Convenient Synthesis of 3-Methyl-1-(4-pyridinyl)-2-butanone using Phenyllithium as a Metalating Agent

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3-Methyl-1-(4-pyridinyl)-2-butanone has been synthesized *via* a short and convenient method based upon acylation of 4-picoline by phenyllithium followed by reaction with ethyl isobutyrate. This procedure can be extended to the preparation of various alkyl pyridyl ketones, intermediates in the synthesis of potential antitumor 6-substituted 7*H*-pyridocarbazole dimers.

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Introduction.

In the search for new drugs endowed with high antitumor properties, several DNA bis-intercalating 7*H*-pyridocarbazole dimers were prepared in our laboratory [1-3]. One of them, ditercalinium (NSC 366241) is presently under clinical trials. In relation to their DNA intercalating ability, it was of great interest to investigate structure-activity relationship studies in the ditercalinium series and therefore to prepare analogs substituted on the intercalating unit by a wide range of alkyl groups of increasing size.

Among the different substitution positions, position 6 appeared crucial [3] and it was therefore necessary to develop a convenient and short chemical pathway for the preparation of 6-alkylated 7*H*-pyridocarbazole dimers with a high yield. The total synthesis of the 7*H*-pyridocarbazole ring that we have previously published [4] satisfies this purpose. Briefly, this method is based on the condensation of an appropriate alkyl pyridyl ketone on the indole nucleus, yielding an ethylenic precursor which is photocyclized to afford the 6-alkylated 7*H*-pyridocarbazole ring. Since the condensation step is the limiting one [4], it was crucial to optimize the synthesis of the required alkyl pyridyl ketone.

According to the literature, such compounds can be obtained through a general procedure based upon acylation of 2-, 3- or 4-picoline with an appropriate ester, after metalation of the methyl group of the picoline isomer. Our purpose was to synthesize the 6-isopropyl substituted 7*H*-pyrido[4,3-*c*]carbazole ring and therefore to prepare 3-methyl-1-(4-pyridinyl)-2-butanone **3** in good yield, using a short and simple method. The general synthetic pathway is presented in Figure 1. Each procedure is discussed in terms of the yield of ketone **3** and of the various by-products obtained which were characterized.

Results and Discussion.

Several different metalating agents have been used in the synthesis of alkyl pyridyl ketones, depending on the picoline isomer. These are: i) Sodium diisopropylamide (SDIA), obtained by reaction of diisopropylamine (DA) with phenyl sodium [5], or lithium diisopropylamide [5,7]. ii) Organolithium reagents, *i.e.* methyllithium [6-8], *t*- or *n*-butyllithium [6] or phenyllithium [6-13]. Attempts to metalate picoline using organomagnesium reagents failed [6]. iii) Sodium amide in liquid ammonia [8,14], or potassium amide [5].

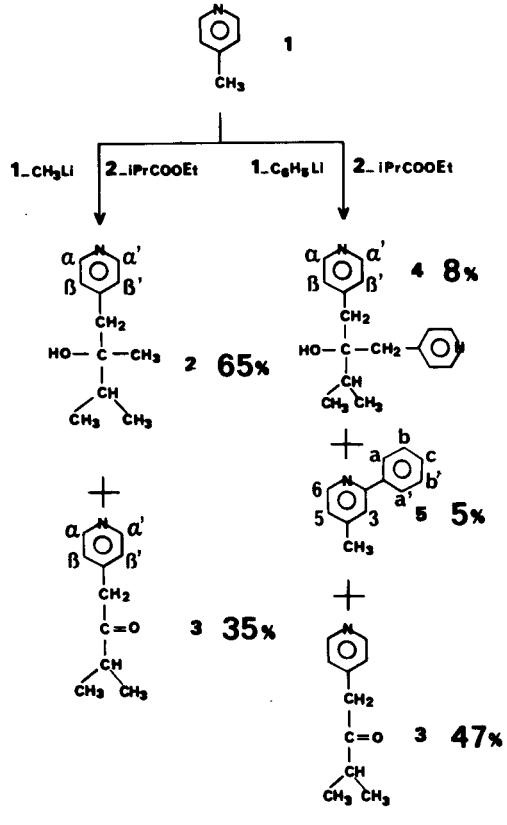

Figure 1. General synthetic pathway for synthesis of 3-methyl-1-(4-pyridinyl)-2-butanone **3**.

Among these procedures, 3-methyl-1-(4-pyridinyl)-2-butanone **3** has been previously prepared by using 4-picoline and ethyl isobutyrate after metalation of 4-picoline by either sodium amide [5], SDIA [5] or methyllithium [6]. Although the procedure using SDIA was

