Activated Nitriles in Heterocyclic Synthesis: A Novel Synthesis of Tetrazole Derivatives

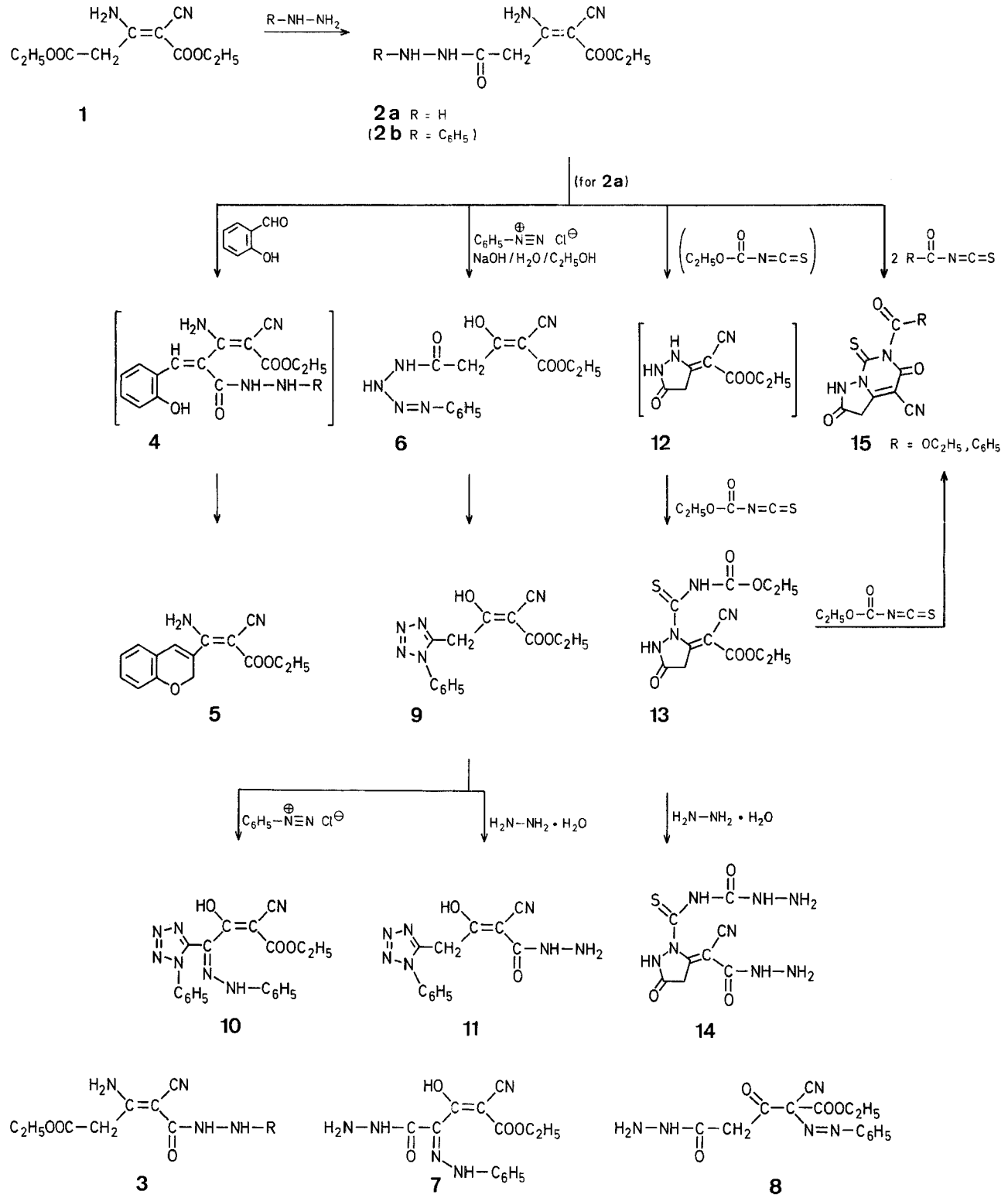
Sherif Mahmoud FAHMY*, Rafat Milad MOHAREB

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

As part of our investigations on the use of 3-amino-2-alkenenitriles (enamino nitriles) in heterocyclic synthesis[1,2], we reported that diethyl 3-amino-2-cyano-2-pentenedioate[3] **(1)** reacts with hydrazine hydrate to give a monohydrazide to which the structure **2a** was assigned[4]. However, critical re-evaluation of the data used for this assignment showed that structure **3** could not be excluded with certainty so that further study of the chemistry of the monohydrazide was necessary to establish its structure unambiguously. We present here a satisfactory proof of the structure of compound **2a** as well as some of its chemical properties. The work has resulted in the synthesis of several new, otherwise difficultly accessible, heterocyclic derivatives of potential biological and synthetic interest.

