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# HETEROCYCLIC SYSTEMS CONTAINING BRIDGEHEAD NITROGEN ATOM . PART LXVI STUDIES OF ORIENTATION OF CYCLIZATION IN THE SYNTHESIS OF 8-FLUOROTHIAZOLO[3,2-a]BENZIMIDAZOL-3(2H)-ONE

RAJINDER DAHIYA and H.K PUJARI

Department of Chemistry, Kurukshetra University,
Kurukshetra - 132 119 (India)

## SUMMARY

2-Fluoro-6-nitroaniline, obtained by nitration of 2-fluoroacetanilide, on reduction with Raney nickel and hydrazine hydrate followed by treatment of the resulting diamine with carbon disulphide *in situ* gives 4-fluorobenzimidazolyl-2-thione. This thione on condensation with chloroacetic acid gives 4-fluorobenzimidazol-2-thiolacetic acid which on cyclization with a mixture of acetic anhydride and pyridine furnishes 8-fluorothiazolo[3,2-a]benzimidazol-3(2H)-one and not the alternate possible isomer, 5-fluorothiazolo[3,2-a]benzimidazol-3(2H)-one as revealed by $^1$H-NMR spectroscopy The condensation of 4-fluorobenzimidazolyl-2-thione with 1,2-dibromoethane yields 2,3-dihydro-8-fluorothiazolo[3,2-a]benzimidazole and sym-bis-(4-fluorobenzimidazol-2-ylmercapto)ethane

## INTRODUCTION

As a part of the research programme of our laboratory directed towards studies of the orientation of cyclization, it was reported that the cyclization of the acid (V, Me in place of F), (V, Cl in place of F) and (V, $NO_2$ in place of F) yielded 8-methyl- (VI, Me in place of F) [1], 8-chloro- (VI, Cl in place of F) [2], 8-nitrothiazolo[3,2-a]benzimidazol-3(2H)-one (VI, $NO_2$ in place of F) [3] and not the other possible isomers, 5-methyl- (X, Me in

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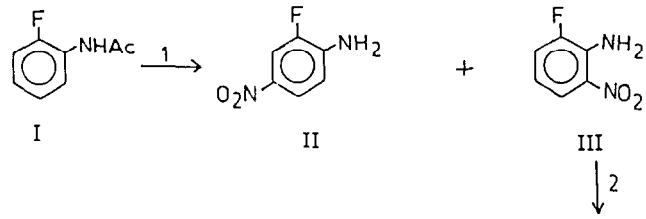
place of F), 5-chloro- (X, Cl in place of F) and 5-nitro-thiazolo[3,2-a]benzimidazol-3(2H)-one (X, $NO_2$ in place of F) respectively. In the present investigation, the cyclization of the acid (V) was undertaken with a view to studying the directive influence of the fluorine atom on the cyclization. We report herein that the structural assignment of the cyclized product has been secured by comparative study of the observed and calculated chemical shifts of the aromatic protons of the cyclized structures (VI and X), the comparative study of the chemical shifts of the aromatic protons in VI and X with those in VII (or XI) and by the shift value of $C_5$-H of the cyclized product VI.

