Improved Preparation of 3-Substituted Pyridines from 3-Picoline, Lithium Diisopropylamide, and Electrophiles

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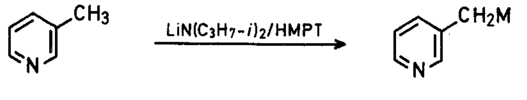
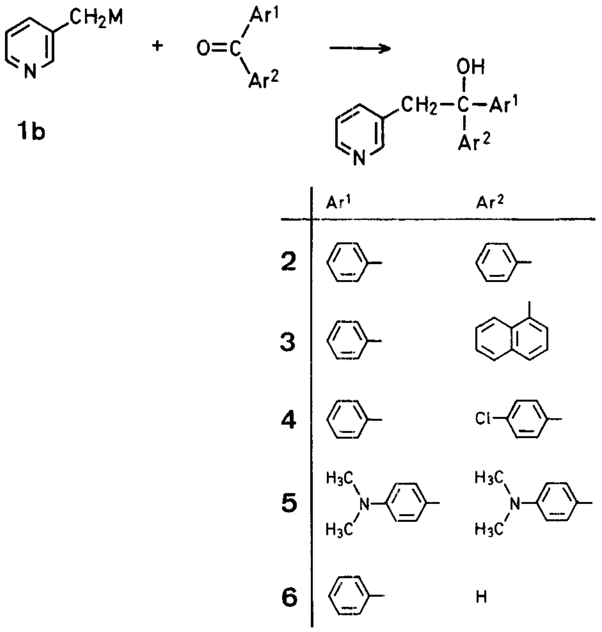
3-Picoline (**1a**) has been metalated by sodium amide[1], potassium amide[2], and lithium amide[3] in liquid ammonia, by sodium diisopropylamide and phenylsodium in benzene[4], and by lithium diisopropylamide in ether[2, 5]. The resulting picolyl organometallics (**1b**) have been alkylated[1, 3], acylated[2, 4], and reacted with aldehydes and ketones[6]; however, in most cases, the yields of the resulting products were only fair to poor. Moreover, in the metalations effected by lithium diisopropylamide, either specifics were not listed[2] or long reaction periods were necessary to afford **1b** in poor yield[5].

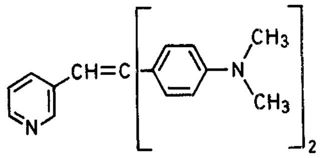


1a **1b** (M = Li)

This note indicates that 3-picoline (**1a**) may be conveniently converted to its lithio salt **1b** by means of a 1:1 complex of lithium diisopropylamide/hexamethylphosphoric triamide in tetrahydrofuran; subsequent condensations with a variety of electrophiles affords a facile synthesis of 3-substituted pyridines in good to excellent yields. The results are summarized in the Table. Specifically, treatment of **1a** with lithium diisopropylamide/hexamethylphosphoric triamide for only 30 min at 0° followed by the addition of 0.5 equivalents of benzophenone afforded **2** (75%) after 1 h at 25°; **2** has previously been prepared in a yield of 27%[6]. In related condensations of **1b** (M = Li), α-naphthyl phenyl ketone, *p*-chlorobenzophenone, and 4,4′-dimethylaminobenzophenone gave **3** (64%), **4** (52%), and **5** (79%), respectively. Previously, treatment of **1b** (M = K) with the latter ketone afforded only olefin **7** (27%), a compound currently obtained (89%) from **5** and cold, concentrated sulfuric acid. Lithium salt **1b** was also reacted with benzaldehyde to give **6** (40%); **6** was formerly prepared in a yield of 17%[6].

Lithium salt **1b** likewise was alkylated with ethyl and *n*-propyl bromides to afford **8** (73%) and **9** (77%), respectively; these yields are again higher than those (50% and 60%, respectively) previously realized[3]. Finally, **1b** (M = Li) was acylated by methyl benzoate using a 3:3:1 ratio of reagents to give **10** (90%); **10** was formerly obtained in a yield of 78%[4].





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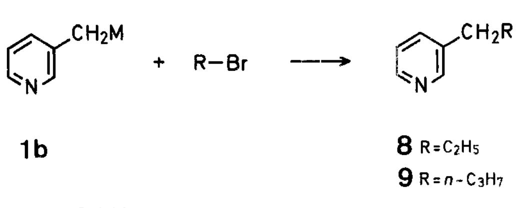

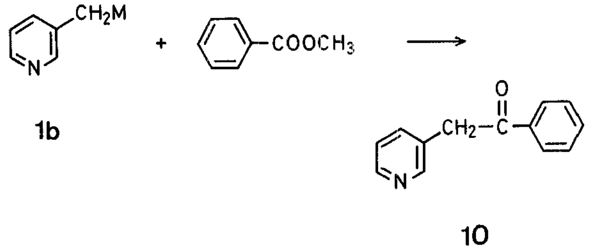

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Clearly, lithium diisopropylamide/hexamethylphosphoric triamide in tetrahydrofuran is the best and most convenient metalating agent to date for the preparation of 3-substituted pyridines via organometallic intermediates not only because of the shorter reaction periods employed but also because of the higher yields of products obtained.

