A SIMPLE METHOD FOR INTRODUCTION OF ACYL GROUPS INTO PYRIDINE NUCLEI *VIA* TRIMETHYLSTANNYL-PYRIDINES AND -QUINOLINES.[1)]

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Abstract —— *The 2-trimethylstannyl (TMSn) derivatives of pyridine and quinoline were directly treated with acyl chlorides to afford the corresponding 2-acyl-pyridines and -quinolines in good yields. On the other hand, replacement of the 3- and 4-TMSn groups by acyl groups was satisfactorily achieved by catalysis of palladium compound such as* $PdCl_2$ *or* $PdCl_2(PPh_3)_2$.

The preceeding paper[2)] from this laboratory demonstrated a general method for preparation of trimethylstannyl (TMSn) derivatives of pyridine and quinoline by treatment of chloro (or bromo)-pyridines and -quinolines with trimethylstannyl sodium. In the course of our investigation on the behavior of the TMSn group, it was found that each TMSn groups at 2-, 3-, and 4-positions in pyridine and quinoline could be replaced by acyl group to give the corresponding pyridyl and quinolyl ketones (4-11) in satisfactory yields, respectively. The preliminary results are described herein.

The substitution of acyl group for TMSn group at the 2-position on pyridine nucleus was smoothly accomplished. For example, 2-TMSn-quinoline (1b) was allowed to react with benzoyl chloride (2d) in dry benzene at room temperature with stirring for 3 hr to afford phenyl 2-quinolyl ketone (5d) in a high yield. Various 2-pyridyl (4b,d) and 2-quinolyl ketones (5a-c) were similarly prepared. The results are summarized in Table 1.

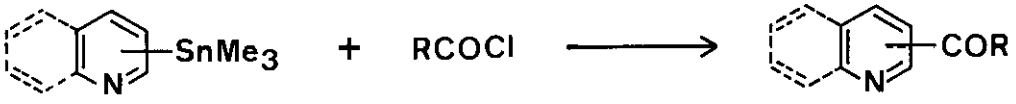

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Table 1. Preparation of 2-Acyl-pyridines (4b,d) and -quinolines (5a-d) from the 2-Trimethylstannyl Derivatives (1a,b)*.

2-TMSn Deriv.	Copmd. No.	RCOCl R	RCOCl No.	Reaction Condition Temp.(°C)	Time(hr)	2-Py and -Quin Ketones[3] mp(°C) or bp(°C/torr) [lit.mp(°C) or bp(°C/torr)]	Yield(%)	Product No.
2-Py	1a	c-hex	2b	r.t.	3	138-140/10 (111-116/0.8)[4]	77	4b
2-Py	1a	Ph	2d	r.t.	3	166-169/10 (165/7)[5]	68	4d
2-Quin	1b	Me	2a	0°-r.t.	5	50-52 (52-53)[5]	39[a]	5a
2-Quin	1b	c-hex	2b	r.t.	5	88-90 (---)[6]	76	5b
2-Quin	1b	*t*-Bu	2c	reflux	8	97-99/0.25	95	5c
2-Quin	1b	Ph	2d	r.t.	3	109-110 (111)[5]	74	5d

* Abbreviations : TMSn ; trimethylstannyl , Py ; pyridyl , Quin ; quinolyl , c-hex ; cyclohexyl , r.t. , room temperature .

a) The lower yield of 5a should be resulted from polymerization involved in the exothermic reaction.

On the other hand, similar treatment of 3-TMSn-pyridine (1c) and -quinoline (1d) with acyl chloride resulted in recovery of the respective starting 1c and 1d in high yields. In these reactions, employment of either $PdCl_2(PPh_3)_2$ (3a) or $PdCl_2$ (3b) as a catalyst led successfully to the formation of 3-pyridyl (6b,d) and 3-quinolyl ketones (7a-d) in good yields.[7] Thus, a mixture of 1d with cyclohexanecarbonyl chloride (2b) in dry benzene was heated for 8 hr under reflux in the presence of 3a as a catalyst to give rise to cyclohexyl 3-quinolyl ketone (7b) in an excellent yield together with a trace of 3,3'-biquinoline (12).[8]

In contrast, 4-TMSn-quinoline (1g) considerably resisted the acylation and required much longer reaction time, whereas 4-TMSn-pyridines (1e,f) readily reacted likewise in the cases of 1c,d. Furthermore, it was found that 3a was uneffective as a catalyst in the acylation of 1g, while 3b was capable of catalyzing the reaction. Thus, the reaction of 1g with 2b necessitated heating for 4 days under reflux in the presence of 3b to form cyclohexyl 4-quinolyl ketone (10b) in a fair yield along with a trace of 4,4'-biquinoline (13). The experimental data for the acylation of 1c-g are listed in Table 2.

Similar treatment of 4-TMSn-pyridine (1h) with 2 in the presence of 3a or 3b led to a viscous substance, hardly purified, without any isolable products. However, 4-TMSn-pyridine (1h), when subjected to the reaction with an equimolar amount of $PdCl(COC_6H_{11})(PPh_3)_2$ (3c) prepared from $Pd(PPh_3)_4$ (3d) and 2b, underwent the conversion into cyclohexyl 4-pyridyl ketone (11b) in a quantitative yield.

