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Simple Synthesis of a Weak Nucleophilic Base (4-Ethyl-2,6-diisopropyl-3,5-dimethylpyridine) Evidencing a Double Janus Group Effect

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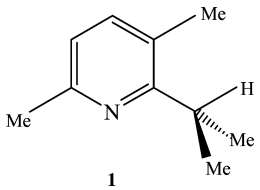
By analogy with 2,6-di-*tert*-butylpyridine and its 4-methyl-substituted derivatives, which are nonnucleophilic bases, 4-ethyl-2,6-diisopropyl-3,5-dimethylpyridine (**4**) is also such a base. The isopropyl groups (Janus-like groups) are forced by the neighboring methyl groups to turn their "*tert*-butyl-analogue face" toward the heteroatom, thereby protecting it sterically against electrophilic attack. The synthesis proceeds in two stages via the corresponding pyrylium salt **3** that is obtained by alkene diacylation. X-ray data for **4**, its picrate, and the hexafluorophosphate of **3** confirm that the ground-state conformation agrees with the Janus effect prediction. The chemical behavior of **4** indicates that it is indeed a weak nucleophilic base, which is able to substitute the nonnucleophilic bases in organic syntheses. The compound **3** reacts at normal pressure with methylamine or ethylamine, forming *N*-alkylpyridinium salts. The cationic polymerization of isobutene in the presence of **4** was also investigated.

Introduction

Freely rotating isopropyl groups offer two kinds of faces, like the mythological god Janus who looked toward both the past and the future (bridging the months of two consecutive years), hence the name Janus group effect.[1−4] One face of an isopropyl group is *tert*-butyl-like, associated with a considerable steric effect, and the other two faces are ethyl-like. Previously, we had tested this effect in two isomeric-substituted pyridines, 2-isopropyl-3,6-dimethylpyridine (**1**) and 6-isopropyl-2,3-dimethylpyridine (**2**).[4]



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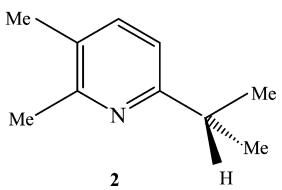

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It was shown earlier[5] that lanthanide shift reagents (LSRs) such as Eu(dpm)$_3$, Eu(fod)$_3$, Pr(dpm)$_3$, or Pr(fod)$_3$ complexed normally with pyridines substituted in the α positions (2 and 6) with one methyl group and one isopropyl group but not with those having one methyl group and one *tert*-butyl group. It was found that there was a normal complexation of such LRSs with pyridine **2**, where the isopropyl group could rotate freely, but practically none with the isomeric pyridine **1**, where the isopropyl was constrained by the neighboring methyl group to turn its *tert*-butyl-like face toward the site of the complexation with the LSR.[4]

Starting from this observation, we now report the simple synthesis of a new nonnucleophilic base, 4-ethyl-2,6-diisopropyl-3,5-dimethylpyridine (**4**), starting from inexpensive reagents in only two reaction steps. In addition to the Janus effect, a gear effect[2,6] may also take place in a pentasubstituted pyridine such as **4**.

Earlier, one of us had reported a synthesis of 2,6-di-*tert*-butyl-4-methylpyridine from its pyrylium analogue obtained by the diacylation of isobutene (IB) (actually, *tert*-butyl chloride, which is easier to handle) with pivaloyl chloride in the presence of tin tetrachloride.[7] Other

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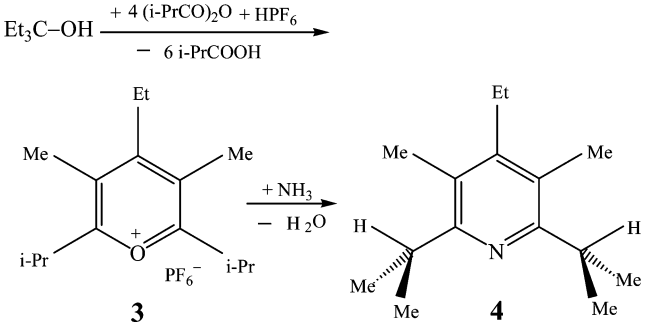
Lewis acids cause the decarbonylation of pivaloyl chloride, but an expensive Brønsted acid (triflic acid) can also be employed.[8] The workup is tedious, and the yields are not high. The synthesis of pyrylium salts via alkene diacylation has been called the Balaban−Nenitzescu−Praill reaction.[9]

