

ENVIRONMENTALLY BENIGN AND EXPEDIENT SYNTHESIS OF 1, 2-DIALKYL PYRIDAZINE-3, 6-DIONE DERIVATIVES**M. M. V. Ramana* and Sanjay C. Pawar**

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ABSTRACT

3, 6-dialkoxypyridazines underwent Chapman rearrangement under conventional heating as well as on microwave irradiation to afford corresponding 1, 2-dialkylpyridazine-3, 6-diones.

KEYWORDS: 1, 2-disubstituted, pyridazine-3, 6-diones, 3, 6-dialkoxypyridazines, microwave irradiation, imidates, Chapman rearrangement.

INTRODUCTION

Pyridazinones are the derivatives of pyridazine which belong to an important group of heterocyclic compounds containing nitrogen atoms at 1 and 2 positions in a six membered ring. It is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. An assessment of various literature reports, one can collect information about the different structure form of pyridazinone that has been utilized as a part of a large number of complex compounds and these compounds exhibit diversified pharmacological activities due to presence of pyridazinone moieties.^[1]

In recent years a substantial number of pyridazines and pyridazinones containing the different moiety or substituent have been demonstrated to possess antipyretics^[2], anti-inflammatory and analgesic^[3, 4], antiplatelet^[5], anticancer^[6], antidepressant and anxiolytic^[7], antidiabetic^[8], antihypertensive^[9], anticonvulsant^[10], bronchial asthma and allergy^[11], antifungal, antibacterial, antitubercular^[12] and many other anticipated biological properties.

Large numbers of pyridazinone derivatives are well known as intermediates for agrochemicals also.^[13]

The most common method for the preparation of alkyl or acyl-substituted pyridazine consists of the direct one step cyclization from an unsaturated diketone and hydrazine. 1-Phenyl-1, 2-dihydropyridazine-3, 6-dione have been synthesized by boiling a mixture of maleic anhydride and phenylhydrazine in glacialacetic acid^[13]. Reaction of diketone in dimethyl formamide with cyanoacetohydrazide gives corresponding pyridazine.^[14] β -aroylpropionic acid derivatives containing the different aromatic moiety react with different hydrazine derivatives for the synthesis of pyridazine and pyridazinone derivatives.^[15] In another method for formation of the pyridazine ring involves addition of a hydrazine molecule to an anhydride or to 1, 4 ketoesters or ketoacids to form pyridazinones.^[16] Reaction of diketone in DMF with cyanoacetohydrazide gives corresponding pyridazine.^[17] Reaction of a mixture of substituted phenyl/ appropriate hydrocarbon and succinic anhydride/ methyl succinic anhydride/ itaconic anhydride with stirred solution of aluminum chloride in carbon disulphide followed by acidification gave β -4-substituted benzoyl propionic acid/ 4-(4-substitutedphenyl)-4-oxobutyric acid/ β -4-substituted benzoyl-2-methylene propionic acid. Reaction of these with hydrazine hydrate/ hydrazine derivative afforded different pyridazinone derivatives.^[18] Most preparation of the pyridazinone derivatives depend on the nucleophilic substitution of the starting material of these derivatives prepared from mucochloric acids. 4, 5-dihalo-3-(2H)-pyridazinone derivatives were prepared by different reactions such as direct ring synthesis, alkylation, and halogen- exchange reaction. 4-(O-hydroxyphenyl)-3-(2H)-pyridazinones can be prepared by 1, 3-dipolar cycloaddition of the in situ prepared diarylnitrilimines and 3-arylidine-2-(3H)-benzofuranones.^[19]

Attempts of direct N-alkylation of 3, 6-pyridazinedione derivatives are tedious and involve substrates that are not easily accessible.

Although most of the methodologies have their own synthetic values, some limitations mainly due to the use of as solvent like dimethyl formamide 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 their synthesis by simple and eco-friendly method. The present communication describes their

synthesis 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.^[20]

MATERIALS AND METHODS

The melting points were determined using capillary tube and are uncorrected. 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. 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 SiO₂ gel (200mesh). Modified LG microwave laboratory oven was used for microwave irradiation. The solvents were purified by distillation before use.