Preparation and Condensations of 3-Picolyllithium (1b):

To a solution of diisopropylamine (2.53 g, 0.025 mol) in tetrahydrofuran (10 ml) at 0° contained in a 300 ml, three-necked flask, equipped with a magnetic stirrer, constant pressure addition funnel, and a rubber septum, was added 1.6*M* *n*-butyllithium (16 ml, 0.025 mol) in hexane via a syringe. The resulting pale yellow solution was maintained at 0° for 30 min, then treated with hexamethylphosphoric triamide (4.5 g, 0.025 mol). The bright yellow solution was stirred at 0° for 15 min, then treated during 5 min with a solution of 3-methylpyridine (2.3 g, 0.025 mol) in tetrahydrofuran (10 ml). After 30 min at 0°, the mixture containing **1b** was treated during 5 min with an electrophile (0.025 mol) in tetrahydrofuran (15 ml). The resulting solution was stirred for 1 h at 25° and poured into 10% hydrochloric acid (100 ml). In the case of the condensations with carbonyl compounds, the solid was removed by filtration, washed with diethyl ether, and subsequently suspended in water (100 ml). The suspension was made basic with potassium hydroxide pellets and the solution was extracted with three 20-ml portions of diethyl ether. The combined organic extracts were washed with two 25-ml portions of water, dried over calcium chloride, and concentrated to afford a white solid. The crude product was recrystallized from an appropriate solvent (Table) to give pure product.

In the case of the alkylations with ethyl and *n*-propyl bromides and the acylation with methyl benzoate, neutralization with 10% hydrochloric acid gave a two-layered system. The layers were separated and the aqueous layer was made basic with solid potassium hydroxide pellets. The basic solution was extracted with three 20-ml portions of diethyl ether and the combined extracts were worked-up as above. Distillation of the crude product gave pure material (Table).

Table. Preparation of 3-Substituted Pyridines by Lithium Diisopropylamide/Hexamethylphosphoric Triamide

Product	Yield (%)	M.P. [B.p.]	Lit. M.p. [B.p.]
2	75 (27)[a]	143–144°[b]	143.8–144.4°[a]
3	64 (—)	205–206°[c, d]	—
4	52 (—)	124–126°[b, d]	—
5	79 (—)	181–182°[c, d]	—
6	40 (17)[a]	120–121°[e]	120.6–121°[a]
8	73 (50)[f]	[184–186°]	[182–184°][f]
9	77 (60)[f]	[74–76°/7.0 torr]	[75–76°/7.0 torr][f]
10	90 (78)[g]	47–48°[h]	47–48°[g]

[a] Value is that reported in reference 6.

[b] Recrystallized from benzene: petroleum ether (b.p. 30–60°).

[c] Recrystallized from aqueous ethanol.

[d] This compound gave a satisfactory elemental analysis (±0.3%) for carbon and hydrogen.

[e] Recrystallized from petroleum ether (b.p. 30–60°).

[f] Value is that reported in reference 3.

[g] Value is that reported in reference 4.

[h] Obtained by vacuum distillation of crude product at 165 to 170°/2.5 torr.

Preparation of 1,1-Bis[4-dimethylaminophenyl]-2-(3-pyridyl)-ethene (7):

A solution of 1,1-bis[4-dimethylaminophenyl]-2-(3-pyridyl)-ethanol (1.0 g, 0.0027 mol) in 98% sulfuric acid (50 ml) was heated to 60°. The solution was stirred for 1.5 h, partially cooled, and poured onto crushed ice (200 g). The solution was cooled with an ice bath and made basic with potassium hydroxide pellets. The solid potassium sulfate was removed by filtration, washed with three 15-ml portions of diethyl ether, and discarded. The aqueous layer was extracted with three 15-ml portions of diethyl ether. The extracts and washings were combined, washed with water, dried over calcium chloride, and concentrated to yield a yellow solid. The crude product was recrystallized from 95% ethanol to give the product; yield: 0.83 g (89%); m.p. 129–130° (lit.[6] m.p. 129.4–130°).

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