It has long been known that 2,6-di-*tert*-butylpyridine (DTBP)[10] or 2,6-di-*tert*-butyl-4-methylpyridine,[7,8] which are commercially available at the present time at a fairly high cost, are nonnucleophilic bases. This fact makes them useful for many applications, e.g., as proton traps for living cationic polymerizations, inhibiting chain branching, and lowering the polydispersity.[11−21] Such pyridines distinguish between Brønsted acids, which are able to protonate them, and Lewis acids such as BF_3 or SO_3, which do not interact with them.[8,22−24] From NMR data, one can infer how protonated pyridines interact with anions or how the bases are chemisorbed on solid surfaces.[25] Benzylic triflates can be prepared with triflic anhydride in the presence of DTBP and are used in situ for the living polymerization of tetrahydrofuran.[26] Highly isotactic poly(isobutyl vinyl ether) was obtained with titanium-based Lewis acids and 2,6-di-*tert*-butyl-4-methylpyridine.[27] On the other hand, the electrochemical polymerization of pyrrole is inhibited by DTBP, owing to proton scavenging.[28] Rate constants between the vinylic cations and DTBP are the lowest among all pyridines.[29] Enolizable aldehydes and ketones afford enolic triflates with triflic anhydride and these nonnucleophilic bases;[30] such enolic esters are important in carbohydrate research;[31] other similar esters can be used for palladium-catalyzed couplings.[32] Radical cations of thianthrene[33] or anthracene[34] act as one-electron oxidants in the presence of these nonnucleophilic bases. An interesting biological application of the two nonnucleophilic pyridines mentioned above is to use them as hypolipaemic agents for lowering cholesterol levels.[35]

Synthesis of 4-Ethyl-2,6-diisopropyl-3,5-dimethylpyrylium Salts and 4. Upon dropwise addition of concentrated hexafluorophosphoric acid into a mixture of isobutyric anhydride and 3-ethyl-3-pentanol (triethylcarbinol), a rapid exothermal diacylation takes place. On cooling, 4-ethyl-2,6-diisopropyl-3,5-dimethylpyrylium hexafluorophosphate (**3**) crystallizes (admixed with a small amount of the hexafluorophosphate of the monoacylation product, 5-ethyl-2,4-dimethylhept-4-en-3-one) and can be separated by filtration and washing with diethyl ether. Recrystallization from ethanol or acetic acid and washing with ethyl ether give **3**, mp 235 °C. In the reaction, a sufficient amount of isobutyric anhydride needs to be present both for the diacylation and for binding of the water that comes with the 60% hexafluorophosphoric acid (5.4 mol of water for each mole of HPF_6).



Triethylcarbinol was selected in this synthesis because its dehydration affords a single alkene, namely, 3-ethyl-2-pentene. In theory, other tertiary or secondary alcohols, e.g., tri-*n*-propylcarbinol, may also be employed, leading to the pentasubstituted compounds related to **3** or **4**, but triethylcarbinol is the simplest one.

