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Studies on 5-Aminoisoxazole Derivatives: Synthesis of Some New Fused Isoxazoles

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Several new fused isoxazole derivatives could be obtained utilising 5-amino-4-ethoxycarbonyl-3-ethoxycarbonylmethyl and 5-amino-4-cyano-3-trichloromethyl-isoxazoles as starting components.

(Keywords: Isoxazolo[2,3—a]pyridines; Isoxazolo[4,3—c]pyridines; Pyrazolo[3,4—c]isoxazoles; Trichloromethyl-amino-methylenemalononitrile)

Untersuchungen an 5-Aminoisoxazol-Derivaten: Synthese einiger neuer kondensierter Isoxazole

Es konnten einige neue Isoxazolderivate über 5-Amino-4-ethoxycarbonyl-3-ethoxycarbonylmethyl- und 5-Amino-4-cyano-3-trichlormethyl-isoxazol als Ausgangsverbindungen erhalten werden.

Introduction

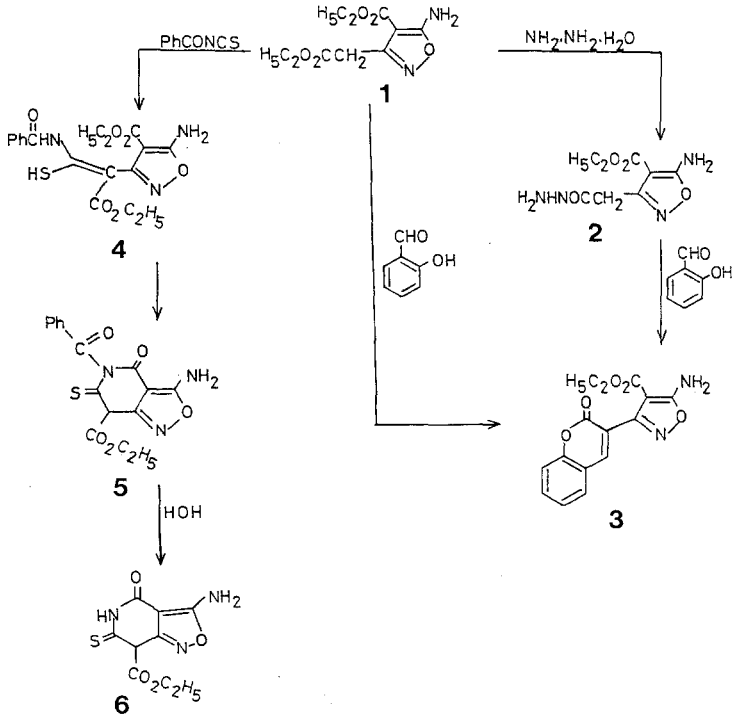
Aminoazoles are synthetically useful compounds and their utilities in heterocyclic synthesis have received considerable attention[1—4]. In spite of the enormous literature reported for this class of compounds, relatively few studies have been conducted on the chemistry of 5-aminoisoxazoles[5,6]. The lack of interest in the synthetic potentialities of these compounds is perhaps due to the reported ready hydrolysis of known 5-aminoisoxazole derivatives into the corresponding 2-isoxazolin-5-ones under mild conditions[6]. Recently, however, and as a part of our program directed for developments for new syntheses procedures of fused azoles, we have reported on the chemistry of 5-

amino-3-phenylisoxazole[6]. In the present paper we report on the synthetic potentialities of 5-amino-4-ethoxycarbonyl-3-ethoxycarbonylmethylisoxazole, recently synthesised by us[7] and on the synthesis and chemistry of 5-amino-4-cyano-3-trichloromethylisoxazole.

