Activated Nitriles in Heterocyclic Synthesis. A Novel Synthesis of Pyrazine Derivatives

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A novel synthesis of pyrazine derivatives from the reaction of α-tosyloximinonitriles with several active methylene enaminonitrile derivatives is reported. The reaction sequence is discussed.

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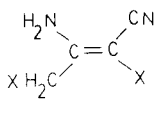
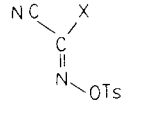
In the last few years our group was involved in a program directed for development of new efficient procedures for the syntheses of polyfunctionally substituted azoles, azines and azoloazines from simple, laboratory available intermediates [1,2]. During this phase of our work, we have reported several new syntheses of azole and azine derivatives utilizing the readily obtainable enaminonitrile derivatives Ia,b as starting components [3].

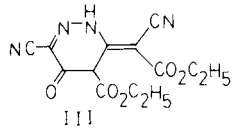
In conjunction with this work we report here a novel synthesis of pyrazines from the reaction of Ia,b and ethyl *O*-tosyloximinoglyoxalate (IIa) and *O*-tosyloximinomesoxalonitrile (IIb). Thus, it has been found that Ia reacts with IIa to yield a product of molecular formula $C_{13}H_{12}N_4O_5$. Two theoretically possible isomeric structures were considered (see structures III and IV, Chart 1). Structure III was readily eliminated based on the ^1H nmr spectrum of the product which revealed the absence of any resonance for pyrazine 4-H and revealed a pattern that can be reasonably interpreted in terms of structure IV. The formation of IV from the reaction of Ia and IIa is assumed to proceed *via* condensation at the active methylene group in Ia to yield the acyclic derivative V. Compound V readily underwent cyclization *via* ethanol elimination to yield the final isolable IV. Similar to the behaviour of Ia and IIa, compound IIb reacted with Ia to yield the pyrazine derivative VI. The pyrazine derivative VII could be obtained from the reaction of Ib and IIa under conditions similar to those utilized to effect condensation of Ia and IIa,b.



Ia, X=$CO_2C_2H_5$
b, X=CN



IIa, X=$CO_2C_2H_5$
b, X=CN



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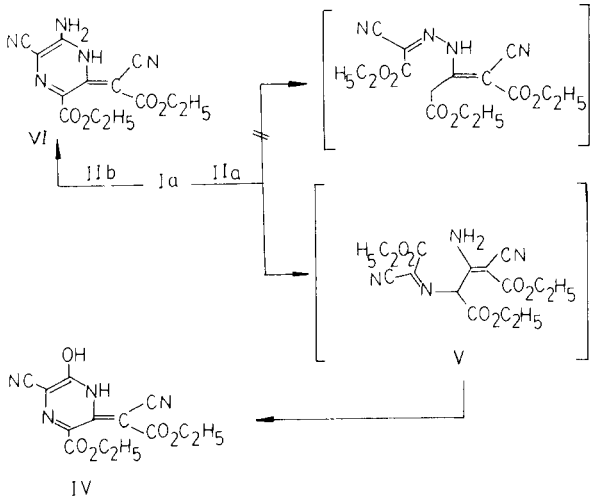
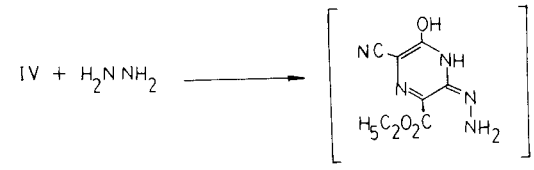
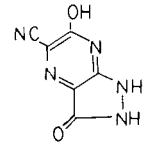


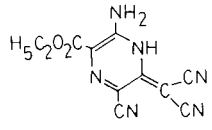
IV



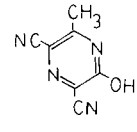
XI



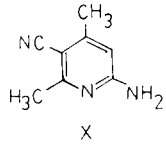
IX



VII



VIII



X

2-Aminocrotononitrile also reacted with IIa at 5° to yield the pyrazine derivative VIII. The formation of VIII

Table 1

Characterization Data of the Newly Synthesised Compounds

Compound	Yield %	Mp, °C (Solvent)	Molecular Formula	Analysis % Calcd./(Found) C	H	N
IV [a]	70	205 (ethanol)	$C_{13}H_{12}O_5N_4$	51.3 (51.1	3.9 3.8	18.4 18.2)
VI [b]	75	235 (ethanol)	$C_{13}H_{13}O_4N_5$	51.5 (51.2	4.3 4.1	23.1 22.9)
VII [a]	50	172 (ethanol)	$C_{11}H_8O_2N_6$	51.3 (51.3	3.1 3.1	32.4 32.2)
VIII [b]	60	168 (ethanol)	$C_7H_4ON_4$	52.5 (52.3	2.5 2.2	35.0 34.9)
IX [b]	80	>300	$C_6H_3O_2N_5$	40.7 (40.4	1.7 1.5	39.5 39.2)

[a] The compound is yellow in colour. [b] The compound is pale brown in colour.

