REACTION IN OXIMES OF 2-HYDROXYACETOPHENONE, CHALCONE, FLAVANONE AND FLAVONE

M.B. BAGADE and B.J. GHIYA*

Department of Organic Chemistry
Institute of Science, Nagpur-440 001, India

Oximes of 2-hydroxyacetophenone, chalcone, flavanone and flavone were prepared by the action of hydroxylamine hydrochloride on the respective compounds. The oximes gave back the starting material by the action of HCl, nitrous acid or CrO_3 in AcOH. 2-Hydroxyacetophenone oxime with $POCl_3$ cyclized to give benzoxazole. 2-Hydroxyacetophenone oxime also condensed with aldehyde to give chalcone oxime. With sulphuric acid chalcone oxime gave chalcone, flavanone oxime. With sulphuric acid chalcone oxime gave chalcone, flavanone oxime, flavanone and flavone oxime, isoxazole respectively. The reactions by the oximes in oxygen- nitrogen synthesis are discussed.

INTRODUCTION

A review[1] on less familiar reactions of oximes mostly deals with the usual ketoximes and aldoximes. Recently we have reported the formation of chalcone, flavanone and flavone oximes[2] from our laboratory as side product in the synthesis of isoxazolines and isoxazoles by the action of hydroxylamine on chalcone and dibenzoylmethanes respectively. 2'-Hydroxychalcone with hydraxylamine hydrochloride gave a number of products, depending upon the reaction conditions, including isoxazoline, chalcone oxime and flavanone oxime[2]. 2-Hydroxydibenzoylmethane as well as flavone with hydroxylamine hydrochloride mostly give isoxazole[3]. However, under special conditions flavone oxime can be obtained by refluxing flavone and hydroxylamine hydrochloride in pyridine for 4 hrs.

RESULTS AND DISCUSSION

Acetophenone oxime (**5**), chalcone oxime (**6**), flavanone oxime (**7**) and flavone oxime (**8**) when heated with dil. HCl gave acetophenone (**1**), chalcone (**2**), flavanone (**3**) and flavone (**4**) respectively. Action of nitrous acid ($NaNO_2$/HCl) in cold gave similar results. With polyphosphoric acid (PPA) (**6**) gave (**2**), (**7**) gave a phosphorus containing compound and (**8**) remained unchanged. Chromic acid and acetic acid gave original compounds from their respective oximes. The reaction of oxime in silica-gel was interesting: (**5**) on stirring with silica-gel in ethylene chloride remained unchanged, however (**6**) gave cyclic product 2-styryl-1,2-benzisoxazole[4] (**12**) while (**7**) and (**8**) remained unchanged.

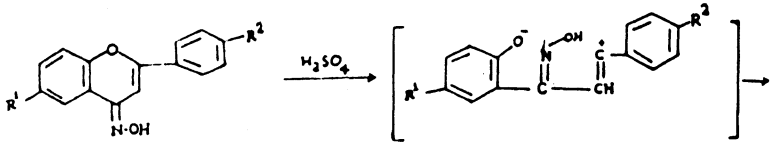
(**5**) with phosphorous oxychloride in DMF gave benzoxazole (**10**) which condensed with aldehyde to form 2-styryl benzoxazole (**11**). (**5**) condensed with aldehyde to give (**6**). Thus 2-styryl benzisoxazole and 2-styryl benzoxazole

syntheses are achieved from common starting material (**5**). (**6**) on treatment with sodium carbonate in alcoholic medium gave 2-styryl benzoxazole (**11**); similar result was obtained, as $POCl_3$ with (**6**) gave (**11**).

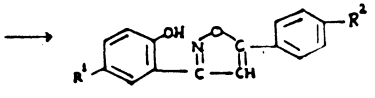
The formation of (**11**) from (**6**) can be explained on the basis of Beckmann transformation of (**6**) followed by intermol cyclodehydration.

