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Activated Nitriles in Heterocyclic Chemistry

A Novel Synthesis of Pyridones, Pyrazolo[1,5-*a*]pyrimidines and Pyrazolo[1,5-b]oxazines

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Several new pyridones, pyrazolo[1,5-*a*]pyrimidines and pyrazolo[1,5-*b*]oxazines were prepared from the cyanoacetohydrazide derivatives **1**, **11** and the cinnamonitrile derivatives **2a–c**.

Aktivierte Nitrile in der heterocyclischen Chemie: Eine neue Synthese von Pyridonen, Pyrazolo[1,5-a]pyrimidinen und Pyrazolo[1,5-b]oxazinen

Einige neue Pyridone, Pyrazolo[1,5-a]pyrimidine and Pyrazolo[1,5-b]oxazine werden hergestellt aus den Cyanoacethydrazid-Derivaten **1** und **11** und den Cinnamonitril-Derivaten **2a–c**.

The considerable biological activities of both pyridones and pyrazoles have stimulated enormous interest in the synthesis and chemistry of this class of compounds[1,2]. As a part of a medicinal chemistry program[3,5] in our laboratories, the syntheses of several pyridones, pyrazolo[1,5-a]pyrimidines and pyrazolo[1,5-b]oxazines were required.

In conjugation of this work, we report here on the reaction of cyanoacethydrazide **(1)** with the cinnamonitrile derivatives **2a–c**. Thus, it has been found that **1** reacts with benzylidenemalononitrile **(2a)** to yield an 1:1 adduct. Several isomeric cyclic and acyclic structures seemed possible for the reaction product. Acyclic structures **3** and **4** were readily eliminated based on the ^{1}H-NMR spectrum of the product which revealed only one singlet proton at $\delta = 5.6$ ppm. Acyclic structures **3** and **4** should have revealed multiplets for more

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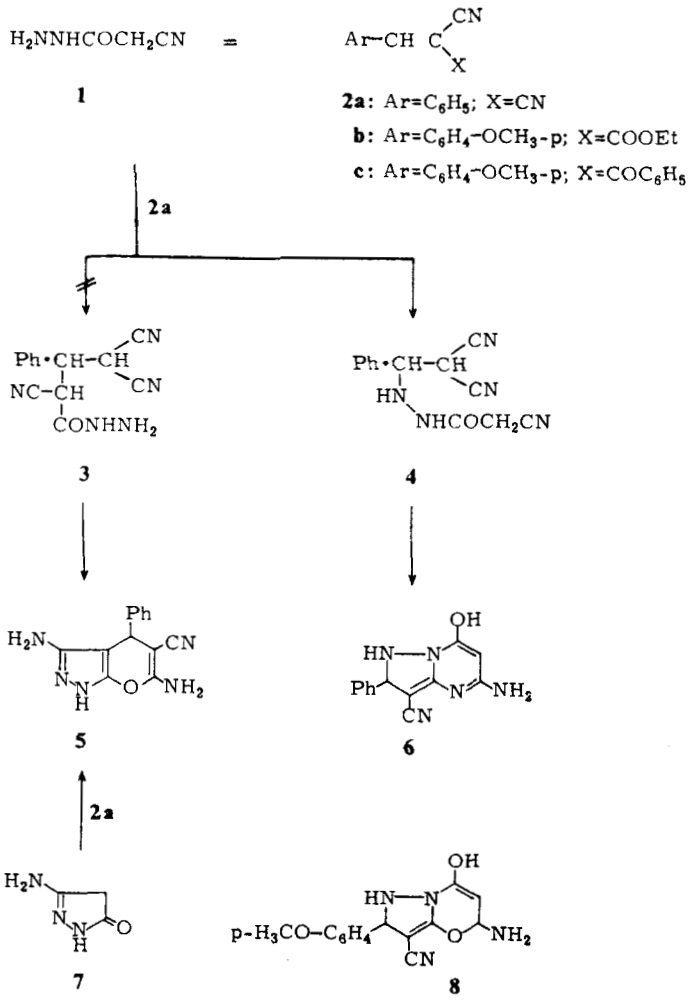
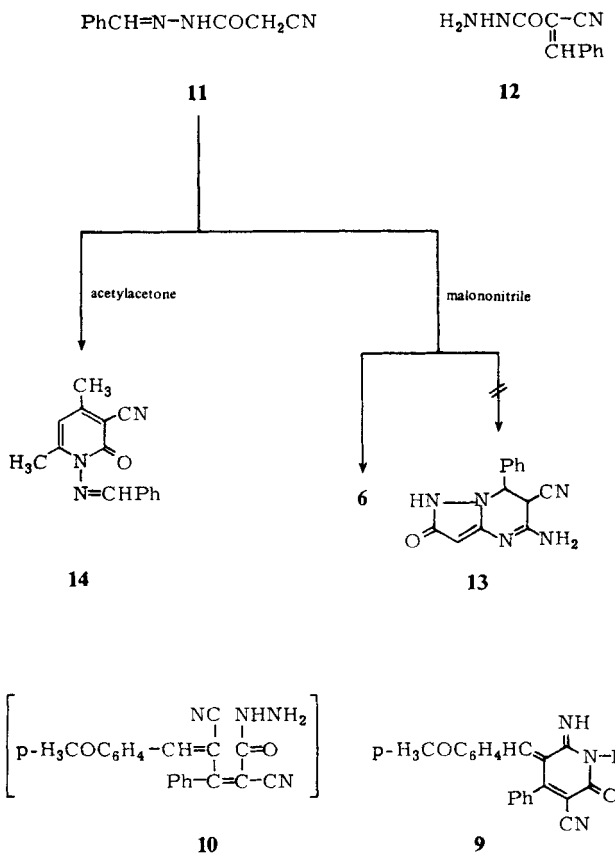
than one proton linked to sp^3 carbons. Thus, structures **5** and **6** were considered and spectroscopy seemed to be of little help for discrimination of both structures. Structure **5** could be eliminated based on the non-identity of the reaction product with the product of the reaction of **2a** with 3-amino-2-pyrazolin-5-one (**7**). Thus, structure **6** was established for the reaction product. Compound **6** is assumed to be formed via initial addition of the hydrazide NH to the activated double bond in **2a** and subsequent cyclisation of the formed **4** into **6** (cf. chart. 1).



