

SYNTHESIS AND REACTIVITY OF 2-CHLORO-4-PHENYL-6-P-TOLYL-NICOTINONITRILE TOWARDS SOME NUCLEOPHILES

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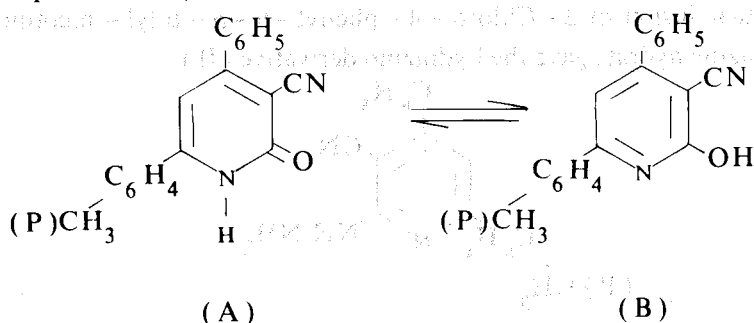
ABSTRACT

The synthesis and reaction of 2-Chloro-4-phenyl-6-p-tolyl- nicotinonitrile (I) with hydrazine hydrate, sodium azide and urea to give the corresponding hydrazino tetrazolopyridine and urea derivatives respectively, are studied. The reaction of (I) with compounds containing active methylene group is reported. The mode of formation and structure of the various products are also discussed.

INTRODUCTION

It has been reported that fusion of p-methylbenzalacetophenone with ethyl cyanoacetate in the presence of ammonium acetate led to the formation of 3-cyano-4-phenyl-6-p-tolyl-2(1H)-pyridone (A) (Sammour *et al.* 1970, 1971).

This pyridone (A) is found to be in equilibrium with the tautomeric form 2-hydroxy-4-phenyl-6-p-tolyl-nicotinonitrile (B), due to the Lactam-Lactim phenomena (Sammour *et al.* 1970, 1971).



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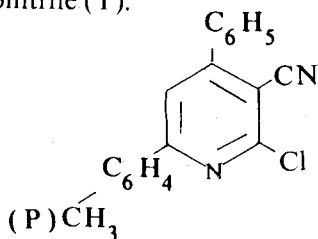
The oxygen of 2-pyridone was found to be replaced by sulphur when treated with P_2S_5 to give 2-mercapto-derivative (Renault 1953).

N-alkyl pyridine thione was prepared by reaction of N-alkyl pyridone with P_2S_5 (Becher *et al.* 1984).

It has also been reported (Dehnert and Lamm 1973, and Fleckenstein and Mohr 1974) that 2-Chloro-3-Cyano-4,6-dimethylpyridine reacts with hydrazine hydrate in ethylene glycol to give the pyrazolopyridine derivative.

RESULTS

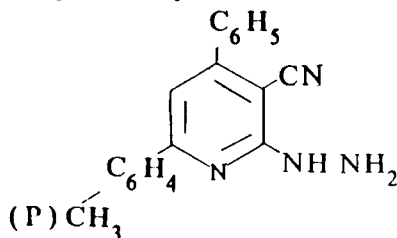
In the present work, we would like to report our results on the synthesis of the corresponding chloride by the reaction of pyridone (A) with a phosphorus pentachloride / phosphorus oxychloride mixture to yield 2-chloro-4-phenyl-6-p-tolyl-nicotinonitrile (I).



(I)

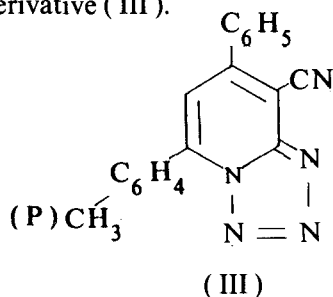
The reactivity of (I) towards some nucleophilic reagents has been investigated and the structure of the products as well as their formation are reported in this study.

We found that fusion of 2-Chloro-4-phenyl-6-p-tolyl-nicotinonitrile (I) with hydrazine hydrate gave the hydrazino derivative (II).

