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Activated Nitriles in Heterocyclic Synthesis: Novel Syntheses of 3H-1,2,4-Triazolo-[1,5-a]pyridine Derivatives

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ABSTRACT

A new route for the synthesis of 3H-1,2,4-triazolo[1,5-a]pyridines **7a–j**, **12a,b**, *and* **17a,b** *utilizing the reaction of the hydrazones of cyanoethanoic acid hydrazide* **3a,b** *with ylidene malononitriles* **2a–e**, *malononitrile, and 3-aminocrotononitrile is described.*

Triazolopyridines are interesting compounds due to their pronounced biological activity, as they can be used as antidepressants [1,2]; however, their synthetic approaches are rather limited [3–5]. In continuation of our previous work concerning the use of α,β-unsaturated nitriles in heterocyclic synthesis [6–11], we report here a facile and efficient route for the synthesis of 3H-1,2,4-triazolo[1,5-a]pyridine derivatives utilizing cyanoethanoic acid hydrazide (1) and ylidene malononitrile (2) as readily obtainable starting materials. Thus, aromatic aldehydes condense with 1 to yield the Schiff's bases **3a,b** [12]. The latter compounds undergo reaction with the cinnamonitriles **2a–c** in pyridine under reflux to afford the 3H-1,2,4-triazolo[1,5-a]pyridine dicarbonitriles **7a–f** in moderate to good yields (Scheme 1).

The structures of compounds **7a–f** were confirmed on the basis of their elemental analyses and spectral data. For example, the IR spectrum of compound **7a** revealed an absorption band at 3340 cm^{-1} (NH) 2222, 2220 (CN), 1680 cm^{-1} (C=O), and at 1640 cm^{-1} (C=N). ^1H NMR spectroscopy revealed the NH signal at δ 10.82 besides the aromatic protons at δ 7.8–7.3 (Table 2). Furthermore, the mass spectrum of compound **7a** revealed a molecular ion peak m/z 337 (M^+), indicating that the isolated product is **7** and not its tetrahydro derivative **6**.

The formation of compounds **7a–c** is assumed to take place via initial Michael addition of the methylene group in **3** to the activated double bond in **2** to form the acyclic nonisolable intermediates **4** which cyclize into the pyridine derivatives **5**. The latter undergo further cyclization into the tetrahydro-1,2,4-triazolo[1,5-a]pyridines **6** which, in turn, undergo auto-oxidation under the experimental conditions to afford the final isolable products **7a–f** (Scheme 1). Similar cyclizations have been recorded in the literature [13].

Similarly, compounds **3a,b** reacted with the alkylidene-malononitriles **2d,e**, generated in situ from the reaction of malononitrile with formaldehyde or with acetaldehyde, to afford the 1,2,4-triazolo[1,5-a]pyridines **7g–j**.

An alternative route to the 1,2,4-triazolo[1,5-a]pyridines **7** is to react compounds **3a,b** with malononitrile (**8**) and then to subject them to subsequent treatment with aldehydes; however, it was found that, when compounds **3a,b** were allowed to react with malononitrile in dioxane under reflux, they afforded directly the 3H-1,2,4-triazolo[1,5-a]pyridine derivatives **12a,b**. Formation of compounds **12a,b** is illustrated in Scheme 2.

Also, compounds **3a,b** reacted with 3-aminocrotononitrile (**13**) under the same experimental

Dedicated to Prof. Shigreu Oae on the occasion of his seventy-fifth birthday.