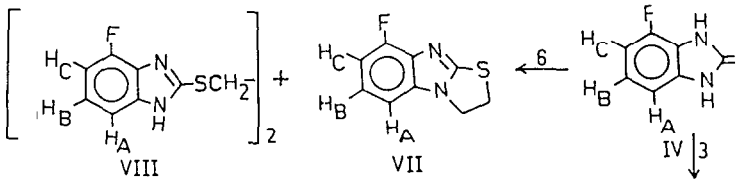
## RESULTS AND DISCUSSION

2-Fluoroacetanilide (I) on successive nitration, hydrolysis and subject to steam distillation gave 2-fluoro-6-nitroaniline (III) as a steam-volatile compound and 2-fluoro-4-nitroaniline(II). The former on reduction with Raney nickel and hydrazine hydrate followed by treatment of resulting diamine with carbon disulphide *in situ* gave 4-fluorobenzimidazolyl-2-thione (IV). The thione (IV) when condensed with chloroacetic acid yielded 4-fluorobenzimidazolyl-2-thiolacetic acid (V). The acid being unsymmetrical, on cyclization was expected to give 8-fluorothiazolo[3,2-a]benzimidazol-3(2H)-one (VI) or 5-fluorothiazolo[3,2-a]benzimidazol-3(2H)-one (X) or both depending upon the direction of cyclization (Scheme). The acid (V), whose structure was characterized by IR, $^1$H-NMR, $^{19}$F-NMR and Mass spectra (see Experimental), however, when heated in acetic anhydride-pyridine mixture underwent cyclization furnishing a single product (TLC). The appearance of a band at 1735 $cm^{-1}$ ( $>$N-C(=O)-) in the IR spectrum and the exhibition of a molecular ion peak $[M]^+$ at m/z 208 (100%) in the mass spectrum of TLC-pure product suggested that cyclization had indeed occurred. The structural assignment for the cyclization product was finally secured as 8-fluorothiazolo[3,2-a]benzimidazol-3(2H)-one (VI) in preference to the other alternative structure (X) on the basis of $^1$H-NMR spectral data.

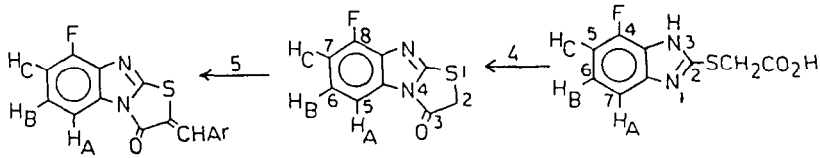
The assignment of $^1$H-NMR signals of aromatic protons in VI and X were derived from calculations by taking into considera-



I II III

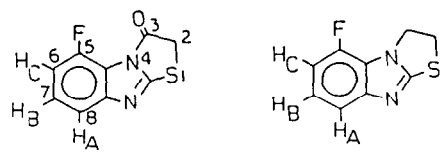


VIII VII IV



IX VI V

a Ar = 3 4 $(MeO)_2C_6H_3$
b Ar = p-$Me_2NC_6H_4$



X XI

XII

1 : Conc $HNO_3$ $Ac_2O$ gl AcOH II HCl steam distillation
2 : Raney Nickel $H_2NNH_2H_2O$ II $CS_2$ KOH,3 $ClCH_2CO_2H$
4 $Ac_2O$, Pyridine, 5 ArCHO NaOAc gl AcOH, 6 $BrCH_2CH_2Br$

Scheme

tion the shielding effect of fluorine atom (fluorine shields ortho-, meta- and para protons by δ 0 30, 0 02 and 0 22 respectively) [4] on the values of the corresponding protons of the parent compound (XII) In the $^1$H-NMR spectrum (TFA) of the parent compound (XII), the signals at δ 8.22, 7 62, 7 62 and 7.77 were assigned to $C_5$-H, $C_6$-H, $C_7$-H and $C_8$-H protons respectively [5] The most downfield resonance of $C_5$-H was due to the deshielding effect on this proton by the thiazolidinone ring This deshielding effect has its origin in the magnetic anisotropy of the carbonyl group with little contribution from the rest of the ring If the structure VI is correct, then the calculated chemical shifts for $C_5$-H ($H_A$), $C_6$-H ($H_B$), and $C_7$-H ($H_C$) would be at δ 8 00 (8.22 - 0 22), 7 60 (7 62 - 0.02) and 7 32 (7 62 - 0 30) respectively (Set-A) On the other hand, if the structure X is correct, the calculated values for $C_6$-H ($H_C$), $C_7$-H ($H_B$) and $C_8$-H ($H_A$) protons would be δ 7 32 (7 62 - 0 30), 7.60 (7 62 - 0 02) and 7 55 (7.77 - 0.22) respectively (Set-B) The observed $^1$H-NMR signals of the cyclized product obtained from the acid (V) at δ 8 06, 7.70 and 7.47 may be due to $C_5$-H ($H_A$), $C_6$-H ($H_B$) and $C_7$-H ($H_C$) protons respectively (Set-C) if the structure VI is correct On the other hand, the observed $^1$H-NMR signals at δ 8 06, 7.70 and 7 47 may be due to $C_7$-H ($H_B$), $C_8$-H ($H_A$) and $C_6$-H ($H_C$) protons respectively (Set-D), if the structure X is correct Since the Set-A is very close to Set-C and Set-B does not tally with Set-D (Table 1) the structure VI is correct