Table 2

IR and ^1H NMR for the Newly Synthesised Compounds

Compound	IR (cm^{-1})	^1H NMR (ppm)
IV	1650 (ester CO), 2200 (CN), 2940 (CH_2), 3200, 3500 (NH, OH)	1.16 (m, 6H, $2CH_3$), 4.16 (m, 4H, $2CH_2$), 10.5 (s, 1H, OH), 12.0 (m, 1H, NH)
VI	1680, 1730 (ester CO), 2215 (CN), 2960 (CH_2CH_3), 3200 ~ 3500 (NH, NH_2)	1.16 (m, 6H, $2CH_3$), 4.16 (m, 4H, $2CH_2$)
VII	1725 (ester CO), 3200, 3400 (NH_2), 2225 (CN)	1.16 (m, 3H, CH_3), 4.16 (m, 2H, CH_2), 8.28 (m, 2H, NH_2), 10.8 (m, 1H, NH)
VIII	2220 (CN), 2850, 2950 (CH_3), 3300 (OH)	3.2 (m, 3H, CH_3), 6.1 (s, 1H, OH)
IX	1700 (amide CO), 2215 (CN), 3100 ~ 3200 (NH)	

is assumed to proceed *via* a sequence similar to that reported above. It is interesting to report here that when 2-aminocrotononitrile was treated with IIa at room temperature, the dimerization product X was the only isolable product [4].

Compound IV reacted with hydrazine hydrate to yield the pyrazolo[3,4-*b*]pyrazine derivative IX. The formation of IX in this reaction represents the first synthesis of this biologically interesting ring system from a pyrazine intermediate. Moreover, known synthetic approaches of this system from azole intermediates are few and limited in scope both by the difficulty of access to the required pyrazole intermediates and by the nature of reagents needed for the formation of the pyrazolo[3,4-*b*]pyrazine end products. The reaction of IV with hydrazine hydrate is assumed to proceed *via* ylidine group cleavage of IV to yield the hydrazine derivative XI. The latter then cyclizes readily into the final end product IX. The scope and limitation of this new synthesis is now under investigation.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded in potassium bromide on a Pye Unicam Sp 1100. The ^1H nmr spectra were measured in DMSO-d_6 on a Varian A-60 HZ using TMS as internal standard and chemical shifts are expressed as δ in ppm. Analytical data were obtained from the analytical data unit at Cairo University.

5-Cyano-6-hydroxy-3-ethoxycarbonyl-2-(ethoxycarbonylcyano)methylene-1*H*-pyrazine (IV).

A solution of Ia (0.1 mole) in acetonitrile (30 ml) was treated with ethyl *O*-tosyloximinoglycoxalate (IIa, 0.1 mole) and triethylamine (2 ml). The reaction mixture was left at room temperature for two days then acidified with concentrated hydrochloric acid (5 ml). The solid product which formed was collected by filtration and crystallized from the suitable solvent to give IV (see Tables 1 and 2).

6-Amino-3-carboxyethyl-5-cyano-2-(ethoxycarbonylcyano)methylene-1*H*-pyrazine (VI).

A solution of Ia (0.1 mole) in acetontrile (30 ml) was treated with *O*-tosyloximinomesoxalonitrile (IIb, 0.1 mole) and triethylamine (2 ml). Then the same procedure used for isolation of compound IV was followed. The solid product was crystallized from the suitable solvent and was identified as VI (see Tables 1 and 2).

6-Amino-3-cyano-2-dicyanomethylene-5-ethoxycarbonyl-1*H*-pyrazine (VII).

A mixture of Ib (0.1 mole) in acetonitrile (30 ml), IIa (0.1 mole) and triethylamine (1 ml) was left at room temperature for two days. The reaction mixture was then acidified and the solid product which formed was filtered off. The solid was recrystallized from the suitable solvent and identified as VII (see Tables 1 and 2).

3,5-Dicyano-2-hydroxy-6-methylpyrazine (VIII).

To a solution of 2-aminocrotononitrile (0.1 mole) in acetonitrile (30 ml) was added IIa (0.1 mole) and triethylamine (2 ml). The reaction mixture was left for two days at 5°, acidified with concentrated hydrochloric acid and the solid product which formed was collected by filtration. The pro-

duct was recrystallized from the suitable solvent and identified as VIII (see Tables 1 and 2).

5-Cyano-6-hydroxy-3-oxo-1,2-dihydropyrazolo[3,4-*b*]pyrazine (IX).

A solution of IV (0.1 mole) in ethanol (20 ml) was treated with hydrazine hydrate (1 ml, 99%) and the reaction mixture was refluxed for two hours. The solvent was then evaporated *in vacuo* and the remaining product was triturated with ethanol. The solid product which formed was collected by filtration, crystallized from the suitable solvent and identified as IX (see Tables 1 and 2).

REFERENCES AND NOTES

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