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HILBERT-JOHNSON REACTION UNDER HIGH PRESSURE: A FACILE PREPARATION OF 2-PYRIDONES

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Dedicated to Professor Yoshito Kishi on the occasion of his 70th birthday

Abstract – For the first time, a facile synthesis of 2-pyridones utilizing a classical Hilbert-Johnson reaction of 2-methoxypyridines with haloalkanes under high pressure has been achieved. The reactions were sensitive to steric hindrance of haloalkanes.

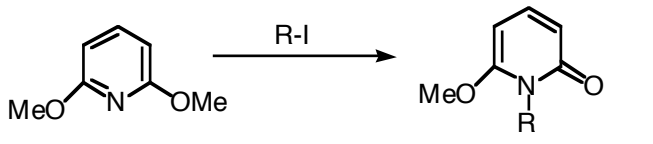
INTRODUCTION

Irreversible lactim-lactam tautomerization has been recognized a long time ago and generally either achieved by heat or catalysts. One of the synthetic applications was reported by Knorr as early as 1897.[1] Later, this reaction was first applied to synthesis of pyrimidine-nucleoside by Johnson and Hilbert,[2] thus being called as Hilbert-Johnson reaction (HJR). The reactions have been employed as one of protocols for preparations of pyrimidine-nucleosides.[3] The biological and medicinal interest in pyrimidines[4] affords further impetus to prepare new types of their derivatives.[5] Because of synthetic utilities of HJR for synthesis of pyrimidine-nucleosides, a more sophisticated version of HJR has been developed employing silyloxypyrimidines rather than alkoxypyrimidines with aids of Lewis acids such as $AlCl_3$, $SnCl_4$, and $Me_2SiSO_3CF_3$ by Vorbrüggen (the silyl HJR:VHJR).[6] In particular, the VHJR was used, as one of key steps, for total synthesis of the anthelmintic agent hikizimycin.[7] The classical HJR is not limited to 2,4-dialkoxypyrimidines with haloalkanes and halogenoses. Specifically, reaction of 3,5-diethoxy-1,2,4-thiadiazole with benzyl bromide gave benzylethoxy-thiazolinone.[8] The HJR is amenable to dimethoxypyridines but requires more harsh conditions probably because of less electron deficient nature than pyrimidines. Therefore, as an initial stage of studies on HJR, we performed HJR under high pressure because we needed for some time pyridones which undergo Diels-Alder reaction with such reactive dienophiles as dimethyl acetylenedicarboxylate to give the corresponding adducts that could serve as an

isoquinuclidine skeleton.[9, 10]

RESULTS AND DISCUSSION

An initial and dramatic example would be 2,6-dimethoxypyridine (**1**) with iodomethane. Thus, reaction of **1** with an excess of iodomethane at 0.6 GPa and 40 ºC for 24 h afforded 6-methoxy-1-methyl-2-pyridone (**2a**) quantitatively, whereas at 0.1MPa and 80 ºC for 24 h the same reaction yielded 35 % of **2a**.[11] Since the first step of HJR is clearly quaternization (Menschutkin reaction) of **1** which has two methoxy groups at *ortho*-positions, the reaction would be sensitive to structures of iodoalkanes.[12] This was indeed the case as shown in Table 1. 1-Iodopropane with **1** even at higher pressure and temperature and for a longer reaction time gave **2c** only in moderate yield. Unfortunately, 2-iodopropane and 2-iodobutane were almost inert to **1** under the same conditions (0.8 GPa, 100 ºC, 48 h).