TABLE 1

Observed and calculated chemical shifts (in δ ppm) for the aromatic protons in XII and the cyclized products VI and X

| Structure | $C_5$-H | | $C_6$-H | | $C_7$-H | | $C_8$-H | |
|---|---|---|---|---|---|---|---|---|
| | Calc | Obs | Calc | Obs | Calc | Obs | Calc | Obs |
| XII (TFA) | - | 8 22 | - | 7 62 | - | 7 62 | - | 7.77 |
| VI (TFA) | 8.00 | 8.06 | 7.60 | 7 70 | 7 32 | 7 47 | - | - |
| X (TFA) | - | - | 7.32 | 7 47 | 7.60 | 8 06 | 7.55 | 7.70 |

The correct structural assignment for the cyclization product as VI and not as X was also arrived at by comparing the chemical shifts of the aromatic protons of the cyclized product obtained from the acid (V), with that of the product obtained from the reaction of IV with 1,2-dibromoethane. The reaction of IV with 1,2-dibromoethane gave in addition to the bis compound (VIII), a cyclized product which can be represented by either structure (VII or XI) In either structure (VII or XI) the $^1$H-NMR signals at δ 7 27 was assigned to $H_C$ and δ 7 60 to both $H_B$ and $H_A$ because $H_C$ is shielded by fluorine and $H_B$ is not affected by fluorine while the shielding effect of fluorine on $H_A$ is almost neutralised by the deshielding effect of adjacent nitrogen overall resulting in $H_A$ and $H_B$ resonating at the same field If structure X is correct for the cyclized product obtained from the acid (V), then $H_A$, $H_B$ and $H_C$ would resonate almost in the same position as in case of VII (or XI) On the other hand if structure VI is correct, $H_A$ would be deshielded by the thiazolidinone ring and as a consequence, $H_A$ would resonate downfield in comparison to either $H_B$ and $H_C$ The signal at δ 8.06 (due to $H_A$) supported the structure VI and ruled out structure X from which such a downfield shift would not be expected.

The same conclusion was also arrived at from the comparison of chemical shifts of the respective aromatic protons in the acid V and its cyclization product VI (or X) In the acid V, the signals at δ 7 38, 7 61 and 7 61 were assigned to $C_5$-H, $C_6$-H and $C_7$-H protons respectively. In the structure VI, $C_5$-H would be deshielded by the carbonyl group and $C_6$-H and $C_7$-H would resonate almost at the same position as in the acid (V). This was, in fact, found to be true thus confirming the structural assignment for the cyclization product as VI The shift value of $C_5$-H δ 0.45 tallies well with the shift value, ca δ 0.40 reported by Murakami and co-workers [6] (Table 2), in similar systems

Thus the structure VI was established by three different methods Establishment of the structure VI for the cyclized products obtained from the acid V lends support that the direction of cyclization in case of acid V (Me in place of F)[1], V (Cl in place of F) [2], V ($NO_2$ ir place of F) [3] is similar suggesting that the cyclization is governed by steric hindrance

TABLE 2

Proton shifts [7] (δ values) of 8-fluorothiazolo[3,2-a]benzimidazol-3(2H)-one (VI) from the corresponding protons of the acids (V)

| Structure | Chemical shifts of protons | | |
|---|---|---|---|
| VI | 8 06 ($C_5$-H) ($H_A$), | 7.70 ($C_6$-H) ($H_B$), | 7.47 ($C_7$-H) ($H_C$) |
| V | 7 61 ($C_7$-H) ($H_A$), | 7 61 ($C_6$-H) ($H_B$), | 7 38 ($C_5$-H) ($H_C$) |
| Shift value | 0 45 | 0.09 | 0.09 |

and not by the electron-donating or electron-withdrawing nature of the substituent. After having established the structure VI, structure VII (and not XI) for the cyclized product obtained from the reaction of IV with 1,2-dibromoethane, was assigned by analogy to structure VI. Elemental analysis of the other product obtained from the reaction of IV with 1,2-dibromoethane showed the participation of 1 mole of 1,2-dibromoethane and 2 moles of IV. The appearance of a band at 3380 $cm^{-1}$ (NH) in the IR spectrum and one singlet at δ 3.99 integrated for four methylene protons and two multiplets at δ 7.25 and 7.54 integrated for two and four aromatic protons respectively was compatible with the bis-structure (VIII)

The 2-arylidenethiazolidinones (IXa,b) were prepared by the condensation of VI with 3,4-dimethoxybenzaldehyde and p-dimethylaminobenzaldehyde respectively. The structures of thiazolidinone (VI) and arylidenethiazolidinone (IX) were further characterized by their IR spectral data The thiazolidinone (VI) absorbed at 1735 $cm^{-1}$ ( >N-C=O), but the unsaturation at 2-position being conjugated with the carbonyl group at 3-position as in the case of arylidenethiazolidinones (IXa,b) showed a bathochromic shift [8]

The carbonyl absorption bands appeared at 1715 and 1700 $cm^{-1}$ in the IR spectra of IXa and IXb respectively The absence of $SCH_2$ signal and appearance of a benzal proton at δ 8.55 in the $^1$H-NMR spectrum of the product obtained from the reaction of VI with 3,4-dimethoxybenzaldehyde corroborated that aldehyde condensation had taken place at the methylene carbon of thiazolidinone (VI).

