

# Beckmann Rearrangement of 2-Hydroxy-5-Methylacetophenone Oxime using Vilsmeier-Haack Reagent (POCl<sub>3</sub>/ DMF): Synthesis of Some New Heterocycles

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## ABSTRACT

Synthesis of some new heterocyclic derivatives **3a-3g** has been reported by the condensation of suitable reagents with malondialdehyde **2**. The malondialdehyde **2** was synthesized by Beckmann rearrangement of 2-hydroxy-5-methylacetophenone oxime **1** using Vilsmeier-Haack reagent (POCl<sub>3</sub>/ DMF), followed by cyclization.

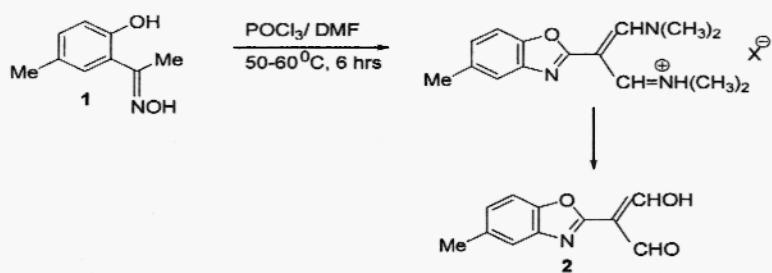
## INTRODUCTION

Utility of Vilsmeier-Haack reagent to bring about formylation of aromatic, non-aromatic and heteroaromatic compounds is well-established.<sup>1-11</sup> Besides this, Vilsmeier-Haack reaction is reported to have utility to bring about Beckmann rearrangement from several compounds.<sup>12-13</sup> One of the significant example of Vilsmeier-Haack reagent is reported to bring about beckmann rearrangement of *o*-hydroxyacetophenone oxime, followed by cyclization to afford malondialdehyde.<sup>14</sup> Reaction of malondialdehyde obtained leads to the formation various heterocyclic derivatives on reaction with suitable reagents. In view of our ongoing research programme related to utility of Vilsmeier-Haack reagent in organic synthesis, we hereby report synthesis of some new heterocyclic compounds by obtaining malondialdehyde from 2-hydroxy-5-methylacetophenone oxime **3**.

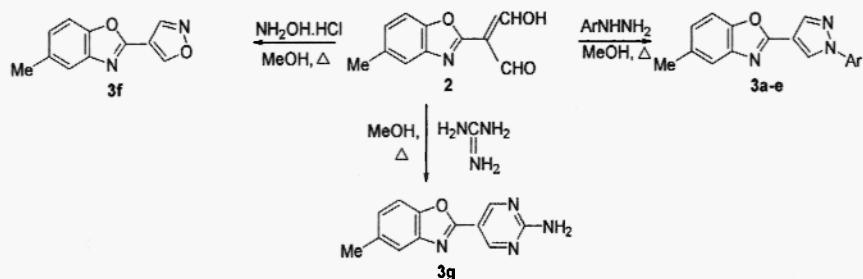
## RESULTS AND DISCUSSION

Vilsmeier-Haack reagent, prepared from phosphorous oxychloride (POCl<sub>3</sub>) and N,N-dimethylformamide (DMF) in cold, was added to a solution of 2-hydroxy-5-methyl acetophenone oxime **1**. The resulting mixture was allowed to stir for 6 hrs at 60-70°C. Usual workup followed by purification gave the desired malondialdehyde **2** (Scheme 1).

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**Scheme 1:** Synthesis of malondialdehyde **2** from 2-hydroxy-5-methyl acetophenone oxime **1**

Malondialdehyde **2**, so obtained was refluxed with methanolic solution of phenylhydrazine for 30 min. On cooling a crystalline product was obtained which was characterized as 1-phenyl-4-(5-methyl-2-benzoxazolyl)pyrazole **3a** by thoroughly analyzing its spectral (IR,  $^1\text{H}$ NMR & mass) as well as elemental data. Other heterocyclic derivatives **3b-3g** were synthesized in a similar way by condensation of **2** with other reagents (Scheme 2).

**Scheme 2.** Synthesis of heterocycles **3a-3g** from malondialdehyde **2**

**Table 1**  
Physical data of heterocycles **3a-3g**

Sr. No.	Compound	Yield (%)	M.p. ( $^\circ\text{C}$ )
1.	3a	68	156-158
2	3b	76	178-180
3	3c	70	196-198
4.	3d	72	182-184 (dec)
5	3e	65	170-172 (dec)
6	3f	64	138-140
7	3g	64	248-249

## EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. The <sup>1</sup>H NMR spectra were recorded on Brucker 300 MHZ instrument. The chemical shifts are expressed in ppm units downfield from an internal TMS standard. Elemental analyses were performed on Perkin-Elmer 2400 instrument. 4-Methyl-2-quinolyl hydrazine<sup>15-17</sup> and 2-(5-methylbenzthiazolyl) hydrazine<sup>18-19</sup> were synthesized according to literature procedure.

