Activated Nitriles in Heterocyclic Synthesis. A Novel Synthesis of 1,2,4-Triazol-3-oyl Nitriles

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Synthesis of 1,2,4-triazoloyl nitriles *via* reaction of 4-phenylhydrazono-2-phenyl-2-oxazolin-5-one and 4-phenylhydrazono-2-ethoxy-2-thiazolin-5-one with active methylene nitriles was accomplished. Some of the chemical properties of the nitriles obtained are reported.

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Oxonitriles are versatile reagents and have been extensively utilised in heterocyclic synthesis (1-3). Continuing our interest in the chemistry of β-oxonitriles, we became interested in the synthesis of certain azoloyl nitriles in order to investigate their chemical and biological activities. Generally oxonitriles are obtained either by hydrolysis of the corresponding enamino nitrile (4), Friedel-Crafts acylation of nitriles (5) or by reaction of cyanide ion with α-halonitriles (6). All these approaches seemed unsuitable for the synthesis of azoloyl nitriles. The difficulty of getting access to the required azoloylenaminonitriles, azole carboxylic acid or azoloylhaloketones precluded attempted synthesis of azoloylnitriles *via* the above approaches. Consequently alternate new routes for synthesis of the required azoloylnitriles were investigated. In the present paper we report a new efficient procedure for synthesis of 1,2,4-triazol-3-oylnitriles. The compounds obtained carry latent functional substituents and appear interesting for further chemical transformations and for biological studies.

Thus, it has been found that 2-phenyl-4-phenylhydrazono-2-oxazolin-5-one (I) reacts with ethyl cyanoacetate and with benzoylacetonitrile to yield 1,2,4-triazol-5-oylnitrile derivatives II and III, respectively. The formation of these products is assumed to proceed by ring opening and recyclization *via* elimination of water to yield the final isolable products. The rearrangement of I by the action of activated nitriles finds a parallel in the previously reported rearrangement of I into 1,2,4-triazoles by the action of acids (7), amines and hydrazines (8).

Compounds II and III can, theoretically exist in more than one tautomeric form. Spectral data revealed the existence of more than one tautomeric form in solutions that the position of equilibrium is highly dependent on the *p*H

Table I

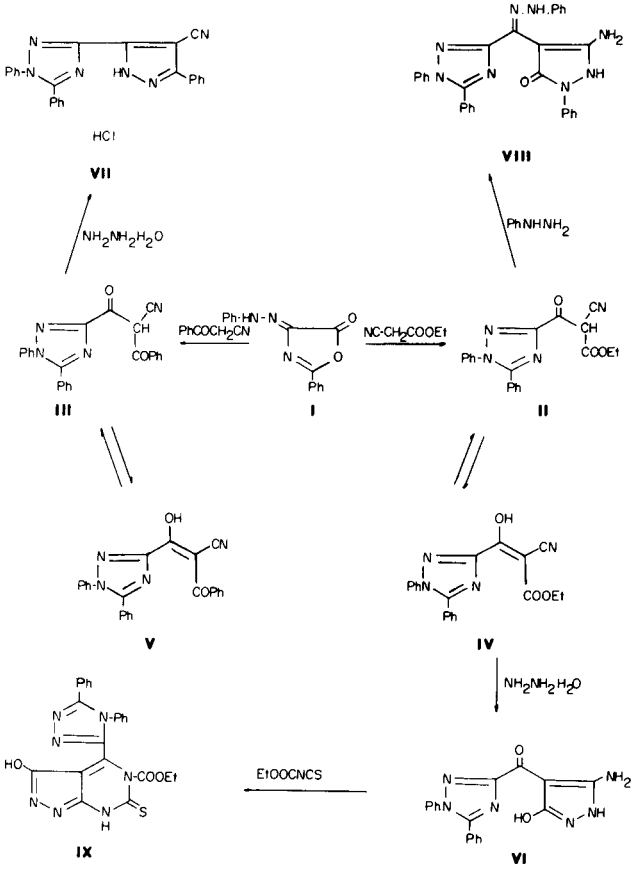
Compounds, II, III, VI-IX, XIa-c and XII