Flavone oxime with sulphuric acid (Beckmann rearrangement condition) gave oxygen-nitrogen heterocyclic compound (80%) and was found to be isoxazole (**11**). It was observed that 2-acetoxychalcone oxime can better be prepared by acetylation of 2-hydroxychalcone and then reacting with hydroxylamine hydrochloride instead of the reaction of chalcone with hydroxylamine hydrochloride

TABLE 1



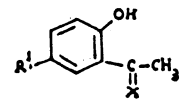
(4)



(10)

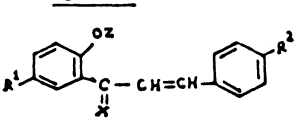
a, $R^1 = CH_3, R^2 = OCH_3$; b, $R^1 = H$, $R^2 = OCH_3$; c, $R^1 = CH_3$, $R^2 = H$

Table II



(1), X=O

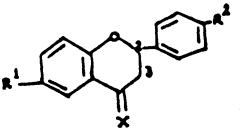
(5), X=NOH



(2), X = O, Z=H.

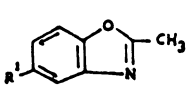
(6), X= NOH, Z=H

(9), X= NOH, Z=COCH$_3$

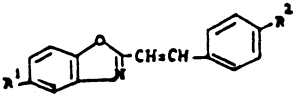


(3), X = O (4) double bond at 2,3

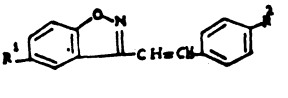
(7), X=NOH (8)



(10)



(11)



(12)

a, $R^1 = CH_3$, $R^2 = OCH_3$; b, $R^1 = H$, $R^2 = OCH_3$; c, $R^1 = Cl$, $R^2 = OCH_3$.

to get chalcone oxime and then acetylating the oxime or condensing the 2-hydroxyacetophenone with aldehyde to get chalcone oxime and acetylating it. 2'-Acetoxychalcone oxime remained unchanged in pyridine, silica-gel but with ethanolic sodium hydroxide gave original chalcone. The results of the action of phosphorous pentachloride on chalcone oxime (**6**) and sodium bicarbonate in ethanol on 2'-acetoxychalcone oxime (**9**) were as per reported earlier[4], i.e. formation of styrylbenzoxazole (**10**). However, with sodium bicarbonate in ethanol (**9**) gave (**3**). The above findings are important in the reactivity of oximes.

The formation of isoxazole from flavone oxime can be schematized as in Table 1.

EXPERIMENTAL

Homogeneity of the product was checked on silica-gel G tlc plates, m.pt. (uncorrected) were determined on electrically heated m.pt. apparatus, nmr spectra were recorded on a Varian XL-100A high resolution nmr spectrophotometer using TMS as internal standard (chemical shifts in δ, ppm), ir spectra (KBr/nujol) as a pye-linicam SP 2000 IR spectrophotometer (λ_{max} in nm) and uv-vis on Varian DMS 80 (λ_{max} in nm).

(I) 2-Hydroxyacetophenones (**1**) were prepared from corresponding phenol derivatives (*p*-cresol, phenol, *p*-chlorophenol) by acetylation.

(II) Phenol derivatives (of *p*-cresol, phenol and *p*-chlorophenol) were acetylated and the acetyl derivatives were subjected to Fries migration using anhydrous aluminium chloride to get the required 2-hydroxyacetophenones (**1a–c**) as reported earlier.

(III) *Preparation of 2-hydroxy-5-methyl acetophenone oxime* (**5a**): 2-Hydroxy-5-methyl acetophenone (**1a**) (0.01 mole) was dissolved in ethanol (20 ml) and hydroxylamine hydrochloride (0.01 mole) was added. Reaction mixture was refluxed for 1 hr. The contents were cooled and poured into ice-cold water. Crude product was filtered at the pump and crystallised from dil. ethanol (1 : 1) to get white crystals of ketone oxime (**5a**) (80%), m.pt. 127°C. It gave colour reaction with ferric chloride solution.