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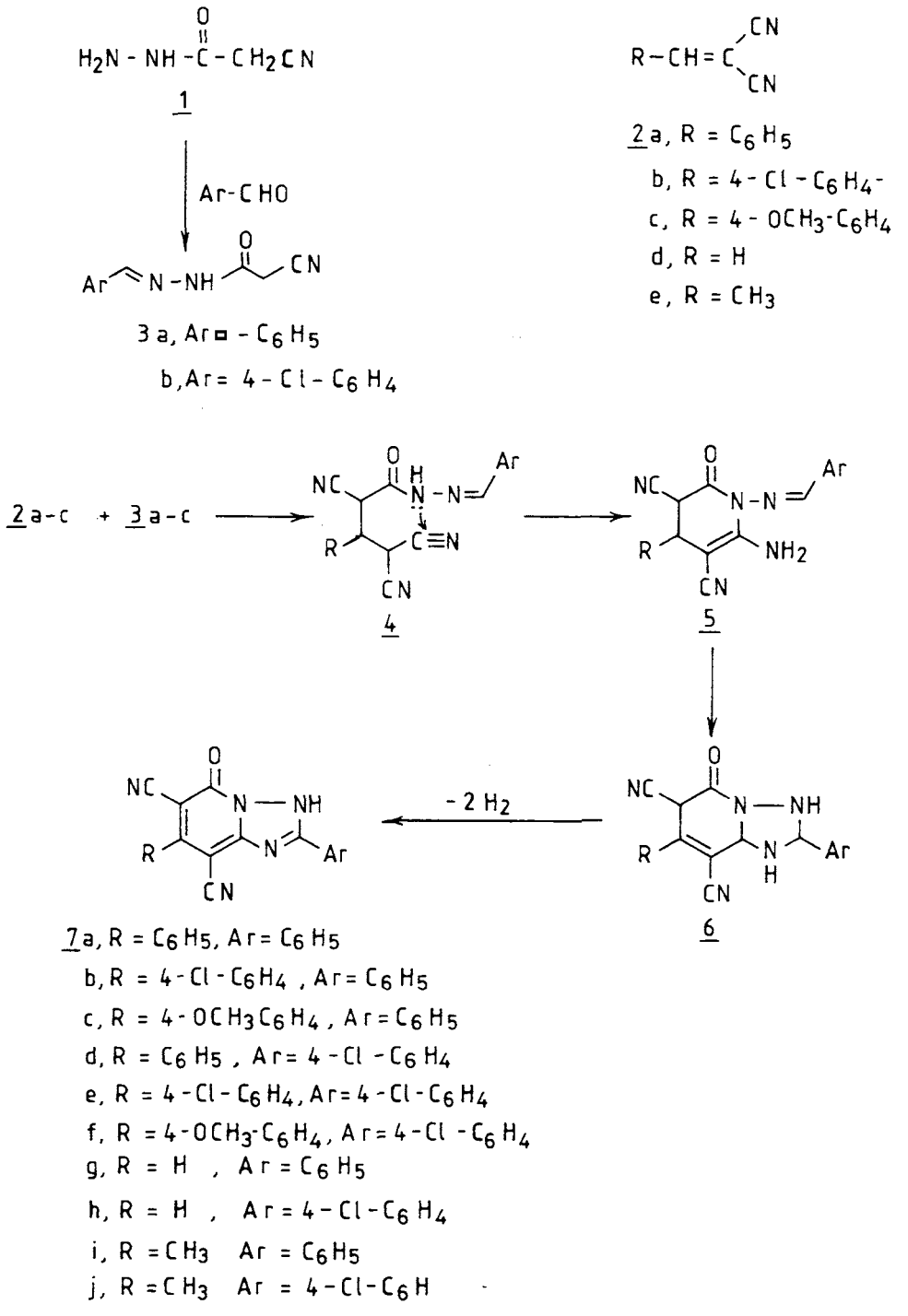
SCHEME 1



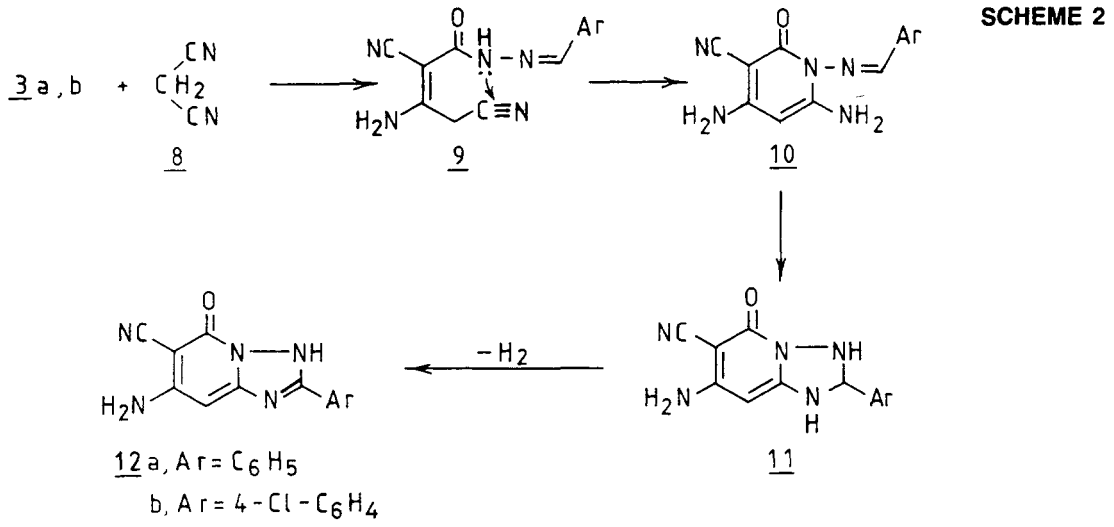
conditions to afford the triazolopyridine derivatives **17a,b**.