Ethyl 3-amino-2-cyano-5-hydrazino-5-oxo-2-pentenoate (hydrazide **2a**) reacts with an equimolecular amount of salicylaldehyde to give a coumarin derivative which was found to be identical with ethyl 3-amino-3-(3-coumarinyl)-2-cyanopropenoate **(5)** prepared according to Ref.[5]. This results proves that hydrazine hydrate reacts with diester **1** to give the hydrazide ester **2a,** not the isomeric compound **3.**

Attempts to couple **2a** with benzenediazonium chloride in the presence of sodium acetate were unsuccessful. However, on conducting the reaction in the presence of excess ethanolic sodium hydroxide a deep red product was obtained. The three isomers **6, 7,** and **8** were considered as possible reaction product. Structure **7** was eliminated on the basis of ^{1}H-N.M.R. spectrometry which revealed a methylene signal at $\delta = 4.1$ ppm indicating that the reaction did not occur at the methylene group. Moreover, the phenylhydrazide **2b** failed to couple with benzenediazonium chloride under a variety of conditions indicating that the methylene group in the hydrazides is not reactive in the coupling reaction so that the possible formation of the isomer **8** can be excluded. Therefore, derivative **6** is proposed as the reaction product. Similar coupling reactions of hydrazides have previously been reported[6].



The acyltetrazene **6** undergoes cyclodehydration in boiling ethanol to give the tetrazole derivative **9** which couples readily with benzenediazonium chloride to afford the hydrazone **10**. Reaction of **9** with hydrazine hydrate gives the 2-alkenoic hydrazide **11**.

The reaction of compound **2a** with ethoxycarbonyl isothiocyanate depends on the reaction conditions. Thus, with an equimolecular amount of ethoxycarbonyl isothiocyanate the pyrazolidine derivative **13** is obtained, presumably via initial cyclocondensation of **2a** to give **12** and reaction of **12** with the isothiocyanate. On the other hand, when compound **2a** is treated with 2 equivalents of ethoxycarbonyl isothiocyanate or benzoyl isothiocyanate the pyrazolo[1,5-*c*]pyrimidine derivatives **15** ($R=OC_2H_5$) or **15** ($R=C_6H_5$), respectively, are obtained as the only isolable products.

All melting points are uncorrected. Analytical data were obtained from the Analytical Data Unit at Cairo University and from El-Nasar Pharmaceutical Chemical Company Analytical Data Unit. The I.R. spectra were obtained (KBr) on a Pye-Unicam SP-1000 Spectrophotometer. The ^{1}H-N.M.R. spectra were recorded on a Varian A-90 Spectrometer. Compounds **1** and **2a, b** were prepared according to Ref.[4,5] and afforded analytical and spectral data in agreement with their structures.

Ethyl 3-Amino-3-(3-coumarinyl)-2-cyanopropenoate (5):
2-Hydroxybenzaldehyde (1.22 g, 0.01 mol) and piperidine (0.2 ml) are added to a solution of ethyl 3-amino-2-cyano-5-hydrazino-5-oxo-2-pentenoate (**2a**; 2.12 g, 0.01 mol) in dimethylformamide (20 ml). The mixture is refluxed for 1 h, then allowed to cool. The solid product is isolated by suction and recrystallized from ethanol/dimethylformamide; yield: 1.3 g (52%); m.p. 244–245 °C, yellow (Ref.[5]; m.p. 245–246 °C).

$C_{15}H_{12}N_2O_4$	calc.	C 63.38	H 4.26	N 9.86
(284.3)	found	63.33	4.52	9.69

I.R. (KBr): ν=3420, 3300 (NH_2); 3050 (aromatic CH); 2980, 2960 (CH_2 and CH_3); 2210 (CN); 1710 (conjugated ester CO); 1685 (ring CO); 1630 cm^{-1} (NH_2 deformation).

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ=1.16 (t, 3H, CH_3); 3.22 (s, 1H, coumarin 4-H); 4.06 (q, 2H, CH_2); 7.2, 7.85 (m, 4H_{arom}); 8.8–9.0 ppm (br. m, 2H, NH_2).

