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An Improved Synthesis of 4-Vinyl-2,6-di-*tert*-butylpyridine and Its Suspension Copolymerization with Styrene and Divinylbenzene

Michael E. Wright* and Shon R. Pulley

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300

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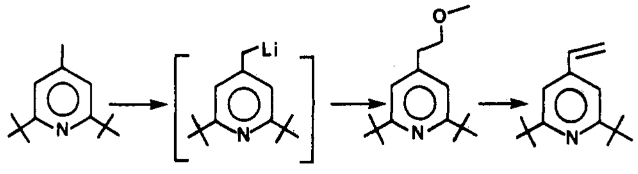
Polymer-supported organic reagents often provide several advantages over their homogeneous counterparts.[1] For instance, ease of workup, higher yields, and sometimes enhanced product selectivity have largely contributed to their popularity. In the case of expensive reagents, recovery of the reagent is important from an economical viewpoint.

Nonnucleophilic organic bases represent an important class of organic reagents that have been utilized in a variety of applications.[2] Although polymer-bound pyridine has received considerable attention,[3] the more sterically hindered organic base 2,6-di-*tert*-butylpyridine has only been incorporated into a polymer in a single instance.[4] The complete lack of nucleophilic character associated with 4-methyl-2,6-di-*tert*-butylpyridine (**1**) has permitted **1** to be utilized as a Lewis base in reactions even with the most reactive electrophiles (e.g., triflic anhydride, Tf_2O). Indeed, Stang and co-workers have shown **1** to be the base of choice in the preparation of vinyl triflates from the appropriate ketone or aldehyde and Tf_2O.[5]

Previously, 4-vinyl-2,6-di-*tert*-butylpyridine (**4**) was prepared in $\cong$5% yield from **1** (reaction sequence: (a) PhLi, (b) CO_2, (c) LAH, P_2O_5), and then monomer **4** was copolymerized with styrene and divinylbenzene to give a copolymer powder containing the hindered pyridine base.[4] We present a new and highly efficient synthesis of **4** and the suspension polymerization of **4** with styrene and divinylbenzene to give polymer beads.

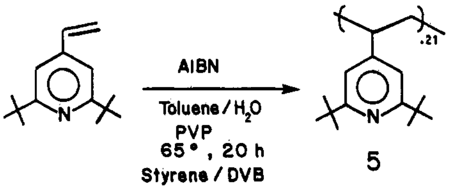
Reaction of 4-methyl-2,6-di-*tert*-butylpyridine[6] with 1.1 equiv of *s*-BuLi in tetrahydrofuran (THF) at −78 °C for 30 min leads to complete deprotonation of **1** and precipitation of the metalated species **2**. Treatment of the slurry with 1.2 equiv of chloromethyl methyl ether at −78 °C followed by warming to 25 °C and finally an aqueous workup affords **3** in 96% crude yield. NMR spectroscopy shows the purity at this point to be ≥95%, which is sufficiently pure for the next step in the reaction sequence. However, analytically pure **3** is easily obtained in 90% yield by subjecting the crude product to column chromatography on basic alumina.



1 2 3 4

Recently, Abruna and co-workers described the direct conversion of a (2-methoxyethyl)bipyridine derivative to the corresponding vinylbipyridine analogue using potassium *tert*-butoxide (KO-*t*-Bu) in THF.[7] We find similar reaction conditions, with the exception of a longer reaction time, can be used in the synthesis of **4**. The reaction of **3** with KO-*t*-Bu was monitored by TLC; little reaction occurs at −78 °C after 30 min, and formation of **4** does not appear complete until after 2 h at 25 °C. Aqueous workup of the mixture and flash chromatography on alumina affords analytically pure **4** as a colorless oil in 82% yield.

Compound **4** was copolymerized[8] with styrene and divinylbenzene by the procedure of Stille and Parrinello[9] to give spherical beads (**5**; 80–300 μm) containing 21 mol % of the 2,6-di-*tert*-butylpyridine monomer (1.6 mequiv/g). Nitrogen analysis confirmed that the pyridine was cleanly incorporated into the polymerization process.



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Currently our research efforts are focused on applications of the supported base in organic synthesis.

Experimental Section

General Procedures. All manipulations of compounds and solvents were carried out by using standard Schlenk techniques. Solvents were degassed and purified by distillation under nitrogen from standard drying agents.[10] Spectroscopic measurements utilized the following instrumentation: ^1H NMR, Varian XL 300; ^{13}C NMR, Varian XL 300 (at 75.4 MHz). NMR chemical shifts are reported in δ vs. Me_4Si, assigning the $CDCl_3$ resonance in ^{13}C spectra to be at 77.00 ppm. The KO-*t*-Bu and polyvinylpyrrolidone (av MW 40 000) (PVP) were purchased from Aldrich Chemical Co. and used as received. The chloromethyl methyl ether was freshly distilled from P_2O_5, and the styrene and divinylbenzene (50% purity) were also freshly distilled before use. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA.

