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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS : SYNTHESIS OF 1,2,4-TRIAZOLO [1,5-a] PYRIDINES

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ABSTRACT

New routes for the synthesis of 1,2,4-triazolo [1,5-a] pyridines are described. The reaction of the hydrazone 6 with arylidine malononitrile (2a-c)gives the 1,2,4-triazolo [1,5-a] pyridines (10a-c). Alternately reactions of 6 with benzoyl acetonitrile and malononitrile afford also 1,2,4-triazolo [1,5-a] pyridines.

1,2,4-Triazolo [1,5-a] azines are biologically interesting molecules.[1-3] and their synthesis is now receiving considerable interest.[4,5] 1,2,4-Triazolo [1,5-a] pyridines are generally obtained via treating 1,2-diaminopyridines with acid chlorides or with aldehydes.[1,3] This method however has its limitation as substituted 1,2-diaminopyridines are expensive and not readily obtainable compounds. Recenty Soto *et al.*[6] have reported synthesis of 3 via reacting 1 with arylidene malononitriles 2. Again this synthetic approach has its limitation. Compounds 3 are produced in low yields and are always contaminated with 4, resulting from cyclization of 1 prior to reaction with cinnamonitrile.

In this paper we report a new and efficient synthesis of

1,2,4-triazolo [1,5-a] pyridines that seem superior to all other reported syntheses. Benzylidene cyanoethanoic acid hydrazide reacted with arylidene malononitrile in refluxing ethanol in presence of piperidine to yield the 1,2,4-triazolo [1,5-a] pyridines 10a-c. Compounds 10 are assumed to be formed via initial addition of active methylene moiety in 5 to activated double bond yielding acyclic Michael adduct 7 that first cyclises to 8, aromatises to 9 then further cyclises to 10. Alternately one may assume initial addition of NH across the C=C linkage affording 11. However, this possibility as well as other alternate possibilities were readily ruled out based on the fact that 10a proved to be identical with a product obtained recently by soto *et al.* [6] via cyclization of 12. Similar to the behavior of 6 toward arylidine malononitrile, it reacted also with ethyl arylidine cyanoacetate 13a-c to give the 1,2,4-triazolo [1,5-a] pyridines 17a-c respectively. These compounds are assumed to be formed via intermediacy of 14-16 in the sequence shown in Chart 3.

