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DOUBLE *CHAPMAN REARRANGEMENT* OF 2, 4-DIALKOXYPYRIMIDINES: A NEW FACILE SYHTHESIS OF 1, 3-DIALKYLPYRIMIDINEDIONES.

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ABSTRACT

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

KEYWORDS: 2, 4-dialkoxypyrimidines, 1, 3-dialkyl-(1H, 3H)-pyrimidine-2, 4-diones, imidates, microwave irradiation, Chapman rearrangement.

INTRODUCTION

The chemistry of pyrimidines is a blossoming field for the study of their pharmacological uses. Many 1, 3-disubstituted pyrimidine-2, 4-dione analogues are biologically important since they possess Antihistaminic[1], antibacterial[2], anticonvulsants[3], anti-inflammatory[4], antiviral[5], antihypertensive[6], stomach ulcers[7], anticancer[8], Central Nervous System (CNS) depressant[9], antidiabetic[10], antioxidants[11] and many other properties.

Some pyrimidinedione derivatives are well known for their use as pesticides, herbicides, and insecticides.[12]

N1, N3-disubstituted pyrimidinediones are interesting as these compounds have required scaffold to consider as intercalating and alkylating agents.[13] The intercalating and alkylating agents nowadays have critical role in cancer chemotherapy.[14]

1, 3-Dialkylpyrimidine derivatives are generally prepared by N3-alkylation of N1-alkylpyrimidines or N1, N3- dialkylation of pyrimidine nucleobases with various alkyl halides in the presence of tetrabutylammonium bromide, potassium fluoride, and potassium

carbonate.[15] For this purpose, several bases, such as sodium hydride[16], magnesium oxide[17] and potassium hydroxide[18] have been used.

Although most of the above methodologies have their own synthetic values but there are some limitations mainly due to the use of dimethyl formamide as solvent with cumbersome workup of the reaction mixture, long reaction times, harsh reaction conditions in which the use of low boiling point alkylating agent is difficult, tedious preparation procedures, use of solvents etc.; 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)-pyrimidine-2, 4-diones in two steps through *Chapman rearrangement* under conventional heating 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.[19]

MATERIALS AND METHODS

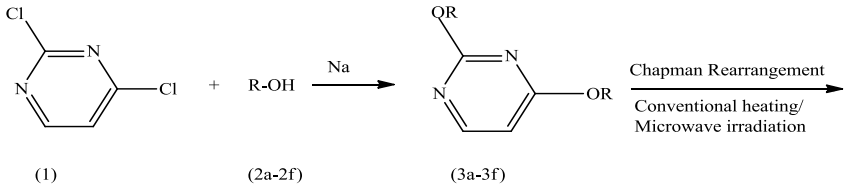
The melting points were determined using capillary tube and are uncorrected. The FTIR spectra were recorded on Spectrum One Perkin Elmer (US). The 1H-NMR spectra were recorded on a Bruker AVANCE (300MHz) spectrometer (with TMS as internal references). 13C-NMR spectra were recorded on Bruker AVANCE (75 MHZ) spectrometer. Mass spectra were recorded on API-3000MD-series (US). UV spectra were recorded on Shimaduz 2401 PC and Shimaduz 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 (200mesh). Modified LG microwave laboratory oven was used for microwave irradiation. The solvents were purified by distillation before use.

In view of the biological importance of pyrimidinediones, we were interested to prepare them from readily available chemicals. The present paper reports the synthesis of 1, 3-dialkyl-(1H, 3H)-pyrimidine-2, 4-diones via Chapman rearrangement of 2, 4-dialkoxypyrimidines. The thermal conversion of aryl N-arylbenzimidates to N-aroyldiphenylamines is known as the

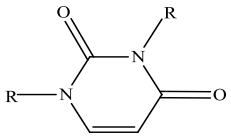
Chapman rearrangement.[20] Though imidates of many classes of compounds have been subjected to *Chapman rearrangement*, 2, 4-dialkoxypyrimidines have not been investigated. In light of the observations from literature survey as well as our interest in evolving new, simpler, ecofriendly, convenient methodologies in organic synthesis and absence of reports on the *Chapman rearrangement* of 2, 4-dialkoxypyrimidines led us to undertake the present work.