(IV) *Condensation of* (**5**) *with anisaldehyde: formation of chalcone oxime:* (**5**) (0.01 mol) and anisaldehyde (0.01 mol) were dissolved in ethanol (25 ml) and sodium hydroxide solution (3 ml, 40%) was added. The reaction mixture was cooled in ice-bath, stirred and after 8 hrs it was treated with dil. HCl. A solid obtained was filtered, washed with sodium bicarbonate solution, again with water and crystallized from rectified spirit to get yellow needle-shaped crystals of compound (**6a**), m.pt. 66°C, yield 70–80%. It gave colour reaction with ferric chloride solution.

(**6b**) and (**6c**) were prepared similarly from (**1a**) and (**1b**).

(**6**) in dichloroethane in presence of silica-gel gave benzisoxazole derivative as reported earlier[4]. However, under similiar experimental conditions, (**5**) remained unchanged.

(V) *Preparation of chalcone oxime, (6)*: Chalcone oximes (**6a–c**) were prepared by the method reported earlier.[4] (**6a**), m.pt. 66°, (**6b**), m.pt. 70°, (**6c**), m.pt. 70°.

(VI) *Acetylation of* **(6a–c)**: **(6)** (1.5 gm) was dissolved in acetic anhydride (6 ml) and a little fused sodium acetate was added. The mixture was refluxed for 1 hr. and poured into cold water, filtered, washed with water and crystallized from rectified spirit to get **(9a–c)**, m.pts. 108°C, 85°C and 85°C respectivelly. **(9)** did not give colour with ferric chloride solution (yield *ca.* 100%).

(VII) *Reaction with pyridine on* **(9a–c)**: **(9a–c)** (1 g) was dissolved in pyridine (10 ml) and refluxed for 3 hrs. The reaction mixture was diluted with cold water, acidified with dil. HCl and a solid separated was crystallized from rectified spirit. **(9a–c)** remained unchanged.

(VIII) *Reaction with alcoholic NaOH on* **(9a–c)**: **(9a–c)** (1 g) was dissolved in ethanol (10 ml). NaoH solution (1 ml, 10%) was added and the mixture was warmed. After 1 hr it was diluted with water, and acidified with dil. HCl. Crude product separated was filtered. Corresponding original chalcones, **(2a-c)**, m.pts. 98°C, 95°C and 90°C respectively were recovered to the extent of 80%.

(9) was prepared in better yields by first acetylating chalcone to 2′-acetoxychalcones (m.pts. 120, 117, 116°C respectively) and then allowing them to react with hydroxylamine hydrochloride in benzene in presence of sodium bicarbonate. These 2′-acetoxychalcone oximes remained unchanged in pyridine but gave original chalcones on NaOH treatment.

(IX) *Preparation of flavanone oxime* **(7)** : Chalcone **(2a)** (1 g) was dissolved in ethanol (20 ml) and to this pyridine (5 ml) and $NH_2OH.HCl$ (1 gm) were added. The reaction mixture was heated on water bath for 15 min. Then it was poured into cold water; a sticky mass separated which was crystallized from rectified spirit to get 4′-methoxy-6-methyl flavanone oxime, **(7)**, m.pt. 208°C (lit. 208), yield *ca.* 70%.

Found: C, 72.44; H, 6.33; required for $C_{17}H_{17}O_3N$: C, 72.1, H, 6.01%.