4-(2-Methoxyethyl)-2,6-di-*tert*-butylpyridine (3). To a chilled (−78 °C) THF (30 mL) solution containing **1** (3.00 g, 14.6 mmol) was added *s*-BuLi (14 mL, 1.1 M in cyclohexane) dropwise by syringe. The mixture was stirred at −78 °C for an additional 30 min, and then the chloromethyl methyl ether (*caution*: chloromethyl methyl ether is highly toxic) (1.52 mL, 1.61 g, 20 mmol) was added in one portion. The mixture was allowed to warm to 25 °C and then diluted with pentanes (200 mL). The mixture was washed with H_2O (2 × 150 mL) and then brine (100 mL). The organic layer was dried (K_2CO_3), and the solvents were removed under reduced pressure to afford crude **3** [3.51 g (96%)] as a pale yellow clear oil. The crude product was diluted with hexanes (2 mL) and applied onto a basic alumina column eluted with a gradient of 0–5% ethyl acetate in hexanes (v/v). Fractions of eluant were collected and analyzed by TLC. The fractions

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containing pure **3** were combined, and the solvent was removed under reduced pressure to yield pure **3** [3.28 g (90%)] as a colorless oil: ^{1}H NMR (CDCl$_3$) δ 6.94 (s, py H-3, 2 H), 3.61 (t, J = 7.1 Hz, CH$_2$O, 2 H) 3.36 (s, OCH$_3$, 3 H), 2.84 (t, J = 7.1 Hz, 2 H, py CH$_2$, 2 H), 1.33 (s, CCH$_3$, 18 H); ^{13}C NMR (CDCl$_3$) δ 167.4 (py C-2), 147.2 (py C-4), 115.7 (py C-3), 72.8 (CH$_2$O), 58.6 (OCH$_3$), 37.6 (CCH$_3$), 36.2 (py-CH$_2$), 30.3 (CCH$_3$). Anal. Calcd for $C_{16}H_{27}NO$: C, 77.06; H, 10.91. Found: C, 77.13; H, 10.93.

4-Vinyl-2,6-di-*tert*-butylpyridine (4). To a chilled (−78 °C) THF (150 mL) solution containing **3** (3.50 g, 14.0 mmol) was added, in one portion, potassium *tert*-butoxide (3.15 g, 28.0 mmol). The cooling bath was removed, and the mixture was allowed to warm to room temperature and react for 2.5 h. The mixture was diluted with diethyl ether (200 mL) and H$_2$O (75 mL), and the layers were separated. The aqueous layer was back-extracted with diethyl ether (75 mL). The diethyl ether solutions were combined and washed with H$_2$O (100 mL) and finally brine (100 mL). The organic layer was dried (K$_2$CO$_3$) and filtered, and the solvents were removed under reduced pressure to afford crude **4** [2.60 g (85%)] as a colorless oil. Purification of **4** was achieved by flash chromatography on basic alumina (4 × 8 cm) with hexanes. Removal of the solvent under reduced pressure gave analytically pure **4** [2.49 g (82%)] as a clear oil: ^{1}H NMR (CDCl$_3$) δ 7.08 (s, py H-3, 2 H), 6.67 (dd, J = 10.8, 17.6 Hz, C*H*=CH$_2$, 1 H), 5.91 (d, J = 17.6 Hz, =CH$_2$, 1 H), 5.38 (d, J = 10.8 Hz, =CH$_2$, 1 H), 1.33 (s, CCH$_3$, 18 H); ^{13}C NMR (CDCl$_3$) δ 167.9 (py C-2), 144.6 (py C-4), 136.3 (*C*H=CH$_2$), 116.6 (=CH$_2$), 112.5 (py C-3), 37.7 (*C*CH$_3$), 30.3 (C*C*H$_3$). Anal. Calcd for $C_{15}H_{23}N$: C, 82.89; H, 10.67. Found: C, 82.85; H, 10.71.

Suspension Polymerization of 4 with Styrene and Divinylbenzene. A 250-mL three-neck Morton flask equipped with a mechanical stirrer and condenser was charged with a degassed aqueous (60 mL) solution of PVP (500 mg) and then vigorously stirred. A degassed solution containing styrene (490 mg, 4.8 mmol), divinylbenzene (119 mg), and **4** (357 mg, 1.6 mmol) was cannulated into the rapidly stirred PVP solution to form an emulsion. With continued stirring, a degassed toluene (2 mL) solution of AIBN (50 mg, 4 mol %) was added by cannula, and the suspension was heated at 65 °C for 20 h. The suspension was cooled and diluted with methanol (50 mL). Stirring was continued for 30 min, and then the mixture was transferred to a beaker. The beads were allowed to settle, and the supernatant liquid was decanted. The beads were washed/stirred/decanted with methanol (2 × 50 mL), tetrahydrofuran (2 × 150 mL), benzene (100 mL), and finally methanol (100 mL). The polymer was dried under reduced pressure at 65 °C for 24 h to afford beads [0.52 g (52%)] ranging in size from 80 to 300 μm. Anal. Calcd: N, 2.21. Found: N, 2.25.

