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MICROWAVE ASSISTED RAPID PREPARATION OF *N*-ALKYL-2-PYRIDONES UNDER NEUTRAL CONDITIONS BY HILBERT-JOHNSON REACTION

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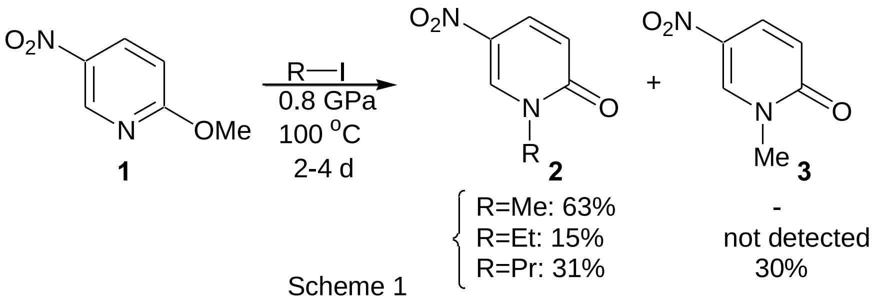
Abstract – The reactions of 2-methoxypyridine with haloalkanes without solvent and catalyst under microwave irradiation (100-200 °C, 5 min) yielded the corresponding *N*-alkyl-2(1*H*)-pyridones in good to moderate yields. However, the reactions were sensitive to length of haloalkanes. In contrast, the reactions of 2-alkoxypyridines with corresponding iodoalkanes under microwave irradiation (150 °C) proceeded rapidly without catalyst and solvent, and were complete within 5 min to afford *N*-alkyl-2(1*H*)-pyridones in good to excellent yields.

INTRODUCTION

N-Alkyl- and *N*-aryl-2(1*H*)-pyridones have been screened for their biological activity.[1-3] Recently, it was reported that the *N*-phenyl-2(1*H*)-pyridone derivative, perampanel acted as a noncompetitive and selective AMPA-receptor (subtype of ionotropic glutamate receptors) antagonist and that it demonstrated evidence of efficacy in reducing motor symptoms in animal models of Parkinson's disease.[4] From the synthetic view point, *N*-alkyl-2(1*H*)-pyridones are also useful as building blocks.[5,6]

The synthesis of *N*-alkyl-2(1*H*)-pyridones is feasible by alkylation of 2-pyridones. In this case selectively switching the reaction course is required to induce the *N*- or *O*-alkylation. In general, *N*-alkylation is performed via the sodium salt and *O*-alkylation via the silver salt, but a mixture of *N*- and *O*-alkylation was obtained in almost all cases.[7] Since these reactions were performed under basic conditions, a milder procedure using the Mitsunobu reaction was reported.[8] This method gave *O*-alkylation products mainly accompanied with lower ratio of *N*-alkylation products (<3.5:1). The other promising method for the synthesis of *N*-alkyl-2(1*H*)-pyridones under milder conditions is the use of Hilbert-Johnson type reaction.

The Hilbert-Johnson reaction[9] involves a coupling of 2-methoxypyridine and iodoalkane for the synthesis of *N*-alkyl-2-pyridones on the basis of irreversible lactim-lactam tautomerization, and was applied to the synthesis of pyrimidine-nucleoside.[10] We have applied the Hilbert-Johnson reaction to the synthesis of *N*-alkyl-2(1*H*)-pyridones (**2**) (Scheme 1). Reaction of 2-methoxy-5-nitropyridine **1** with iodoalkanes afforded the corresponding *N*-alkyl-5-nitro-2-pyridone **2** in moderate to poor (63-15%) yields accompanied by the *N*-methyl form **3** as a by-product under high pressure (0.8 GPa, 80-100 °C) and with long reaction times (2 d - 4 d).[11] These results suggested that *N*-alkyl-2(1*H*)-pyridones were obtained under neutral conditions using the Hilbert-Johnson reaction, but formation of side product **3**, *N*-methyl-2-pyridone and the long reaction time were problematic.



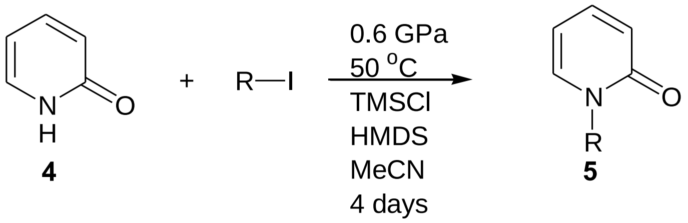
Scheme 1

In order to optimize reaction conditions, we investigated the effect of microwave irradiation on the Hilbert-Johnson reaction. We have also been interested in the reaction in the absence of solvent and catalyst. We have reported[12,13] that microwave irradiation might assist such 1,2- and/or conjugate additions using TMSCN without catalyst and additive. We applied the method of microwave irradiation without catalyst and solvent to Hilbert-Johnson reaction for the synthesis of *N*-alkyl-2(1*H*)-pyridones possessing long alkyl chains.