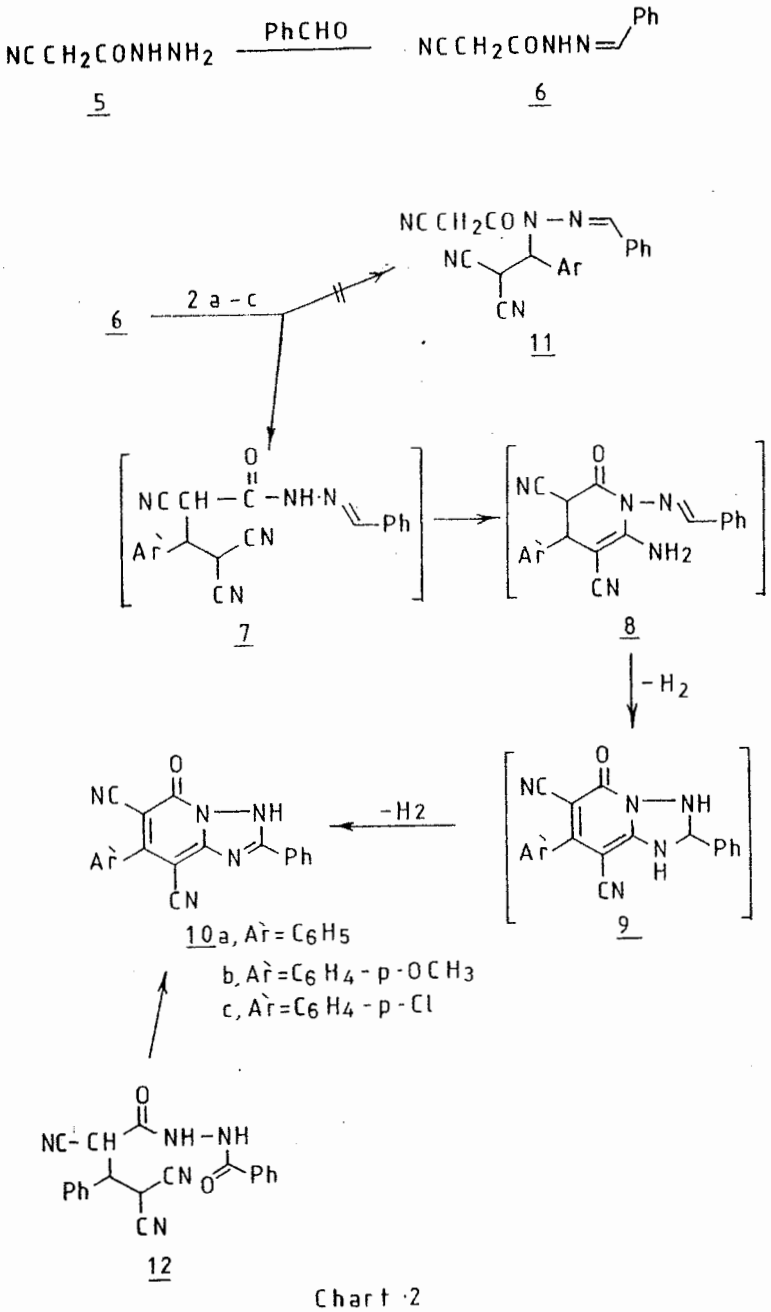
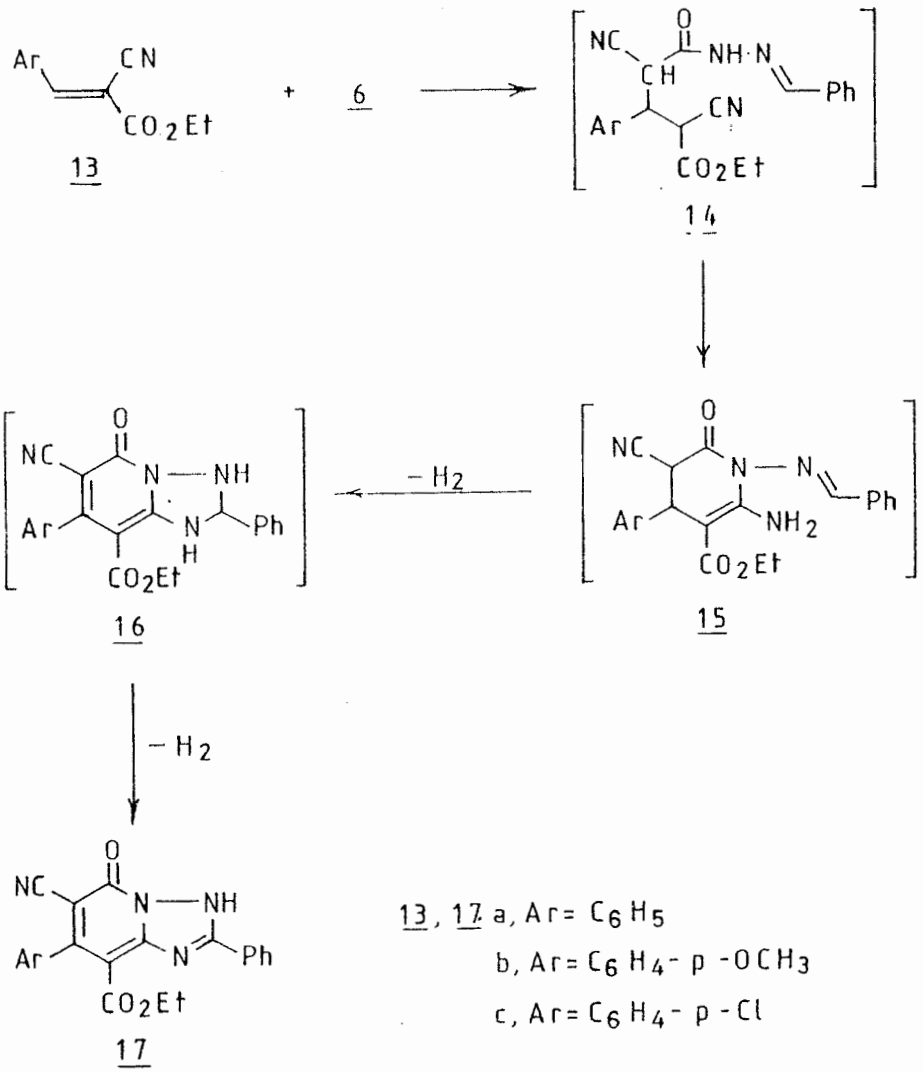