1

2a: R=Me
2b: R=Et
2c: R=n-Pr

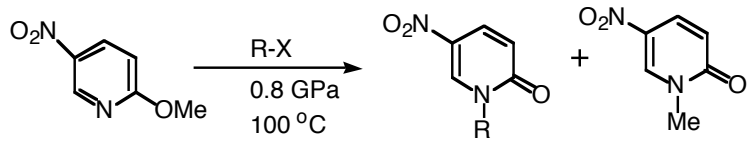
Scheme 1. HJR of 2,6-dimethoxypyridine (**1**) with iodoalokanes (**2**)

Table 1. Reaction of iodoalkanes with **1**

R	Pressure (GPa)	Temperature (ºC)	Reaction time (h)	Yield[a] (%)
Me	0.6	40	24	100
Et	0.8	80	48	35
Et	0.8	100	48	83
n-Pr	0.8	100	48	56

a) Isolated yield based upon **1** and not optimized. Starting materials are recovered except in the case of reaction with iodomethane

To help clarify further scope and limitations, a commercially available 2-methoxy-5-nitropyridine (**3**) was chosen as a substrate and at 100 º the reactions were performed C and 0.8 GPa. The results are Summarized in Table 2.[13] Reaction of iodomethane and iodoethane with **3** afforded **4a** and **4b** albeit only



3

4a: R=Me
4b: R=Et
4c: R=n-P**r**
4d: R=Bn

4a

Scheme 2. HJR of 2-methoxy-5-nitroypyridine (**3**) with haloalkanes

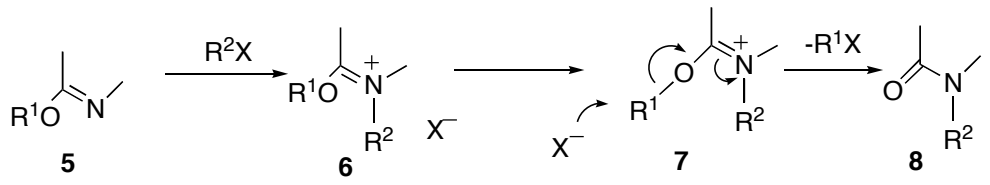
Table 2. HJR of 2-methoxy-5-nitropyridine (**3**) with haloalkanes[a)]

R	X	Time (days)	Yield (%)	
			4	**4a**
Me	I	2	63	---
Et	I	4	15	nd[b]
n-Pr	I	3	31	30
$PhCH_2$	Br	3	70	12

[a] Isolated yields based upon **3** and not optimized. In all the cases starting materials were recovered.
[b] Not detected.

in low yield in the latter case. However, iodopropane and benzyl bromide gave **4c** and **4d** in moderate yields along with **4a**.

The postulated mechanism of the HJR for pyrimidine nuleoside synthesis is an initial quaternization of nitrogen heterocycles **5**, followed by halide assisted lactim-lactam tautomerization of **7** (Scheme 3).[14] In view of this mechanism, **4a** presumably formed by reaction of liberated MeX with **2** in the cases of relatively larger groups such as n-Pr and Bn than Me because of a long reaction time.



Scheme 3. Postulated mechanism of HJR

Further studies on a classical HJR and, in particular VHJR, ***under neutral conditions*** for exploration of synthetic applications to pyrimidine-nucleosides are underway and will be reported in due course.

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13. A typical experimental procedure: A mixture of **3** (0.462 g, 3 mmol) and iodomethane (6 mL) is placed in an 8 ml Teflon capsule and compressed to 0.8 GPa , then heated to 100 ^{o}C for 2 days. After cooling to room temperature, the capsule was taken from the high pressure instrument. The precipitate (0.2803 g) was filtered. The solid was already pure **4a**. After evaporation of excess iodomethane, the residue was subject to a short column chromatography on SiO_2 (ethyl acetate/benzene=1/10). Thus, additional **4a** (0.0150 g). Total isolated yield: 63 %: colorless solid: mp 168-169 ^{o}C; ^{1}H-NMR ($CDCl_3$) δ 3.59 (s, 3H), 6.45 (d, 1H, J=10 Hz), 8.00 (dd, 1H, J=2.7, 10 Hz), 8.53 (d, 1H, J=2.7 Hz). Anal. Calcd for $C_6H_6N_2O_3$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.45; H, 3.74; N,18.33.
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