RESULTS AND DISCUSSION

The present paper reports the synthesis of 1, 2-dialkylpyridazine-3, 6-diones via *Chapman rearrangement* of 3, 6-dialkoxypyridazines.

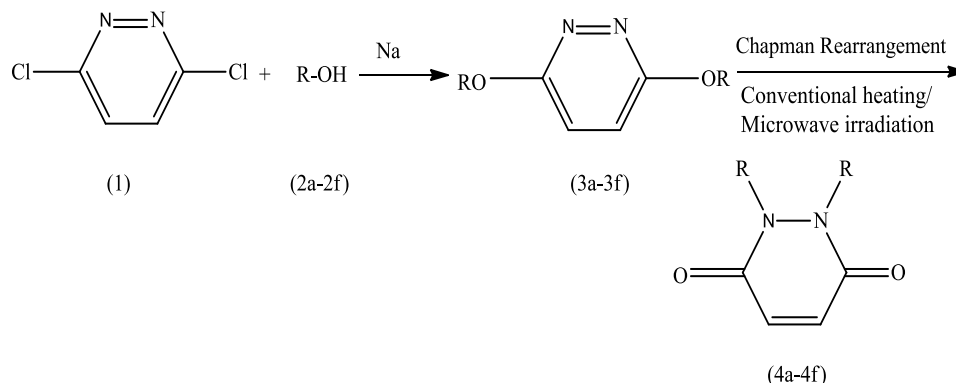
The thermal conversion of aryl N-arylbenzimidates to N-aryldiphenylamines is known as the *Chapman rearrangement*.^[21] Though imidates of many classes of compounds have been subjected to *Chapman rearrangement*, 3, 6-dialkoxypyridazines have not been investigated.

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 3, 6-dialkoxypyridazines led us to undertake this work in continuation with earlier work.^[22, 23, 24, 25, 26]

For this purpose, 1, 2-dihydropyridazine-3, 6-dione was visualized as the starting substrate. This on chlorination followed by condensation with various alcohols yielded the respective imidates. These were then subjected to *Chapman rearrangement* to afford the corresponding 1, 2-dialkyl-pyridazine-3, 6-diones. (**Scheme**)

3, 6-dichloropyridazine (**1**) has been synthesized as per literature procedure.^[27]

Scheme: Synthesis of 1, 2-dialkylpyridazine-3, 6-diones.



Compounds	R
2a, 3a, 4a	
2b, 3b, 4b	CH ₃ -CH ₂ -CH ₂ -CH ₂ -
2c, 3c, 4c	CH ₃ -CH ₂ -CH ₂ -
2d, 3d, 4d	(CH ₃) ₂ CH-
2e, 3e, 4e	CH ₃ -
2f, 3f, 4f	CH ₃ -CH ₂ -

General Procedure for preparation of 3, 6-dialkoxypyridazines (3a-3f)

Pieces of sodium (0.025M) were added to anhydrous alcohol (**2a-2f**) (50ml). After all sodium had reacted, 3, 6-dichloropyridazine (**1**) (0.01M) was added in small lots at 0°C. The reaction was allowed to warm at room temperature and stirred at 55°C-60°C for 6-7 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 3, 6-dialkoxypyridazines (**3a-3f**) as solid/ oil.

3, 6-di-(2-butoxy)-pyridazine (3a).

