Pak. j. sci. ind. res., vol. 33, no.12, December 1990

ORGANIC REACTIONS IN THE AQUEOUS MEDIUM
Part-IV. Simple Methods for the Synthesis of N-Unsubstituted Salicylaldehyde-Imine, Hydrosalicylamide and Tricyclobenzoxine

SHAFIULLAH KHAN, C. M. ASHRAF AND A. EHSAN

PCSIR Laboratories Complex, Lahore-54600, Pakistan

(Received March 25, 1990; revised January 15, 1991)

A stable N-unsubstituted imine, salicylaldehyde-imine (II) has been synthesised in good yield (90%) for the first time. Interaction of salicylaldehyde with ammonia and ammonium salts in protic and aprotic solvents yielded salicylaldehydeimine (II), hydrosalicylamide (III) and tricyclobenzoxine (IV). The synthesis of hydrosalicylamide has been carried out in water and the yields are identical or better than those in organic solvents. Optimum conditions for the synthesis of (II), (III) and (IV) in 90, 92 and 62% yields, respectively, have been established by varying parameters of the reactions involved. A possible mechanism for their formation has also been discussed.

Key words: Synthesis, Salicylaldehyde-imine, Benzoxine.

Introduction

Condensation reactions of salicylaldehyde with different compounds bearing active methylene groups have been investigated in the presence of ammonium acetate [1-5]. We intended to extend such reactions to different β-diketones, which have not been investigated previously. During our preliminary investigations, it was observed that such a reaction in the presence of acetylacetone yielded a large number of products as indicated by thin layer chromatography. Their resolution into pure components by ordinary methods was difficults. Repeated separations by TLC failed to afford pure components [6].

Moreover, salicylaldehyde has also been reported to yield the analogue of hexamine and hydrosalicylamide on reaction with excessive amount of ammonium carbonate in water [7]. Attempts to reproduce all these results were not encouraging. Hence, it was decided to investigate systematically the reaction of salicylaldehyde with gaseous ammonia and ammonium salts by changing various parameters of the reaction such as molar ratio, molar concentration, solvent, pH and duration of the reaction.

Experimental

All the chemicals used were of analytical grade. The solvents used were distilled before use. Distilled water was used for all experiments. The experiments were performed at room temperature (23 ± 2°) in conical flasks stoppered with loose cotton so as to facilitate the escape of gaseous products. Experiments were carried out in aqueous and non-aqueous media. pH was recorded on a Henna H-8417 digital pH meter. Initial pH was recorded by mixing and shaking the reactants. Since the reaction commenced just after mixing the reactants, no values of the pH could be obtained during the condensation. The final pH was actually the pH of mother liquor after the products were isolated by filtration. Products were dried at room temperature in a vacuum desiccator. These were purified by crystallization from the appropriate solvents. Melting points were determined on a Kofler microscope hot state. Infrared absorption spectra were recorded on a Beckman Acculab-10, Infrared spectrophotometer. The NMR spectra were recorded on a Hitachi Perking Elmer R-24, 60 MHz spectrophotometer using TMS as internal reference.

N-Unsubstituted salicylaldehyde-imine (II). 30 ml each of benzene, *n*-hexane and diethyl ether were taken in different flasks followed by addition of salicylaldehyde (1ml; 1.043 g). Gaseous ammonia was bubbled till the contents got saturated with it. The product formed was isolated using vacuum filtration. Its characteristic IR (KBr disc) absorptions for NH and C=N were at 3350 and 1630 cm^{-1} respectively. The formation of salicylaldehyde-imine (II), C_7H_7NO requires: C, 69.42%; H, 5.79%; N, 11.57% and the elemental analysis gave C, 69.39%; H, 5.75% and N, 10.98%. The same product resulted in all cases and yield of (II) were 0.93 g (89.9%) in diethyl ether, 0.89 g (86%) in benzene and 0.91 g (87%) in *n*-hexane respectively.

Hydrosalicylamide (III): N, N'-bis (2-Hydroxybenzylidene)-2-Hydroxy-α, α-Tolyldiamine.

Gaseous ammonia. In each of four flasks, 30 ml of water, dioxan, methanol and ethanol were taken followed by addition of salicylaldehyde (1 ml, 1.043 g). Gaseous ammonia was passed till the contents became saturated with it. Bright yellow product, hydrosalicylamide (III), resulted in all the solvents used. It was filtered, recrystallized from acetone (m.p. 163-164° dec) (lit. 164°) (8) and the yields were (0.912 g, 92.4%) in water, (5.891 g, 86%) in dioxan, (0.861 g, 85.1%) in methanol and (0.837 g, 84.3%) in ethanol. Its mixed m.p. with an authentic sample remained undepressed and their IR spectra were also superimposable.