Compound (Colour)	Solvent of crystallisation	Mp (°C)	Molecular formula (Molecular weight)	Analysis % Found/Calcd. C	H	N
II (Colourless)	1-Propanol	214	$C_{20}H_{16}O_3N_4$ (360)	67.0 66.6	4.6 4.4	15.3 15.6
III (Colourless)	Ethanol	213	$C_{24}H_{16}O_2N_4$ (392)	73.3 73.4	4.3 4.1	14.1 14.3
VI (Yellow)	Methanol	185	$C_{16}H_{14}O_2N_6$ (346)	62.0 62.4	4.5 4.0	24.0 24.3
VII (Colourless)	Ethanol	268	$C_{24}H_{17}N_6Cl$ (424.5)	68.2 67.8	4.5 4.0	19.4 19.7
VIII (Yellow)	Ethanol	195	$C_{30}H_{24}ON_8$ (512)	70.6 70.3	5.0 4.7	21.6 21.9
IX (Colourless)	Ethanol	278	$C_{22}H_{17}O_3N_7S$ (459)	57.8 57.5	4.0 3.7	21.0 21.3
XIa (Colourless)	Ethanol	142	$C_{12}H_7O_2N_5$ (253)	56.9 56.9	2.8 2.8	28.0 27.6
XIb (Colourless)	Ethanol	201	$C_{14}H_{12}O_4N_4$ (300)	55.7 56.0	4.4 4.0	18.2 18.6
XIc (Brown)	Ethanol	145	$C_{18}H_{12}O_3N_4$ (320)	66.5 66.1	3.3 3.5	16.1 16.4
XII (Colourless)	Dioxan	192	$C_{19}H_{15}O_3N_5$ (361)	63.5 63.1	4.2 4.2	19.1 19.4

of the solution. In solid state the enol forms IV and V predominate. The detailed structural investigation of these compounds will be published separately in connection with an investigation of other physical characteristics.

Compounds II and III (or alternate tautomeric IV and V) reacted with hydrazine hydrate to yield the 1,2,4-triazol-3-oylpyrazole derivative VI and the 1,2,4-triazol-3-ylpyrazole derivative VII, respectively. On the other hand the phenylhydrazone VIII was obtained from the reaction of II (or tautomeric IV) with phenylhydrazine. Compound II also reacted with ethoxycarbonyl isothiocyanate to yield the pyrazolo[4,3-*d*]pyrimidine derivative IX. To our knowledge this is the first reported synthesis of these biologically important (9,10) derivatives *via* a similar route.

Similar to the behaviour of I, 2-ethoxy-4-phenylhydrazono-2-thiazolin-5-one (X) rearranged by the action of active methylene reagents, namely, malononitrile, ethyl cyanoacetate, benzoylacetonitrile and 3-methyl-1-phenyl-2-pyrazolin-5-one to yield 1,2,4-Δ^2-triazolin-5-one derivatives XIa-c and XII. The formation of these products is assumed to proceed *via* ring opening to yield the acyclic intermediate by loss of ethyl mercaptan into the final isolable products. A similar reaction sequence has been previously reported by one of us for the reaction of 4-substituted-2-alkoxy and 2-benzylmercapto-2-thiazolin-5-ones with aliphatic amine (11-13).