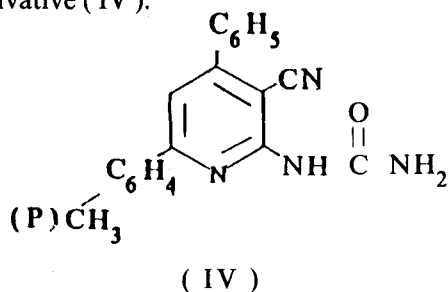


(II)

Reaction of (I) with sodium azide in dimethylformamide afforded the formation of tetrazolopyridine derivative (III).



Treatment of (I) with urea in the presence of sodium ethoxide gave the corresponding urea derivative (IV).



The chlorine atom in 2-chloro-4-phenyl-6-p-tolyl-nicotinonitrile (I) was readily replaced on refluxing with compounds containing active methylene compounds in dimethylformamide as a medium and sodamide as catalyst.

Thus, treatment of (I) with diethylmalonate and ethyl acetoacetate in dimethylformamide and in the presence of sodamide yielded the substituted products V_a and V_c respectively, in a major amount. The corresponding hydrolysed derivatives V_b and V_d were respectively detected in small amounts. An authentic sample of V_b was obtained by refluxing a solution of V_a with 10% KOH for 3 hours.

On the other hand, reaction of (I) with acetyl acetone, diphenylmethyl cyanide, ethyl methyl ketone, methyl isopropyl ketone, ethyl cyanoacetate, ethyl phenylacetate, di-isobutyl ketone, fluorene, benzyl cyanide and acetonyl acetone in dimethyl formamide and sodamide gave (V_{e-n}) respectively.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were taken on a Pye Unicam SP 1200 spectrophotometer using the KBr Wafer technique and are listed in Table 2. ^1H NMR spectra were obtained on a Varian A-60 spectrometer using 20 % solutions in deuterio-chloroform. Chloroform was utilized as the internal standard. Mass spectra were obtained on a Hitachi Rmv 9 E Mass Spectrometer.

Preparation of 2 - chloro - 4 - phenyl - 6 - p - tolyl - nicotinonitrile (I)

A mixture of 3 - cyano - 4 - phenyl - 6 - p - tolyl - 2 (1H) - pyridone (A) (0.01 mole), 3 g PCl_5 and 5 ml POCl_3 was heated under nitrogen atmosphere on a water bath for 5 hrs. The reaction mixture was then poured onto crushed ice. The yellow solid product obtained was filtered off, washed several times with water, dried and crystallized from ethyl alcohol to give the corresponding product (I) as yellow crystals (50 % yield). It has the following properties : mp $184 - 186^\circ\text{C}$; ^1H NMR δ (in ppm) 2.50 (s, 3H), 7.30 - 8.30 (m, 10H); IR ν 1585cm^{-1} (C = C), 2250cm^{-1} (C \equiv N); MS, m/e (relative intensity) 304.5 (100, M^+), 289.5 (83.3, $\text{M}^+ - 15$), 254 (66.5), 240 (53.3); Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{N}_2\text{Cl}$: C, 74.87; H, 4.26; N, 9.19. Found : C, 74.58; H, 4.21; N, 9.08.

Reaction of (I) with hydrazine hydrate. Formation of (II)

A mixture of (I) (1g) and hydrazine hydrate (10 ml) was fused for 6 hrs. at 130°C . The solid product obtained was crystallized from ethyl alcohol to give the hydrazine derivative (II) as yellow crystals (62 % yield). It has the following properties mp $234 - 236^\circ\text{C}$; ^1H NMR δ (in ppm) 2.50 (s, 3H), 4.15 (s, 3H), 7.20 - 8.10 (m, 10H); IR ν 1590cm^{-1} (C = C), 2110cm^{-1} (C \equiv N), 3165cm^{-1} (N - H); MS, m/e (relative intensity) 300 (100, M^+), 285 (34.4, $\text{M}^+ - 15$), 271 (95.5), 255 (53.1); Anal. Calcd. for $\text{C}_{19}\text{H}_{16}\text{N}_4$: C, 76.00; H, 5.33; N, 18.66. Found : C, 75.58; H, 5.10; N, 18.25.