Table 1

Compound	BP °C/mm Hg or MP °C	Formula	^{1}H NMR [1]	MS
2	BP, 120°/0.7 mm Hg	$C_{11}H_{17}NO$ Calcd. C: 73.70 % H: 9.56 N: 7.81 O: 8.93 Found: C: 73.41 % H: 9.35	0.86 (m, 9H, CH_3COH; 2 x CH_3 1.52 (h, 1H, CH) 2.58 (d, 2H, CH_2-pyr*) 4.14 (s, 1H, OH) 7.19 (d, 2H, $H_{\beta,\beta'}$) 8.34 (d, 2H, $H_{\alpha,\alpha'}$)	180 (M+) 162, 136 120, 106 93, 87 71, 69 51
3	BP, 101°/1 mm Hg Lit [6] 95°-97°/1 mm Hg	$C_{10}H_{13}NO$ Calcd. C: 73.59 % H: 8.03 N: 6.24 O: 9.80 Found: C: 73.26 % H: 8.17	1.03 (d, 6H, 2 x CH_3) 2.73 (h, 1H, CH) 3.87 (s, 2H, CH_2CO) 7.17 (d, 2H, $H_{\beta,\beta'}$) 8.44 (d, 2H, $H_{\alpha,\alpha'}$)	163 (M+) 149, 107 93, 71 51
4	MP, 154°	$C_{16}H_{20}N_2O$ Calcd. C: 74.97 % H: 7.86 N: 10.93 O: 6.24 Found: C: 74.72 % H: 7.82 N: 10.66 O: 6.50	0.87 (d, 6H, 2 x CH_3) 1.44 (h, 1H, CH) 2.73-2.47 (d, 4H, CH_2-pyr*) 4.48 (s, 1H, OH) 7.21 (d, 4H, $H_{\beta,\beta'}$) 8.37 (d, 4H, $H_{\alpha,\alpha'}$)	257 (M+) 213, 195 164, 146 120, 106 94, 71 51
5	BP, 105°/1 mm Hg Lit. [6] 113°-115°/2 mm Hg	$C_{12}H_{11}N$ Calcd. C: 85.20 % H: 6.52 N: 8.28 Found: C: 85.03 H: 6.74	2.34 (s, 3H, CH_3) 7.11 (d, 1H, H_5) 7.28 (m, 3H, $H_{b,b',c}$) 7.74 (s, 1H, H_3) 8.01 (d, 2H, $H_{a,a'}$) 8.44 (d, 1H, H_6)	169 (M+) 141, 127 91, 77 51

[1] Chemical shifts (in parts per million from HMDS) in DMSO-d_6. Numbering of protons is indicated in Figure 1. * pyr = pyridine.

reported to give the best yield, we only obtained a very weak yield of ketone **3** (3%) following the described experimental conditions [5]. The method using sodium amide as a metalating agent requires on the other hand the use of liquid ammonia [5]. Since our purpose was to prepare **3** using a short and simple method, organolithium reagents (*e.g.* methyllithium or phenyllithium) were preferred.

1) Synthesis of **3** using Methyllithium as a Metalating Agent.

Osuch *et al.* [6] have obtained the desired ketone **3** in a 60% yield using methyllithium as a metalating agent of 4-picoline. With this reagent no by-products were formed whereas azomethine addition compounds, resulting from lateral metalation of 4-picoline were obtained when using phenyllithium instead of methyllithium [6]. We therefore followed this procedure using 4-picoline/methyllithium/-ester in the ratio 2/2/1, described as being the optimal conditions. In our case, after treatment and distillation of the crude product, the reaction yielded 35% of the desired ketone **3** and 65% of the alcohol **2** whose characteristics are given in Table 1 (yields calculated from the molar quantity of ester used).

A likely hypothesis, accounting for the formation of alcohol **2**, which was not reported by Osuch *et al.* [6], might be that the exchange of the metal between methyllithium and 4-picoline was incomplete, allowing the excess of unreacted methyllithium to react immediately with the formed ketone **3**, thus giving alcohol **2**. This assumption is reinforced by the concomittant appearance of alcohol **2** and ketone **3**, as shown by ^{1}H nmr analysis of aliquots of the reaction mixture (data not shown). Furthermore, to ascertain the mechanism of formation of **2**, ketone **3** was reacted separately with methyllithium under the experimental conditions of acylation of 4-picoline with ethyl isobutyrate/methyllithium. The nmr analysis of the crude product (data not shown), and separation by flash chromatography of the compounds formed in the reaction, showed that after 20 minutes at room temperature the reaction of ketone **3** with methyllithium yielded 50% of alcohol **2**.

Attempts to increase the yield of ketone **3** by using 4-picoline/methyllithium/ester in the ratio 1/1/1 failed. Indeed, in this latter case only 18% of the desired ketone **3** was isolated, whereas 75% of alcohol **2** was obtained.

2) Synthesis of **3** using Phenyllithium as a Metalating Agent.

Phenyllithium was subsequently tested, since this organolithium reagent has been widely used for the synthesis of various alkyl pyridyl ketones [6-13]. It has never been employed, however, for the preparation of 3-methyl-1-(4-pyridinyl)-2-butanone **3**. Three different assays were performed by varying either the ratio 4-picoline/phenyllithium/ester, or the mode of addition, (Standard addition, S.A., *i.e.* 4-picoline added to phenyllithium; Reverse addition, R.A., *i.e.* phenyllithium added to 4-picoline).