Results and Discussion

5-Amino-4-ethoxycarbonyl-3-ethoxycarbonylmethylisoxazole (**1**) reacted with hydrazine hydrate to yield a hydrazide that can result from reaction of hydrazine with either the ester group at C-4 or the ethoxycarbonylmethyl moiety at C-3. Structure **2** could be readily established for the reaction product based on its conversion into the coumarin-3-ylisoxazole derivative **3** on reaction with salicylaldehyde. The same coumarin derivative could be directly obtained from the reaction of **1** with salicylaldehyde under almost the same experimental conditions. Compound **1** also reacted with benzoylisothiocyanate to

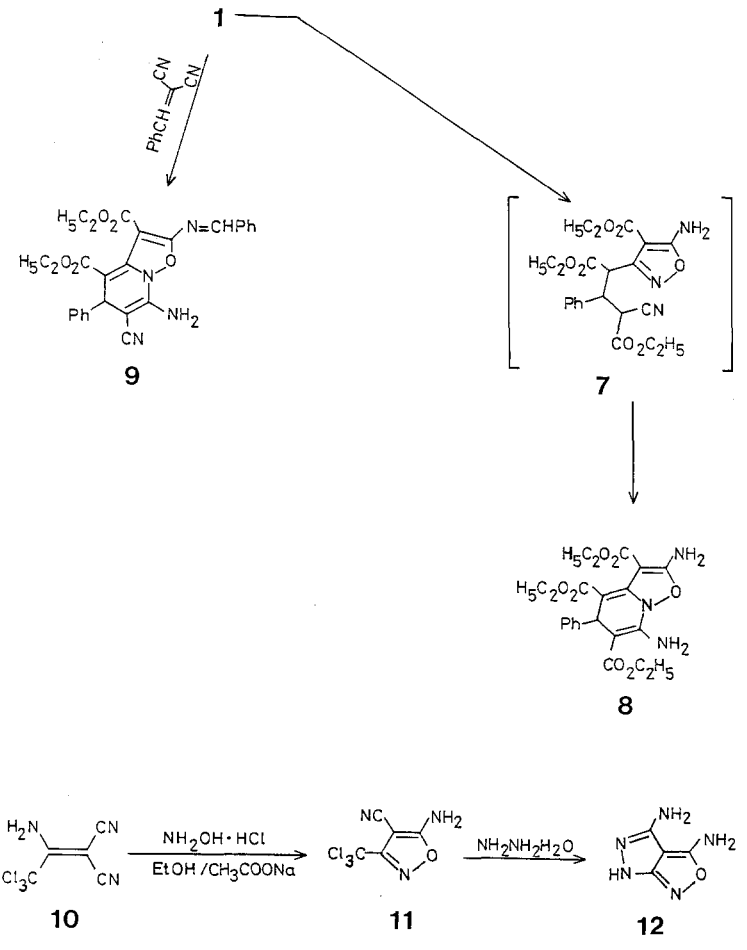
Scheme 1



yield a product of molecular formula $C_9H_9N_3O_4S$. Structure **6** was established for this compound based on ^{1}H-NMR which revealed the absence of methylene protons at $\delta\,3\sim5$ ppm and revealed the existence of a NH_2 singlet at 7.66 ppm. The formation of **6** in this reaction might be assumed to proceed via addition of benzoylisothiocyanate to yield the intermediate diadduct **4**, the latter cyclises under the reaction condition into **5**, which then decomposes into the finally isolated product **6**.

Compound **1** reacted with ethyl 2-cyanocinnamate to yield a 1 : 1 adduct. Several isomeric structures seemed possible for this adduct. The IR spectra revealed, however, the absence of a CN group absorption,

Scheme 2



thus excluding the possibility that the reaction product is an acyclic *Michael* adduct. Structure **8** was considered for the reaction product. Compound **8** is assumed to be formed via the formation of the intermediate *Michael* adduct **7**. The formation of **8** may be assumed to be a new approach for the synthesis of isoxazolo[2,3−a]pyridines.

In contrast to the behaviour of **1** toward ethyl 2-cyanocinnamate, it reacted with benzylidenemalononitrile to yield the isoxazole derivative **9**. This derivative is assumed to be formed via reaction of **1** with two moles of benzylidenemalononitrile followed by cyclization and loss of malononitrile to yield **9**. Similar phenomena has been previously observed by us[8]. Also formation of *Schiff* bases on reacting 5-aminoisoxazoles with ylidenemalononitrile has been recently reported[6].