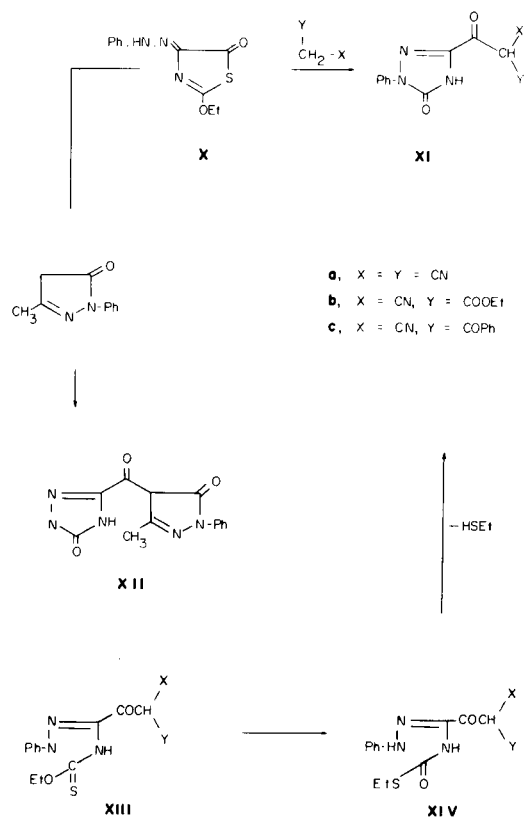


Table II

IR and ^1H NMR Data for Compounds in Table I

Compound	IR cm^{-1} (selected bands)	^1H NMR δ (ppm)
II	3500, 3350 and 2960 (CH, CH_2 and CH_3), 2230 (CN), 1680 (C=O) and 1620 (C=N)	1.33 (t, 3H, CH_3), 4.2 (m, 3H, CH_2 and OH) and 7.2-7.66 (m, 10H, $2C_6H_5$)
III	3500-3350 and 3070 (OH), 2230 (CN) and 1620 (C=N)	7.2-8.3 (m, 15H, $3C_6H_5$)
VI (a)	3600-3350 (OH and NH), 1700-1680 (C=O) and 1620 (C=N)	
VII (a)	3500-2800 (NH), 2220 (CN) and 1620 (C=N)	
VIII (a)	3300, 3100 (NH), 1680 (C=O) and 1620 (C=N)	
IX	3300-2400 (NH and OH), 1720ester C=O) and 1620 (C=N)	1.3 (t, 3H, CH_3), 4.3 (q, 2H, CH_2), 7.5-7.66 (m, 10H, $2C_6H_5$)
XIa (a)	3400-2700 (NH and OH), 2220 (CN) and 1650 (ring C=O)	
XIb	3500, 3050 (NH and OH), 2220 (CN), 1670 (ester C=O) and 1620 (C=N)	1.33 (t, 3H, CH_3), 4.4 (q, CH_2), and 7.3-8.2 (m, 5H,
XIc (a)	3050, 3000 (NH and OH), 2220 (CN), 1640 (C=O) and 1620 (C=N)	
XII	3090, 2970, 2910 (CH_3 and CH), 1650 (ring C=O)	2.05 (s, 3H, CH_3) and 6.4-7.7 (m, 11H, $2C_6H_5$ and NH)

(a) Insoluble in most commonly used ^1H nmr solvents.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Pye Unicam SP 1000 spectrophotometer. The ^1H nmr spectra were recorded on a Varian A-60 spectrometer in DMSO using TMS as an internal standard. Chemical shifts are expressed in δ units (ppm). Microanalytical data were performed by the Microanalytical Data Unite at Cairo University.

Reaction of I or X With Active Methylene Reagents.

To a solution of the appropriate active methylene reagent (0.01 mole) in dioxane (100 ml), finely divided sodium metal (0.23 g) was added. The reaction mixture was kept overnight at room temperature, then treated with 0.01 mole of either I or X. The reaction mixture was refluxed for eight hours. The solvent was then removed *in vacuo* and the remaining solid product was triturated with an ethanol/water mixture (1:2, 150 ml) and was acidified with hydrochloric acid. The resulting solid product was collected by filtration and crystallised from the proper solvent (*cf.* Tables I and II).

Reaction of II or III With Hydrazine Hydrate.

A mixture of either II or III (0.01 mole) and hydrazine hydrate (0.015 mole) was heated at 100° (bath temperature) for five hours, then triturated with ethanol, poured into cold water and acidified with hydrochloric acid. The resulting solid was collected by filtration and crystallised from a proper solvent.

Reaction of II With Phenylhydrazine.

A solution of II (0.01 mole) in ethanol (30 ml) was treated with phenylhydrazine (1 ml) and the reaction mixture was refluxed for three hours. The solid product obtained after concentration of this solution was collected by filtration and crystallised from the proper solvent.

Reaction of II With Ethoxycarbonyl Isothiocyanate.

To a suspension of ammonium thiocyanate (0.01 mole) in dry dioxane (30 ml), ethyl chloroformate (0.01 mole) was added. The reaction mixture was refluxed for five minutes, then treated with 0.01 mole of II. The reaction mixture was refluxed for five hours and poured over ice. The resulting solid product was collected by filtration, washed with water and crystallised.

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