For this purpose, (1H, 3H)-pyrimidine-2, 4-dione was visualized as the starting substrate. This on chlorination followed by condensation with various phenols yielded the respective alkoxy products. These were then subjected to double *Chapman rearrangement* to afford the corresponding 1, 3-dialkylpyrimidine-2, 4-diones. **(Scheme)** 2, 4-dichloropyrimidine **(1)** has been synthesized as per literature procedure.[21]

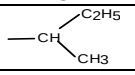
Scheme: Synthesis of 1, 3-dialkyl-(1H, 3H)-pyrimidine-2, 4-dione



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



(4a-4f)

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

General Procedure for preparation of 2, 4-dialkoxypyrimidine (3a-3f)

Pieces of sodium (0.025M) were 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-alkoxypyrimidines **(3a-3g)** as solid/ oil.

2, 4-di-(1-butoxy)-pyrimidine (3a).

Yield: 49%, Oil, IR (KBr, cm^{-1}): 1135 (C-O-C stretch.), 1342 (C-N stretch.), 1610 (C=C stretch. Ar), 2898-2996 (-CH_2, -CH_3 stretch.), 3088 (C-H stretch. Ar-H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.5 (m, 6H), 0.9 (m, 4H), 1.2 (m, 4H), 3.3(m, 4H), 6.5, 6.7 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 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* (%): 224 (29), 219 (41), 197 (26), 184 (43), 178 (33), 164 (42), 149 (21), 134 (100), 128 (33), 110 (36), 89 (34), 73 (41), 61 (34), 58 (49). UV spectrum: λ_{max} 236.4, 207.3 abs. 0.171, 0.872. Molecular formula: $C_{12}H_{20}N_2O_2$. Elemental analysis: Calculated: C (64.29%), H (8.93%), N (12.50%). Found: C (64.38%), H (8.97%), N (12.59%).

2, 4-dimethoxypyrimidine (3b).

Yield: 69%, Oil (Lit.[22] bp: 204-205^{o}C).

2, 4-di-(2-butoxy)-pyrimidine (3c).

Yield: 74%**,** Oil, IR (KBr, cm^{-1}): 1148 (C-O-C stretch.), 1344 (C-N stretch), 1617 (C=C stretch. Ar), 2890-2923 (-CH, -CH_2, -CH_3 stretch.), 3088 (C-H stretch. Ar-H). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.1 (m, 6H), 1.2 (m, 6H), 1.5 (m, 4H), 3.7 (m, 2 H), 6.9, 7.2 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.51, 17.32, 19.54, 21.32, 36.11, 37.52, 65.37, 67.61, 110.20, 111.65, 147.54, 159.82, 165.60, 171.51. MS: *m/z* (%): 224 (29), 212 (32), 199 (42), 188 (27), 180 (27), 172 (41), 161 (39), 155 (100), 140 (25), 133 (31), 127 (32), 107(26), 91 (34), 77 (37), 59 (34). UV spectrum: λ_{max} 249.20, 211.81 abs. 0.198, 0.112. Molecular formula: $C_{12}H_{20}N_2O_2$. Elemental analysis: Calculated: C (64.29%), H (8.93%), N (12.50%). Found: C (64.37%), H (9.01%), N (12.58%).

2, 4-diethoxypyrimidine (3d).

Yield: 71%, Oil (Lit.[23] bp: 270°C).

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

Yield: 66%, Oil (Lit.[24] bp: 301-302^{o}C).

2, 4-di-(2-propoxy)-pyrimidine (3f).

Yield: 65%, Oil (Lit.[22] bp:210-211^{o}C).