Ethyl 2-Cyano-3-hydroxy-5-oxo-5-(1-phenyltetrazen-4-yl)-2-pentenoate (6):
A solution of benzenediazonium chloride [prepared from aniline (0.93, 0.01 mol) and the appropriate quantity of hydrochloric acid and sodium nitrite] is added to a stirred solution of compound **2a** (2.12 g, 0.01 mol) in ethanol (50 ml) + aqueous 10% sodium hydroxide (20 ml). The mixture is left at room temperature for 15 min. The resultant solid is isolated by suction and recrystallized from ethanol; yield: 2.6 g (82%); m.p. 144–146 °C, deep red.

$C_{14}H_{15}N_5O_4$	calc.	C 52.99	H 4.77	N 22.07
(317.3)	found	52.67	4.44	22.32

I.R. (KBr): ν=3450–3320 (NH, OH); 3000, 2980, 2960 (CH, CH_2, CH_3); 2220 (CN); 1700, 1690 (ester and amide CO); 1620 cm^{-1} (C=C).

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ=1.16 (t, 3H, CH_3); 3.15 (s, 2H, CH_2); 4.1 (q, 2H, CH_2); 6.9 (br, 2H, NH, OH); 7.2–7.4 (s, 5H, C_6H_5); 11.5 ppm (br, 1H, NH).

Ethyl 2-Cyano-3-hydroxy-4-(1-phenyltetrazol-5-yl)-2-butenoate (9):
A solution of compound **6** (3.17 g, 0.01 mol) in ethanol (30 ml) is refluxed for 30 min and then evaporated in vacuo. The remaining product is triturated with water (20 ml). The resultant solid is isolated by suction and recrystallized from ethanol; yield: 1.89 g (80%); m.p. 275–277 °C, deep red.

$C_{14}H_{13}N_5O_3$	calc.	C 56.18	H 4.38	N 23.40
(299.3)	found	56.35	4.63	23.51

I.R. (KBr): ν=3400, 3320 (NH, OH); 2980, 2960 (CH_2, CH_3); 2220 (CN); 1690 (ester CO); 1640 cm^{-1} (C=C).

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ=1.16 (t, 3H, CH_3); 3.5 (br, 3H, CH_2, OH); 4.16 (q, 2H, CH_2); 7.2–7.7 ppm (m, 5H, C_6H_5).

Ethyl 2-Cyano-3-hydroxy-4-phenylhydrazono-5-(1-phenyltetrazol-5-yl)-2-butenoate (10):
A solution of benzenediazonium chloride [prepared from aniline (0.93 g, 0.01 mol) and the appropriate quantity of hydrochloric acid and sodium nitrite] is added to a stirred solution of compound **9** (2.99 g, 0.01 mol) in ethanol (70 ml) containing anhydrous sodium acetate (5.0 g). The mixture is stirred at room temperature for 30 min. The resultant precipitate is isolated by suction and recrystallized from ethanol/dioxan; yield: 3.5 g (87%); m.p. 159–160 °C, brown.

$C_{20}H_{19}N_7O_3$	calc.	C 59.25	H 4.69	N 24.19
(405.4)	found	58.95	4.52	23.97

I.R. (KBr): ν=3420–3300 (NH, OH); 3000, 2960 (CH_2, CH_3); 2220 (CN); 1690 (ester CO); 1630 cm^{-1} (C=C).

2-Cyano-3-hydroxy-4-(1-phenyltetrazol-5-yl)-2-butenoic Acid Hydrazide (11):
To a solution of compound **9** (5.6 g, 0.02 mol) in ethanol (50 ml) an equivalent amount of hydrazine hydrate (1.2 ml, 0.02 mol) is added. The mixture is refluxed on a boiling water bath for 30 min. The solid product is isolated by suction, washed several times with water, and recrystallised from ethanol; yield 2.2 g (78%); m.p. 261–262 °C, deep violet.

$C_{12}H_{11}N_7O_2$	calc.	C 50.52	H 3.89	N 34.37
(285.3)	found	50.43	3.99	34.54

I.R. (KBr): ν=3450, 3400–3200 (NH, OH); 2980 (CH, CH_2); 2220 (CN); 1650 cm^{-1} (CO).

^{1}H-N.M.R. (DMSO-d_6/TMS_{int}): δ=3.12 (br, 2H, NH_2); 4.5 (s, 2H, CH_2); 6.8 (br, 1H, OH); 7.2–8.0 ppm (m, 5H, C_6H_5).

