

Beckmann Rearrangement of 2-Hydroxy-5-Methylacetophenone Oxime using Vilsmeier-Haack Reagent (POCl₃/ 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 (POCl₃/ DMF), followed by cyclization.

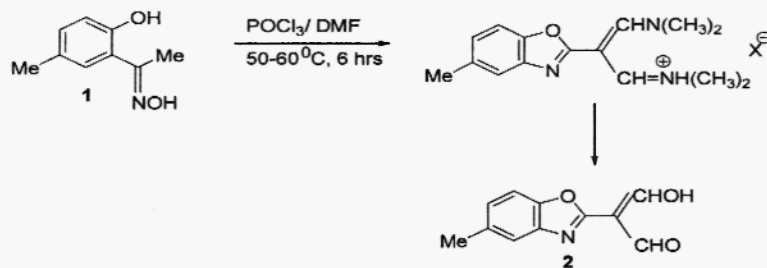
INTRODUCTION

Utility of Vilsmeier-Haack reagent to bring about formylation of aromatic, non-aromatic and heteroaromatic compounds is well-established.¹⁻¹¹ Besides this, Vilsmeier-Haack reaction is reported to have utility to bring about Beckmann rearrangement from several compounds.¹²⁻¹³ 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.¹⁴ 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

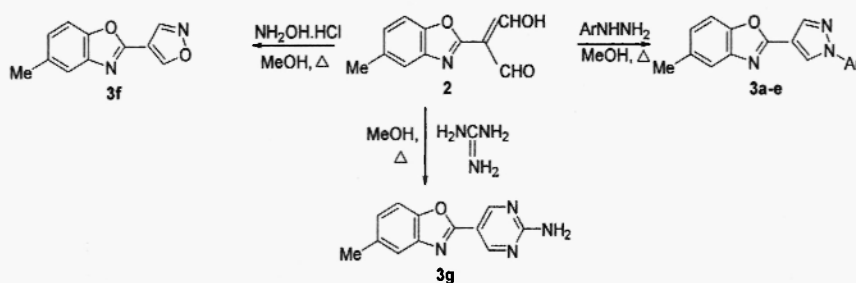
Vilsmeier-Haack reagent, prepared from phosphorous oxychloride (POCl₃) and N,N-dimethylformamide (DMF) in cold, was added to a solution of 2-hydroxy-5-methyl acetophenone oxime **1**. The resulting mixture was allowed to stir for 6 hrs at 60-70°C. Usual workup followed by purification gave the desired 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, ¹HNMR & 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. (°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 ^1H NMR spectra were recorded on Bruker 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 hydrazine¹⁵⁻¹⁷ and 2-(5-methylbenzthiazolyl) hydrazine¹⁸⁻¹⁹ 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_3) 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_3) 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 (ν_{max} , KBr): 1643.8 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz, δ): 2.419 (s, 3H), 8.281 (s, 1H), 8.555 (s, 1H), 7.06-7.17 (m, 8H); Mass: 275 $\{\text{M}^+\}$; 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 (ν_{max} , KBr): 1635.9 cm^{-1} , 3408.7 (NH stretch); ^1H NMR (CDCl_3 , 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 $\{\text{M}^+\}$; 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 (ν_{max} , KBr): 1647.8 cm^{-1} ; ^1H NMR (CDCl_3 , 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 $\{\text{M}^+\}$; 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 (ν_{max} , KBr): 1641.9 cm^{-1} ; ^1H NMR (CDCl_3 , 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 $\{\text{M}^+\}$; 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-Dinitrophenyl)-4-(5-methyl-benzoxazol-2-yl)pyrazole 3e:

Yield 65%, M.p. 170-172°C; IR (ν_{max} , KBr): 1647.3 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz, δ): 2.516 (s, 3H), 8.805 (s, 1H), 9.123 (s, 1H), 7.214-8.608 (m, 6H); Mass: 364 $\{\text{M}^+\}$; 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 FeCl₃) 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. 138-140^oC; IR (ν_{max}, KBr): 1658 cm⁻¹; ¹HNMR (CDCl₃, 300 MHz, δ): 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 {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 FeCl₃) 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.248-249^oC;IR (ν_{max}, KBr): 3385 & 3428.5cm⁻¹(NH stretch); ¹HNMR (CDCl₃, 300 MHz, δ): 2.43 (s, 3H); 7.417-7.461(m, 2H); 7.539 (s, 2H); 7.636 (d, 1H); Mass: 226 {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)