Reaction of (I) with sodium azide. Formation of (III)

To a solution of (I) (0.01 mole) in dimethylformamide (10 ml), a solution of sodium azide (1 g) in water (5 ml) was added, and the reaction mixture was

refluxed for 3 hrs. After cooling, a crystalline product was separated, which was crystallized from benzene to give the tetrazolopyridine (III) as yellow crystals (37 % yield). It has the following properties mp 167–168°C; $^1\text{H NMR } \delta$ (in ppm) 2.40 (s, 3H), 7.25–8.15 (m, 10H); IR \checkmark 1530, 1620 cm^{-1} (N=N), 2220 cm^{-1} (C \equiv N); MS, m/e (relative intensity) 311 (53.3, M^+), 283 (100, $\text{M}^+ - \text{N}_2$), 269 (29.6), 255 (25), 240 (21.9); Anal. calcd. for $\text{C}_{19}\text{H}_{13}\text{N}_5$: C, 73.31; H, 4.18; N, 22.50. Found: C, 73.05; H, 4.07; N, 22.24.

Reaction of (I) with urea. Formation of (IV)

To metallic sodium (0.02 mole) in 20 ml of absolute ethanol was added 0.6 g of powdered urea (0.01 mole) and 3 g of (I). The reaction mixture was then refluxed for 4 hrs., filtered while hot, washed with ethanol and dried. The crude product obtained was crystallized from pet. ether (b.p. 60–80) to give (IV) as yellow crystals (35 % yield). It has the following properties: mp 93–95°C; $^1\text{H NMR } \delta$ (in ppm) 2.45 (s, 3H), 4.50 (s, 2H), 4.85 (s, 2H), 7.20–8.00 (m, 10H); IR \checkmark 1590 cm^{-1} (C=C), 2215 cm^{-1} (C \equiv N), 3000 cm^{-1} (N–H); Anal. calcd. for $\text{C}_{20}\text{H}_{16}\text{ON}_4$: C, 73.17; H, 4.87; N, 17.07. Found: C, 72.81; H, 4.38; N, 16.66.

Reaction of (I) with compounds containing active methylene groups. Formation of ($\text{V}_{\text{a-n}}$):

To a solution of (I) (0.01 mole) in 20 ml dimethylformamide, active methylene compound (0.02 mole) (diethyl malonate, ethyl acetoacetate, acetyl acetone, diphenylmethyl cyanide, ethyl methyl ketone, methyl isopropyl ketone, ethyl cyanoacetate, ethyl phenyl acetate, di-isobutyl ketone, fluorene, benzyl cyanide and acetyl acetone) and sodamide (0.04 mole) were added, and the reaction mixture was refluxed for 3 hrs. The cooled product was poured into 100 ml cold water and acidified with dilute hydrochloric acid. The solids obtained were crystallized from proper solvent to give ($\text{V}_{\text{a-n}}$) respectively (cf. Tables 1, 2, 3).

Preparation of an authentic sample of (V_{b}):

A solution of V_{a} (0.01 mole) in 15 ml 10 % KOH was refluxed for 3 hrs. The reaction mixture was then poured into an ice/HCl mixture. The solid product obtained was crystallized from pet. ether to give a product which proved to be (V_{b}) from the melting point and mixed melting point determinations.

Table 1
The adducts (V_{a-n})

Compound	m.p. (Solvent)*	Colour	Molecular Formula	Yield %	Elemental Analysis %	
					Found	Calculated
V_a	240 – 242 (E)	Brown	$C_{26}H_{24}O_4N_2$	72	C 72.47 H 5.32	72.89 5.59
V_b	88 – 91 (P)	Yellow	$C_{21}H_{16}O_2N_2$	24	C 76.27 H 4.52	76.82 4.87
V_c	245 (E)	Yellow	$C_{25}H_{22}O_3N_2$	51	C 75.10 H 5.23	75.37 5.52
V_d	116 – 117 (P)	Yellow	$C_{22}H_{18}O N_2$	22	C 80.53 H 5.04	80.98 5.53
V_e	223 – 224 (E)	Green	$C_{24}H_{20}O_2N_2$	58	C 78.12 H 5.16	78.26 5.43
V_f	98 – 100 (P)	Yellow	$C_{33}H_{23}N_3$	43	C 85.48 H 4.53	85.90 4.98
V_g	237 (B)	Yellow	$C_{23}H_{20}O N_2$	52	C 80.96 H 5.38	81.17 5.88
V_h	241 (B)	Pale Yellow	$C_{24}H_{22}O N_2$	44	C 80.72 H 6.12	81.35 6.20