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Registry No. 1, 38222-83-2; 3, 107082-94-0; 4, 81869-04-7; ClCH$_2$OCH$_3$, 107-30-2; (divinylbenzene)(styrene)(4-vinyl-2,6-di-*tert*-butylpyridine)(copolymer), 107054-29-5.

Conjugate Reduction of α,β-Acetylenic Ketones and Esters by Diisobutylaluminum Hydride–Hexamethylphosphoric Triamide

Tetsuo Tsuda,* Tsutomu Yoshida, Tadashi Kawamoto, and Takeo Saegusa*

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

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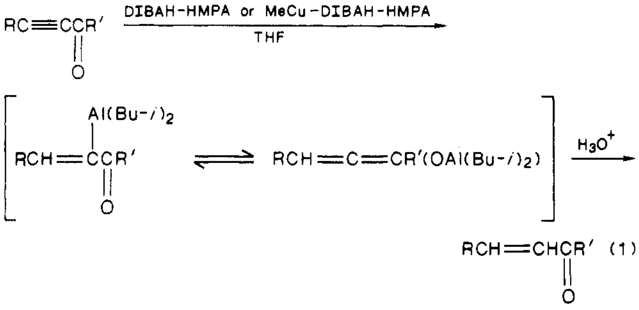
Recently we have reported an efficient and selective methylcopper- (MeCu-) catalyzed conjugate reduction of α,β-olefinic carbonyl compounds by diisobutylaluminum hydride (DIBAH) in the presence of hexamethylphosphoric triamide (HMPA) as a ligand to aluminum, where aluminum enolate intermediates generated by the hydralumination of α,β-unsaturated carbonyl compounds by DIBAH are involved.[1] In the present study, we tried to extend the scope of this novel reducing reagent; i.e., we investigated the conjugate reduction of α,β-acetylenic ketones and esters by the DIBAH–HMPA and the MeCu–DIBAH–HMPA systems (eq 1). Although catalytic hydrogenation has been known to effect the cis-conjugate reduction of α,β-acetylenic carbonyl compounds (vide post),[2] only a few examples of the conjugate reduction by metal hydrides or complex metal hydrides are known. The reduction of methyl propiolate with the Bu$_3$SnH–MeOH system gives methyl acrylate in a low yield.[3] The conjugate reduction of methyl 2-butynoate and methyl phenylpropiolate is effected by the use of a large amount of the reducing reagent NaAlH$_2$(OCH$_2$CH$_2$OCH$_3$)$_2$–CuBr,[4] while the complex metal hydrides such as LiCuHR[5] and LiBH(s-Bu)$_3$[6] have been reported not to be able to accomplish the conjugate reduction of α,β-acetylenic carbonyl compounds.



First, factors influencing the conjugate reduction of α,β-acetylenic ketone were examined using 2-methyl-4-nonyn-3-one (**1**) as a representative substrate. The results are summarized in Table I. In the presence of 3 equiv of HMPA to 1 equiv of aluminum, the conjugate reduction of **1** by DIBAH alone took place smoothly at 0 °C to give 2-methyl-4-nonen-3-one (**9**) quantitatively. At −50 °C the reduction proceeded very slowly. Addition of a catalytic amount of MeCu (10 mol %) to the DIBAH–HMPA system accelerated the reaction remarkably to effect the quantitative conjugate reduction at −50 °C. The reduction by DIBAH alone without HMPA caused the usual carbonyl reduction to give the corresponding propargyl alcohol. Thus, HMPA alters remarkably the reducing reactivity of DIBAH to suppress completely the carbonyl reduction and to effect the conjugate reduction selectively. An equimolar amount of HMPA to DIBAH is sufficient to manifest its effect. This finding suggests that HMPA functions not as a cosolvent but as a ligand to aluminum.[1] Stereochemistry of the resultant carbon–carbon double bond of the conjugate reduction product **9** depends on the presence or absence of MeCu. The (E) isomer predominates in the DIBAH–HMPA system. On the other hand, the MeCu–DIBAH–HMPA system favors the formation of the (Z) isomer, although the selectivity is not high. Several attempts to improve the (Z) stereochemistry by employing other copper(I) compounds and solvents (toluene, diethyl ether) were unsuccessful. The stereochem-

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