General procedure for preparation of 1, 3-dialkyl-(1H, 3H)-pyrimidine-2, 4-diones (4a-4f) by double *Chapman rearrangement* of 2, 4-dialkoxypyrimidines (3a-3f) under conventional heating.

In a flask, equipped with water condenser 2, 4-dialkoxypyrimidine **(3a-3f)** (0.01M) was heated under stirring in nitrogen atmosphere at 155^{o}C-180^{o}C for 35-80 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-dilkoxypyrimidines **(3a-3f)** smoothly underwent *Chapman rearrangement* but the reaction times were larger and percentage yields were moderate. It was therefore thought worthwhile to carryout 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.[19]

General procedure for preparation of 1, 3-dialkyl-(1H, 3H)pyrimidine-2, 4-dione (4a-4f) by double *Chapman rearrangement* of 2, 4-dialkoxypyrimidines (3a-3f) under microwave irradiation.

In a flask, equipped with water condenser 2, 4-dialkoxypyrimidine **(3a-3f)** (0.01M) was irradiated (900 W) in a microwave oven for 14-20minutes. 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-di-(1-butyl)-(1H, 3H)-pyrimidine-2, 4-dione (4a).

Oil (Lit.[18] bp: 282^{o}C).

1, 3-dimethyl-(1H, 3H)-pyrimidine-2, 4-dione (4b).

mp: 122°C (Lit.[25] mp: 122-123°C).

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

Oil, IR (KBr, cm^{-1}): 1334 (C-N stretch), 1613 (C=C stretch. Ar), 1681, 1690 (N-C=O stretch.), 2855-2989 (-CH, -CH_2, -CH_3 stretch.), 3084 (C-H stretch. Ar-H). ^{1}H NMR (300

MHz, $CDCl_3$): δ 0.9 (m, 6H), 1.1 (m, 6H), 1.6 (m, 4H), 3.6 (m, 2 H), 6.6, 7.0 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.91, 18.02, 19.14, 20.92, 36.31, 38.01, 66.01, 67.43, 109.31, 111.65, 145.05, 152.32, 164.52. MS: *m/z* (%): 224 (41), 218 (13), 202 (32), 193 (22), 181 (29), 168 (31), 160 (40), 152(31), 138 (100), 121 (32), 112 (41), 98 (23), 81 (33), 74 (27), 67 (24), 49 (24), 40 (23). UV spectrum: λ_{max} 223.56, 202.22 abs. 0.163, 0.103. Molecular formula: $C_{12}H_{20}N_2O_2$. Elemental analysis: Calculated: C (64.29%), H (8.93%), N (12.50%). Found: C (64.16%), H (9.06%), N (12.39%).

1, 3-diethyl-(1H, 3H)-pyrimidine-2, 4-dione (4d).

Oil (Lit.[22] bp: 290-292^oC).

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

Oil (Lit.[25] bp: 215^oC).

1, 3 –di-(2-propyl)-(1H, 3H)-pyrimidine-2, 4-dione (4f).

Oil (Lit.[25] bp: 267^oC).

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

	Conventional heating		Microwave irradiation	
	Time (minutes)	**Yield (%)**	**Time (minutes)**	**Yield (%)**
4a	45	41	15	55
4b	35	44	15	52
4c	45	46	14	51
4d	65	47	19	58
4e	80	42	20	53
4f	50	44	17	53

RESULTS AND DISCUSSION

2, 4-dialkoxypyrimidines for the first time smoothly underwent double *Chapman rearrangement* to afford the corresponding 1, 3-dialkyl-(1H, 3H)-pyrimidine-2, 4-diones under conventional heating. Same reaction under microwave irradiation underwent facile double *Chapman rearrangement* under green chemistry conditions in less time and good yield compared to conventional heating.

CONCLUSION

2, 4-dialkoxypyrimidines for the first time underwent facile double *Chapman rearrangement* to afford the corresponding 1, 3-dialkyl-(1H, 3H)-pyrimidine-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 new pyrimidine derivatives reported in this paper has the potential of exhibiting biological activities.

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