HETEROCYCLES, Vol 14, No 4, 1980

CONVENIENT METHOD FOR THE PREPARATION OF 2-PHENACYLPYRIDINES[1]

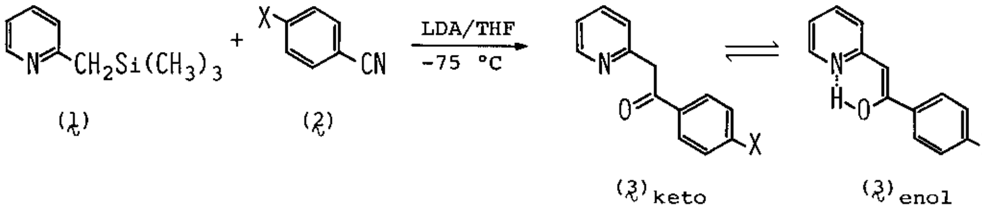
Takeo KONAKAHARA* and Yukio TAKAGI
Department of Applied Chemistry, Science University of Tokyo,
Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

Abstract — 2-Phenacylpyridines (**3**) were prepared from 2-(trimethylsilylmethyl)pyridine (**1**) and *p*-substituted benzonitriles (**2**) (X = H, Cl, CH_3, OCH_3) in high yields (70 ∿ 99%) under a mild condition (LDA/THF, -75 °C). The method was compared with a reaction of α-picoline with (**2**) under the same condition. The keto-enol tautomerism of (**3**) were also discussed by means of the nmr spectra.

The reaction of metalated α-silyl compounds with carbonyl compounds (the Peterson reaction)[2] has been investigated by many workers in a comparison with the Wittig reaction.[3] Leij *et al.* have reported the reaction of α-silyl carbanions with sulfur dioxide to give the corresponding sulfines.[4] This was the first observation on the reaction of α-silyl carbanion with an unsatulated compound except for carbonyl compounds including esters and amides. In the course of our investigation of 2-(trimethylsilylmethyl)pyridine (**1**), we have reported a preparation of 2-alkenylpyridines from (**1**) and carbonyl compounds, and shown the reaction of (**1**) is superior to that of α-picoline to prepare the corresponding alkenes.[5]

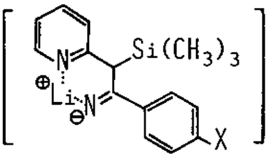
We now wish to report a convenient method to prepare 2-phenacylpyridines (**3**) from (**1**) and substituted benzonitriles (**2**).[6] Treatment of (**1**) with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -75 °C afforded an orange-colored solution of the corresponding lithio derivative, which reacted with an equivalent of benzonitrile (**2a**), *p*-chlorobenzonitrile (**2b**), *p*-methylbenzonitrlie (**2c**), and *p*-methoxybenzonitrile (**2d**) to give 2-phenacylpyridine (**3a**), 2-(*p*-chlorophenacyl)pyridine (**3b**), 2-(*p*-methylphenacyl)pyridine (**3c**), and 2-(*p*-methoxyphenacyl)pyridine (**3d**) in high yield, respectively (see Eq. 1). The yield obtained and mp are shown in Table.

Generally, (**3**) has been prepared by a reaction of metalated α-picoline with esters. In the method, two equivalents of α-picoline are required to complete the reaction.[8] Wolfe *et al.* developed a new method to prepare (3) from an equivalent amount of α-picoline and esters.[9] In their method, although (3) was obtained in high yield, a plolonged reaction time and excess sodium hydride were required (3a: 48 h, 92%). Recently, they have prepared (3) through a reaction of α-picolyllithium with *N,N*-dimethylcarboxyamides under a molar ratio of 1 : 1. The reaction of aromatic *N,N*-dimethylcarboxyamide, however, has given a low yield.[10]



(Eq. 1)

	a	b	c	d	e
X	H	Cl	CH_3	OCH_3	NO_2



(4)

TABLE YIELDS AND PHYSICAL PROPERTIES OF (3)[a]

Compds.	Yield (%) This work[b]		Lit. method[c]		Mp (°C)	Keto %[d]
	[A]	[B]	[C]	[D]		
a	82 (99)	71	80	51	60 ∿ 61.5[e]	56.5
b	71 (77)	—	80, 68[f]	—	86 ∿ 87[f]	42.7
c	75 (80)	—	80[g]	—	68.5 ∿ 70[g]	69.3
d	71 (72)	63	75[h]	—	79.5 ∿ 80.5[h]	82.5
e	0	—	—	—	—	—

a) All compounds obtained exhibited spectral properties in accordance with assigned structures. *b)* Yield of the pure product isolated by recrystallization from benzene-hexane, UV-yield in parentheses. Method A: the reaction of (1) with (2), method B: used α-picoline instead of (1). *c)* Method C: values reported in Ref. 8, method D: a value reported in Ref. 10. *d)* Determined by NMR in $CDCl_3$ at an ambient temperature. *e)* Lit.[15] 52.5 ∿ 54 °C. *f)* Lit.[15] 89 °C. *g)* Lit.[15] 67 °C. *h)* Lit.[15] 84.5 °C.

