yield of phenacylaniline in the above reaction is 40% based on unrecovered **3**.

Preparation and Reduction of *cis*- and *trans*-1. The cis and trans anils were prepared as described previously and observed to have the reported spectral characteristics.[2] Each of the anils was reduced with $NaBH_4$ in the manner indicated for reduction of phenacylaniline. The hydrochlorides (34% from *cis*-**1** and 46% from *trans*-**1**) were compared to each other and to the hydrochloride of **6**. All three compounds proved to be the same by virtue of melting point, mixture melting point, and identity of IR spectra.

The cis anil was reacted with aniline in the manner described by Yates for reaction of phenylglyoxal with aniline.[1] A 4.5% yield of impure **3** was obtained; mp 169–173 °C.

Reaction of Phenylglyoxal with Aniline. Phenylglyoxal hydrate[7] was reacted with freshly distilled aniline using the procedure described by Proctor.[2] In a typical run, 7.70 g (50.6 mmol) of phenylglyoxal hydrate, 4.17 g (50.6 mmol) of aniline, and 10 mL of acetic acid in 50 mL of 95% ethanol were heated on a steam bath for 30 min to give 10.80 g of an orange oil. TLC showed that a minimum of seven compounds were present in the oil which was chromatographed on 100 g of Florisil.[8] Elution with 2:1 hexane–benzene gave, after crystallization from acetone, 34 mg (0.3%) of impure **3**, mp 165–168 °C. The IR spectrum of this material was identical to that of pure **3** obtained in other ways and it also did not depress the melting point of pure **3**.

The majority of the product was eluted with benzene in several fractions. Crystallization of the early benzene fractions yielded 2.54 g of yellow crystals, mp 68–76 °C. Recrystallization of the material from heptane failed to change the melting point significantly. The substance had the spectral properties described by Proctor for his major product but its mass spectrum was very complex. All of the ions observed for **5** were also observed for this material; in addition, ions were seen at *m/e* (rel intensity) 518 (23), 354 (5), 313 (11), 222 (5), 122 (5), and 120 (6). The compound of mass 518 is unstable. After standing for 1 month, no ion above *m/e* 389 was observed. Instead, an intense peak at *m/e* 93 was detected, probably due to aniline released in the decomposition.

When the mother liquors from the crystallization of the above product were allowed to evaporate slowly, rounded domes of yellow crystals were formed. Crystallization of these from 95% ethanol yielded 1.07 g (13%) of **5**: mp 173–175 °C. The anlytical sample melted at 175.5–176.5 °C: IR (Nujol) 1695, 1660, 1590, 1205 cm^{-1}; UV λ_{max} (EtOH) 243 (ϵ 34 400), 285 nm (ϵ 12 900); NMR ($CDCl_3$) δ 5.85 (s, 1 H), 6.47 (s, 1 H), 6.6–8.0 (m, 25 H); MS *m/e* (rel intensity)388 (57), 195 (12), 182 (100), 180 (10), 105 (21), 104 (24), 77 (57), 51 (8). High resolution mass measurements gave *m/e* 388.1824 ($C_{27}H_{22}N_3$ requires 388.1815) and *m/e* 182.0869 ($C_{12}H_{10}N_2$ requires *m/e* 182.0844).

Anal. Calcd for $C_{34}H_{27}N_3O$: C, 82.72; H, 5.52; N, 8.51. Found: C, 83.06; H, 5.61; N, 8.39.

Compound **5** underwent reaction when boiled in ethanol containing 10% concentrated HCl and also absorbed H_2 at atmospheric pressure in the presence of a Pd on charcoal catalyst. Apparent mixtures of products were formed.

The final homogeneous fraction was eluted from the column with 1:1 $CHCl_3$–MeOH. Low-temperature (−80 °C) crystallization from ethanol gave 0.68 g (9%) of **4**, mp 125–128 °C. The melting point is not indicative of the purity of the compound since an odor of aniline begins to emanate from the solid well below the melting temperature. TLC of the sample on silica gel gave one well defined spot while older, decomposed samples gave at least four spots. The substance had: IR (Nujol) 3410, 1695, 1590, 1215 cm^{-1}; UV λ_{max} (EtOH) 246 (ϵ 24 100), 286 nm (ϵ 3650); NMR ($CDCl_3$) δ 4.56 (broad, 2 H), 6.39 (s, 1 H), 6.6–8.1 (m, 15 H). Addition of D_2O caused the signal at δ 4.56 to disappear. MS *m/e* (rel intensity) 197 (28), 195 (10), 122 (24), 120 (22), 105 (94), 104 (11), 77 (100), 51 (24). High resolution measurements gave *m/e* 197.1076 ($C_{13}H_{13}N_2$ requires 197.1080). Compound **4** could not be dried adequately without decomposition so the mass spectrum had a water peak at *m/e* 18.