The formation of compounds **17a,b** is assumed to take place by initial condensation of **3** with **13** via loss of ammonia to afford the nonisolable intermediate **14** that cyclizes into **15**. The latter compounds undergo further cyclization under the reaction conditions to afford compounds **16** that then aromatize to yield the final isolable products **17a,b** (Scheme 3). Thus, the aforementioned reactions provide a simple route to 3H-1,2,4-triazolo[1,5-a]pyridine derivatives.

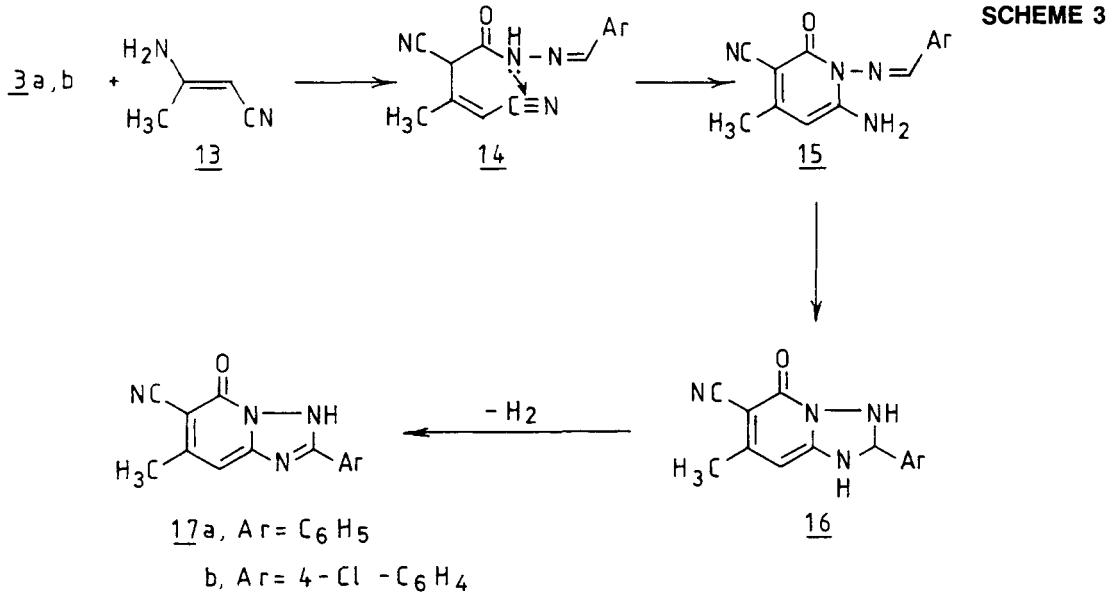
EXPERIMENTAL

Melting points were measured on a Gallen-Kamp melting point apparatus and are uncorrected. IR

SCHEME 2



SCHEME 3



spectra were taken as KBr discs on a Pye-Unicam Sp 1100 spectrometer. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) instrument for solutions in $CDCl_3$ or DMSO-d6, with TMS as an internal standard. Mass spectra were obtained on a GCMS-QP 1000 Ex mass spectrometer with ionization potential of 70 eV. Microanalyses were performed at the Microanalytical Center of Cairo University.

Aldehyde cyanoacetylhydrazones **3a,b**. To a solution of **1** (9.9 g, 0.01 mol) in ethanol (100 mL) was added either benzaldehyde (10.6 g, 0.1 mol) or *p*-chlorobenzaldehyde (14.15 g, 0.1 mol) followed by a catalytic amount of piperidine. The reaction mixture was stirred at room temperature for 1 hour. The solid products, so formed, were collected by filtration, washed with ethanol, and then crystallized from the appropriate solvent. Compound **3a**, colorless crystals from ethanol (yield 70%), mp 180°C. Compound **3b**, yellowish crystals from dioxane (yield 60%), mp 205°C.

