 3H, SCH₃), 1.79(t, 3H, Ar-CH₂CH₃), 1.18(t, 3H, CH₂CH₃ of ester). MS: 395(M⁺), Anal. Calcd. for C₁₅H₁₇N₂O₅S: C, 57.71; H, 4.33; N 17.32, Found: C, 57.63; H, 4.23; N 17.44.

Ethyl 10-S-methyl-4-oxo-8-(4-chlorophenyl) pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3e):

Overall yield: 57% (Method I), 85% (Method II), mp: 249-259°C, IR(KBr) cm⁻¹: 1733, 1697(C=O), 1622, 1515(C=C, C=N). ¹H NMR(DMSO): δ 9.6(s, 1H, ArH at C6), δ 7.49-8.86(m, 5H, ArH), 4.29(q, 2H, CH₂CH₃ of ester), 2.7(s, 3H, SCH₃), 1.31(t, 3H, CH₂CH₃ of ester). MS: 416(M⁺), Anal. Calcd. for C₁₆H₁₄ClN₂O₅S: C, 51.99; H, 3.39; N, 18.13; Found: C, 51.78; H, 3.55; N, 18.18.
Ethyl 10-S-methyl-4-oxo-8-(2-fluorophenyl) pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3f) : Overall yield: 55% (Method I), 81% (Method II), mp: 233-235°C, IR(KBr) cm⁻¹: 1733, 1697(C=O), 1622, 1525(C=C, C=N). ¹H NMR(DMSO): δ 9.6(s, 1H, ArH at C6), δ 7.49-8.86(m, 5H, ArH), 4.29(q, 2H, CH₂CH₃ of ester), 2.7(s, 1H, ArH), 1.31(t, 3H, CH₂CH₃-ester). MS: 399(M⁺), Anal. Calcd. for C₁₈H₁₄F₂N₄O₃S: C, 54.13; H, 3.53; N, 17.53; Found: C, 54.19; H, 3.65; N, 17.44.

Ethyl 10-S-methyl-4-oxo-8-(4-fluorophenyl)pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3g) : Overall yield: 51% (Method I), 82% (Method II), mp: 241-243°C, IR(KBr) cm⁻¹: 1732, 1695(C=O), 1623, 1524(C=C, C=N). ¹H NMR(DMSO): δ 9.59(s, 1H, ArH at C6), δ 7.4-8.8(m, 5H, ArH), 4.27(q, 2H, CH₂CH₃-ester), 2.69(s, 1H, ArH), 1.31(t, 3H, CH₂CH₃ of ester). MS: 399(M⁺), Anal. Calcd. for C₁₈H₁₄F₂N₄O₃S: C, 54.13; H, 3.53; N, 17.53; Found: C, 54.19; H, 3.65; N, 17.44.

Ethyl 10-S-methyl-4-oxo-8-(2,4-dinitrophenyl) pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3h) : Overall yield: 52% (Method I), 81% (Method II), mp: >300°C, IR(KBr) cm⁻¹: 1740, 1699(C=O), 1629, 1529(C=C, C=N). ¹H NMR(DMSO): δ 9.4(s, 1H, ArH at C6), δ 7.4-8.81(m, 4H, ArH), 4.27(q, 2H, CH₂CH₃-ester), 1.9(s, 3H, Ar-CH₃), 1.31(t, 3H, CH₂CH₃ of ester). MS: 471(M⁺), Anal. Calcd. for C₁₈H₁₄N₄O₇S: C, 45.86; H, 2.78; N, 20.80; Found: C, 45.94; H, 2.84; N, 20.67.

Ethyl 10-S-methyl-4-oxo-8-(2-nitropyridin-4-yl)pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylate (3i) : Overall yield: 51% (Method I), 81% (Method II), mp: 245-247°C, IR(KBr) cm⁻¹: 1735, 1698(C=O), 1619, 1525(C=C, C=N). ¹H NMR(DMSO): δ 9.6(s, 1H, ArH at C6), δ 7.49-8.86(m, 3H, ArH), 4.29(q, 2H, CH₂CH₃-ester), 1.31(t, 3H, CH₂CH₃ of ester). MS: 428(M⁺), Anal. Calcd. for C₁₅H₁₈N₄O₃: C, 47.66; H, 3.29; N, 22.89; Found: C, 47.48; H, 3.36; N, 22.77.

Ethyl 10-S-methyl-4-oxo-8-(pyridine-3-carboxylate-4-yl)pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylates (3j) : Overall yield: 51% (Method I), 81% (Method II), mp: 261-263°C, IR(KBr) cm⁻¹: 3395(b, OH), 1739, 1720, 1699(C=O), 1630, 1529(C=C, C=N). ¹H NMR(DMSO): δ 12.1(s, 1H, H of COOH), δ 9.6(s, 1H, ArH at C6), δ 7.49-8.88(m, 4H, ArH), 4.29(q, 2H, CH₂CH₃-ester), 1.9(s, 3H, ArCH₃), 1.31(t, 3H, CH₂CH₃ of ester). MS: 427(M⁺), Anal. Calcd. for C₁₅H₁₈N₄O₇S: C, 45.86; H, 2.78; N, 20.80; Found: C, 45.94; H, 2.84; N, 20.67.