The other fractions obtained from the chromatography were solids or oils which could not be characterized.

Acknowledgment. The author is grateful to Mr. Kenneth Brown for experimental assistance and to the Department of Chemistry of Indiana University, Bloomington, Indiana for the determination of the mass spectra.

Registry No.—*cis*-**1**, 66749-85-7; *trans*-**1**, 66749-86-8; **3**, 66749-87-9; **4**, 66749-88-0; **5**, 66749-89-1; **6**, 31121-09-2; **6**·HCl, 3099-27-2; phenacylaniline, 5883-81-8; phenacyl bromide, 70-11-1; aniline, 62-53-3; phenylglyoxal, 1074-12-0.

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Palladium-Catalyzed Reaction of 3-Bromopyridine with Allylic Alcohols: A Convenient Synthesis of 3-Alkylpyridines

Yoshinao Tamaru, Yoshimi Yamada, and Zen-ichi Yoshida*

Department of Synthetic Chemistry, Kyoto University, Yoshida, Kyoto 606, Japan

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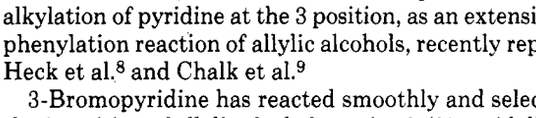
Compared with a wide variety of convenient methods for 2- and 4-alkylpyridines, the synthesis of 3-alkylpyridines is less common and rather laborious.[1] 3-Alkylpyridines have usually been prepared either by the alkylation of 3-pyridyllithium[2] or 3-picolyllithium[3] or by elaboration of nicotinic acid.[4] Therefore, and because of their particular pertinence to the alkaloids[5] and use in synthesis[6] (e.g., as a precursor of 1,5-diketones), a convenient preparative method for 3-alkylpyridines would be desirable.

In this context, we have examined the palladium-catalyzed alkylation of pyridine at the 3 position, as an extension to the phenylation reaction of allylic alcohols, recently reported by Heck et al.[8] and Chalk et al.[9]

3-Bromopyridine has reacted smoothly and selectively at the 3 position of allylic alcohols to give 3-(3′-pyridyl) ketones or aldehydes in the presence of 1 mol % of $Pd(OAc)_2$ (based on 3-bromopyridine, eq 1). In some cases, depending on the



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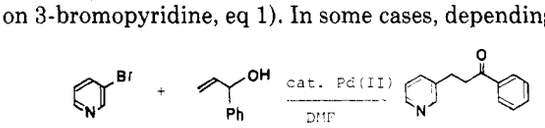

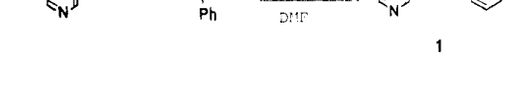

(2)

2 3 4

structure of the allylic alcohols and the reaction conditions, the positional isomer [2-(3′-pyridyl) ketone or aldehyde, **5**] and unsaturated alcohol **6** were also obtained as minor prod-

5 6

ucts. In Table I are summarized the reaction conditions and product distribution obtained with five kinds of allylic alcohols. Alcohols examined were allyl alcohol, α-, β-methallyl

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Table I. Reactions of 3-Bromopyridine with Allylic Alcohols