## EXPERIMENTAL

Melting points were determined in conc. sulphuric acid bath and are uncorrected. TLC was performed on silica gel-G plates using acetone-benzene (1:3) as irrigant except in VII and VIII where AcOEt-benzene (1.4) was used. IR spectra ($\nu_{max}$ in $cm^{-1}$) were recorded in nujol mull on a Beckman IR-20 spectrophotometer, $^1$H-NMR on a Perkin-Elmer 90 MHz spectrometer using TMS as internal reference (chemical shift in δ, ppm) and $^{19}$F-NMR spectra were obtained on a Jeol FX 90 Q, 84.25 MHz spectrometer with hexafluorobenzene as external reference. Mass spectra were scanned on an E.I./L.R. instrument at 70 eV.

### 2-Fluoroacetanilide (I)

2-Fluoroaniline (27 78 g, 0.25 mole) in a mixture of glacial acetic acid (30 ml) and acetic anhydride (30 ml) was heated on a steam bath for half an hour, and then poured into ice-cold water with vigorous stirring to give 2-fluoroacetanilide (I), m.p. 79°C (Lit. [9] m.p. 80°C).

### Nitration of o-fluoroacetanilide (I) : Preparation of 2-fluoro-6-nitroaniline (III) and 2-fluoro-4-nitroaniline (II)

Compounds (II) and (III) were prepared by the nitration of I with conc. $HNO_3$ in acetic anhydride-acetic acid (1:1 by vol.) at 0-5°C and subsequent hydrolysis with HCl following the method of Kavalek [10]. The fluoronitroanilines (II and III) were separated by steam distillation. III was isolated as a steam-volatile distillate while II remained in the flask and was isolated through usual

work up III, m.p. 130°C (Lit. [10] m.p. 130.5-32°C); II, m.p. 138°C (Lit. [11] m.p. 135-36°C).

4-Fluorobenzimidazolyl-2-thione (IV)

(IV) was prepared in 69% yield by the reduction of III with Raney nickel and hydrazine hydrate followed by the reaction of the resulting diamine with carbon disulphide *in situ* following the method of Van Allan and Deacon [12] for the synthesis of benzimidazolyl-2-thione, m.p. 297°C, IR : 1620, 1640 (C=C and C=N), 3160 (NH). $^1$H-NMR ($CDCl_3$+TFA) : 7.27 (m, 1H, $H_C$), 7.51 (m, 2H, $H_A$ and $H_B$). $^{19}$F-NMR (DMSO) : -127.537 ppm (s, 1F, $C_4$-F). Analysis: Found: S, 18.6; N, 16.4. $C_7H_5FN_2S$ requires S, 19.1; N, 16.7%.

4-Fluorobenzimidazol-2-thiolacetic acid (V)

A mixture of IV (1.68 g, 0.01 mol), chloroacetic acid (0.94 g, 0.01 mol) and anhyd. sodium acetate (0.82 g, 0.01 mol) in anhyd. ethanol (60 ml) was heated, under reflux, on a steam bath for 3 h. The reaction mixture was concentrated almost to dryness and allowed to cool to room temperature. The solid, thus separated, was filtered and washed well with water and crystallized from ethanol to give V as dirty white crystals, m.p. 190°, IR : 1595, 1615 (C=C and C=N), 1660 (CO in $CO_2H$), 2560-2750 ($CO_2H$), 3160 (NH). $^1$H-NMR (TFA) : 4.34 (s, 2H, $SCH_2$), 7.38 (m, 1H, $H_C$), 7.61 (m, 2H, $H_A$ and $H_B$). $^{19}$F-NMR (DMSO) : -125.915 ppm (s, 1F, $C_4$-F). MS : m/z 226 ($M^+$, 22%), Analysis : Found : S, 13.9; N, 12.0. $C_9H_7FN_2O_2S$ requires S, 14.2; N, 12.4%.