### Synthesis of Malondialdehyde 2

Vilsmeier-Haack reagent was prepared in cold by adding 5 equivalents of phosphorous oxychloride (POCl<sub>3</sub>) in excess of N,N-dimethylformamide (DMF). To this reagent was added 1 equivalent of 2-hydroxy-5-methylacetophenone oxime 1 and allowed to heat for 6 hrs at temperature of 50-60°C. On cooling the reaction mixture was poured over crushed ice, basified with KOH, heated on water bath for 1 hr and filtered hot. The hot alkaline solution was neutralized with dil HCl to give 2.

**Synthesis of heterocycles 3a-3e: General Procedure:** A mixture of malondialdehyde 2 (10 mmol) and hydrazine (10 mmol) in methanol was refluxed in methanol on water bath (till the mixture fails to give violet colour with FeCl<sub>3</sub>) and poured on ice cold water. The solid, thus obtained, was dried and recrystallized to give pure heterocycle 3a-3f.

### Characterization data of the compounds 3a-3e

#### *1-Phenyl-4-(5-methylbenzoxazol-2-yl)pyrazole 3a:*

Yield 68%; M.p. 156-158°C; IR (v<sub>max</sub>, KBr): 1643.8 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.419 (s, 3H), 8.281 (s, 1H), 8.555 (s, 1H), 7.06-7.17 (m, 8H); Mass: 275 {M<sup>+</sup>}; Elemental Analysis: obs. C 73.94%, H 4.67%, N 15.11%, calcd C 74.18%, H 4.72%, N 15.27%

#### *4-(5-Methylbenzoxazol-2-yl)pyrazole 3b:*

Yield 76%; M.p. 178-180°C; IR (v<sub>max</sub>, KBr): 1635.9 cm<sup>-1</sup>, 3408.7 (NH stretch); <sup>1</sup>HNMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.411 (s, 3H), 8.220 (s, 2H), 7.051-7.126 (dd, 1H), 7.327(d, 1H), 7.423 (d, 1H); Mass: 200 {M<sup>+</sup>}; Elemental Analysis: obs. C 66.19%, H 4.37%, N 20.1%, calcd C 66.33%, H 4.52%, N 21.1%

#### *1-(4-methyl-2-quinolyl)-4-(5-methylbenzoxazol-2-yl)pyrazole 3c:*

Yield 70%, M.p. 196-198°C; IR (v<sub>max</sub>, KBr): 1647.8 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.371 (s, 3H), 2.419 (s, 3H), 8.313 (s, 1H), 9.077 (s, 1H), 7.084-7.897 (m, 9H); Mass: 341 {M<sup>+</sup>}; Elemental Analysis: obs. C 73.85%, H 4.59%, N 16.33%, calcd C 73.9%, H 4.69%, N 16.42%

#### *1-(5-Methyl-2-benzthiazolyl)-4-(5-methylbenzoxazol-2-yl)pyrazole 3d:*

Yield 72%, M.p. 182-184°C; IR (v<sub>max</sub>, KBr): 1641.9 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.417 (s, 3H), 2.725 (s, 3H), 8.328 (s, 1H), 9.391 (s, 1H), 7.059-8.021 (m, 6H); Mass: 347 {M<sup>+</sup>}; Elemental Analysis: obs. C 65.89%, H 3.96%, N 16.11%, calcd C 65.89%, H 4.04%, N 16.18%

#### *1-(2,4-Dintrophenyl)-4-(5-methylbenzoxazol-2-yl)pyrazole 3e:*

Yield 65%, M.p. 170-172°C; IR (v<sub>max</sub>, KBr): 1647.3 cm<sup>-1</sup>; <sup>1</sup>HNMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.516 (s, 3H), 8.805 (s, 1H), 9.123 (s, 1H), 7.214-8.608 (m, 6H); Mass: 364 {M<sup>+</sup>}; Elemental Analysis: obs. C 55.64%, H 2.97%, N 19.08%, calcd C 55.89%, H 3.01%, N 19.17%

**Synthesis of compound 3f:**

A mixture of **2** (10 mmol), hydroxylamine hydrochloride (1mmol) in methanol was refluxed on a water bath (till the mixture failed to give violet colour with alcoholic  $\text{FeCl}_3$ ) and poured into water. The solid, so obtained, was filtered, washed, dried and recrystallised from MeOH to afford pure 4-(5-methylbenzoxazol-2-yl) isoxazole (**3f**).