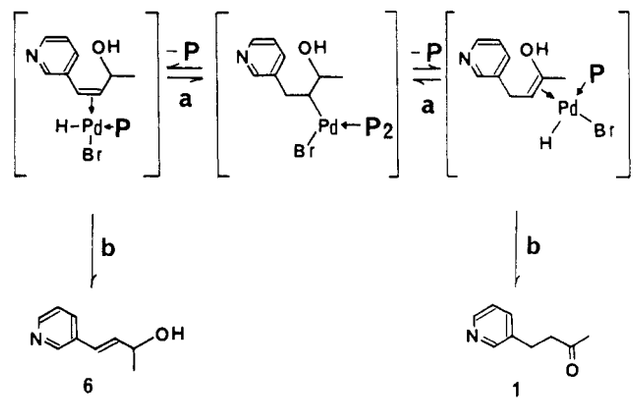
entry	alcohol	registry no.	reaction conditions[a] solvent	additive	temp, °C	time, h	conv, %	product distribution[b] 3-(3′-pyridyl)[c]	2-(3′-(pyridyl)[c]	others
1	CH_2=$CHCH_2$-OH	107-18-6	HMPA	PPh_3	95	9	100	45 (17)		17 (5)[d] 8 (2)[e] 18 (5)[f] 12[g]
2	CH_2=$C(CH_3)$-CH_2OH	513-42-8	HMPA	PPh_3	100	48	100	96 [100/0] (50)		4[h] (2)
3	CH_2=$C(CH_3)$-CH_2OH		DMF	PPh_3	100	50	100	97 [100/0]		3[h]
4	CH_2=$CHCH(CH_3)OH$	598-32-3	HMPA	PPh_3	120	5	100	92 [90/10] (44)	8 (4)	
5	CH_2=$CHCH(CH_3)OH$		HMPA	NaI	120	10	77	85 [99/1]	15	
6	CH_2=$CHCH(CH_3)OH$		HMPA	none	120	6	96	82 [99/1]	18	
7	CH_2=$CHCH(CH_3)OH$		DMF	PPh_3	120	7	97	90 [82/18]	2	9[g]
8	CH_2=$CHCH(CH_3)OH$		DMF	none	120	9	97	93 [100/0] (87)	7 (7)	
9	CH_3CH=$CHCH(CH_3)OH$	1568-50-2	HMPA	PPh_3	120	24	100	84 [98/2] (62)	16 [95/5] (13)	
10	CH_3CH=$CHCH(CH_3)OH$		HMPA	none	120	24	100	61 [98/2]	39 [99/1]	
11	CH_3CH=$CHCH(CH_3)OH$		DMF	PPh_3	120	10	93	87 [83/17]	4 [63/37]	9[g]
12	CH_3CH=$CHCH(CH_3)OH$		DMF	none	120	24	99	77 [99/1] (71)	21 [100/0] (18)	2[g]
13	CH_2=$CHCH(Ph)OH$	4393-06-0	HMPA	PPh_3	120	6	100	93 [93/7] (80)		7[g]
14	CH_2=$CHCH(Ph)OH$		HMPA	none	120	24	100	93 [100/0]		7[g]
15	CH_2=$CHCH(Ph)OH$		DMF	PPh_3	120	5	100	91 [76/24]		9[g]
16	CH_2=$CHCH(Ph)OH$		DMF	none	120	24	99	93 [100/0] (91)		7[g]

[a] The usual reaction scale is as follows: 3-bromopyridine (4.0 mmol), allylic alcohol (6.0 mmol), $Pd(OAc)_2$ (0.04 mmol), $NaHCO_3$ (4.8 mmol) in 3 mL of a solvent. As an additive, PPh_3 (0.12 mmol) or NaI (0.14 mmol) was added in the cases indicated. Bath temperatures were controlled within ±0.5 °C. Conversion is based on 3-bromopyridine consumed. [b] Calcd from the area intensities on VPC (SiDC 550, He). The values in the parentheses refer to the isolated yields. The values in the brackets refer to the ratio of carbonyl to alcohol. [c] 3-(3′-Pyridyl) and 2-(3′-pyridyl) refer to the products 3-(3′-pyridyl)carbonyl and alcohol, and 2-(3′-pyridyl)carbonyl and alcohol, respectively. [d] 2-Propylidene-3-(3′-pyridyl)propanal; registry no. 66702-64-5. [e] 5-(3′-Pyridyl)-2-methylpent-2-enal; registry no. 66702-65-6. [f] 2-Methyl-2-(3′-pyridyl)pent-4-enal; registry no. 66702-66-7. [g] Unknowns consist of more than one peak of less than 5%.