RESULTS AND DISCUSSION

At first, we investigated direct *N*-alkylation of 2-pyridone under high pressure conditions. Under neutral conditions, we have not succeeded in introduction of long alkyl chains. However, the reaction of **4** with iodoethane and iodopropane proceeded in the presence of TMSCl and HMDS in MeCN under high pressure (0.6 GPa and 50 °C) for 4 d to afford the corresponding *N*-alkyl-2-pyridones (**5**) in moderate yields, 65 and 70% respectively (Table 1). Using longer iodoalkanes (R=*n*-Bu, *n*-Hex, *n*-Hept) under similar conditions, the reaction yielded the corresponding *N*-alkyl-2-pyridones in moderate yields (45-63%, isolated yields) (Table 1). We succeeded in the synthesis of *N*-alkyl-2(1*H*)-pyridones possessing long alkyl chain as above. However these reactions were not complete in 4 days.

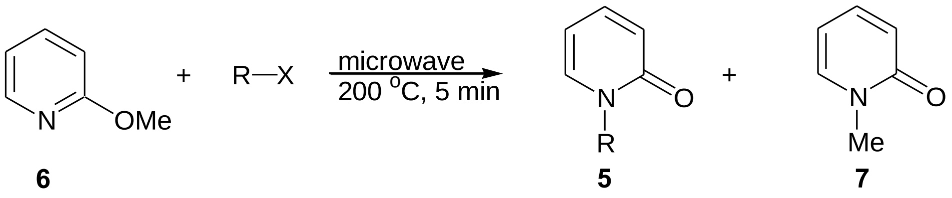
Table 1. Reaction of iodoalkanes with **4** under high pressure



R	Isolated yield of **5** (%)
Me	74
Et	65
Pr	70
n-Bu	63
n-Hex	56
n-Hept	45

In order to improve yields and shorten reaction times, we investigated the effect of microwave[14] irradiation for Hilbert-Johnson reaction using 2-methoxypyridine (**6**) without catalyst and solvent (Table 2). Reaction of **6** with iodomethane was complete within 5 min to afford **5a** (equal to **7** in this case) in excellent yield (94%) under microwave irradiation (200 ^{o}C) (Table 2, entry **a**).[14] We succeeded in shortening the reaction time dramatically for preparation of *N*-methyl-2(1*H*)-pyridone **5a** under neutral conditions. Using iodoethane and iodopropane, similar reactions gave **5b** and **5c** respectively in lower yields, along with **7** (Table 2, entries **b** and **c**).[11] Using bromoalkanes instead of iodoalkanes, the yields of **5** decreased remarkably (Table 2, entries **d**-**f**). And yet these reactions were not completed within 5 min.

Table 2. Reaction of **6** with haloalkanes under microwave irradiation

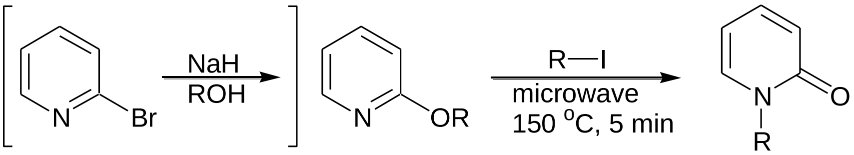


Entry	R	X	**6** : **5** : **7***	Isolated yield of **5**
a	Me	I	0 : 1 : -	94 %
b	Et	I	0 : 3 : 2	60 %
c	Pr	I	10 : 2 : 1	32 %
d	Et	Br	0 : 1 : 2	31 %
e	Pr	Br	10 : 2 : 1	24 %
f	Bu	Br	10 : 2 : 1	10 %

* Determined by ^{1}H NMR.

