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Synthesis of some tetrazolo [1,5-a]- pyrimidines & β-ketoamine derivatives

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Abstract
The synthesis of tetrazolo [1,5-a] pyrimidines (IIIa-c, IV), ketoamine derivatives (Va-c), enolimino derivative (VI), and ketoimino derivatives (VII) of tetrazole) is done by the reaction of 5-aminotetrazole (II) with fluorinated 1,3-diketones (Ia-c) in different media have been investigated. These compounds were found to be solvent-dependent. All new fluorinated tetrazole have been characterised by elemental analysis as well as IR, PMR, 19F NMR & mass spectrometry.

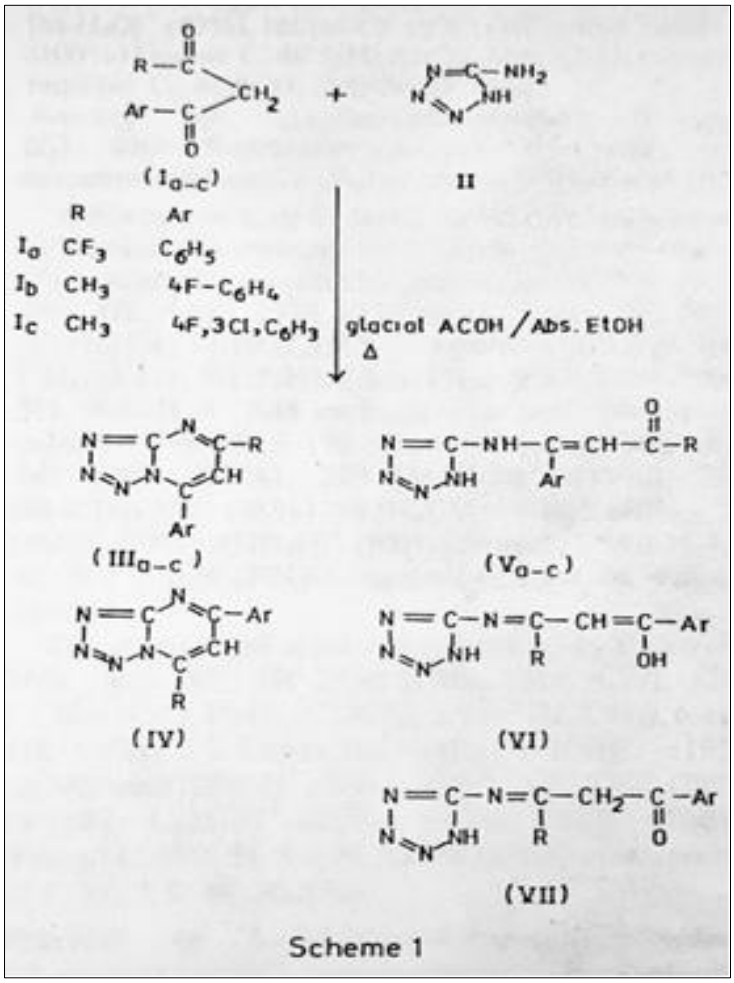
Keywords: some tetrazolo, mass spectrometry, aminotetrazole

Introduction
The importance of 1,3-diketones in synthetic organic chemistry is difficult to overestimate. Their accessibility, stability, and often unique properties make them promising for use in various fields of human activity. High reactivity of 1,3-diketones opens wide prospects for the design of a variety of organic compounds, including those structurally related to natural ones. Continuously growing interest in β-dicarbonyl compounds is observed among researchers working in various fields of medicinal chemistry and chemistry of metal complexes.

β-diketones can be used for the preparation of ketoimine (by condensation with amine) and various heterocyclic compounds (E.g., pyrimidine derivatives). β-diketones are well known for its antioxidant capability associated with the corresponding enol tautomer. They are valuable compound in the treatment of many pathological disorders, such as cardiovascular diseases, liver diseases, hypertension, obesity, diabetes, neurological disorders, inflammation, skin diseases etc.
Tetrazole derivatives are well known for various biological activities. For example; antibacterial, antifungal[1], anticancer[2], analgesic[3], antimflammatory[4], antidiabetic, antihyperlipidemic[5], antitubercular activities[6]. A great number of medicinally tetrazole moiety has been approved by USFDA[7].

Synthesis of tetrazolo [1,5-a] pyrimidines and related β-ketoamine derivatives has been accomplished in the present study in view of the paucity of literature8-10 on the subject. Besides, the reaction of equimolar amount of fluorinated 1,3-diketones (I a-c) and 5-amino tetrazol have been investigated in different solvent for the first time. This was done in few of five possibilities (Scheme 1) offered by the reaction, *viz*. formation of tetrazolo [1,5-a] pryimidines (III a-c, IV), ketoamino derivatives (V a-c), enolimino derivatives (VI), and ketoimino derivatives (VII) of tetrazole.
Our investigation revealed that in acetic acid medium, compound IIIa-c are mainly formed while in abs. ethanol, β-ketoamine derivatives (V a-c) of the tetrazole are obtained as major product along with IIIa-c as minor products.