The results shown in Table indicate the superiority of the present method for the preparation of (3). In comparison with the reported method,[8~10] the present method has the advantages of a lower molar ratio of the tar base to the reactant, a higher yield and/or a shorter reaction time. In Levine-Raynolds' method, two equivalents of α-picoline was required (molar ratio of 2 : 1) to give (3) in the yield shown in Table, but in our method, only one equivalent of (1) was required (molar ratio of 1 : 1) to give (3) in the same yield as those of their method (see Table). For example, benzonitrile (2a) gives (3a) quantitatively (99% UV-yield). When α-picoline was employed instead of (1), the yield of (3) was decreased (see Table).[11] The phenomenon is explained by a stabilization effect of trimethylsilyl group on an *alpha*-positioned charged carbon atom of the carbanion. The preparation of (3e) (X = NO_2) by the same method resulted in failure, because of a strong reactivity of nitro group itself for organometalics.[12] Nitrobenzene reacted with the lithiated (1) at -75 °C to give many products.[13] The reaction of propionitrile with (1) under the same conditions was also performed to obtain the corresponding ketone, but gave an unsatisfactory result (30% of ethyl 2-pyridylmethyl ketone).

The reaction (Eq. 1) is considered to proceed through the intermediate ketimines (4), and the detailed investigation is in progress.

Nmr spectra in $CDCl_3$ showed that the compound (3) exists as keto-enol tautomeric mixtures as shown in Eq. 1 and the values of keto % are summerized in Table.[14] A linear relationship exists between $\log(K_T)_{rel}$ and Hammett's σ values for the substituents X except for the methoxyl group ($\rho = 1.26$).[15] The methoxyl derivative (3d) exists predominantly in the keto form more than expected from the above relationship. This predominance in the keto form with respect to the enol form in (3d) results from a *n*-π conjugation between O atom and phenylene ring, which prevents the enolization.[16]

In a typical procedure, a 15% solution of *n*-butyllithium (8.6 g, 0.02 mol) in hexane was added to a solution of diisopropylamine (0.02 mol) in THF (54 ml) at -75 °C with stirring under oxygen-free, dry nitrogen. To the solution, (1) (0.02 mol) is added slowly and stirred for an additional 10 min.[6] The mixture was treated with a THF solution of (2) (0.02 mol) and stirred for 1 h at -75 °C and for 2 h at room temperature. The mixture quenched with aq. ammonium chloride was extracted with ether, and the ethereal solution was then extracted with dil. hydrochloric acid. The acidic solution of the product was worked up as usual after a neutralization to give (3). From the remained ethereal solution was obtained an unreacted

(**2**) after an evaporation of the solvent.

We thank Atsuo Koide for a partial support in the Experimental work.

References and Footnotes

1. A preliminary report of this work was presented at the 40th National Meeting of the Chemical Society of Japan, Fukuoka, October 1979.
2. D. J. Peterson, *J. Org. Chem.*, 1968, **33**, 780.
3. K. Shimoji, H. Taguchi, K. Oshima, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1974, **96**, 1620; S. L. Hartzel, D. F. Sullivan and M. W. Rathke, *Tetrahedron Lett.*, 1974, 1403; I. Ojima, M. Kumagai and Y. Nagai, *Tetrahedron Lett.*, 1974, 4005; T. H. Chan and M. Moreland, *Tetrahedron Lett.*, 1978, 515; R. P. Woodbury and M. W. Rathke, *Tetrahedron Lett.*, 1978, 709.
4. M. van der Leij, P. A. T. W. Porskamp, B. H. M. Lammerink and B. Zwanenburg, *Tetrahedron Lett.*, 1978, 811.
5. T. Konakahara and Y. Takagi, *Synthesis*, 1979, 192.
6. 2-(Trimethylsilylmethyl)pyridine (**1**) was prepared from α-picoline (0.25 mol) and trimethylchlorosilane (0.125 mol) in LDA/THF medium at -75 °C in good yield (77 ∿ 80% isolated). In comparison with Musker-Scholl's method, the present method has the advantages of a higher yield, a lesser formation of polysilylated compounds, and a simple work-up.[7]
7. Musker and Scholl obtained (**1**) in phenyllithium-ether system in a *ca.* 40% yield (W. K. Musker and R. L. Scholl, *J. Organometal. Chem.*, 1971, **27**, 37).
8. R. Levine and S. Raynolds, *J. Org. Chem.*, 1960, **25**, 530.
9. J. F. Wolfe, D. E. Portlock and D. J. Feuerbach, *J. Org. Chem.*, 1974, **39**, 2006.
10. R. P. Cassity, L. T. Taylor and J. F. Wolfe, *J. Org. Chem.*, 1978, **43**, 2286.
11. W. B. Edwards, III, *J. Heterocycl. Chem.*, 1975, **12**, 413.
12. P. Buck and G. Köbrich, *Tetrahedron Lett.*, 1967, 1563.
13. One of them was identified as 1,2-bis(2-pyridyl)ethene (T. Konakahara and Y. Takagi, unpublished data).
14. Klose and Uhlemann have reported that an enamine tautomer (or its ionic form) is formed at higher temperatures in addition to the keto and the enol tautomers (**3**) (G. Klose and E. Uhlemann, *Tetrahedron*, 1966, **22**, 1373). Assignment of structure (**3**) to the enol form in this paper is based on precidents established by Elguero *et al.*, because the spectra were recorded at an ambient temperature (J. Elguero, C. Marzin, A. R. Katritzky and P. Linda, "Advances in Heterocyclic Chemistry, Supplement 1, The Tautomerism of Heterocycles," eds. A. R. Katritzky and A. J. Boulton, Academic Press, New York(1976), p. 187.
15. In a series of alkyl 2-pyridylmethyl ketones, the K_T values were correlated with Taft steric substituent constants by Wursthorn and Sund (K. R. Wursthorn and E. H. Sund, *J. Heterocycl. Chem.*, 1972, **9**, 25).
16. R. F. Branch, A. H. Beckett and D. B. Cowell, *Tetrahedron*, 1963, **19**, 401; and references cited therein.

Received, 21st November, 1979