Ammonium carbonate. Ammonium carbonate (0.96 g, 0.1 mole) was added to four different flasks containing water (10 ml), followed by addition of (1.043 g, 0.1 mole), (2.086 g, 0.2 mole), (3.13 g, 0.3 mole) and (4.17 g, 0.4 mole) of salicylaldehyde in each flask. Identical experiments were run in methanol using ammonium carbonate and salicylaldehyde in the molar ratio 1:1, 1:2, 1:3 and 1:4 respectively. Hydrosalicylamide (III) formed both in water and methanol. Its yields in four such experiments after 48 hrs were (0.98 g, 30%), (1.85 g, 56%), (2.35 g, 71%), (2.54 g, 77%) in water and (1.56 g, 48%), (2.26 g, 69%), (2.22 g, 67%) and (2.06 g, 63%) respectively in methanol.

The experiments were repeated using other ammoniating agents like ammonium phosphate, ammonium acetate and ammonium bicarbonate in water and methanol. The yields of product (III) obtained under various conditions is given in Table 2. However, the reaction of salicylaldehyde with ammonium acetate in water gave no product even if the duration of reaction was extended upto two weeks.

Tricyclobenzoxine (IV)

Ammonium acetate. The reaction of ammonium acetate (0.77 g, 0.1 mole) with aldehyde (3.13 g, 0.3 mole) when carried out in methanol in the molar ratio 1:3 yielded a mixture of (III) and (IV). These two were separated by dissolving (III) in acetone, while the (IV) was practically insoluble in this solvent. The yields, thus, obtained were 0.966 g (III) (55.6%) and 0.823 g (IV) (25%). However, when the reactants were in the molar ratio 1:4, (IV), m.p. 244-245° predominated (2.1 g, 62%). Its mass spectrum indicated molecular ion peak at *m/z* 329, corresponding to its molecular formula, $C_{21}H_{15}O_3N$.

Ammonium bicarbonate. Ammonium bicarbonate (0.79 g, 0.1 mole) and salicylaldehyde (3.13 g, 0.3 mole; 4.17 g, 0.4 mole) at molar ratios 1:3 and 1:4 gave a mixture of (III) and (IV) in methanol and the yields were (0.4 g (III) 22%; 0.31 g (IV) 9% and (0.103 g (III) 7%; 0.478 g (IV) 14% respectively.

Discussion

The reactions of salicylaldehyde and ammonia/ammonium salts have been carried out and three products, (II), (III) and (IV), have been obtained under various conditions and the results are shown in Table 1 and 2.

The reactions of various aldehydes and ammonia/amines usually yield N-substituted imines (Schiff's bases) which are quite stable [9-10]. On the other hand, N-unsubstituted imines have never been obtained in the stable form. Their existence has been explained on the basis of spectroscopic observations [11]. However, such unstable N-unsubstituted imines have been stablished through complex formation with metals like iron, copper and cobalt [12,13]. A stable N-unsubstituted salicylaldehyde-imine (II), formed by the reaction of salicylaldehyde and gaseous ammonia at room temperature, has been isolated for the first time in non-polar solvents and results have been reported in Table 1. In the present investigations, (II) m.p. 68-70° has been obtained in different aprotic solvents e.g., *n*-hexane, benzene and diethyl ether in good yields (86-90°). The formation of this N-unsubstituted-imine has been confirmed through its IR spectrum which indicated C=N absorption at 1630 cm^{-1} in conformity with the literature [13].

It is pertinent to point out that (II) can be kept in the stable form as long as desired in aprotic solvents like benzene, *n*-hexane and diethyl ether. The use of such solvents provides a useful procedure for keeping unstable imine in the pure state since in such solvents, side reactions like condensation and hydrolysis do not take place.

It was observed that (II) was converted into (III) in protic solvents like methanol, ethanol and water, while in the open it also transformed to (III) with evolution of ammonia and also when heated alone at 120°.

The reactants in polar solvents are not free from solvation, hydrolysis, self-condensation and polymerization [12]. Consequently, when gaseous ammonia was passed in protic

TABLE 1. SYNTHESIS OF N-UNSUBSTITUTED SALICYLALDEHYDE-IMINE (II) AND HYDROSALICYLAMIDE (III) IN WATER AND ORGANIC SOLVENTS.