2,6-Diaryl-4-oxo-3H-1,2,4-triazolo[1,5-a]pyridine-5,7-dicarbonitriles **7a–f**. *General Procedure.* A solution of **3a** or **3b** (0.01 mol) in pyridine (20 mL) was treated with the arylidenemalononitriles **2a–c** (0.01 mol). The reaction mixture in each case was heated under reflux for 8 hours, then left to cool. The solvent was removed under reduced pressure and the residue was poured into ice-water, acidified by concd HCl. The formed solid product in each case was collected by filtration, washed with water,

TABLE 1 Physical and Analytical Data of the Prepared Compounds

Compound No.	Mp (°C)	Yield (%)	Crystal Solvent	Formula (MW)	Found Calcd	Analysis % C	H	N
7a	205–207	45	ethanol	$C_{20}H_{11}N_5O$ (337.34)		71.3 71.21	3.5 3.29	20.7 20.79
7b	215–216	54	iso-propanol	$C_{20}H_{10}N_5OCl$ (371.79)		64.9 64.61	2.6 2.71	18.5 18.84
7c	202	55	ethanol	$C_{21}H_{13}N_5O_2$ (367.37)		68.8 68.66	3.5 3.57	18.9 19.06
7d	192	53	dioxane	$C_{20}H_{10}N_5OCl$ (371.79)		64.5 64.61	2.9 2.71	19.0 18.84
7e	180	56	DMF	$C_{20}H_9N_5OCl_2$ (406.23)		59.4 59.13	2.5 2.23	17.3 17.24
7f	215–216	50	dioxane	$C_{21}H_{12}N_5O_2Cl$ (401.81)		62.8 62.77	3.0 3.01	17.6 17.43
7g	>300	46	DMF	$C_{14}H_7N_5O$ (261.24)		64.4 64.37	2.9 2.70	26.4 26.81
7h	>300	48	DMF	$C_{14}H_6N_5OCl$ (295.69)		57.0 56.87	2.1 2.04	23.7 23.69
7i	208	61	dioxane	$C_{15}H_9N_5O$ (275.27)		65.6 65.45	3.3 3.29	25.6 25.44
7j	237	60	dioxane	$C_{15}H_8N_5OCl$ (309.72)		58.1 58.17	2.8 2.60	22.7 22.61
12a	300	68	DMF	$C_{13}H_9N_5O$ (251.25)		62.0 62.15	3.8 3.61	27.9 27.87
12b	>300	57	DMF	$C_{13}H_8N_5OCl$ (285.69)		54.5 54.65	3.0 2.82	24.6 24.51
17a	150–151	50	ethanol	$C_{14}H_{10}N_4O$ (250.26)		67.3 67.19	3.9 4.03	22.5 22.30
17b	185	53	ethanol	$C_{14}H_9N_4OCl$ (284.71)		59.0 59.06	3.3 3.19	19.8 19.68