In addition to the role of solvent, the nature of R and Ar also influences the reaction in view of the change in the direction of enolization. Thus, while the condensation of symmetrical 1,3- diketones with 5-amino tetrazole can lead to only one isomer, in unsymmetrical 1,3-diketones (I a-c), there are five possibilities as listed earlier. The formation of exclusive product (III a-c) may be explained by the direction of enolization taking place towards the phenyl ring11



Scheme 1

Typical spectral data is given below. For example, in case of IIIa, the IR spectrum displayed absorption bands around 2920 cm-1 (CH) and 1600 cm-1 (C=N). The 1H NMR spectrum (CDCl3) showed signals at δ6.5 (s, 1H, =CH) and 7.5-7.8 (m, 5H, Ar—H) and 19F NMR spectrum showed a singlet at δ -68.457 due to CF3 attached to the pyrimidine ring. The mass spectrum showed the molecular ion peak at *m/z* 265 (41.5%) with respect to the base peak at *m/z* 68 [CN4] and the fragment ion peak at *m/z* 170 [M-- CF3—C≡N] + (25%). Structure IV was ruled out based on the mass fragmentation pattern which support IIIa.

In the case of β-ketoamine derivatives, for example, Va, the IR spectra showed broad absorptions around 3200, 3150, 3080 (NH) and 1655 cm-1 (C=O). 1H NMR spectrum (CDCl3 +

DMSO-*d6*) showed signals at δ2.54 (s, 1H, NH), 6.6 (s, 1H, =CH) and 7.6-8.13 ppm (m, 6H, 5 aromatic protons + NH, exchangeable with deuterium oxide), 19F NMR spectrum showed a doublet (δ-77.55 and -78.18) due to CF3. The mass spectrum exhibited the molecular ion peak at *m/z* 283 (28%) with respect to the base peak at *m/z* 69 [CN4H] and the other fragment ion at *m/z* 265 [M—H2O] + (40%), 186 [M—CF3C=O]+ (20%).

Structure VI (enolimino-form) was ruled out by IR and PMR data due to the absence of the hydrogen bonded OH vibrations near 2700 cm-1 and no signal at δ 13-15 ppm of hydrogen bonded OH respectively. Structure VII (ketoimino-form) was similarly ruled out by IR and PMR data due to absence of C=O at 1700 cm-1 and no signal in PMR at δ 4.2-3.8 due to the protons of CH2 group of the ketoimino-form.

Experimental

All melting points were determined in open capillaries and are uncorrected. IR spectra were recorded (KBr) on a Perkin-Elmer (Model 337) spectrophotometer (υmax in cm-1), PMR spectra in CDCl3 or DMSO-d6 on a JEOL FX 90Q MHz instrument (chemical shifts in δ, ppm) using TMS as internal standard, and mass spectra on a M-S 30 Kratos mass spectrometer at 70eV. Carbon and hydrogen analysis were carried out on a coleman 'C' and 'H' analyzer. Nitrogen analyses were done on a Carlo Ebra N-analyzer 1106.

All the reactions were carried out in gl. acetic acid and ab. ethanol and the products separated by column chromatography and preparative TLC over silica gel. Fluorinated 1,3-diketones (Ia- c) were prepared by literature methods17-18.

Reaction of 4,4,4-trifluoro-l-phenyl-1,3-dione (Ia) with 5-aminotetrazole (II): Formation of tetrazolo [1,5- a] pyrimidine (IIIa) and ketoamino derivative (Va) of tetrazole

A mixture of Ia (0.01 mole) and II (0.01 mole) was refluxed separately for 4-5 hr in gl. acetic acid and abs. ethanol. TLC indicated the formation of only one compound (IIIa) in gl. acetic acid and two compounds (IIIa and Va) in abs. ethanol. These products were separated by column chromatography. The orange compound, obtained from benzene-ethyl acetate (9:1) fraction, was identified as IIIa, yield 76% (in gl. acetic acid), 26% (in abs. ethanol), m.p. 78º; IR: 2920 (CH), 1600 (CN), 1555 (--N=N--) and 1270 (CF3); PMR (CDCl3): 6.5 (s, 1H, =CH), 7.5-7.8 (m,

5H, Ar-H); 19F NMR: -68.457(s); MS: *m/z* 265 [M]+ (26%), 170[M—CF3—C=N]+ (25%), 144 [170—CN]+ (38%), 68 [CN4] (100%) (Found C,49.9; H, 2.4; N, 26.5. C11H6N5F3 requires C, 49.8; H, 2.3; N, 26.4%).