Similar to the behaviour of **2a**, compound **2b** reacted with **1** to yield the pyrazolo[1,5-b]oxazine derivative **8**. In contrast to the behaviour of **2a**, **b**, compound **2c** reacted with **1** to yield the condensation product **9**. The formation of **9** in this reaction is assumed to proceed via condensation of **1** with **2c** to yield the intermediate **10** which then cyclises via addition to the cyano group to yield the final isolable product **9**.



The behaviour of **2a–c** towards **1** is different than their behaviour towards other active methylene reagents. This may indicate that the hydrazino moiety in **1** is the most active nucleophilic center in the molecule. This assumption was supported by our observation that **1** reacts with benzaldehyde to yield the Schiff's base **11** rather than the ylidene derivative **12**.

The behaviour of **11** towards a variety of active methylene nitriles has been investigated. It has been found that **11** reacts with malononitrile to yield a product of molecular formula $C_{13}H_{11}N_5O$. Two isomeric structures seemed possible (cf. structures **13** and **6**). Structure **6** was readily established based on identity of the reaction product with a sample of **6** prepared from the reaction of **1** with **2a**. Similarly the pyridine derivative **14** was formed from the reaction of **11** with acetylacetone. Now the behaviour of **11** towards a variety of activated double bond systems is under investigation.

Experimental Part

MP: uncorr. *IR Spectra* (KBr): Unicam Sp-1000. *^{1}H-NMR* (DMSO-D_6), TMS int. stand., chemical shifts: δ (ppm). *Analytical data:* microanalytical center at Cairo University.

Table 1: *Characterisation data of compounds* **5, 6, 8, 9, 11** *and* **14**

Product	Colour	Yield (%)	M.P.[°C] (Solv.)	Molecular formula	% Analysis C	H	Calc. Found N
5	brown	50	> 300	$C_{13}H_{11}N_5O$ (253)	61.7 61.5	4.3 4.1	27.7 27.5
6	pale yellow	70	> 280 (acetic acid)	$C_{13}H_{11}N_5O$ (253	61.7 61.3	4.3 4.1	27.7 27.1
8	Colourless	73	200 (ethanol)	$C_{14}H_{14}N_4O_3$ (286)	58.7 58.5	4.8 4.6	19.6 19.4
9	colourless	68	> 300 (ethanol)	$C_{20}H_{16}N_4O_2$ (344)	69.8 69.5	4.6 4.4	16.3 16.0
11	colourless	78	173 (ethanol)	$C_{10}H_9N_3O$ (187)	64.2 63.9	4.8 4.6	22.5 22.1
14	Colourless	65	198 (ethanol)	$C_{15}H_{13}N_3O$ (251)	71.7 71.4	5.2 5.0	16.7 16.5