NC CH2CONHNH2
PhCHO
NC CH2CONHN=CHPh
5
6
2 a - c
NC CH2CO N - N=CHPh
NC
Ar
CN
11
NC CH - C - NH·N=CHPh
Ar
CN
CN
7
8
-H2
9
-H2
10a, Ar = C6H5
b, Ar = C6H4 - p - OCH3
c, Ar = C6H4 - p - Cl
NC - CH
NH - NH
Ph
CN
O
Ph
CN
12

Chart 2



13, 17 a, Ar = C_6H_5

b, Ar = C_6H_4-p-OCH_3

c, Ar = C_6H_4-p-Cl

Chart 3

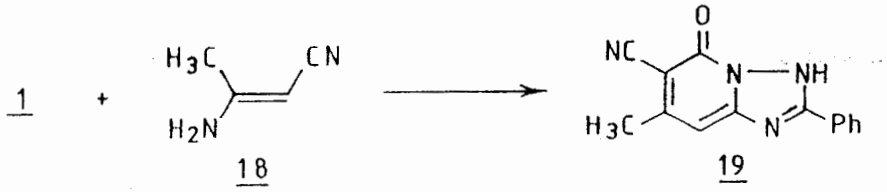


Chart 4

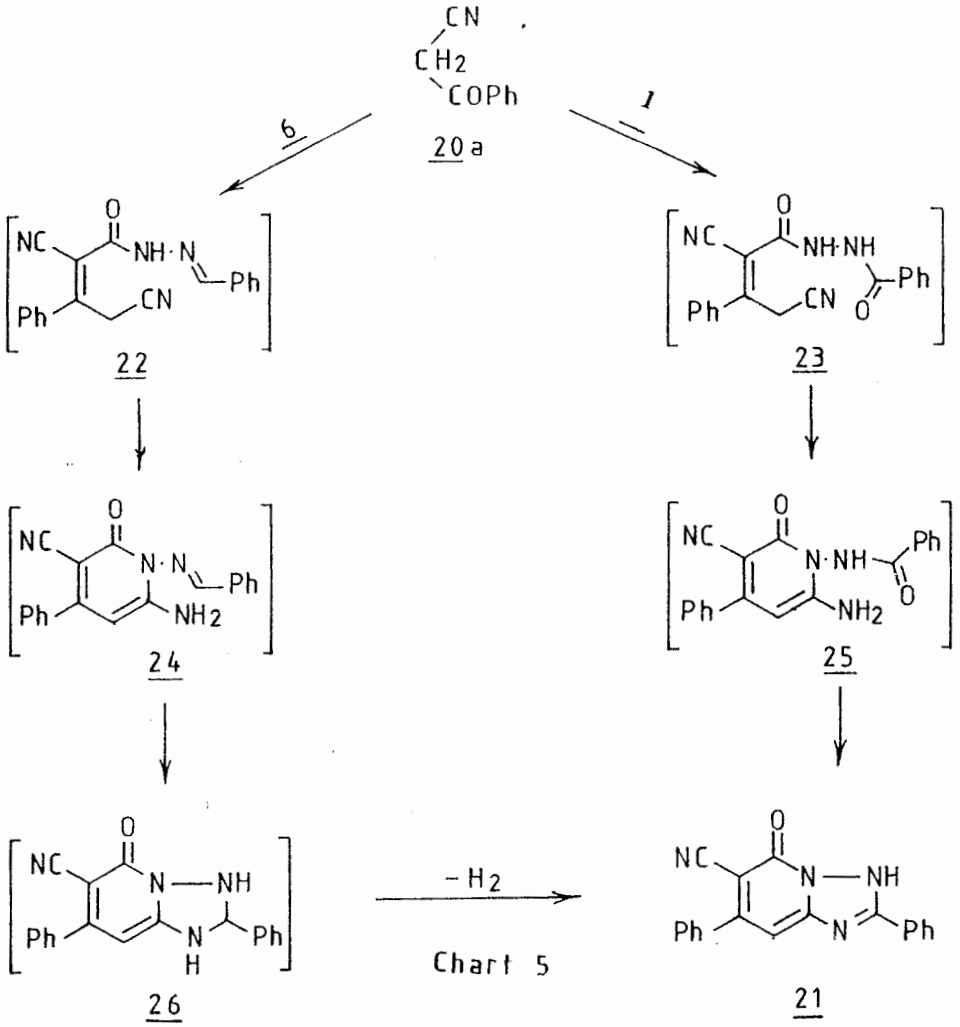
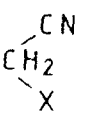