3-Amino-4-trichloro-2-cyanocrotonate (**10**) reacted with hydroxylamine to yield the isoxazole derivative **11**. This derivative is formed via addition of the hydroxylamine to the α,β-unsaturated linkage and cyclization. Compound **11** reacted with hydrazine hydrate to yield the pyrazolo[3,4−c]isoxazole derivative **12**. Compound **12** is assumed to be formed via displacement of the trichloromethyl function in **10** by hydrazine and cyclization of the resulting hydrazino isoxazole derivative into the finally isolated **12**. The ready elimination of a trichloromethyl moiety in heterocyclic derivatives by hydrazines has been recently observed by us[2,9–12] and utilised for the synthesis of a variety of otherwise difficult obtainable polyfunctionally substituted azoles and fused azole derivatives from readily obtainable azole intermediates having a trichloromethyl substituent. The mechanisms of these displacements have been previously commented by *Elnagdi* et al.[11] and also by *Gravelinko* and *Miller*[13].

Experimental

All melting points are uncorrected. IR spectra (cm^{-1}) were recorded (KBr) on a Pye Unicam Sp-1000. ^{1}H-NMR Spectra were obtained on an EM-360 MHz spectrometer in *DMSO* using *TMS* as internal standard and chemical shifts are expressed as δ/ppm. Analytical data were performed by the microanalytical unit, Cairo University.

5-Amino-3-carboxyhydrazinomethyl-4-ethoxycarbonylisoxazole (**2**)

A solution of **1** (2.42 g, 0.01 mol) in ethanol (20 ml) is treated with hydrazine hydrate (0.6 ml, 0.01 mol). The reaction mixture is refluxed for 5 h and then left to cool. The solid product so formed is collected by filtration and crystallised from *Et*OH; m. p. 214–216°C (colourless); yield: 85%.

IR: 3 480, 3 320, 3 320 (NH_2 and NH), 1 700, 1 680 (2 CO), 1 590 (C=N and NH_2).

^{1}H-NMR: 1.31 (t, 3 H, CH_3), 3.44 (s, 2 H, CH_2), 4.22 (q, 2 H, CH_2), 7.72 (s, 2 H, NH_2), 9.15 (s, 1 H, NH), 11.21 (s, 2 H, NH_2).

$C_8H_{12}N_4O_4$ (228). Calcd. C 42.1 H 5.3 N 24.6.
Found. C 41.9 H 5.6 N 24.3.

5-Amino-3-(coumarin-3-yl)-4-ethoxycarbonylisoxazole (**3**)

A solution of either **1** or **2** (0.01 mol) in ethanol (20 ml) is treated with salicylaldehyde (0.01 mol). The reaction mixture is refluxed for 5 h, then evaporated in vacuo. The remaining product is triturated with water and the resulting solid product is collected by filtration and crystallised from *Et*OH; m. p. 184 °C (colourless); yield: 90%.

IR: 3 500, 3 300 (NH_2), 1 720, 1 690 (2 CO), 1 650 (C=C), 1 610 (C=N and δ NH_2).

^{1}H-NMR: 1.11 (t, 3 H, CH_3), 4.18 (q, 2 H, CH_2), 7.42–8.00 (m, 5 H, C_6H_4 and CH), 8.32 (s, 2 H, NH_2).

$C_{15}H_{12}N_2O_5$ (300). Calcd. C 60.0 H 4.0 N 9.3.
Found. C 59.8 H 4.2 N 9.6.

1-Amino-4-ethoxycarbonyl-5-thioxo-7-oxo-4,5,6,7-tetrahydroisoxaxolo[4,3—c]pyridine (**6**)

A solution of **1** (0.01 mol) in dry dioxan (20 ml) was added to a solution of benzoylisothiocyanate (0.01 mol). The reaction mixture was refluxed for 6 h and the solvent was then evaporated in vacuo. The remaining solid product was then triturated with water, collected by filtration and crystallised from *Et*OH-*DMF*; m. p. > 270 °C (brown); yield 65%.

IR: 3 500 (NH_2 and NH), 1 700–1 650 (2 CO).