As the reaction of 2-methoxypyridine with iodomethane gave an excellent yield while the reaction using other haloalkanes yielded **7** as by-products, we changed starting materials to 2-alkoxypyridine and corresponding iodoalkanes. Starting 2-alkoxypyridines were prepared from the reactions of 2-bromopyridine and alcohols according to the method reported previously.[15] Reaction of the synthesized 2-propoxypyridine **8b** with 2 molar equivalents of iodopropane without catalyst and solvent under microwave irradiation (150 °C) proceeded smoothly, and was completed within 5 min to afford *N*-propyl-2-pyridone **5b** exclusively in 99% yield (Table 3, entry **b**). Generally, reaction of the 2-alkoxypyridine **8** with corresponding iodoalkanes (R=Me, *n*-Bu, *n*-Pent, *n*-Hex, *n*-Hept) under similar conditions yielded corresponding *N*-alkyl-2-pyridones **5**, exclusively in good to excellent yields (75-99%) (Table 3, entries **a**-**f**).[16] However, the reaction of **8a** with an excess of iodomethane under high pressure (0.6 GPa, 100 °C) yielded **5a** in 93% yield, but long reaction time (4 d) was required to complete the reaction. Now, we succeeded in the high yield and short reaction time preparation of *N*-alkyl-2(1*H*)-pyridones **5** including long alkyl chain under neutral conditions by microwave irradiation.

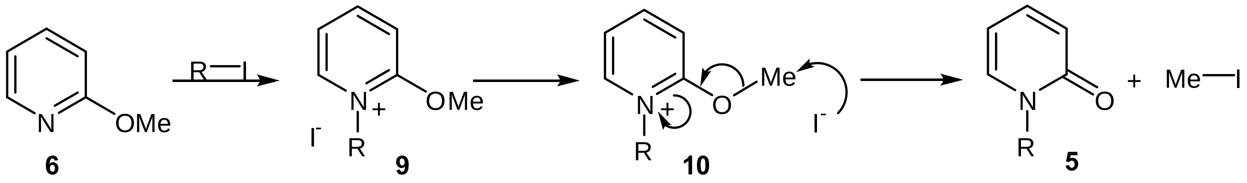
Table 3. Reaction of **8** with corresponding iodoalkanes under microwave irradiation



8 **5**

Entry	R	Isolated yield of **5**
a	Me	94 %
b	Pr	99 %
c	*n*-Bu	99 %
d	*n*-Pent	75 %
e	*n*-Hex	94 %
f	*n*-Hept	98 %

In order to understand the reaction mechanism, 2-methoxypyridine (**6**) was treated under microwave conditions in the absence of iodoalkanes, but no reaction occurred at all. This result indicated that the reaction requires iodoalkanes. Next, **6** was allowed to react with iodoethane for 1 day at rt, and then was microwave irradiated affording mainly pyridinium salt. On the basis of above result, the proposed mechanism of this reaction is an initial quaternization of pyridine nitrogen (**9**), followed by lactim-lactam tautomerization assisted by the attack of iodide ion (**10**) successively, under microwave irradiation (Scheme 2).[17] *N*-Methyl-2-pyridone **7** was presumably formed in the reaction of liberated MeI with **6** (Table 2).



Scheme 2. Proposed mechanism of Hilbert-Johnson reaction

In conclusion, we have demonstrated that reaction of 2-alkoxypyridine with corresponding iodoalkanes is suitable for the synthesis of *N*-alkyl-2-pyridones under neutral conditions by Hilbert-Johnson reaction. Microwave irradiation method made it possible to perform the reaction without solvent and catalyst and to reduce reaction time markedly. Reactions of halogenosugars and alkoxypyrimidines in microwave irradiation under neutral conditions for the synthesis of nucleoside will be reported in due course.

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14. Representative experimental procedure: Iodomethane (568 mg, 4 mmol) and 2-methoxypyridine (218 mg, 2 mmol) were thoroughly mixed in a CEM vial. This was capped and irradiated in a CEM Discover microwave to keep reaction temperature at 150 ^{o}C for 5 min. After cooling to rt, the mixture was evaporated *in vacuo* and the resulting oil was subjected to a short column chromatography on SiO_2 using EtOAc and MeOH (10:1) as an eluent to afford **10a** (205 mg, 94%). *N*-methyl-2(1*H*)-pyridone (**10a**): colorless oil, ^{1}H NMR ($CDCl_3$) δ: 3.28 (3H, s), 5.92 (1H, dt, *J*=14.4, 1.2 Hz), 6.27 (1H, d, *J*=9.2 Hz), 7.06-7.10 (1H, m), 7.10-7.15 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 37.4 105.8, 120.1, 138.4, 139.5, 162.9, IR (neat) 3401, 1652, 1565 cm^{-1}; *Anal.* Calcd for C_6H_7NO: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.31; H, 6.49; N, 12.74. All other isolated products in each reaction gave satisfactory elemental and spectral data (^{1}H NMR, ^{13}C NMR, IR) and were in agreement with those reported in the literature.[16-18] Yields were isolated ones after SiO_2 column chromatography and not optimized.
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