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단신

4,6-Dimethyl-2-oxo/Thio-nicotinonitrile의 N-, O-알킬화 반응

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N- *vs.* O-alkylation on 4,6-Dimethyl-2-oxo/Thio-nicotinonitrile

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주제어: 락탐-락팀 호변이성질체, 치환반응

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INTRODUCTION

3-Cyano pyridine i.e. nicotinonitrile, over last decades had been synthesized using nicotinamide.[1] Presence of prototropic tautomerism in pyridone moiety they forms N alkyl and O alkylated products, and N-alkylated pyridones are useful in synthesizing alkaloids.[2] Pyridone moieties having both donor and acceptor properties and due to their characteristic features they dimerised easily. Tautomeric effect in pyridone moiety have a prototropic tautomerism,found in many heterocyclic systems.[3] In non polar medium enol tautomeric form predominates where as in polar solvents N-alkylated product have been obtained in maximum yield.[4] N *vs*. O alkylation of 2- pyridone[5] and other heterocyclic ambident anions[6] has been extensively investigated. The ratio of products formed selectively depends on solvent, cation and alkylating agents.

Several authors[7,8] have discussed the formation of N *vs*. O alkylation product on pyridone but a reliable assessment of the factors which govern product distribution was limited by the absence of a sufficient body of comparable data.

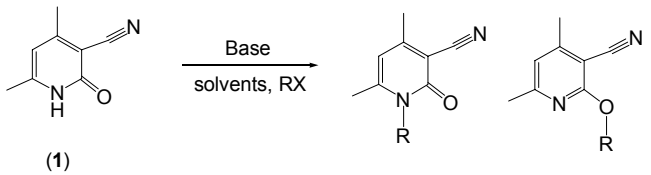
Alkylation on 2-pyridone[9] is influenced by steric factors to result the formation of O-alkylated or N-alkylated product but it has been illustrated that oxygen alkylation was favored when a methyl group occupied the 6- position of 2-pyridone and bulky alkylating agents were employed.[10] It has also been proposed that electron withdrawing substituents on ortho and para positions to 2-oxo group favored alkylation at nitrogen in 2 pyridones.[9]

RESULT AND DISCUSSION

Present paper reports a systematic study of the sensitivity of the alkylation site of the 4,6-dimethyl-2-oxo-nicotinonitrile[11] i.e. 3-cyano-4,6-dimethyl-2-oxo-pyridone (**1**) and 4,6-dimethyl-2-thio-nicotinonitrile[12] i.e. 3-cyano-4,6-dimethyl-2-thio pyridone (**2**) towards a number of factors known to have influence in other ambident anion systems.[13-16] Factors such as solvent, leaving groups, bases and alkyl halide structure were systematically varied during the reaction (*Scheme* 1 and 2).

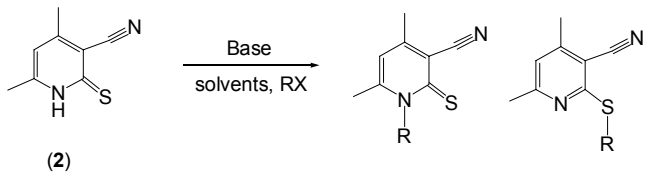
Table 1 summarizes the data which show the influence of alkylating agent, base and solvent in determining the reaction site in compound **1** while *Table* 2 shows the similar summarized data for compound **2**.

In case compounds **1** and **2** the heterocyclic moiety having an electron withdrawing CN group at ortho to oxo and thio while two bulkier methyl groups at position 4 and 6 acts as electron releasing group, balanced the electronic environment and encourages us for describing a new observation in alkyl-



(**1**)

Scheme 1



(**2**)

Scheme 2

Table 1

Alkylating agents	Bases	Solvents	Ratio of product		
			N-alkyl	O-alkyl	Starting/NO
MeI	KOH	MeOH	68.63%	0%	…….
MeI	KOH	DMF	85%	0.02%	…….
MeI	K_2CO_3	DMF	45%	28%	…….
MeI	KOH	Dry DMF	99%	0.5%	…….
MeI	KOH	DCM	2.27%	0.68%	65%
MeI	KOH	Toluene	0.45%	0%	75%
EtI	KOH	MeOH	76.65%	0.2%	……
EtI	KOH	DMF	58%	0.28%	……
EtI	K_2CO_3	DMF	48%	22.9%	…….
EtI	KOH	Dry DMF	27.27%	6.81%	…….
EtI	KOH	DCM	3.23%	0.48%	59.5%
$BrCH_2CH_2Br$	K_2CO_3	DMF	0.93%	3.6%	36%
$BrCH_2CH_2Br$	KOH	DMF	0%	2.56%	32%
$BrCH_2CH_2Br$	K_2CO_3	Dry DMF	1.03%	0%	16.58%
$BrCH_2CH_2CH_2Br$	K_2CO_3	DMF	1.8%	16.95%	20%
$BrCH_2CH_2CH_2Br$	KOH	DMF	0%	1.06%	25.2%
$BrCH_2CH_2CH_2Br$	K_2CO_3	Dry DMF	2.4%	0.8%	20%
$BrCH_2CH_2CH_2Br$	NaH	DMF	0.6%	1.86%	23.87%
$PhCH_2Cl$	K_2CO_3	DMF	68.18%	34.04%	……
$PhCH_2Cl$	KOH	DMF	70.28%	20.56%	…....