3-[Cyano(ethoxycarbonyl)-methylene]-1-ethoxycarbonylaminothiocarbonyl-5-oxopyrazolidine (13):
To a solution of ethoxycarbonyl isothiocyanate [prepared from ammonium isothiocyanate (0.62 g, 0.01 mol) and ethyl carbonochloridate (1.07 g, 0.01 mol) in acetone (30 ml)] compound **2a** (2.12 g, 0.01 mol) is added. The mixture is refluxed for 3 h and then evaporated in vacuo. The remaining product is triturated with water (20 ml) and the resultant solid product is isolated by suction and recrystallized from dioxan; yield: 2.04 g (63%); m.p. 165–166 °C, colorless.

$C_{12}H_{14}N_4O_5S$	calc.	C 44.17	H 4.29	N 17.17
(326.3)	found	44.19	4.35	17.19

I.R. (KBr): ν=3270–3200 (NH); 2220 (CN); 1725, 1690 cm^{-1} (ester and ring CO).

3-[Cyano(hydrazinocarbonyl)-methylene]-1-ethoxycarbonylaminothiocarbonyl-5-oxopyrazolidine (14):
Hydrazine hydrate (0.5 ml, 0.01 mol) is added dropwise to a stirred solution of compound **13** (1.65 g, 0.005 mol) in ethanol (20 ml). The mixture is heated on a boiling water bath for 40 min, and then allowed to cool. The solid product formed on standing is isolated by suction and recrystallized from ethanol; yield: 1.23 g (83%); m.p. 259–260 °C, colorless.

$C_8H_{10}N_8O_3S$	calc.	C 32.21	H 3.35	N 37.58
(298.2)	found	32.00	3.67	37.88

I.R. (KBr): ν=3500–2500 (NH); 2220 (CN); 1660–1640 cm^{-1} (CO).

6-Ethoxycarbonyl- or 6-Benzoyl-2,5-dioxo-7-thioxo-1,2,3,5,6,7-hexahydropyrazolo[1,5-*c*]pyrimidine (15, R = OC_2H_5 or C_6H_5):
A solution of ethoxycarbonyl or benzoyl isothiocyanate is prepared from ammonium thiocyanate (0.761 g, 0.01 mol) and ethyl carbonochloridate (1.086 g, 0.01 mol) or benzoyl chloride (1.406 g, 0.01 mol) in acetone (50 ml). Compound **2a** (1.06 g, 0.005 mol) is added to this solution, the mixture is refluxed for 3 h, and then evaporated in vacuo. The remaining product is washed several times with ethanol/water mixture. It is isolated by suction and recrystallized from ethanol or dioxan.

15, R = OC_2H_5; yield: 1.95 g (74%); m.p. 189–190 °C, colorless (ethanol).

$C_{10}H_8N_4O_4S$	calc.	C 42.86	H 2.88	N 19.99
(280.3)	found	42.71	2.93	19.88

I.R. (KBr): ν=3380–3300 (NH); 2200 (CN); 1690–1610 cm^{-1} (CO).

15, R = C_6H_5; yield: 1.52 g (53%); m.p. 240–241 °C, colorless (dioxan).

$C_{14}H_8N_4O_3S$	calc.	C 53.84	H 2.58	N 17.94
(312.3)	found	54.13	2.81	18.22

I.R. (KBr): ν=3420–3300 (NH); 2200 (CN); 1680–1670 (benzoyl and ester CO); 1620 cm^{-1} (C=C).

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* Address for correspondence.

1 M. H. Elnagdi, S. M. Fahmy, M. R. H. Elmoghayer, M. A. M. Ilias, *Z. Naturforsch.* [b] **30**, 778 (1975).
2 M. H. Elnagdi, M. R. H. Elmoghayer, D. H. Fleita, E. M. Hafez, S. M. Fahmy, *J. Org. Chem.* **41**, 3781 (1976).
3 H. Junek, F. Frosch, *Z. Naturforsch.* [b] **26**, 1124 (1971).
4 S. M. Fahmy, N. Abed, R. M. Mohareb, *Synthesis* **1982**, 490.
5 H. Yasuda, H. Midorikawa, *Bull. Chem. Soc. Jpn.* **39**, 1754 (1966).
6 O. Dimroth, G. De Montmollin, *Ber. Dtsch. Chem. Ges.* **43**, 2904 (1910).

F. Babudri, L. Di Nunno, S. Florio, *Synthesis* **1983** (3), 230–231:

The title compounds **5** and **7** should be named (*Z*)-2-alkylidene-4-methyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines; compound **10** as 11-methyl-3-(2-methylaminophenylthio)-2-oxo-4,5-diphenyl-2,5-dihydro-11*H*-oxepino[3,2-*b*][1,4]benzothiazine.