Sr. No.	Solvents	Products	%Yield
1.	Diethyl ether	II	90
2.	Benzene	II	86
3.	Hexane	II	87
4.	Methanol	III	85
5.	Ethanol	III	84
6.	Dioxane	III	86
7.	Water	III	92

TABLE 2. PERCENTAGE YIELDS OF HYDROSALICYLAMIDE (III) AND TRICYCLOBENZOXINE (IV) FROM AMMONIUM SALTS.

Molar-ratios Ammonium salt:salicyl-aldehyde		1:1	1:2	1:3		1:4	
Ammonium salts		III	III	III	IV	III	IV
Ammonium	H_2O	17	34	34	—	35	—
phosphate	CH_3OH	26	33	33	—	34	—
Ammonium	H_2O	30	56	71	—	77	—
carbonate	CH_3OH	48	69	67	—	63	—
Ammonium	H_2O						
acetate	CH_3OH	57	81	56	25	—	64
Ammonium	H_2O	38	59	59	—	61	—
bicarbonate	CH_3OH	33	72	22	9	7	14
Ammonium	H_2O	—	—	—	—	—	—
dihydrogen	CH_3OH	—	—	—	—	—	—
phosphate							
Ammonium	H_2O	—	—	—	—	—	—
chloride	CH_3OH	—	—	—	—	—	—

solvents like methanol, ethanol and water, initial formation of (II) was observed but the ultimate product was hydrosalicylamide (III), which was obtained in good yields (84-92%) in all the cases. Hence, this also provides an excellent method of obtaining (III) (92%) even in water [4,5].

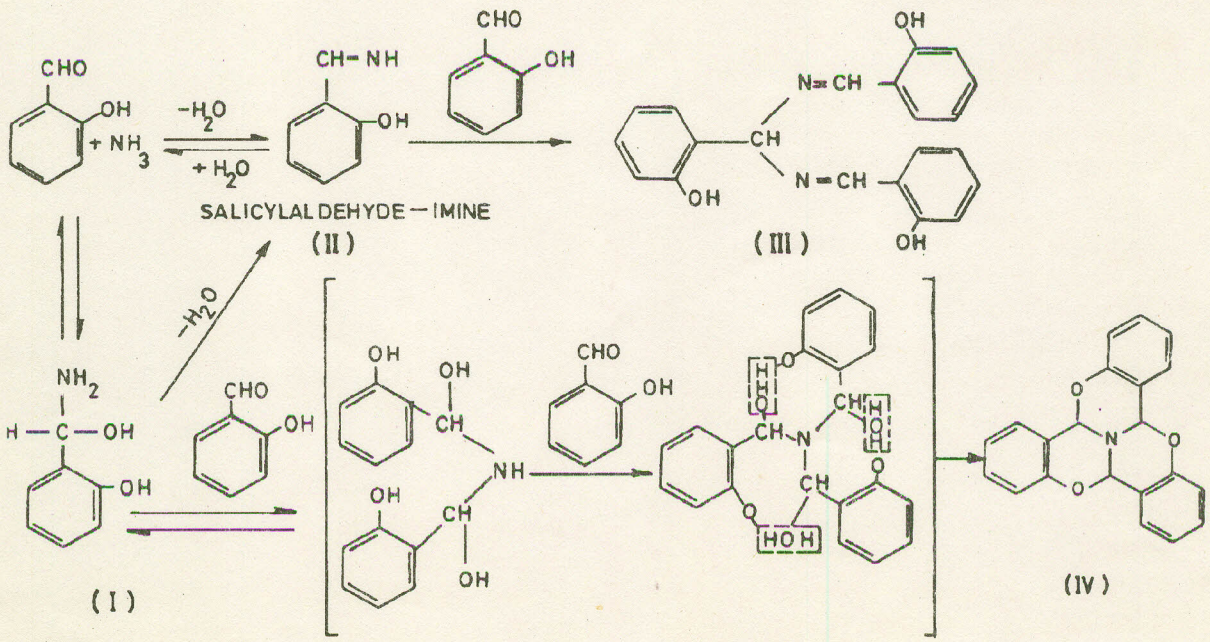
The reaction of salicylaldehyde with different ammonium salts in varying molar ratio has been studied in water and methanol and the results have been recorded in Table 2. It is obvious that ammonium carbonate, ammonium bicarbonate and tri-ammonium phosphate in different molar ratios yielded hydro-salicylamide (III) in water as well as in methanol. However, the reaction of ammonium bicarbonate with salicylaldehyde in the molar ratios of 1:3 and 1:4 gave a mixture of (III) and (IV) only in methanol. The pH values ranged from 7-8.5 in these reactions. In the presence of acidic salts like ammonium chloride and ammonium dihydrogen phosphate, salicylaldehyde did not yield any of the three products in these solvents. It suggests that under the acidic conditions the nucleophilic attack by these ammoniating agents may not be possible.