Table 2: *I.R. and* ^{1}*H-NMR data of compounds* **5, 6, 8, 9, 11** *and* **14**

Product	IR (KBr) [cm^{-1}]	^{1}H-NMR (DMSO-d_6/TMS_{int}) δ [ppm]
5	3300, 3200, 3400 (NH_2); 2940 (CH) and 2210 (CN).	5.66 (s, 4H, NH_2); 7.4 (m, $5H_{arom.}$); 8.3 (s, br, 1H, NH), 7.9 (s, 1H, CH).
6	3400, 3320, 3200 (NH_2); 2940 (CH) and 2200 (CN).	5.66 (s, 2H, NH_2); 7.5 (m, $5H_{arom.}$); 8.34 (s, br, 2H, CH and NH) and 11.9 (s, 1H, OH).
8	3450, 3300, 3200 (NH_2); 2970, 2950 (CH and CH_3) and 2225 (CN).	
9	3460, 3300, 3210 (NH and NH_2); 2950 (CH and CH_3); 2220 (CN) and 1750 (ring CO).	3.3 (s, 3H, NH and NH_2); 4.0 (s, 3H, OCH_3) and 6.9 ~8.0 (m, $9H_{arom.}$)..
11	3200 (NH); 2940 (CH_2); 2220 (CN) and 1700 (CO).	4.2 (s, 2H, CH_2); 7.3 ~7.8 (m, $5H_{arom.}$); 7.9 (s, 1H, CH) and 12.3 (s, br, 1H, NH).
14	3025, 2900 (CH and CH_3) 2200 (CN) and 1680 (CO).	3.3 (s, 6H, two CH_3); 6.38 (s, 1H, pyridine H-3) and 9.8 (s, 1H, azomethine CH).

5-Cyano-3,6-diamino-4-phenyl-pyrazolo[1,5-a]-4H-pyran **(5)**

A solution of 0.99 g 3-amino-5-pyrazolone **(7)** in 100 ml ethanol was heated under reflux with 1.5 g benzalmalononitrile (**2a**) and 1 ml of triethylamine for 5 h, the solvent was removed, the residue was triturated with ethanol and the resulting solid product was crystallized to give **5** (cf. Table 1 and 2).

5-Amino-3-cyano-7-hydroxy-2-phenylpyrazolo[1,5-a]pyrimidine **(6)**

Method A: A solution of 0.99 g cyanoacethydrazide in 100 ml ethanol was treated with 1.54 g **2a** and 1 ml of triethylamine. The reaction mixture was heated under reflux for 5 h and then the solvent was removed. The residue was triturated with ethanol and the resulting solid product was crystallised to give **6** (cf. Tables 1 and 2).

Method B: Compound **6** could also be prepared by the reaction of 1.87 g **11** and 0.66 g malononitrile applying the same procedure described in method A.

5-Amino-3-cyano-7-hydroxy-2-(p-methoxyphenyl)-pyrazolo[1,5-b]oxazine **(8)**

A solution of 0.99 g **1** in 100 ml ethanol was treated with 2.31 g anisalethyl cyanoacetate and 2 ml triethylamine. The reaction mixture was heated under reflux for 7 h, then the solvent was evaporated i.vac. The residue was triturated with ethanol and the resulting solid product was crystallised to give **8** (cf. Tables 1 and 2).

1-Amino-5-anisylidene-3-cyano-6-imino-4-phenylpyridin-2-one **(9)**

9 was prepared by the reaction of 0.99 g **1** with 2.63 g **2c** applying the same procedure as for synthesis of compound **8** (cf. Tables 1 and 2).

Benzal cyanoacethydrazide **(11)**

A mixture of 0.99 g **1** and 1.06 g benzaldehyde was heated on a boiling water bath for 20 min. The oily layer that formed readily solidified on cooling and was crystallised to give **11** (cf. Tables 1 and 2).

1-N-(Benzalamino)-3-cyano-4,6-dimethylpyridin-2-one **(14)**

A solution of 1.87 g **11**, 1 g acetylacetone and 2 ml triethylamine in 100 ml ethanol was heated under reflux for 7 h. The solvent was removed i.vac. and the residue crystallised to give **14** (cf. Tables 1 and 2).

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[Ph 721]