alcohols, methylpropenylcarbinol, and phenylvinylcarbinol. In these reactions, 3,3′-bipyridyl formation reaction did not occur to a detectable extent. The reactivity and regioselectivity depend on the structure of allylic alcohols. The methyl substituent on the olefinic carbon of allyl alcohol markably suppressed the reaction rate as observed in the reactions with β-methallyl alcohol and methylpropenylcarbinol. The size of the alkyl and aryl groups at the 1 position of the allyl alcohol did not affect their reactivity. While there was no significant solvent effect on the reactivity between dimethylformamide (DMF) and hexamethylphosphoric triamide (HMPA), the former is the best choice of solvents as judged by selectivity for the 3 position. For example, the C-3/C-2 ratio changed from 82:18 (in HMPA, entry 6) to 93:7 (in DMF, entry 8). DMF was also a satisfactory solvent for practical reasons since the products could be isolated without an aqueous workup by distillation of the filtered reaction mixture. With aqueous workup, the isolated yields fall to half owing to the high water solubility of products (especially with a short alkyl chain; entries 1, 2, 4, and 13).

Triphenylphosphine raised the reactivity and the 3-pyridylation selectivity, but in the presence of this cocatalyst, an appreciable amount of **6** was produced. The latter effect is amplified in DMF. The unsaturated alcohol formation is characteristic of this pyridylation, not observed to such a large extent for the arylation[9] or thienylation[7] of allylic alcohols under similar conditions. In the pyridylation reaction, pyridine as well as triphenylphosphine seems to act to displace the olefinic group from the metal (path b, Scheme I), before the complete addition–elimination sequences of hydridopalladium complex to give carbonyl compound (path a). Thus

Scheme I



formed free metal hydride cannot isomerize the olefin and decomposes rapidly in the presence of base.

A particularly interesting feature of the reaction with allyl alcohol, not observed with other allylic alcohols, is the formation of aldol condensation products **2** and **3** (eq 2, entry 1), a process that has been postulated to explain the low isolated yield of 3-phenylpropionaldehyde.[9] Apparently these products arise from 3-(3′-pyridyl)propionaldehyde and propionaldehyde, formed in situ by olefin migration. Furthermore the isolation of 2-methyl-2-(3′-pyridyl)pent-4-enal (**4**) suggests that under the present reaction conditions the π-allylpalladium complex, probably formed by the oxidative addition of Pd(0) to allyl alcohol, reacted with the enolate of 2-(3′-pyridyl)propionaldehyde.[10]

In conclusion, the present palladium-catalyzed reaction is a good method to prepare the 3-alkylpyridines, with the following advantages. (a) The manipulation is very easy (not rigorously sensitive to moisture) and applicable to a large scale reaction. (b) By the combination with an appropriate allylic alcohol, we can modify the alkyl substituent with a carbonyl group at the 3′ position, permitting further transformations.

Experimental Section

General Procedure for the Reactions of 3-Bromopyridine and Allylic Alcohols. The general procedure was exemplified by the reaction of 3-bromopyridine and α-methallyl alcohol (entry 4, Table I). Into an argon purged mixture of $Pd(OAc)_2$ (9 mg, 0.04 mmol), PPh_3 (31.5 mg, 0.12 mmol), and $NaHCO_3$ (404 mg, 4.8 mmol) were added 3-bromopyridine (632 mg, 4 mmol), α-methallyl alcohol (432 mg, 6 mmol), and 3 mL of HMPA by means of a syringe. The slurry mixture was stirred and heated at 120 °C for 5 h. The reaction was monitored by means of VPC (SiDC 550, He) by sampling 2 μL from the reaction mixture at an appropriate interval. The reaction mixture was poured into 20 mL of water and extracted with ether (30 + 20 + 20 mL). The combined ether extracts were washed with 10 mL of saturated NaCl and dried over $MgSO_4$. Evaporation of a solvent and the subsequent distillation (Kugelrohr 150 °C (15–5 mmHg)) gave a colorless oil (48% isolated yield), which consisted of 83% of 2-(3′-pyridyl)ethyl methyl ketone, 9% of 1-(3′-pyridyl)-1-buten-3-ol, and 8% of 1-(3′-pyridyl)-ethyl methyl ketone.

