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A NOVEL AND EXPEDIENT SYNTHESIS OF 1, 3-DIALKYL-6-METHYLPYRIMIDINEDIONES

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ABSTRACT

2, 4-dialkoxy-6-methylpyrimidines underwent double *Chapman rearrangement* under conventional heating as well as on microwave irradiation to afford corresponding 1, 3- dialkyl-(1H, 3H)-6-methylpyrimidine-2, 4-diones.

KEYWORDS: 2, 4-dialkoxy-6-methylpyrimidines, 1, 3-disubstituted, pyrimidine-2, 4-diones, microwave irradiation, Chapman rearrangement, imidates.

INTRODUCTION

Pyrimidines and pyrimidinediones are biologically important molecules and valuable heterocyclic nuclei for the design of pharmaceutical agents.[1] Various analogs of pyrimidines have been found to posses antibacterial.[2] antiinflamatory activities.[3] antihypertensive.[4] antipyretic.[5] antidiabetic.[6] anticonvulsants.[7] antioxidants.[8] antiviral,[9] anticancer,[10] central nervous system (CNS) depressant.[11] antihistaminic,[12] properties.

Some pyrimidinedione derivatives are well known for their use as pesticides, herbicides, and insecticides.[13]

N1, N3-disubstituted pyrimidinediones are interesting as these compounds have required scaffold to consider as intercalating and alkylating agents.[14] The intercalating and alkylating agents nowadays have critical role in cancer chemotherapy,[15] 1, 3-dialkylpyrimidines are synthesized by N-3 alkylation of N-1 substituted pyrimidine derivatives with various alkyl halides in the presence of several bases, such as sodium hydride,[16] tetrabutylammonium

fluoride.[17] potassium fluoride,[18] potassium carbonate.[19] magnesium oxide.[20] and potassium hydroxide.[21] have been used.

Although most of the above methodologies have their own synthetic values, some limitations mainly due to the use of dimethyl formamide as solvent with cumbersome workup of the reaction mixture, the long reaction times, harsh reaction conditions in which the use of low boiling point alkylating agent is difficult, tedious preparation procedures; which could represent significant drawbacks for preparative purposes. Thus, there is scope for the synthesis of them by simple and eco-friendly method.

The present paper describes the synthesis of 1, 3-dialkyl-(1H, 3H)-6-methylpyrimidine-2, 4-diones in two steps through *Chapman rearrangement* under conventional as well as microwave irradiation in absence of solvent in second step.

Microwave irradiation is one of the most promising non conventional methodologies used in organic synthesis. Use of microwave generally allows to conduct organic reactions in an easy way which also dramatically decreases reaction time, clean work up and better reaction yield with high purity.[22]

OBJECTIVE

To evolve new, simpler, ecofriendly, convenient methodology for the synthesis of 1, 3-dialkyl-(1H, 3H)-6-methylpyrimidine-2, 4-diones.

MATERIALS AND METHODS

The melting points were determined using capillary tube and are uncorrected. The ^{1}H-NMR spectra were recorded on a Brucker AVANCE (300 MHz) spectrometer (with TMS as internal references). ^{13}C-NMR spectra were recorded on Brucker AVANCE (75 MHz) spectrometer. The FTIR spectra were recorded on Spectrum One Perkin Elmer (US). Mass spectra were recorded on API-3000MD-series (US). UV spectra were recorded on Shimadzu 2401 PC and Shimadzu 2450, Japan, Spectrophotometer. Elemental analyses were carried out in EA 3000, Euro Vector, Italy. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (200 mesh). Modified LG microwave laboratory oven was used for microwave irradiation. The solvents were purified by distillation before use.

RESULTS AND DISCUSSION

In view of the biological importance of pyrimidinediones, we were interested to prepare them from readily available chemicals. Herein, we wish to report the synthesis of 1, 3-dialkyl-2, 4-

(1H, 3H)-6-methylpyrimidinediones via Chapman rearrangement of 2, 4-dialkoxy-6-methyl pyrimidines.