The results presented in Table 2 show that the best yield of ketone **3** was obtained when using a 2/2/1 ratio, the optimal conditions reported by Levine *et al.* [7] in the case of 2-picoline, and the reverse addition method. Furthermore, a concomitant decrease in the yield of by-products was observed under these precise experimental conditions. These by-products were isolated in all cases (characteristics given in Table 1), and were shown to be: i) Alcohol **4**, resulting from further reaction of ketone **3** with the metalated 4-picoline (4-$(NC_5H_4)CH_2^-$ Li^+). ii) Azomethine addition product **5**, already observed by Osuch *et al.* [6].

Table 2

Acylation of 4-Picoline by Phenyllithium and Ethyl Isobutyrate

Ratio			Method	Yield			Yield in recovered
4-Pic/ϕ	Li/iPrCOOEt		S.A. or R.A.	**3**	**4**	**5**	**1**
2	2	2	S.A.	34%	21%	28%	17%
2	2	1	S.A.	31%	22%	15%	32%
2	2	1	R.A.	47%	8%	5%	31%

4-Pic: 4-picoline. ϕ Li: phenyllithium. iPrCOOEt: ethyl isobutyrate.

The formation of the bipyridyl by-product **4** contrasts with the studies of Raynolds *et al.* [5] and Osuch *et al.* [6]. Indeed, these authors did not report the formation of bipyridyl by-products when acylating 4-picoline by either SDIA or methyllithium. In the case of 2-picoline, Levine *et al.* [7] suggested that the simultaneous formation of ketone and alcohol might result from intermediates stabilized by interaction of the spatially close pyridinic nitrogen and lithium atom. The present results show that such a mechanism might occur even in the case of 4-picoline, suggesting that the proposed nitrogen-metal interaction is not absolutely required. On the other hand, during the course of this reaction we did not observe the formation of hydroxylated by-product analogous to alcohol **4**, resulting from further reaction of ketone **3** with methyllithium. A possible explanation could be that even if an excess of phenyllithium remained, this reagent was unable to further react with ketone **3**. To test this assumption, phenyllithium was reacted separately with ketone **3**. The nmr analysis of the crude product and isolation of the compounds formed during the reaction showed that after 30 minutes at room temperature, only 20% of the reaction had occured (data not shown). This weak reactivity of phenyllithium toward ketone **3** is likely due to steric parameters which are not encountered with methyllithium. This probably explains the lack of by-products analogous to alcohol **4** when 4-picoline was acylated by means of phenyllithium/ethyl isobutyrate. In addition to this, metalation of 4-picoline by phenyllithium is faster and more complete than with methyllithium.

Conclusion.

Phenyllithium thus appears to be the most convenient metalating agent of 4-picoline and the procedure described in this paper can be extended to the synthesis of various alkyl pyridyl ketones. These intermediates will permit the preparation of a wide range of 6-alkylated 7*H*-pyridocarbazoles, thus allowing exhaustive structure activity relationship studies in these series.

EXPERIMENTAL

All melting points (taken on a Kofler apparatus) and boiling points are uncorrected. The ^1H nmr spectra were recorded on a Bruker WH 270 MHz spectrometer. Chemical shifts (in parts per million ± 0.02) are relative to HMDS (hexamethyldisiloxane) as an internal reference. Mass spectra were performed on a Ribermag R-10-10-C spectrometer. Phenyllithium was commercially available from Janssen and was titrated using the procedure described in reference [15].

Reaction of Phenyllithium with 4-Picoline and Ethyl Isobutyrate. Reverse Addition Method (R.A.): Synthesis of 3-Methyl-1-(4-pyridinyl)-2-butanone **3**.

Freshly distilled 4-picoline **1** diluted in 10 ml of anhydrous and peroxides free diethyl ether. To this stirred solution was added at room temperature (20°) under nitrogen, 48 ml of phenyllithium (20% in diethyl ether-*n*-hexane, 0.1 mole) at such a rate that the ether did not reflux (30 minutes). The resulting brown solution was stirred at 25° for 15 minutes, then ethyl isobutyrate (6.7 ml, 0.05 mole) diluted in 10 ml of anhydrous ether was added at such a rate that the solvent refluxed gently. The red thick suspension thus obtained was refluxed for an additional 30 minutes. After cooling to room temperature, the reaction was poured into a mixture of 500 ml of crushed ice and 10 ml of concentrated hydrochloric acid. The organic phase was extracted with 1 *M* aqueous hydrochloric acid. The combined aqueous extracts were made slightly basic to *p*H 8 with an aqueous solution of sodium carbonate and extracted with ether. The organic extracts were dried over sodium sulphate and the solvent was removed *in vacuo*. The resulting light-yellow viscous oil was further dried *in vacuo* for 5 hours to provide white crystals which were collected by filtration, thoroughly washed with a mixture of ether-*n*-hexane (1:1) to give 1.02 g (8%) of pure **4**, mp 154°. Distillation of the filtrate first at atmospheric pressure to remove unreacted 4-picoline **1**, and then *in vacuo* gave 3.83 g (47%) of 3-methyl-1-(4-pyridinyl)-2-butanone **3**, bp 101° at 1 mm Hg and 0.42 g (5%) of 2-phenyl-4-methylpyridine **5**, bp 105° at 1 mm Hg.

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