**Characterization data of 4-(5-methylbenzoxazol-2-yl)isoxazole (**3f**):**

Yield 64%, M.p.  $138\text{--}140^\circ\text{C}$ ; IR ( $\nu_{\text{max}}$ , KBr):  $1658\text{ cm}^{-1}$ ;  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 300 MHz,  $\delta$ ): 2.418 (s, 3H), 8.819 (s, 1H), 9.065 (s, 1H), 7.108-7.192 (d, 1H), 7.454 (d, 1H), 7.349-7.376 (dd, 1H); Mass: 201  $\{\text{M}^+\}$ ; Elemental Analysis: obs. C 65.89%, H 3.9%, N 14.12%, calcd C 66%, H 4%, N 14%

**Synthesis of compound 3g:**

A mixture of **2** (10 mmol), guanidine hydrochloride (10 mmol) in methanol was refluxed on a water bath (till the mixture failed to give violet colour with alcoholic  $\text{FeCl}_3$ ) and poured into water. The solid, so obtained, was filtered, washed, dried and recrystallised from MeOH to obtain pure 1-(2-minopyrimidin-5-yl)-4-(5-methylbenzoxazol-2-yl) pyrazole (**3g**).

**Characterization data of 4-(5-methylbenzoxazol-2-yl) isoxazole (**3f**):**

Yield 64%, M.p.  $248\text{--}249^\circ\text{C}$ ; IR ( $\nu_{\text{max}}$ , KBr): 3385 &  $3428.5\text{ cm}^{-1}$  (NH stretch);  $^1\text{H}$ NMR ( $\text{CDCl}_3$ , 300 MHz,  $\delta$ ): 2.43 (s, 3H); 7.417-7.461(m, 2H); 7.539 (s, 2H); 7.636 (d, 1H); Mass: 226  $\{\text{M}^+\}$ ; Elemental Analysis: obs. C 63.46%, H 4.36%, N 24.64%, calcd C 63.57%, H 4.41%, N 24.72%

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**REFERENCES**

1. A. Vilsmeier, A. Haack, *Chem. Ber.* **60**, 119 (1927)
2. W.G. Jackson, A.M. Sargeson, P.A. Tucker, A.D. Watson, *J. Am. Chem. Soc.*, **103**, 533 (1981)
3. O. Meth-Cohn, A. Bramha Narine, *Tetrahedron Lett.*, **23**, 2045 (1978)
4. H.L. Bell, M. McGuire, G.A. Freeman, *J. Heterocycl. Chem.*, **20**, 41 (1983)
5. M. Parameswara Reddy, G.S. Krishna Rao, *J. Org. Chem.*, **46**, 5371 (1981)
6. A.R. Katritzky, M. Charles, M. Marson *J. Am. Chem. Soc.*, **105**, 3279 (1983)
7. D.R. Adams, J.N. Dominguez, J.A. Perez, *Tetrahedron Lett.*, **24**, 517 (1983)
8. O. Meth-Cohn, S.P. Stanforth *Org. Synth.*, **2**, 777 (1991)
9. M. Venugopal, P.T. Perumal, *Synth. Commun.*, **21**, 515 (1991)
10. K. Dinakaran, P.T. Perumal, *Ind. J. Chem.*, **39B**, 135 (2000)
11. M.S.C. Pedras, M. Jha, *J. Org. Chem.*, **70**, 1828 (2005)
12. A.S. Ahmed, R.C. Boruah, *Tetrahedron Lett.*, **37**, 8231 (1996)
13. J. Elguero, B. Shimiz, *An. Quim. Sec. C*, **84**, 191 (1988)
14. M.R. Jayanth, H.A. Naik, D.R. Tatke, S. Seshadri, *Ind. J. Chem.*, **11**, 1112 (1973)
15. P.J. Palmer, R.B. Trig, J.V. Warrington, *J. Med. Chem.*, **14**, 248 (1971)

16. T. Kemetani, M. Hiiragi, K. Kigarawa, *Yakugaku Zaashi*, **85**, 836 (1965)
17. K.T. Potts, L.S. Bhattacharya, M.A. Smith, Hrig, C.A. Girag, *J. Org. Chem.*, **37**, 4410 (1972)
18. S.G. Friedman, *J. Gen. Chem. (USSR)*, **20**, 1191 (1950)
19. V.R. Rao, V.R. Srinivasan, *Symp. Syn. Heterocyclic Compounds of Physical Interest*, 137 (1964); *Chem. Abstr.*, **69**, 27312 (1968)