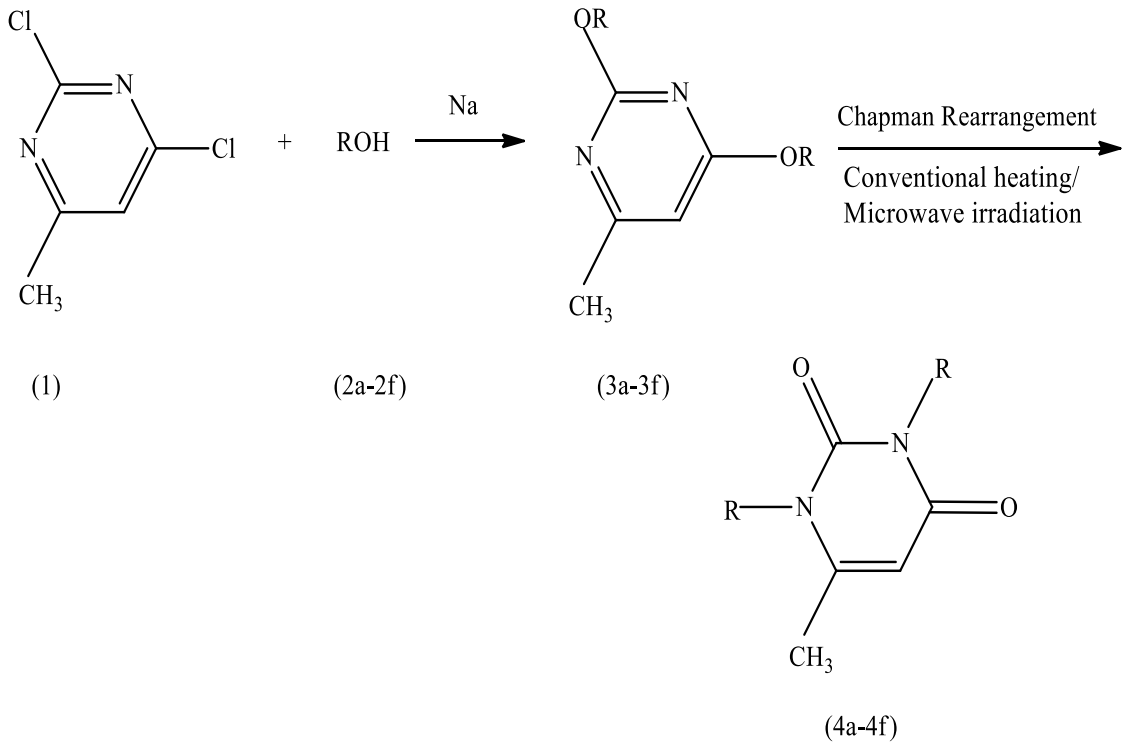
The thermal conversion of aryl N-arylbenzimidates to N-aroyldiphenylamines is known as the *Chapman rearrangement*[23]. Though imidates of many classes of compounds have been subjected to *Chapman rearrangement*, 2, 4-diaryloxy-6-methylpyrimidines have not been investigated.

In light of the observations from literature survey as well as our interest in evolving new, simpler, ecofriendly, convenient methodologies in organic synthesis and absence of reports on the *Chapman rearrangement* of 2, 4-dialkoxy-6-methylpyrimidines led us to undertake the present work.

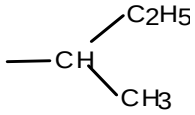
For this purpose, 2, 4-dichloro-6-methylpyrimidine **(1)** was visualized as the starting substrate. This on condensation with various alcohols **(2a-2f)** yielded the respective alkoxy products **(3a-3f)**. These were then subjected to *double Chapman rearrangement* to afford the corresponding 1, 3-dialkyl-6-methylpyrimidine-2, 4-diones **(3a-3f)**. **(Scheme)**

2, 4-dichloro-6-methylpyrimidine **(1)** has been synthesized as per literature procedure from 6-methyl-(1H, 3H)-pyrimidine-2, 4-dione.[24]

Scheme: Synthesis of 1, 3- dialkyl-(1H, 3H)-6-methylpyrimidine-2, 4-diones.