Table 2. Preparation of 3- and 4-Acyl-pyridines (6, 8, 9, and 11) and -quinolines (7 and 10) from the respective 3- and 4-Trimethylstannyl Derivatives (1c-h).*

3-(and 4-)TMSn Derivatives	Compd. No.	RCOCl R	RCOCl No.	Reaction Condition (refluxed in benzene) Catalyst[a]	Time	3-(and 4-)-Py and -Quin Ketones[3] mp(°C) or bp(°C/torr) [lit.mp(°C) or bp(°C/torr)]	Yield(%)	Product No.
3-Py	1c	c-hex	2b	3a	8 hr	164-165/15 (100-103/0.1)[9]	68	6b
3-Py	1c	Ph	2d	3a	8 hr	156-157/7 (154-156/2.5-2.7)[10]	67	6d
3-Quin	1d	Me	2a	3a	8 hr	100-102 (97-101)[11]	70	7a
3-Quin	1d	c-hex	2b	3a	8 hr	72-74	80	7b
3-Quin	1d	c-hex	2b	3b	8 hr	72-74	73	7b
3-Quin	1d	*t*-Bu	2c	3a	8 hr	141-143/0.9	73	7c
3-Quin	1d	Ph	2d	3a	8 hr	74-76 (76-77)[10]	71	7d
4-(2-M-)Py	1e	c-hex	2b	3a	8 hr	156-158/10	67	8b
4-(2-M-)Py	1e	Ph	2d	3a	8 hr	163-165/10 (135-138/2)[12]	60	8d
4-(2,6-DM-)Py	1f	c-hex	2b	3a	8 hr	160-161/9	73	9b
4-(2,6-DM-)Py	1f	Ph	2d	3a	8 hr	158-161/10 (155-159/9)[12]	70	9d
4-Quin	1g	Me	2a	3b	4 day	118-121/1.0 (105/0.5)[13]	24	10a
4-Quin	1g	c-hex	2b	3b	4 day	75-77	50	10b
4-Quin	1g	*t*-Bu	2c	3b	4 day	130-132/1.0	trace	10c
4-Quin	1g	Ph	2d	3b	4 day	163-165/0.25 (154/0.5)[13]	47	10d
4-Py	1h	$PdCl(COC_6H_{11})(PPh_3)_2$[b]			3 hr	170-175(bath temp.)/10 (63-66/0.05)[14]	86	11b

* Abbreviations : TMSn ; trimethylstannyl , Py ; pyridyl , Quin ; quinolyl , 4-(2-M-)Py ; 4-(2-methyl)pyridyl , 4-(2,6-DM-)Py ; 4-(2,6-dimethyl)pyridyl , c-hex ; cyclohexyl.

a) 3a ; $PdCl_2(PPh_3)_2$, 3b ; $PdCl_2$

b) This complex (3c) was prepared from $Pd(PPh_3)_4$ (3d) and 2b by similar method described in the literature[15], and was used instead of 2b.

The pathway to 4 and 5 from 1 presumably involves *N*-acylation and subsequent migration of the acyl group to the 2-position with loss of chlorotrimethylstannane (14). On the other hand, the acylation of 1c-f by the catalysis of 3a would be explained by the following sequence: metathesis between 1d and 3a, followed by reductive elimination, affords 12 and active catalyst $Pd(PPh_3)_2$ (3e). To the resulting 3e, 2b adds oxidatively to form the complex 3c, which then undergoes metathetical replacement of chloride by 3-quinolyl group to yield the complex $Pd(COC_6H_{11})(3\text{-Quin})(PPh_3)_2$ (3f). Subsequently, 7b and 3e are eliminated from 3f, and 3e serves again as a catalyst in the reaction between 1d and 2b.

The action of 3b as a catalyst in the reaction of 1g would essentially be same as that of 3a in the reaction of 1d, although clear explanation for the lower reactivity of 1g than those of 1b,d cannot be given at present.

REFFERENCES AND NOTES

1. A part of this work was presented at the 17th Annual Meeting of Tohoku Branch, Pharmaceutical Society of Japan, Sendai, October 1978, Abstracts of Papers, p.10.
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3. All compounds exhibited IR and NMR data in full accord with their structure and new compounds gave satisfactory microanalysis (C; ±0.27%, H; ±0.29%, N; ±0.29%).
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6. Mp or bp was not designated in the literature, see E. C. Taylor, M. L. Chittenden, and S. F. Martin, *Heterocycles*, 1, 59 (1973).
7. There have been the literatures concerning the palladium catalyzed reactions of organotin compounds with acyl chlorides: (a) M. Kosugi, Y. Shimizu, and T. Migita, *Chem. Lett.*, 1423 (1977), (b) D. Milstein and J. K. Stille, *J. Am. Chem. Soc.*, 100, 3636 (1978), and (c) *Idem*, *J. Org. Chem.*, 44, 1613 (1979). However, no example of π-deficient heteroaromatics was shown in them. In the reaction of 1g with 2b in HMPA in the presence of $C_6H_5CH_2Pd(PPh_3)_2Cl$, according to the procedure described in the paper (c), the coupling product (10b) could not be detected.
8. 3,3'-Biquinoline (12) was quantitatively obtained on heating 1d with a half equivalent of 3a or 3b in dry benzene under reflux for 3 hr.
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