8-Fluorothiazolo[3,2-a]benzimidazol-3(2H)-one (VI)

4-Fluorobenzimidazol-2-thiolacetic acid (V; 1 g) in a mixture of pyridine (3 ml) and acetic anhydride (1 ml) was heated on a boiling steam bath for 10 min. The reaction mixture was cooled to room temperature and poured into water. The compound, thus separated, was filtered and washed well with water and crystallized from ethanol to give VI as colourless needles, m.p. 126°, IR: 1590, 1620 (C=C and C=N), 1735 ($>$N-C(=O)-). $^1$H-NMR (TFA) : 4.86 (s, 2H,

$SCH_2$), 7.47 (m, 1H, $H_C$), 7.70 (m, 1H, $H_B$), 8 06 (m, 1H, $H_A$). $^{19}$F-NMR (DMSO) : -124 178 ppm (s, 1F, $C_8$-F), MS . m/z 208 ($M^+$, 100%) Analysis : Found : S, 15.1, N, 13.1. $C_9H_5FN_2OS$ requires S, 15.4, N, 13.5%.

Reaction of IV with 1,2-dibromoethane. Syntheses of 2,3-dihydro-8-fluorothiazolo[3,2-a]benzimidazole (VII) and sym-bis(4-fluorobenzimidazol-2-yl-mercapto)ethane (VIII)

A mixture of IV (1.68 g, 0.01 mol) and 1,2-dibromoethane (1.88 g, 0.01 mol) in anhyd. ethanol (60 ml) was heated, under reflux, for 4 h. The reaction mixture was concentrated to almost half, poured into water and neutralized with $NaHCO_3$. The solid, thus obtained, was filtered and washed well with water and crystallized from ethanol. TLC on silica gel revealed that the product was a mixture of two compounds, which were separated on a silica gel column using benzene-ethyl acetate (4 1) as eluent. Compound VII as a pale yellow solid was eluted first and the bis compound (VIII) as a white solid recovered later.

VII, m p 150°, IR: 1590, 1620 (C=C and C=N) $^1$H-NMR (TFA): 4.41 (t, 2H, $SCH_2$), 4.79 (t, 2H, $NCH_2$), 7.27 (m, 1H, $H_C$), 7 60 (m, 2H, $H_A$ and $H_B$) Analysis Found . S, 16.2. $C_9H_7FN_2S$ requires S, 16.5%

VIII, m p. 218°, IR 1590, 1625 (C=C and C=N), 3380 (NH) $^1$H-NMR (TFA) 3.99 (s, 4H, $-SCH_2CH_2S-$), 7.25 (m, 2H, $2xH_C$), 7.54 (m, 4H, $2xH_A$ and $2xH_B$). $^{19}$F-NMR (DMSO): -125 799 ppm (s, 2F, $2xC_4$-F). Analysis: Found: S, 17.4, N, 15.3. $C_{16}H_{12}F_2N_4S_2$ requires S, 17.7, N, 15.5%.

8-Fluoro-2-(3,4-dimethoxybenzylidene)thiazolo[3,2-a]benzimidazol-3(2H)-one (IXa)

Thiazolidinone (VI, 0.21 g, 0.001 mol), 3,4-dimethoxybenzaldehyde (0.17 g, 0.001 mol) and anhyd. sodium acetate (0.08 g, 0 001 mol) in glacial acetic acid (15 ml) were refluxed for 2.5 h. The reaction mixture was cooled to room temperature and poured into water The solid, thus separated, was filtered and crystallized from glacial acetic acid to give IXa as brown crystals,

m.p. 219°, IR: 1595, 1625 (C=N, C=C), 1715 ( >N-C=O). $^1$H-NMR (TFA): 4.10 (s, 6H, 2xOCH$_3$), centred at 7.50 (m, 5H, Ar-H), 8.17 (m, 1H, $H_A$), 8.55 (s, 1H, -S-C=CH-). Analysis : Found : N, 7.9. $C_{18}H_{13}FN_2O_3S$ requires N, 7.8%.

Similarly, IXb was prepared from VI and p-dimethylaminobenzaldehyde, m.p. 198°, IR: 1590, 1620 (C=N, C=C), 1700 ( >N-C=O). Analysis : Found: N, 11.9. $C_{18}H_{14}FN_3OS$ requires N, 12.4%.

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