Beckmann Rearrangement of 2-Hydroxy-5-Methylacetophenone Oxime using Vilsmeier-Haack Reagent ($POCl_3$/ 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 ($POCl_3$/ 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 malondialehyde 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 ($POCl_3$) 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^{0}C. Usual workup followed by purification gave the desired malondialdehyde **2 (Scheme 1).**

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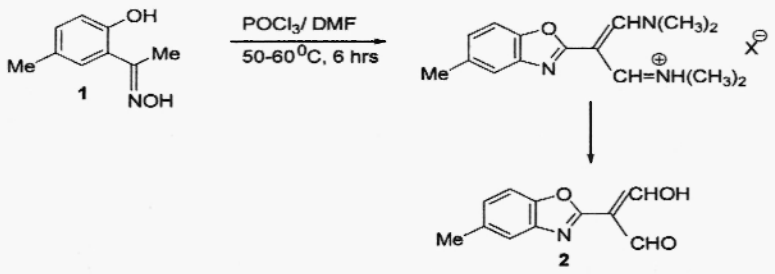
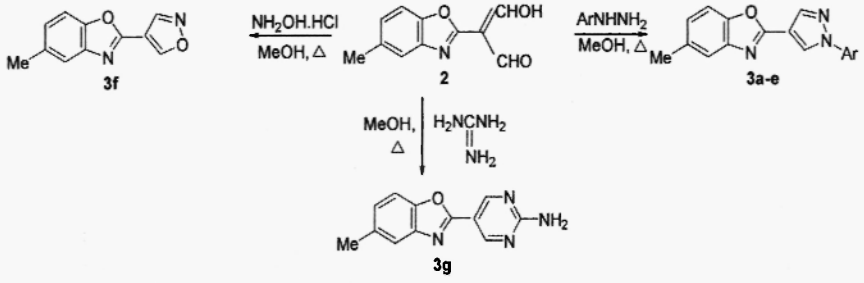


Scheme 1: Synthesis of malondialdehyde **2** from 2-hydroxy-5-methyl acetophenone oxime **1**

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}HNMR & 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 hetercycles **3a-3g** from malondialdehyde **2**

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

Sr. No.	Compound	Yield (%)	M.p. (^{0}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 ^{1}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[15-17] and 2-(5-methylbenzthiazolyl) hydrazine[18-19] 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^{0}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^{0}C; IR (ν_{max}, KBr): 1643.8 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz, δ): 2.419 (s, 3H), 8.281 (s, 1H), 8.555 (s, 1H), 7.06-7.17 (m, 8H); Mass: 275 {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^{0}C; IR (vmax, KBr): 1635.9 cm^{-1}, 3408.7 (NH strech); ^{1}HNMR ($CDCl_3$, 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 {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^{0}C; IR (ν_{max}, KBr): 1647.8 cm^{-1}; ^{1}HNMR ($CDCl_3$, 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 {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^{0}C ;IR (ν_{max}, KBr): 1641.9 cm^{-1}; ^{1}HNMR ($CDCl_3$, 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 {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-Dintrophenyl)-4-(5-methyl-benzoxazol-2-yl)pyrazole* 3e:**

Yield 65%, M.p. 170-172^{0}C ;IR (vmax, KBr): 1647.3 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz, δ): 2.516 (s, 3H), 8.805 (s, 1H), 9.123 (s, 1H), 7.214-8.608 (m, 6H); Mass: 364 {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 $FeCl_3$) 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. 138-140^{0}C ; IR (ν_{max}, KBr): 1658 cm^{-1}; ^{1}HNMR ($CDCl_3$, 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 $FeCl_3$) 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.248-249^{0}C;IR (ν_{max}, KBr): 3385 & 3428.5cm^{-1}(NH stretch); ^{1}HNMR ($CDCl_3$, 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%

ACKNOWLEDGEMENT

We are highly thankful to DST (Grant no. SR/FTP/CS-125/2006), New Delhi for providing financial assistance to accomplish this work.

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