Yield: 65%, Oil. ¹H NMR (300 MHz, CDCl₃): δ 1.2 (m, 6H), 1.3 (m, 6H), 1.5 (m, 4H), 3.6 (m, 2 H), 7.0 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 14.60, 16.98, 19.31, 20.89, 36.24, 36.92, 65.51, 66.82, 111.03, 112.05, 132.61, 157.03. IR (KBr, cm⁻¹): 1146 (C-O-C stretch.), 1347 (C-N stretch), 1611 (C=C stretch. Ar), 2889-2929 (-CH, -CH₂, -CH₃ stretch.) UV spectrum: λ_{max} 232.2 abs. 0.142. Molecular formula: C₁₂H₂₀N₂O₂. Elemental analysis: Calculated: C (64.29%), H (8.93%), N (12.50%). Found: C (64.35%), H (8.86%), N (12.59%). MS: *m/z*

(%): 224 (41), 208 (19), 195 (33), 181 (37), 169 (32), 160 (24), 151 (29), 142 (17), 131 (100), 116 (35), 104 (41), 88 (27), 71 (29), 62 (24), 43 (21).

3, 6-di-(1-butoxy)-pyridazine (3b).

Yield: 70%, Oil (Lit.^[28] bp: 368°C)

3, 6-di-(1-propoxy)-pyridazine (3c).

Yield: 64%, Oil (Lit.^[28] bp: 289 °C)

3, 6-di-(2-propoxy)-pyridazine (3d).

Yield: 64%, Oil (Lit.^[29] bp: 122-124° C at 13 mm/Hg)

3, 6-dimethoxypyridazine (3e).

Yield: 72%, solid, mp: 108 °C (Lit.^[29] mp: 108-109°C)

3, 6-diethoxypyridazine (3f).

Yield: 71 %, solid, mp: 50°C (Lit.^[29] mp: 50-51°C)

General procedure for preparation of 1, 2-dialkylpyridazine-3, 6-diones (4a-4f) by Chapman rearrangement of 3, 6-dialkoxypyridazines (3a-3f) under conventional heating.

In a flask, equipped with water condenser 3, 6-dialkoxypyridazine (**3a-3f**) (0.01M) was heated under stirring in nitrogen atmosphere at 150°C-180°C for 40-70 minutes. After completion (TLC), the reaction mass was cooled to room temperature and petroleum ether (25 ml) was added. It was stirred to afford a sticky mass which was purified by column chromatography using chloroform: hexane (25:75) to obtain solid/ oil.

Thus, 3, 6-dialkoxypyridazines (**3a-3f**) smoothly underwent *Chapman rearrangement* to afford 1, 2-dialkylpyridazine-3, 6-diones (**4a-4f**); 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.^[30]

General procedure for preparation of 1, 2-dialkylpyridazine-3, 6-diones (4a-4f) by Chapman rearrangement of 3, 6-dialkoxypyridazine (3a-3f) under microwave irradiation.

In a flask, equipped with water condenser 3, 6-dialkoxypyridazine (**3a-3f**) (0.01M) was irradiated (900 W) in a microwave oven for 16-25 minutes. After completion (TLC), the reaction mass was cooled to room temperature and petroleum ether (25 ml) was added under stirring. It was purified by column chromatography using chloroform : hexane (25:75) to afford solid/ oil.

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

1, 2-di-(2-butyl)-pyridazine-3, 6-dione (4a).

Oil. ^1H NMR (300 MHz, CDCl_3): δ 0.8 (m, 6H), 1.0 (m, 6H), 1.5 (m, 4H), 3.7 (m, 2 H), 6.8 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 14.02, 17.91, 19.22, 21.03, 36.44, 37.88, 66.21, 68.10, 109.31, 111.65, 134.23, 157.32. IR (KBr, cm^{-1}): 1329 (C-N stretch), 1617 (C=C stretch. Ar), 1680, 1688 (N-C=O stretch.), 2847-2991 (-CH, -CH₂, -CH₃ stretch.). UV spectrum: λ_{max} 222.1 abs. 0.142. Molecular formula: $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$. Elemental analysis: Calculated: C (64.29%), H (8.93%), N (12.50%). Found: C (64.37%), H (9.07%), N (12.59%). MS: m/z (%): 224 (29), 211 (22), 197 (31), 178 (42), 166 (19), 157 (30), 141 (100), 130 (22), 119 (32), 96 (28), 76 (19), 64 (38), 51 (28)

1, 2 –di-(1-butyl)-pyridazine-3, 6-dione (4b).