^{1}H-NMR: 1.18 (t, 3 H, CH_3), 4.20 (q, 2 H, CH_2), 7.66 (s, br, 2 H, NH_2), 10.22 (s, br, 1 H, NH).

$C_9H_9N_3O_4S$ (255). Calcd. C 42.4 H 3.5 N 16.5.
Found. C 42.2 H 3.2 N 16.8.

2,8-Diamino-3,5,7-triethoxycarbonyl-6-phenylisoxazolo[2,3—a]pyridine (**8**)

A solution of **1** (0.01 mol) in ethanol (20 ml) is treated with ethyl-2-cyanocinnamate (0.01 mol) and few drops of piperidine. The reaction mixture is refluxed for 3 h. The solvent is then evaporated and the remaining product is triturated with water, collected by filtration and crystallised from *DMF*; m. p. 230–232 °C (colourless); yield 80%.

IR: 3 500, 3 220 (NH_2), 1 750, 1 700 (3 CO).

^{1}H-NMR: 1.28–1.66 (t, 9 H, 3 CH_3), 3.55 (s, br, 2 H, NH_2), 4.12–4.32 (q, 6 H, 3 CH_2), 4.42 (s, 1 H, pyridine CH), 7.32 (m, 5 H, C_6H_5), 8.68 (s, 2 H, NH_2).

$C_{22}H_{25}N_3O_7$ (443). Calcd. C 59.6 H 5.6 N 9.5.
Found. C 59.6 H 5.4 N 9.2.

8-Amino-7-cyano-3,5-diethoxycarbonyl-6-phenyl-2-phenylazome-thinisoxazolo-[2,3—a]pyridine (**9**)

A solution of **1** (0.01 mol) in ethanol (20 ml) is treated with benzylidenemalononitrile (0.01 mol) and few drops of piperidine. The reaction

mixture is refluxed for 3 h. The solvent is then evaporated, the remaining product is triturated with water, collected by filtration and crystallised from *Et*OH-*DMF*; m. p. 246–248 °C (green); yield 72%.

IR: 3 450, 3 200 (NH_2), 2 200 (CN), 1 690 (2 CO), 1 650–1 600 (C=C, C=N and δNH_2).

^{1}H-NMR: 1.11 (t, 6 H, 2 CH_3), 4.12 (q, 4 H, 2 CH_2), 4.48 (s, 1 H, pyridine CH), 7.42 (m, NH, 2 C_6H_5 and CH), 10.22 (s, 2 H, NH_2), 6.96 (s, 2 H, NH_2).

$C_{27}H_{24}N_4O_5$ (484). Calcd. C 66.9 H 5.0 N 11.6.
Found. C 67.2 H 5.2 N 11.3.

5-Amino-4-cyano-3-trichloromethylisoxazole (**11**)

A solution of **10** (0.01 mol) in ethanol (20 mol) is treated with hydroxylamine hydrochloride (0.01 mol) and sodium acetate (3.0 gm) and then refluxed for 4 h, after which it is poured into water (50 ml). The solid product so formed is collected by filtration and crystallised from *Et*OH; m.p. 122 °C (colourless); yield 65%.

IR: 3 460, 3 400, 3 380, 3 360 (NH_2), 2 220 (CN), 1 640 (C=C), 1 610 (C=N and δNH_2).

$C_5H_2N_3OCl_3$ (226.5). Calcd. C 26.5 H 0.9 N 18.5.
Found. C 26.7 H 1.2 N 18.4.

3,4-Diamino-pyrazolo[3,4—c]isoxazole (**12**)

A solution of **11** (0.01 mol) in ethanol (20 ml) is treated with hydrazine hydrate (0.01 mol). The reaction mixture is refluxed for 3 h. The solvent is then evaporated, the remaining product is triturated with water and the resulting solid product is collected by filtration and crystallised from *Et*OH; m. p. 190 °C (yellow); yield 70%. IR: 3 500–3 000 (chelated NH_2 and NH), 1 610 (δNH_2 and NH).

$C_4H_5N_5O$ (139). Calcd. C 34.5 H 3.6 N 50.0.
Found. C 34.6 H 3.8 N 50.4.

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