For the reaction in DMF (entry 8), the workup was undertaken as follows. The reaction mixture diluted with 20 mL of ether was filtered through a Florisil column (mesh 100–200, 1 cm length). Distillation of filtrate gave 545 mg of colorless oil (94% isolated yield, Kugelrohr 150 °C (13–10 mmHg)), consisting of 93% of methyl 2-(3′-pyridyl)-ethyl ketone and 7% of methyl 1-(3′-pyridyl)ethyl ketone.

Registry No.—**1**, 39976-56-2; **5** (R = H; R = Me), 66702-67-8; **5** (R = R′ = Me), 66702-68-9; **6** (R = H; R′ = Me), 66702-69-0; **6** (R = R′ = Me), 66702-70-3; **6** (R = H; R′ = Ph), 66702-71-4; 3-(3-pyridyl)-propanal, 1802-16-0; 2-methyl-3-(3-pyridyl)propanal, 66417-76-3; (*E*)-2-methyl-3-(3-pyridyl)propenal, 66702-72-5; 4-(3-pyridyl)-2-butanone, 55161-19-8; 4-(3-pyridyl)-3-penten-2-ol, 66702-73-6; 3-(3-pyridyl)-3-penten-2-ol, 66702-74-7.

Supplementary Material Available: ^{1}H NMR, IR, and mass spectra of 3- and 2-(3′-pyridyl)aldehydes and ketones and related compounds (5 pages). Ordering information is given on any current masthead page.

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Magnetic Equivalence and Nonequivalence of Methylene Groups Adjacent to an Asymmetric Center in a Series of γ-Phenyl-γ-butyrolactones[1]

Royston M. Roberts,* Rajiha Al-Naiemi, and Rachanee Chayasirisophon

Department of Chemistry, The University of Texas at Austin, Austin, Texas 78712

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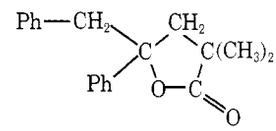
In recent studies, several γ-benzyl-γ-phenyl-γ-butyrolactones were prepared as intermediates in the synthesis of benzyltetralins and benzyltetralols.[2,3] The NMR spectrum of α,α-dimethyl-γ-phenyl-γ-butyrolactone (**1**) attracted our



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interest because it showed a clear AB pattern (centered at ca. δ 3.1) for one of the methylene groups and a sharp singlet (at δ 2.38) for the other. The ring methylene hydrogens would certainly be expected to be nonequivalent, and the benzyl methylene hydrogens might also be expected to be nonequivalent since they are adjacent to an asymmetric center. This spectrum was compared with those of the diastereomers of α-methyl-γ-benzyl-γ-phenyl-γ-butyrolactone[4,5] (*Z*-**2** and *E*-**2**); see Table I. The spectra of *Z*-**2** and *E*-**2** indicate that both the ring methylene and benzyl methylene hydrogens are nonequivalent in these lactones. This aroused our curiosity as to which pair of methylene hydrogens in lactone **1** were the NMR equivalent ones.

To determine this, we first prepared the dideuterio analogue of **1** in which the deuterium atoms were placed unequivocally in the benzyl position. As may be seen in Table I, this lactone (**1d**) had an NMR spectrum identical with that of lactone **1** except that the singlet at δ 2.38 was missing. This proved that this singlet comes from the benzyl methylene hydrogens of lactone **1** and not from the β hydrogens of the lactone ring. Hence the β hydrogens of lactone **1** are nonequivalent, as expected, but the benzyl methylene hydrogens are NMR equivalent.

The same test was applied to lactone *Z*-**2**. Its α,α-dideuteriobenzyl derivative was also synthesized. As may be seen in Table I, this lactone (*Z*-**2d**) had an NMR spectrum virtually identical with that of lactone *Z*-**2** except that the AB signal at δ_A 3.20, δ_B 3.09 was missing, confirming the analysis of the spectrum of lactone *Z*-**2** as presented in Table I. Comparing the assigned NMR signals of lactone **1** with those of *Z*-**2** and *E*-**2** (Table I) reveals the surprising fact that the chemical shifts of the benzyl and methylene hydrogens are virtually reversed in these compounds!

An attempt was made to sort out the ABC signal from the α- and β-hydrogens remaining in lactone *Z*-**2d**. It consisted of two separated multiplets at δ 1.74–2.22 and δ 2.62–3.03,

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