The white compound obtained from ethyl acetate-methanol (1:1) fraction were identified as Va, yield 65%, m.p. 230º; IR: 3200, 3150, 3080 (NH), 1655 (CO), 1555; PMR (CDCl3 + DMSO-

d6): 2.54 (s, 1H, NH), 6.6 (s, 1H, =CH), 7.6-8.13 (m, 6H, 5 ArH +

H exchangeable with

deuterium oxide); 19F NMR: -77.55 – 78.18 *(d)*; MS: *m/z* 283 [M]+ (28%), 265 [M-H2O]+ (40%),

186 [M-CF3CO]+ (20%), 69 [CN4H]+ (100%) Found: C, 46.6; H, 2.8; N, 24.6. C11H8F3N5O requires

C, 46.6; H, 2.8; N, 24.7%).

Reaction of 1-(4-fluorophenyl) butane-1,3-dione (Ib) with 5-aminotetrazole (II): Formation of ketoamino derivative (Vb) of tetrazole along with IIIb.

A mixture of Ib (0.01 mole) and II (0.01 mole) was refluxed in abs. ethanol for 10-12 hr, left over night. The white solid was identified as *Vb*, yield 78%, m.p. 205º; IR: 3440, 3770, 3170 (NH), 3060 (CH), 1630 (CO); 1550; MPMR (CDCl3 + DMSO-*d6*): 1.3 (s, 3H, CH3), 3.1 (s, 1H, NH),

6.6 (s, 1H, =CH), 7.9-8.5 (m, 5H, 4-ArH + NH exchangeable with deuterium oxide); 19F HMR: -

170.275, -170.738 *(d)*; MS: *m/z* 247 [M]+ (26%), 229 [M-H2O]+ (45%), 204 [M-CH3CO]+ (38%),

84 [N4CH=NH]+ (48%), 57 [N4H]+ (70%), 43 [N3H]+ (100%) (Found C,53.2; H, 4.1; N, 28.2.

C11H6FN5O requires C, 53.4; H, 4.0; N, 38.3%).

The orange-red solid was identified as *IIIb* yields 16%, m.p. 82º; IR: 2930 (CH), 1610 (CN), 1560 (--N=N--); PMR (CDCl3): 1.9 (s,3H, CH3), 6.1 (s, 1H, =CH), 7.2-7.8 (m, 4H, ArH); 19F NMR: -195.2 (s); MS: *m/z* 229 [M]+ (32%) 188[M—CH3CN]+ (28%), 68 [188-C8H5F]+ (26%) 53 [68--NH]+

(100%) (Found: C, 57.6; H, 3.4; N, 30.4. C11H8N5 F requires C, 57.6; H, 3.5; N, 30.6%).

Reaction of 1-(3-Chloro-4-fluorophenyl) butane-1,3-dione (Ic) with 5-aminotetrazole (II): Formation of ketoamino derivative (Vc) of tetrazole along with tetrazolo[1,5-a] pyrimidine (IIIc).

A mixture of Ic (0.01 mole) and II (0.01 mole) was refluxed in abs. ethanol for 10-12 hr, left over night. It yielded a white solid crystalline compound which was identified as *Vc*, yield 72%, m.p. 209º; IR: 3400, 3360, 3190 (NH), 1650 (CO), 1560; PMR (CDCl3 + DMSO-*d6*): 1.28 (s, 3H, CH3), 3.2 (s, 1H, NH), 6.6 (s, 1H, =CH), 7.9-8.2 (m, 4H, 3-ArH + NH exchangeable with deuterium oxide); 19F HMR: -164.94 (s); MS: *m/z* 281.5 (32%), 238 [M-CH3CO]+ (55%), 69(CN4H) (62%) (Found: C, 46.9; H, 3.2; N, 24.9. C11H9FN5OCl requires C, 46.9; H, 3.2; N, 24.8%).

The brown solid was identified as *IIIc*, yields 18%, m.p. 95º; IR: 2910 (CH), 1600 (CN), 1565 (-- N=N--); PMR (CDCl3): 2.0 (s,3H, CH3), 6.3 (s, 1H, =CH), 7.26-7.9 (m, 3H, 3 ArH); 19F NMR: -190.2 (s); MS: *m/z* 263.5 (28%), 222 [M—CH3CN]+ (38%), 109 [M-C8H4FCl]+ (32%), 68 [CN4] (100%)

(Found: C, 50.2; H, 2.7; N, 26.5. C11H7FN5Cl requires C, 50.2; H, 2.7; N, 26.6%).

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