Synthesis and reactivity of a Nicotinonitrile derivative

Table 1 Contd.

Compound	m.p. (Solvent)*	Colour	Molecular Formula	Yield %	Elemental Analysis %	
					Found	Calculated
V _i	163 (E)	Brown	C ₂₄ H ₁₉ O ₂ N ₃	60	C 75.46 H 4.81	75.59 4.98
V _j	247 (B)	Yellow	C ₂₉ H ₂₄ O ₂ N ₂	43	C 79.72 H 5.10	80.55 5.55
V _k	120–122 (P)	Yellow	C ₂₈ H ₃₀ O N ₂	32	C 81.36 H 6.80	81.95 7.31
V _l	80–83 (E)	Yellow	C ₃₂ H ₂₂ N ₂	30	C 87.87 H 4.81	88.47 5.06
V _m	178 (E)	Brown	C ₂₇ H ₁₉ N ₃	50	C 83.66 H 4.38	84.15 4.93
V _n	244 (E)	Yellow	C ₂₄ H ₂₂ O ₂ N ₂	53	C 77.63 H 5.73	77.83 5.94

* (B) = Benzene (E) = Ethanol

(P) = Pet. ether (80–100)

Table 2
The infrared spectra for reaction products of (I)
with some compounds containing active methylene groups

Compound	Group frequencies (cm ⁻¹)			
	ν C \equiv N	ν C=O	ν C=C	ν C-H
V _a	2220	1640		
V _c	2215	1640	1575	
V _e	2180	1680, 1700	1605	
V _f	2205		1620	
V _g	2205	1680	1575, 1615	
V _h	2220	1665	1610	
V _j	2210	1720	1615	
V _k	2200	1700	1585	
V _l	2200		1560, 1580	
V _n	2205		1620	2910

Table 3
¹H NMR spectra for reaction products of (I)
with some compounds containing active methylene groups

Compound	Chemical shift (δ) in ppm		Groups
V _d	7.15 – 7.95	(m)	10H, aromatic protons
	3.50	(s)	2H, one CH ₂ group
	2.50	(s)	3H, one CH ₃ group
	1.80	(s)	3H, one CH ₃ group
V _e	7.20 – 8.10	(m)	10H, aromatic protons
	3.35	(s)	1H, one CH group
	2.50	(s)	3H, one CH ₃ group
	1.60	(s)	6H, two CH ₃ group
V _l	6.80 – 7.95	(m)	14H, aromatic protons
	2.95	(s)	1H, one CH group
	2.55	(s)	3H, one CH ₃ group

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تخليق ونشاطية

٢-كلورو-٤-فينيل-٦-بارا-طويليل-نيكوتينونيتريل
تجاه بعض الكواشف النيوكليوفيليه

السيد سليمان و إبراهيم صالح النعيمي

و

بدرية عبد الوهاب حسين

يتناول هذا البحث تخليق وتفاعل مركب ٢ - كلورو - ٤-فينيل - ٦ - بارا - طويليل - نيكوتينونيتريل (I) مع هيدرات الهيدرازين ، أزيد الصوديوم ، واليوريا ليعطي مشتقات الهيدرازينو ، التيترازولوبيريدين واليوريا ، على التوالي ، كذلك فإن هذا البحث يتضمن تفاعل المركب (I) مع مركبات تحتوي على مجموعة مثيلين منشطة ، ويناقش سبل تكوين وأشكال المركبات الناتجة من هذه التفاعلات .