(1) (2a-2f) (3a-3f) (4a-4f)

Compounds	R
2a, 3a, 4a	CH_3-
2b, 3b, 4b	C_2H_5-
2c, 3c, 4c	
2d, 3d, 4d	$(CH_3)_2CH$-
2e, 3e, 4e	CH_3-CH_2 -CH_2-
2f, 3f, 4f	$CH_3CH_2CH_2CH_2$-

General Procedure for preparation of 2, 4-dialkoxy-6-methylpyrimidine (3a-3f)

Sodium (0.025M) was added to anhydrous alcohol **(2a-2f)** (45ml). After all sodium had reacted, 2, 4-dichloro-6-methylpyrimidine **(1)** (0.01M) was added in small lots at 0^{o}C. The reaction was allowed to warm at room temperature and stirred at 50^{o}C-60 ^{o}C for 7-8 hours. After completion of the reaction (TLC), the solvent was evaporated under reduced pressure to dryness. The residue was added to water (50 ml) and extracted with ether (3 x 25 ml). The combined organic extracts were washed with brine and dried over sodium sulfate. The solvent was evaporated under reduced pressure to afford solid/ oil. The product was purified by flash column chromatography using ethylacetate : hexane (10:90) to give 2, 4-di-alkoxy-6-methylpyrimidines **(3a-3g)** as solid/oil.

2, 4-dimethoxy-6-methylpyrimidine (3a).

Yield: 76%. mp: 70^{o}C (Lit[25]. mp: 67-71^{o}C)

2, 4-diethoxy-6-methylpyrimidine (3b).

Yield: 66%. Oil (Lit[26]. bp.: 293-295^{o}C)

2, 4-di-(2-butoxy)-6-methylpyrimidine (3c).

Yield: 70%. Oil (Lit[25]. bp.: 286-287^{o}C)

2, 4-di-(2-propoxy)-6-methylpyrimidine (3d).

Yield: 71%. Oil (Lit[25]. bp.: 272-273^{o}C)

2, 4-di-(1-propoxy)-6-methylpyrimidine (3e).

Yield: 77%.Oil. Molecular formula: $C_{11}H_{18}N_2O_2$. Elemental analysis: Calculated: C (62.83%), H (8.63%), N(13.32%). Found: C (62.30%), H (8.57%), N (13.41%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (m, 6H), 1.6 (m, 4H), 2.3 (s, 3H), 3.6 (m, 4 H), 7.2 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.32, 11.61, 22.34, 24.66, 64.22, 65.11, 159.82, 165.60, 169.51. MS: *m/z* (%):210 (31), 194 (25), 183 (24), 170 (39), 152 (24), 146 (100), 135 (33), 126 (40), 111 (24), 95 (24), 79 (26), 62(36). IR (KBr, cm^{-1}): 1148(C-O-C stretch.), 1464(C-N stretch), 1619(C=C stretch. Ar), 2878-2964 (-CH_2, -CH_3 stretch.). UV

spectrum: λ_{max} 216.66 abs. 0.125.

2, 4-di-(1-butoxy)-6-methylpyrimidine (3f).

Yield: 68%. Oil (Lit[25]. bp: 305-306°C)

General procedure for preparation of 1, 3-dialkyl-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4a-4f) by *Chapman rearrangement* of 2, 4-dialkoxy-6-methylpyrimidines (3a-3f) under conventional heating.

In a flask, equipped with water condenser 2, 4-diaryloxy-6-methylpyrimidine **(3a-3j)** (0.01M) was heated under stirring in nitrogen atmosphere at 160°C-180°C for 35-70 minutes. After completion, (TLC) the reaction mass was cooled to room temperature and petroleum ether (25 ml) was added. It was purified to afford crystals/ oil.

Thus, 2, 4-dilkoxy-6-methylpyrimidines **(3a-3f)** smoothly underwent *Chapman rearrangement* but the reaction times were larger and percentage yields were moderate. It was therefore thought worthwhile to carry out the *Chapman rearrangement* of these compounds under microwave irradiation.

Reduced reaction times, less effect on the environment and better reaction yields are some of the common advantages of using microwave irradiation for chemical reactions.[22]

General procedure for preparation of 1, 3-dialkyl-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4a-4f) by *Chapman rearrangement* of 2, 4-dialkoxy-6-methylpyrimidines (3a-3f) under microwave irradiation.