The crystal and molecular structure of **3** was determined by X-ray crystallography and showed (Figure 1a) that the two isopropyl groups are in a conformation that

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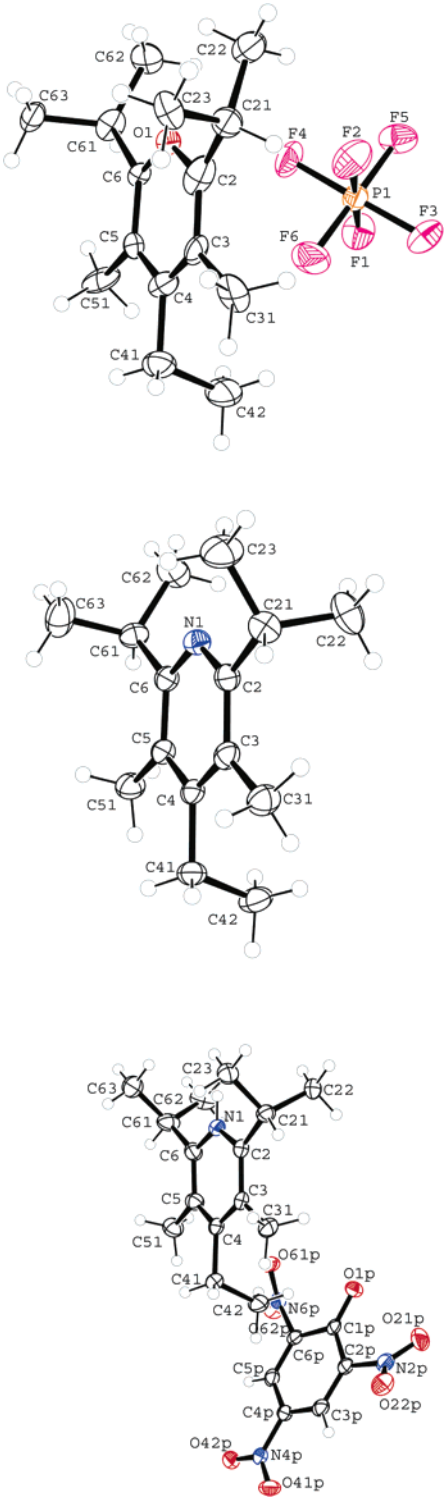

FIGURE 1. From top to bottom: the molecular structures of (a) the pyrylium salt **3**, (b) the pyridine **4**, and (c) its picrate **5**.

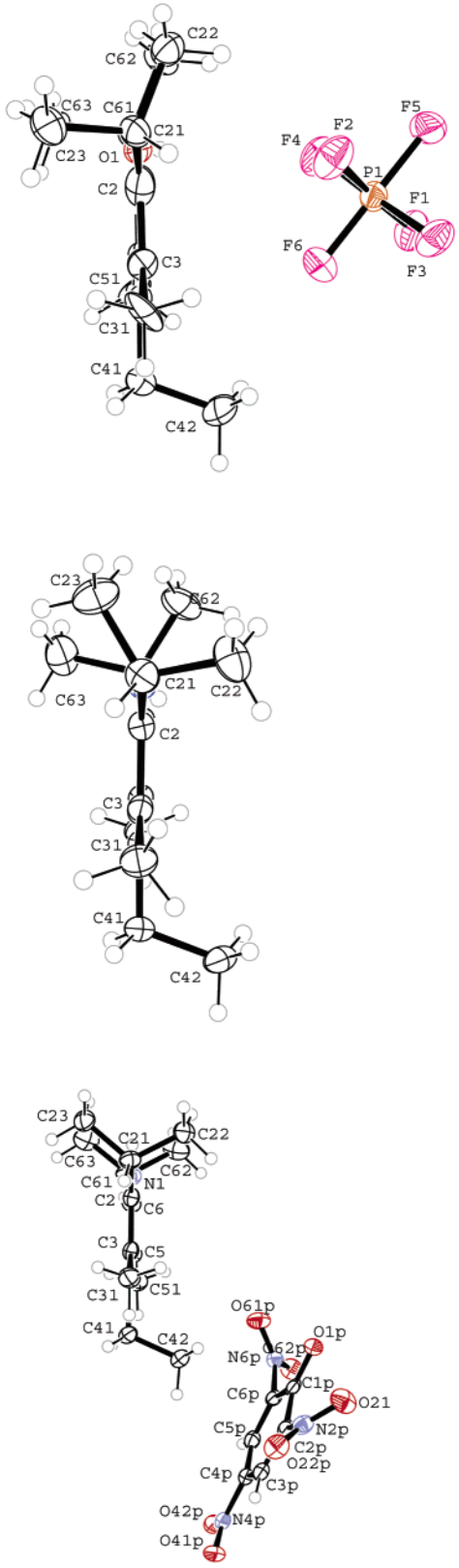

FIGURE 2. From top to bottom: the molecular structures of (a) the pyrylium salt **3**, (b) the pyridine **4**, and (c) its picrate **5** (side views).