Chart 5

It has been reported[2] that 1 reacts with 2-aminorotononitrile 18 to yield 19. Now we have found that 1 reacts with the nitrile 20a, to yield the 1,2,4-triazolopyridine 21. This same compound was also obtained from reaction of 6 with 20a (Chart 5). This compound was assumed to be formed via initial condensation of active methylene group in 1 or 6 with carbonyl function in 20a yielding condensates 22 or 23 that cyclise into 24 or 25 then futher cyclise and aromstise yielding the end product.

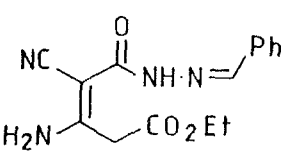
Reaction of active methylene moieties in 1 and 6 with the cyano compounds in 20b,c could also be effected. The adduct 27 was the only insoluble product from reactions with 20b. Reaction of 1 or 6 with 20c afforded the triazolo [1,5-a] pyridine 28.

The structures of the compounds 10, 17, 21, 27 and 28 were confirmed by the spectral and analytical data (Tables 1,2).

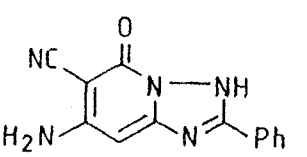


20b, X = CO_2Et

c, X = CN



27



28

Chart 6

Table 1. Physical and Analytical Data.

Comp. No.	M.p. °C*	Yield %	Mol. formula	Analysis Calc./(Found)		
				C%	H%	N%
10_a	317	80	$C_{20}H_{11}N_5O$	71.20 (71.2)	3.26 (3.3)	20.77 (20.8)
10_b	295	60	$C_{21}H_{13}N_5O_2$	68.65 (68.6)	3.54 (3.6)	19.07 (19.1)
10_c	302	73	$C_{20}H_{10}ClN_5O$	64.51 (64.5)	2.68 (2.7)	18.81 (18.7)
17_a	270	68	$C_{22}H_{16}N_4O_3$	68.75 (68.8)	4.16 (4.2)	14.58 (14.5)
17_b	290	82	$C_{23}H_{18}N_4O_4$	66.66 (66.6)	4.34 (4.4)	13.52 (13.4)
17_c	298	70	$C_{22}H_{15}ClN_4O_3$	63.08 (63.0)	3.57 (3.6)	13.36 (13.4)
21	330	70	$C_{19}H_{12}N_4O$	73.08 (73.0)	3.85 (3.8)	17.9 (17.9)
27	222	65	$C_{15}H_{16}N_4O_3$	60.00 (60.1)	5.33 (5.3)	18.66 (18.7)
28	309	69	$C_{13}H_9N_5O$	62.15 (62.1)	3.58 (3.6)	27.88 (27.7)

* All compounds were crystallised from methanol.

Table 2. Spectral Data.