In a flask, equipped with water condenser 2, 4-dialkoxy-6-methylpyrimidine **(3a-3f)** (0.01M) was irradiated (900W) in a microwave oven for 17-23 minutes. After completion (TLC), the reaction mass was cooled to room temperature and petroleum ether (25 ml) was added under stirring. It was purified to afford crystals/ oil.

Percentage Yield and reaction time under conventional heating and microwave irradiation are presented in the **Table**.

1, 3, 6-triimethyl-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4a).

Yield: 56%. mp: 114°C(Lit[27]. m.p.: 113-114°C)

1, 3-diethyl-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4b).

Yield: 53%. Oil (Lit[28]. bp: 290-292°C)

1, 3-di-(2-butyl)-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4c).

Yield: 58%. Oil. Molecular formula: $C_{13}H_{22}N_2O_2$. Elemental analysis: Calculated: C (65.55%), H (9.24%), N (11.76%). Found: C (65.48%), H (9.31%), N (11.64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.9 (m, 6H), 1.0 (m, 6H), 1.5 (m, 4H), 2.1 (s, 3H), 3.7 (m, 2 H), 7.1 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.88, 17.92, 19.44, 21.13, 24.12, 36.35, 37.81, 65.87, 67.23, 108.89, 111.34, 144.78, 152.25, 165.04. MS: *m/z* (%): 238 (32), 221 (42), 213 (24), 201 (29), 192 (20), 174 (24), 163 (33), 151(31), 142 (100), 130 (25), 119 (33), 94 (19), 79 (27), 62 (31), 51 (33), 43 (26). IR (KBr, cm^{-1}): 1333 (C-N stretch), 1613 (C=C stretch. Ar), 1680, 1690 (N-C=O stretch.), 2855-2992 (-CH, $-CH_2$, $-CH_3$ stretch.). UV spectrum: λ_{max} 219.42 abs. 0.189.

1, 3-di-(2-propyl)-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4d).

Yield: 52%. Oil (Lit[28]. bp: 267-268^{o}C)

1, 3-di-(2-propyl)-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4e).

Yield: 58%. Oil (Lit[28]. bp: 293-294^{o}C)

1, 3-di-(1-butyl)-(1H, 3H)-6-methylpyrimidine-2, 4-dione (4f).

Yield: 48%. Oil. Molecular formula: $C_{13}H_{22}N_2O_2$. Elemental analysis: Calculated: C (65.55%), H (9.24%), N (11.76%). Found: C (65.61%), H (9.15%), N (11.65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.5 (m, 6H), 0.9 (m, 4H), 1.2 (m, 4H), 2.1 (s, 3H), 3.3(m, 4H), 6.6 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2, 13.52, 15.21, 20.41, 23.84, 36.34, 37.51, 71.24, 73.83, 102.54, 146.34, 158.71, 165.32, 170.46. MS: *m/z* (%): 238 (27), 227 (31), 219 (39), 204 (16), 190 (33), 181 (19), 169 (33), 156(100), 141 (21), 132 (20), 122 (35), 99 (24), 81 (26), 69 (19), 54 (27), 39 (32). IR (KBr, cm^{-1}): 1339 (C-N stretch.), 1612 (C=C stretch. Ar), 1680, 1687 (N-C=O stretch.), 2882-2991 ($-CH_2$, $-CH_3$ stretch.). UV spectrum: λ_{max} 223.6, abs. 0.153.

Table: Time and yield of the synthesized compounds 4a-4f

No	Conventional heating		Microwave irradiation	
	Time (minutes)	Yield (%)	Time (minutes)	Yield (%)
4a	35	47	20	56
4b	50	42	23	53
4c	70	49	20	58
4d	50	48	20	52
4e	35	43	17	58
4f	45	48	17	54

CONCLUSION

2, 4-dialkoxy-6-methylpyrimidines underwent facile *Chapman rearrangement* for the first time to afford the corresponding 1, 3-disubstituted-(1H, 3H)-6-methylpyrimidine-2, 4-diones under conventional heating as well as microwave irradiation. Microwave assisted method of synthesis provides a simpler and environmental-friendly alternative for the conventional procedures.

The synthesis of novel heterocycles reported in this paper has the potential of exhibiting pharmacological and agrochemical activities.

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