NMR: δ, 2.32, S, 3H, ArCH_3; 3.86, S, 3H, OCH_3; 5.04, dd 1H, –C–*H*; 6.08–7.8, m, Ar–*H*; 1.55, S, O*H*; 2.77 dd H, –C*H*H, IR (nujol) 3300–3200 (H bonded OH), 1660 (C=N str), 1310 (OCH–def), 1250 (Ar–O– str in Ar ether), 1070 (Asym. C–O–C str in 6-membered cyclic ether), 1040 (O–CH_3 in Ar ether), 960 (=N–O str in oximes), 3000, 2880, 1460, 1380 cm^{-1} (nujol peaks). UV, vis., ($CHCl_3$) : λ_{max}, 226 (O.D.O. 22), 244 (O.D.O. 33), 260 (O.D.O. 30), 318 nm (O.D.O. 145), corresponding to π–π* and *n*–π* transitions in molecule.

(X) *Preparation of flavone oxime,* **(8a–c)**: Flavone, **(4a–c)** (0.01 mol, 2 gm) and hydroxylamine hydrochloride (1.5 gm) were dissolved in pyridine (20 ml). The reaction mixture was refluxed for 4 hrs. It was cooled, acidified with dil. HCl. Yellow solid obtained was crystallized from rectified spirit to get **(8a)**, m.pt. 237°C (lit.[2] 237°C), **(8b)**, m.pt. 200°C and **(8c)** m.pt. 215°C (yield 60–70%).

Analysis and spectral data of 4é-methoxy-6-methyl flavone oxime (8a):

Found: C=72.0, H=5.33; for $C_{17}H_{15}O_3N$.

Calculated: C=72.59, H=5.33%.

NMR: δ, 2.34, S, 3H, –CH_3; 3.84, S, 3H, OCH_3; 6.9-8, m, 8H, Ar-*H* and heteroaromatic H, 10.8, S, 1H, OH; 2.5 DMSO-d_s peak, 3.35 absorbed H_2O peaks.

IR (nujol) 3200 broad (OH str); 1640 s (C=N str); 1310 m (O–CH def); 1260 s (Ar–O str in ar. ethers); 1090 s (asym C–O–C str in 6-membered cyclic ethers); 815 s (symm C–O–C); 1020 S (O–CH_3 str in ar. ethers); 960 S (N=O str in oximes) 800 cm^{-1} (=C–H wagging) 3000–2850,1460,1380 nujol peaks with other peaks.

UV, vis.: ($CHCl_3$): λ_{max} 253 (O.D.O. 64), 298 (O.D.O. 85) and 335 nm (O.D.O. 46) corresponding to π–π^* and $n - \pi^*$ transitions in the compound.

Acetyl deriv. of **(8a)** m.pt. 118°C.

(XI) *Action of H_2SO_4 on* **(8)** (Beckmann rearrangement condition): **(8)** (0.01 mol, 2.8 gm) was dissolved in conc. H_2SO_4 (8 ml) and water (2 ml) was added. The mixture was heated on water bath for 15 min., cooled, diluted with water to get a solid. It was crystallized from rectified spirit to get white solid isoxazol **(10)** in yield 80% m.pts. **(10a)**, 150° (Lit. 150°), **(10b)**, 135°; **(10c)**, 106°C.

Analysis and spectral data of 3-(2-hydroxy-5-methylphenyl)-5-(4-methoxyphenyl)-isoxazole, (10a):

Found: C = 72.32, H = 5.39; required for $C_{17}H_{15}O_3N$ C = 72.6; H = 5.3%.

NMR: δ 2.40, S, 3H, Ar–CH_3; 3.94, S, 3H, O–CH_3; 6.83, S, 1H, Heteroaromatic H; 6.9-7–9 m 7H, Ar–H; 9.44, S, 1H, OH.

I.R.: λ_{max} 3210 (broad) intramolecular H-bonding in OH; 1620 (m) C=N & C=C str; 1310 (s), O–CH def ; 1265 (s) Ar–O str in ar. ether; 1185 (s) C–O str in phenol shifts to lower frequency; 1020 (s) OCH_3 str in ether; 950 (m) =N–O str; 790 cm^{-1} (s) =C–H wagging. 3300–2850, 1460, 1380 nujol peaks associated with other peaks.