Comp.	IR, γ, cm^{-1}	^{1}H-NMR, δ ppm
10_a	3300 (NH); 2200 (CN); 1640 (CO-amide)	3.3 (s, 1H, NH); 7.45-7.9 (m, 9H, Ar)
10_b	3345 (NH); 2220 (CN); 1665 (CO-amide)	3.85 (s, 3H, OCH_3); 7.10-7.60 (m, 9H, Ar); 8.50 (s, 1H, NH)
10_c	3350 (NH); 2180 (CN); 1650 (CO-amide)	7.50-7.70 (m, 9H, Ar); 8.58 (s, 1H, NH)
17_a	3390 (NH); 2190 (CN); 1750 (CO-ester); 1630 (CO-amide)	1.0 (t, 3H, CH_3); 3.6 (q, 2H, CH_2O); 7.25-8.10 (m, 9H, Ar); 8.4 (s, 1H, NH)
21	3280 (NH); 2190 (CN); 1650 (CO-amide)	
27	3500-3400 (OH, NH_2); 3200 (NH); 2110 (CN); 1720 (CO-ester)	0.6 (t, 3H, CH_3); 3.8 (q, 2H, CH_2); 7.3-7.4 (m, 6H, Ar, OH); 8.41 (broad s, 3H, NH_2, NH)
28	3400 (NH_2); 2260 (CN); 1670 (CO-amide)	5.6 (broad s, NH_2); 7.40-8.40 (m, 5H, Ar)

EXPERIMENTAL

Preparation of Benzylidene cyanoethanoic acid hydrazide (6) :

A mixture of 0.01 mole of cyanoethanoic acid hydrazide (5) and 0.01 mole of benzaldehyde was stirred at room temperature. A precipitate started to from after 10 minutes. The precipitate was filtered then crystallised from ethanol m.p. 168°C, yield 86%.

Synthesis of the dicyanotriazolo [1.5-a] pyridines 10a-c :

To a solution of 6 (0.01 mole) in 50 ml ethanol was added 0.01 mole of the appropriate arylidene malononitrile 2 and 1 ml of piperidine. The reaction mixture was heated under reflux for 4 hours. The solvent was evaported under reduced pressure and the residu was triturated with ethanol to give 10a-c (Table 1,2).

Synthesis of the carboethoxytriazolo [1,5-a] pyridines 17a-c :

A mixture of 0.01 mole of 6 and 0.01 mole of the appropriate ethyl arylidine cyanoacetate 13 and 1 ml of piperidine was refluxed in 50 ml ethanol for 5 hours. The solvent was concentrated and left to cool. The precipitate so formed was collected by filtration to give 17a-c (Table 1).

Synthesis of the diphenyltriazolo [1,5-a] pyridine 21 :

To 0.01 mole of N-benzoylcyanoethanoic acid hydrazide (1) or of 6 was added 0.01 mole of benzoylacetonitrile (20a) and 1 ml of triethylamine. The reaction mixture was heated under reflux in 50 ml ethanol for 20 hours. The solid formed after cooling was collected by filtration to give 21 (Table 1).

Synthesis of the adduct 27 :

A mixture of 0.01 mole of ethylcyanoacetate (20b) and 0.01 mole of 1 or 6 was refluxed in 50 ml ethanol for 30 hours in presence of 5 drops of piperidine. The solvent was evaporated and the residue was triturated with ethanol to give the adduct 27 (Table 1).

Synthesis of the aminotriazolo [1,5-a] pyridine 28 :

To a solution of 0.01 mole of malononitrile (20c) in 50 ml ethanol was added 0.01 mole of 1 or 6 and 1 ml of piperidine. The reaction mixture was refluxed for 18 hours. After cooling the compound 28 was precipitated, then collected by filtration (Table 1).

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دراسات على الأروميتات غير المتجانسة عديدة المستبدلات الوظيفية : تخليق ١و٢و٤-تريازولو [١وه-أ] بيريدينات

صلاح القوصى – عبد المنعم الترجمان – عبد الحميد إسماعيل – محمد حواطه

ومحمد حلمى النجدى

وصفت فى هذا البحث طرق جديدة لتخليق ١و٢و٤-تريازولو [١وه-أ] البيريدينات. تفاعل الهيدرازون ٦ مع أريليدين المالونونيتريل (٢ أ- جـ). وبالمثل تفاعل المركب ٦ مع بنزويل الأسيتونيتريل والمالونونيتريل فأعطى أيضا ١و٢و٤-تريازولو [١وه-أ] بيرينات.