The reaction of salicylaldehyde with ammonium acetate presents a very interesting picture. It was observed that these reagents do not yield any product in water if kept even for a longer duration. In methanol the molar ratio of the reactants appeared to play a very important role in the synthesis of hydrosalicylamide (III) and tricyclobenzoxine (IV). Thus, when the ratio of salt to the aldehyde was 1:1 or 1:2, exclusively (III) was obtained in methanol. But, when this molar ratio was 1:3, a mixture of (III) and (IV) was obtained in the same solvent. However, at molar ratio 1:4, (IV) was obtained in good yield (62%) with only traces of (III). This method for obtaining (IV) is very simple as compared to previously reported method [14] which required rather vigorous conditions in the presence of extra chemicals like acetic anhydride, benzene etc.

It was also observed that not only the molar ratio but also the molar concentration played a significant role in the reaction of ammonium acetate with salicylaldehyde. At higher dilution, neither (III) nor (IV) could be isolated. However, a maximum yield of (IV) (62%) was obtained only at higher molar concentration of salicylaldehyde.

The mode of formation of products (II), (III) and (IV) has been shown in Scheme 1, where nucleophilic addition of ammonia has been proposed to give the hemiaminal or carbinol amine (I) [7] as the first step in conformity with earlier reports [7,15]. This undergoes dehydration yielding salicylaldehyde-imine (II), which has been isolated in an excellent yield.

The latter on reaction with more of the aldehyde was found to change into hydrosalicylamide (III). Furthermore, (II) when left in open also changed to salicylaldehyde with liberation of ammonia. This suggests that regenerated salicylalhyde on interaction with undecomposed N-unsubstituted-imine may also yield (III) as shown in the Scheme. Moreover, when ammonium acetate and salicylaldehyde were treated in methanol in the molar ratio of 1:4 respectively, (IV)



Scheme 1.

was the major product. Thus, it has been proposed that hemiaminal (I) may react successively with excess salicylaldehyde forming an intermediate which on dehydration yields tricyclobenzoxine (IV).

Acknowledgement. The authors are greatful to Ms. Eva Campi of Chemistry Department, Monash University, Clayton, Victoria-3168 (Australia) for useful discussion and for obtaining mass spectrum of tricyclobenzoxine.

References

1. Akio Skurai and Hiroshi Midori Kawa, J. Org. Chem., **34**, (11), 3612 (1969).
2. Akio Sakurai and Hiroshi Midori Kawa, J. Chem. Soc., Perkin-I, 2025 (1975).
3. Akio Skurai and Hiroshi Midori Kawa, Bull. Chem. Soc. (Japan), **42**, 220 (1978).
4. S. Kambe, T.Takajo and S. Saito, Synthesis, **8**, 802 (1975).
5. B. Shyder, G. Petterson and A. Abrahamson, J. Amer. Chem. Soc., **3**, 5214 (1989).
6. K. Shafiullah, C.M. Ashraf and A. Ehsan, (Unpublished data).
7. Jerry March, *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure* (McGraw-Hill International Book Co., Kasaido Printing Co. Limited Tokyo, Japan, 1977), pp. 816.
8. A. Kamal and A.A. Qureshi, Tetrahedron, **19**, 869 (1963).
9. M.M. Sprung, Chem. Rev., **26**, 301 (1940).
10. W. Robert Layer, Chem. Rev., **63**, 489 (1963).
11. H.S. Mosher and E.J. Blanz. Jr. , J. Org. Chem., **22**, 445 (1957).
12. Beilsteins HandBuch, Band **8**, 46 (1942).
13. Ilsong Rhee, Membo Ryang and Shigeru Tsutsumi, Tetrahedron Letters, 3419 (1970).
14. Kana Karanjan, Raman Krishan and P. Shanmugam, Synthesis, **8**, 501 (1975).
15. Jencks, J. Amer. Chem. Soc., **81**, 475 (1959).