2.2 Present Work

In the present study 3-(Methylthio) 3H-pyrazolo[2,3-d]pyrimidine-4-amin (1) have been treated with EMME under heating at 130-90°C for 3 h to form uncyclized diethyl 2-[3-(methylthio)-1-substituted 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethyl enemalates (2), which in turn cyclized to desired ethyl 10-S-methyl-4-oxo-8-substituted pyrazolo[4,3-e]pyrimido[1,2-c]pyrimidine-3-carboxylates (3), when heated for 1.5-2 h in presence of diphenyl ether (DPO). Microwave accelerated solvent-free synthesis of 3 was also carried out directly from 3-(methylthio) 3H-pyrazolo[2,3-d]pyrimidine-4-amin (1) as one pot preparation within 17-20 min (Scheme 1).

![Scheme 1](https://example.com/scheme1.png)
3. RESULTS AND DISCUSSION

A comparative study of conventional, as well as microwave methodologies, has also been undertaken for the synthesis of pyrazolopyrimidopyrimidines (3). The conventional method involved two steps, in the first step reaction between 1-substituted pyrazolo[2,3-d]pyrimidine-4-aminnes (1) and EMME gave diethyl 2-[3-(methylthio)-1-substituted 1H-pyrazolo[3,4-d]pyrimidin-4-yl]aminomethylenemalonates (2). The second step involved the cyclization of uncyclized compounds (2) in boiling diphenyl ether to provide ethyl 4-oxo-8-substituted pyrazolo[3,2-e]pyrimido[1,2-c]pyrimidine-3-carboxylates (3) in 52-62 % overall yield from pyrazolo[3,4-d]pyrimidine-4-aminnes (1) (Method I), while, one pot microwave assisted cyclocondensation of 2 with EMME under solvent-free condition gave identical compound 3 within 17-20 min in 81-85 % overall yield in a single step (Method II). The microwave assisted one-pot synthesis of pyrazolopyrimidopyrimidines (3) avoided the use of expensive solvent like diphenyl ether, reduced the reaction time drastically from h to min and also improved the product yield (20-30 %). Therefore, microwave accelerated solvent free method for cyclocondensation involving nucleophilic addition of amines 1 to EMME remarkably proved to be advantageous over classical heating procedure because of rapid, solvent free, in situ cleaner reaction with smooth workup and greater yield. The comparison between conventional and microwave methodologies has been shown in Table 1.

IR(KBr) spectra of 2 showed bands near 3386-3350 cm\(^{-1}\) responsible for NH along with two sharp characteristic bands for carbonyl group of two ester functionality at 1715-1674 cm\(^{-1}\). Absorption bands due to C=C and C=N vibrations were found in the region 1622-1523 cm\(^{-1}\). The absence of amino vibrations supported the formation of uncyclized intermediate 2. \(^1\)H NMR(DMSO-d\(^6\)) of 2 exhibited a deuterium exchangeable doublet at δ 11.34-11.4 integrating for 1H for NH proton, a doublet due to the vinyl proton in the region δ 9.15-9.18 and singlet at δ 8.8-8.68 due to pyrimidine ring proton. Aromatic protons appeared as multiplet in the area δ 7.54-7.71. Twin quartet and triplet in the region δ 4.19-4.6 and δ 1.26-1.32 each integrating for 2H and 3H respectively were responsible for two ethyl groups present in malonate functionality of 2. Thiomethyl protons gave singlet at δ 2.7-2.82 integrating for 3H. In IR(KBr) spectra of 3, the absence of band near 3386-3350 cm\(^{-1}\) due to NH vibrations suggested the formation of angular pyrazolopyrimidopyrimidines 3. The carbonyl group of ester exhibited band in the area 1740-1724 cm\(^{-1}\) whereas, absorption due to lactone was found to be shifted 20-30 cm\(^{-1}\) higher wave number as compared to ketones of uncyclized malonates producing a sharp band in the area 1699-1690 cm\(^{-1}\). Pyrimidine protons present at C6 and C2 appeared at δ 8.87-9.1 and δ 7.21-7.25 as singlet each integrating.

Scheme 2
for one proton, whereas ethyl protons of ester group appeared as a triplet at δ 1.37-1.48 integrating for 3H and a quartet at δ 4.35-4.46 integrating for 2H in the 1H NMR(DMSO) spectra of 3. The mass spectrum of ethyl 4-oxo-8-diphenylpyrazolo[3,2-e]pyrimido[1,2-c]pyrimidine-3-carboxylate 3a exhibited a characteristic molecular ion peak at m/e 381. The fragment ion (M–COOC₂H₅) was obtained at m/e = 338(Scheme 2).

Table 1. A comparison between conventional and microwave assisted synthesis of pyrazolo[3,2-e]pyrimido[3,4-d]pyrimidines 4a-j

| Entry | Conventional Method I | Microwave Method II |
|-------|-----------------------|---------------------|
|       | Time H | Yield % | Time Min | Yield % |
| 3a    | 5      | 62      | 17       | 85      |
| 3b    | 5.5    | 60      | 18       | 83      |
| 3c    | 5      | 61      | 19       | 84      |
| 3d    | 5      | 56      | 19       | 83      |
| 3e    | 5      | 57      | 20       | 85      |
| 3f    | 5.5    | 55      | 19       | 82      |
| 3g    | 5.5    | 51      | 20       | 82      |
| 3h    | 5.5    | 52      | 20       | 82      |
| 3i    | 5.5    | 51      | 20       | 81      |
| 3j    | 5.5    | 51      | 20       | 81      |

4. CONCLUSIONS

Utility and versatility of EMME in Gould-Jacob reaction in the synthesis of pyrazolopyrimidopyrimidines from pyrazolopyrimidin-4-amines have been explored with and without microwave assistance, where microwave assisted synthesis of pyrazolopyrimidopyrimidines was proved to be solvent free, rapid, cleaner and yield efficient as well.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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