Table 2

Alkylating agents	Bases	Solvents	Ratio of product		
			N-alkyl	S-alkyl	2/NS
MeI	K_2CO_3	DMF	0%	56.19%	....
MeI	KOH	DMF	0%	58%	....
MeI	K_2CO_3	DCM	0%	48%	52%
EtI	K_2CO_3	DMF	0%	62%	....
EtI	KOH	Dry DMF	0%	64%	....
$PhCH_2Cl$	K_2CO_3	DMF	0%	57%	....
$PhCH_2Cl$	KOH	DMF	0%	60%	....
$BrCH_2CH_2Br$	KOH	DMF	0%	69.89%	....
$BrCH_2CH_2Br$	K_2CO_3	DMF	0%	69.83%	....
$BrCH_2CH_2CH_2Br$	KOH	DMF	0%	72.12%	....
$BrCH_2CH_2CH_2Br$	K_2CO_3	DMF	0%	70.58%	....

ation products.

Lactum-lactim type of tautomerization in 2 pyridone has been earlier studied, where ortho position of oxo group has the capability to form hydrogen bond.[17] In solution, the lactam-lactim ratio depends on the polarity of the solvent. The lactim tautomer is a better hydrogen bond donor and acceptor and predominates as a solvated monomer in polar or protic media.[18] In apolar solvents, the tautomeric equilibrium is influenced by dimerisation. Due to its polar nature, the lactam tautomer exists predominantly as a hydrogen-bonded dimer in apolar media. On the other hand, the less polar lactim tautomer is also found as a monomer in apolar solvent.[19]

In solution the pyridone moiety behaves as ambident anoin which can alkylated both at nitrogen and oxygen atom.[20] The nitrogen atom act as a soft nucleophilic centre and that's why the reaction undergoes *via* SN2 mechanism while oxygen atom acts as hard nucleophilic centre and the alkylation takes *via* SN1 mechanism.[21] In the case of polar protic solvent medium the methylation more favorably takes place on N site with absence of O-methylating compound however when the same condition maintained in case of bulkier ethyl group the formation of O alkylating product has been favoured with maximum amount of N ethylated product. The above fact may be due to the increasing the steric factor of alkylating agent.

However when we move from polar protic to polar aprotic solvent the overall yield of product increases with the formation of O alkylated product in minimum amount. This effect also has been increases in all cases when we use weak base instead of stronger one.

In non polar solvents the reaction has not been completed and major amount of starting material remains in reaction mixture. When dihalides have been used instead of methyl and ethyl iodide the formation of O dimers has been favoured instead of N dimer in solvent medium where as in dry solvent the formation of O dimers are not favorable one. This favors the rule that O alkylation favors SN1 mechanism and formation of bulkier carbocation intermediate favored forward reaction. In case of 1,2-dibromoethane and 1,3-dibromopropane the O alkyl-

ated product have been observed in major amount in DMF however in case of dry DMF the N-alkylated product have been dominating one. An abrupt change observed in these cases that when we used dihalide the formation of NO linked dimers has been found in maximum yield in any case. Formation of benzylated product does not explain the above thought because in this case again the N benzylated product has been found in maximum amount however in strong basic condition the overall yield of products have been increases.

In case of compound **2** just reverse result obtained where S-alkylated product is formed due to the reason that sulfur atom having a greater nucleophilicity than the nitrogen while oxygen atom having less nucleophilicity than nitrogen and more favorable S alkylated product predominated over N alkylated product in each case whether the alkylating agent or base may be bulkier and stronger. Only the effect observed in the yield of product obtained where in presence of stronger base the yield of overall product formation has been found increases.

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11. Cyanoacetamide (4.2 g, 0.05 moles) was dissolved in ethanol and aqueous solution of potassium carbonate (2 g, 0.05 moles) was added. The reaction mixture was followed by adding acetyl acetone (5 g, 0.05 moles). Reaction mixture was left for stirring overnight. Precipitate so obtained was filtered and washed with cold ethanol. Compound was dried in air. m.p. 287 ~ 289 ^{o}C Yield: 4.9g (66.6%) ^{1}H -NMR ($CDCl_3$) δ 2.41 (s, 3H, C<u>H</u>$_3$), δ 2.43 (s, 3H, C<u>H</u>$_3$), δ 6.08 (s, 1H, ArC<u>H</u>). IR (KBr): 639-772 cm^{-1} (C-H bending), 1377 cm^{-1} (C-N stretching), 1657 cm^{-1} (C=O stretching), 2217 cm^{-1} (CN stretching), 2856-2920 cm^{-1} (C-H stretching). M+ ion peak: 148.
12. In a 250 mL R. B. flask attached with reflux condenser in oil bath 30 mL β-picoline was heated up to 120 ^{o}C. In it fractions of phosphorus penta sulfide (16.6 g, 0.075 moles) added up to 0.5 hr with stirring. After complete addition 3-cyano, 4,6-dimethyl-2-oxo-nicotinonitrile (1) was added in it & refluxed at same temperature for 5hr. Removed the extra solvent through rotary evaporator and 50 mL hot water added in it. Refluxed again the reaction mixture for 15 min, cooled and filtered. m.p. above 240^{o} Yield: 2.5 g (53.2%); ^{1}H NMR ($CDCl_3$, 300 MHz); δ 2.44 (s, 3H, C<u>H</u>$_3$), δ 2.46 (s, 3H, C<u>H</u>$_3$), δ 6.41 (s, 1H, HetArC<u>H</u>), IR (KBr, cm^{-1}); 606-842 (CH bending), 1374 (C-N stretching), 1442-1613 (C=C, aromatic stretching), 2217 (CN stretching), 2872-2955 (CH stretching), 3447 (NH stretching). M+ ion peak: 150.
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