TABLE 2 IR and ^1H NMR Spectra of the New Compounds

Compound	IR (ν, cm^{-1})	^1H NMR (δ)
7a	3380 (NH), 2222, 2220 (CN), 1690 (CO)	10.82 (s, 1H, NH), 7.8–7.3 (m, 10H, arom. H)
7b	3390 (NH), 2221, 2220 (CN), 1690 (CO)	10.81 (s, 1H, NH), 7.7–7.3 (m, 9H, arom. H)
7c	3380 (NH), 2223, 2222 (CN), 1680 (CO)	10.75 (s, 1H, NH), 7.8–7.3 (m, 9H, arom. H), 3.7 (s, 3H, OCH_3)
7d	3400 (NH), 2225, 2220 (CN), 1690 (CO)	10.82 (s, 1H, NH), 7.8–7.3 (m, 9H, arom. H)
7e	3400 (NH), 2222, 2218 (CN), 1680 (CO)	10.83 (s, 1H, NH), 7.8–7.2 (m, 8H, arom. H)
7f	3390 (NH), 2225, 2220 (CN), 1690 (CO)	10.72 (s, 1H, NH), 7.8–7.4 (m, 8H, arom. H), 3.74 (s, 3H, OCH_3)
7g	3400 (NH), 2229, 2220 (CN), 1685 (CO)	10.78 (s, 1H, NH), 7.8–7.3 (m, 6H, arom. H)
7h	3410 (NH), 2222, 2220 (CN), 1690 (CO)	10.80 (s, 1H, NH), 7.9–7.5 (m, 5H, arom. H)
7i	3400 (NH), 2225, 2220 (CN), 1685 (CO)	10.85 (s, 1H, NH), 7.8–7.5 (m, 5H, arom. H), 2.38 (s, 3H, CH_3)
7j	3410 (NH), 2222, 2220 (CN), 1690 (CO)	10.75 (s, 1H, NH), 7.8–7.4 (m, 4H, arom. H), 2.39 (s, 3H, CH_3)
12a	3400, 3340 (NH_2), 2220 (CN), 1690 (CO)	10.92 (br, s, 1H, NH), 7.7–7.4 (m, 6H, arom. H + pyridyl H-3), 4.2 (s, 2H, NH_2)
12b	3420–3360 (NH_2), 2222 (CN), 1695 (CO)	10.88 (br, s, 1H, NH), 7.8–7.4 (m, 5H, arom. H + pyridyl H-3), 4.22 (s, 2H, NH_2)
17a	3960 (NH), 2223 (CN), 1690 (CO), 1640 (C=N).	10.82 (br, s, 1H, NH), 7.7–7.2 (m, 6H, arom. H + pyridyl H-3), 2.38 (s, 3H, CH_3)
17b	3400 (NH), 2220 (CN), 1688 (CO), 1645 (C=N)	10.75 (s, 1H, NH), 7.7–7.2 (m, 5H, arom. H + pyridyl H-3), 2.40 (s, 3H, CH_3)

and then recrystallized from the proper solvent (Table 1).

2-Aryl-4-oxo-3H-1, 2, 4-triazolo[1,5-a]pyridine-5,7-dicarbonitriles **7g,h**. To a solution of paraformaldehyde (0.3 g, 0.01 mol) in DMF (20 mL) was added malononitrile (0.66 g, 0.01 mol), followed by a catalytic amount of piperidine and 0.01 mol of either **3a** or **3b**. The reaction mixture in each case was heated under reflux for 5 hours. The solvent was evaporated under reduced pressure, and the remainder was poured into ice-water. The solid product, formed in each case, was collected by filtration, washed with water, and recrystallized from ethanol (Table 1).

2-Aryl-6-methyl-4-oxo-3H-1, 2, 4-triazolo[1,5-a]pyridine-5,7-dicarbonitriles **7i,j**. *General Procedures.* To a solution of malononitrile (0.66 g, 0.01 mol) in ethanol (20 mL) was added acetaldehyde (0.44 g, 0.01 mol) and 2–3 drops of piperidine; then there was added 0.01 mol of either **3a** or **3b**. The reaction mixture was stirred at room temperature for 24 hours, then heated under reflux for 6 hours. The solvent was evaporated under reduced pressure. The solid product, formed in each case on cooling, was collected by filtration, washed with ethanol, and recrystallized from ethanol (Table 1).

6-Amino-2-aryl-4-oxo-3H-1, 2, 4-triazolo[1,5-a]pyridine-5-carbonitriles **12a,b**. A suspension of **3a** or **3b** (0.01 mol) in dioxane (20 mL) and a catalytic amount of piperidine was treated with malononitrile (0.66 g, 0.01 mol). The reaction mixture in each case was heated under reflux for 5 hours. The solvent was evaporated under reduced pressure. The solid product, so formed in each case, was collected by filtration, washed with ethanol, and recrystallized from dioxane (Table 1).

2-Aryl-6-methyl-4-oxo-3H-1, 2, 4-triazolo[1,5-a]pyridine-5-carbonitriles **17a,b**. A suspension of **3a** or **3b** (0.01 mol) in dioxane (20 mL) and a catalytic amount of piperidine was treated with 3-aminocrotononitrile (0.82 g, 0.01 mol). The reaction mixture in each case was then heated under reflux for 6 hours. The solvent was evaporated under reduced pressure, and the remainder was poured into ice-water, neutralized with concd HCl. The solid product, formed in each case, was collected by filtration, washed with water, and recrystallized from ethanol (Table 1).

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