UV, vis.: ($CHCl_3$) λ_{max} 200–254 (O.D.O. 42) and 292 nm (O.D.O.78).

With PPA and orthophosphoric acid **(8)** was recovered unchanged.

The authentic isoxazoles were prepared for comparision by usual method.[2]

(XII) *Action of $POCl_3$ on* **(5)**: *formation of* **(10)**: 2-Hydroxy-5′-methyl acetophenone oxime **(5)** (0.01 mole) was dissolved in dimethyl formamide (10 ml). Mixture was cooled in ice bath at 0°C. To this mixture $POCl_3$ (0.01 mole) was added dropwise with stirring and mixture was kept for 24 hrs. in ice bath. The product was taken out by adding cold water which was filtered at the pump and crystallised from ethanol to get yellowish shining crystals of benzoxazole **(10)**, m.pt. 149° and gave no colouration with neutral ferric chloride solution.

(XIII) *Condensation of* **(10)** *with anisaldeahyde: formation of* **(11)**: Benzoxasole **(10)** (0.01 mole) and anisaldehyde (0.1 mole) were dissolved in ethanol (100 ml), solution was heated to near boiling and sodium hydroxide solution (40%, 30 ml) was added. Reaction mixture was stirred till solidified. Kept the mixture overnight, acidified with dilute HCl, washed with sodium bicarbonate solution followed by water. The product obtained was crystallised from ethanol to get **(11)**, m.pt. 174°. Its alcoholic solution does not give any colouration with neutral ferric chloride solution.

(XIV) *Action of $POCl_3$ on* **(6)**: *Formation of* **(11)**: 2′–Hydroxy-4-methoxy-5′-methyl chalcone oxime **(6)** (0.01 mole) was dissolved in dimethyl formamide (10 ml). The mixture was cooled in ice bath at 0°C. To this mixture $POCl_3$ (0.01 mole) was added dropwise with stirring and mixture was kept for 24 hrs in ice

bath. The product was taken out by adding cold water which was filtered at the pump and crystallised from ethanol to get white crystals of **(11)** m.pt. 174° and gave no colouration with netural ferric chloride solution.

(XV) *Action of sodium carbonate on* **(9)**: *formation of* **(11)**: 2'-Acetoxy chalcone oxime **(9)** (0.01 mole) was dissolved in ethanol (10 ml); to this sodium carbonate solution (20%, 5 ml) was added and reaction mixture was kept for 48 hrs at room temperature. The product was taken out by adding cold water, filtered at the pump and crystallised from ethanol to get white crystals of **(11)** m.pt. 174° and gave no colouration with neutral ferric chloride solution.

(XVI) *Action of sodium bicarbonate on* **(9)**: *Formation of* **(3)**: 2'-Acetoxy chalcone oxime **(9)** (0.01 mole) was dissolved in ethanol (10 ml); to this aqueous solution of sodium bicarbonate (10%, 5 ml) was added and mixture was refluxed for 1/2 hr. The content was cooled and product was taken out by adding water, which was filtered at the pump and crystallised from ethanol to get **(3)**, m.pt. 110° and gave no colouration with neutral ferric chloride solution.

ACKNOWLEDGEMENTS

The authors thank RSIC Lucknow for IR, NMR, UV spectra, RSIC Nagpur for IR and elemental analysis and our Physics Laboratory for UV, VIS spectra.

REFERENCES

1. J.P. Freeman, *Chem. Rev.*, **73**, 283 (1973).

2. S.B. Lohiya and B.J. Ghiya, *Indian J. Chem.*, **25B**, 279, 873 (1986).

3. V.J. Naphade and B.J. Ghiya, *Indian J. Chem*, **26B**, 583 (1987).

4. C. Witczak and M. Krolikowska, *Chem. Abstr.*, **96**, 142837j, 142838k (1982).

[Received: 6 November 1989; Accepted: 7 May 1990] AJC-163