Oil. ^1H NMR (300 MHz, CDCl_3): δ 0.4 (m, 6H), 0.9 (m, 4H), 1.1 (m, 4H), 3.4(m, 4H), 6.6 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 12.42, 14.01, 15.31, 20.47, 24.04, 35.89, 38.64, 71.03, 74.11, 101.45, 135.74, 158.45. IR (KBr, cm^{-1}): 1336 (C-N stretch.), 1612 (C=C stretch. Ar), 1682, 1687 (N-C=O stretch.), 2895-2994 (-CH₂, -CH₃ stretch.). UV spectrum: λ_{max} 241.1 abs. 0.163. Molecular formula: $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}_2$. Elemental analysis: Calculated: C (64.29%), H (8.93%), N (12.50%). Found: C (64.36%), H (9.01%), N (12.40%). MS: m/z (%): 224 (41), 204 (33), 190(17), 181 (27), 170 (24), 158 (21), 147 (30), 132 (19), 121 (100), 108 (44), 92 (19), 79 (32), 63 (31), 48 (21).

1, 2-di-(1-propyl)-pyridazine-3, 6-dione (4c).

Oil. ^1H NMR (300 MHz, CDCl_3): δ 0.9 (m, 6H), 1.6 (m, 4H), 3.5 (m, 4H), 7.1 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 10.21, 26.04, 65.11, 137.03, 157.30. IR (KBr, cm^{-1}): 1346 (C-N

stretch.), 1609 (C=C stretch. Ar), 1682 (N-C=O stretch.), 2895-2994 (-CH, -CH₃ stretch.). UV spectrum: λ_{max} 225.4 abs. 0.141. Molecular formula: C₁₀H₁₆N₂O₂. Elemental analysis: Calculated: C (61.21%), H (8.22%), N (14.27%). Found: C (61.14%), H (8.16%), N (14.36%). MS: m/z (%): 196 (31), 176 (28), 162 (34), 156 (19), 143 (100), 130 (28), 121 (40), 112 (23), 94 (23), 82 (21), 73 (25), 66 (20), 57 (26), 51(22).

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

Oil. ¹H NMR (300 MHz, CDCl₃): δ 1.2 (m, 4H), 4.1 (m, 4H), 7.1 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): 25.11, 64.03, 136.04, 157.31. IR (KBr, cm⁻¹): 1333 (C-N stretch.), 1618 (C=C stretch. Ar), 1683 (N-C=O stretch.), 2878-2986 (-CH, -CH₃ stretch.). UV spectrum: λ_{max} 223.5 abs. 0.140. Molecular formula: C₁₀H₁₆N₂O₂. Elemental analysis: Calculated: C (61.21%), H (8.22%), N (14.27%). Found: C (61.30%), H (8.14%), N (14.34%). MS: m/z (%): 196 (23), 180 (22), 168 (14), 154 (33), 141 (40), 134 (100), 120 (20), 107 (19), 91 (40), 76 (23), 61 (32), 54 (23).

1, 2 –dimethyl-pyridazine-3, 6-dione (4e).

Soild, mp: 137°C (Lit²⁸. mp: 137-138°C)

1, 2-diethyl-pyridazine-3, 6-dione (4f).

Solid , mp: 114°C (Lit²⁸. mp:114-115°C)

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

	Conventional heating		Microwave irradiation	
	Time (minutes)	Yield (%)	Time (minutes)	Yield (%)
4a	65	47	25	58
4b	50	49	18	56
4c	45	42	16	54
4d	70	50	18	55
4e	70	48	22	55
4f	40	45	17	56

CONCLUSION

For the first time 3, 6-dialkoxypyridazines underwent facile double *Chapman rearrangement* to afford the corresponding 1, 2-dialkylpyridazine-3, 6-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. Thus it is a convenient way towards the goal of green, sustainable chemistry, and is strongly recommended to use in organic preparations.

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

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