Y. Kurasawa, Y. Moritaki, A. Takada, *Synthesis* **1983** (3), 238–240:

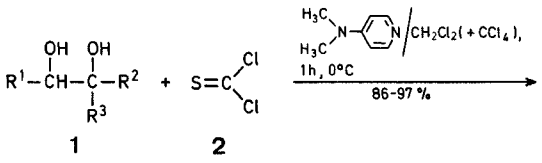
The title compounds **6** and **7** should be named 3-(1-ethoxyalkylidenehydrazinocarbonylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines and 3-(1,3,4-oxadiazol-2-ylmethylene)-2-oxo-1,2,3,4-tetrahydroquinoxalines, respectively.

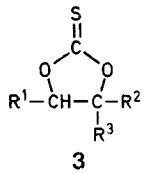
Abstract **6589**, *Synthesis* **1983** (3), 247:

The title should be *N*-(1-Aroyloxyalkyl)-pyridinium and *P*-(1-Aroyloxyalkyl)-phosphonium Salts.

Abstract **6593**, *Synthesis* **1983** (4), 335:

The formula scheme **1** + **2** ⟶ **3** should be:



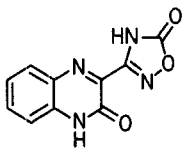


Y. Otsuji, S. Nakanishi, N. Ohmura, K. Mizuno, *Synthesis* **1983** (5), 390:

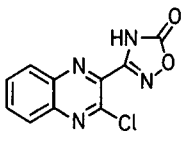
The substituents for compound **2g** (Table) should be R=H, X=H, n=1.

Y. Kurasawa, M. Ichikawa, A. Sakakura, A. Takada, *Synthesis* **1983** (5), 399–400:

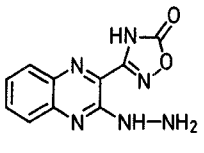
The structures of products **4, 8, 9,** and **10** given have since been found to be erroneous, the corrected structures are given below. A revision will be published in *Chem. Pharm. Bull.* in 1984.



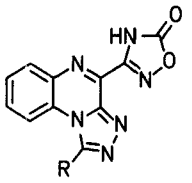
4



8



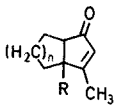
9



10a R = H
b R = CH_3

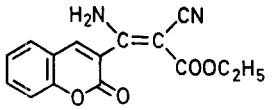
C. Santelli-Rouvier, M. Santelli, *Synthesis* **1983** (6), 429–442:

The structure of the third product in Table 4 (p. 435) should be:



S. M. Fahmy, R. M. Mohareb, *Synthesis* **1983** (6), 478–480:

The structure of product **5** should be:



L. Jacob, M. Julia, B. Pfeiffer, C. Rolando, *Synthesis* **1983** (6), 451–452:

The first three entries in Table 1 (p. 451) should be as follows:

Table 1. Demethylation of Mixed Alkyl Methyl Phosphates **(1, 3, 4)** and of Dimethyl Heptanephosphonate **(5)** using Dimethyl Sulfide (2.5 equiv) and Methanesulfonic Acid (10 equiv)

Substrate	Product	Reaction conditions		Yield[a] [%]	m.p. [°C][b] (solvent)	Molecular formula[c] or m.p. [°C] reported
		Scale [mmol]	Time [h]			
1a $n\text{-}C_6H_{13}\text{–O–P(O)(OCH}_3\text{)(OCH}_3\text{)}$	**2a** · $H_2N\text{–}C_6H_5$	10	22	82 (93)	133–134° (ethanol)	$C_{12}H_{22}NO_4P$ (275.3)
1b $n\text{-}C_8H_{17}\text{–O–P(O)(OCH}_3\text{)(OCH}_3\text{)}$	**2b** · $H_2N\text{–}C_6H_5$	5	7	(88)	135–137° (acetone)	129–130[c,22] (ethanol)
		5	12	(93)		
		5	48	(98)		
		5	19	65		
		10	92	83		
		10	52[c]	83		
1c $n\text{-}C_6H_{13}\text{–CH(CH}_3\text{)–O–P(O)(OCH}_3\text{)(OCH}_3\text{)}$	**2c** · $H_2N\text{–}C_6H_5$	5	19	68	154° (ethanol)	$C_{14}H_{26}NO_4P$ (303.3)
		10	92	79		