has the pairs of methyl groups mirroring each other and being oriented toward the heteroatom but not bisecting exactly the heterocyclic ring, with the anion probably being responsible for the incomplete alignment of the isopropyl hydrogens with the 3- and 5-methyl groups.

Subsequent treatment with aqueous ammonia converted **3** into the title product **4** in high yield. After extraction with diethyl ether, **4** can be purified by distillation at reduced pressure, and being a little soluble in *n*-pentane, it can be recrystallized for attaining high

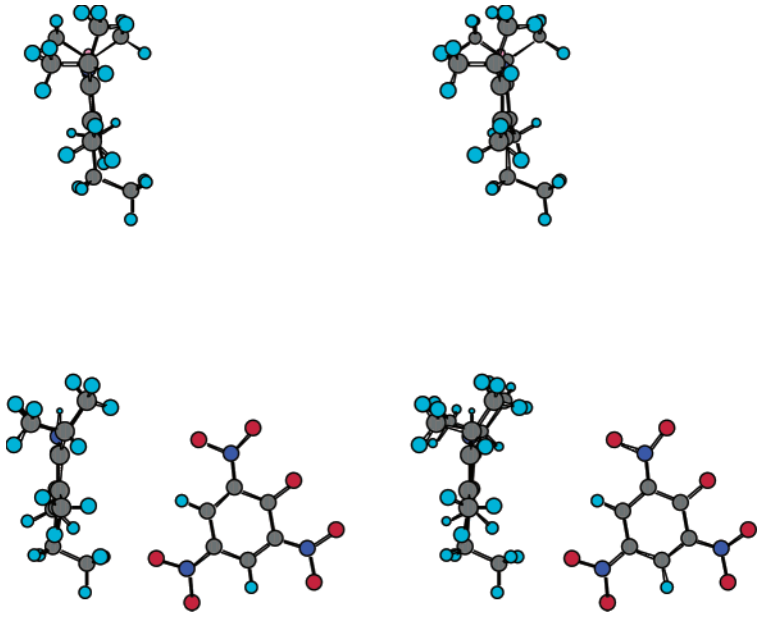

FIGURE 3. Stereoviews (side oriented for the heterocycle) of the structure of pyridine **4** (top) and its picrate **5** (bottom) calculated by MM2.

purity. Its X-ray structure is shown in Figure 1b, revealing that the two isopropyl groups are also shielding the heteroatom but in intercalated conformations. A crystalline picrate **5** of this pyridine was prepared; its crystal and molecular structures were determined by X-ray crystallography and showed (Figure 1c) that the two isopropyl groups are in an "eclipsed conformation", which has their two methyl groups oriented toward the heteroatom, bisecting exactly the planar pyridinium ring, i.e., in a conformation in which the isopropyl groups exert the same steric shielding as the *tert*-butyl groups. The only difference is that in **4** the isopropyl groups may turn (provided that the molecule has sufficient energy), alleviating the shielding, as shown by the quaternization that can proceed at normal pressure. Side views of the three molecular structures along the plane of the heterocycle illustrate the notable differences between the conformations of the pair of isopropyl groups (Figures 2a−c).

Interestingly, the molecular mechanics (MM2) calculations reproduce not only the Janus-like orientation of isopropyl groups but also their "staggered" conformation in the pyridine **4**, as well as their "eclipsed" conformation in the corresponding pyridinium picrate **5** (Figure 3).

Neither $Eu(fod)_3$ nor $Pr(fod)_3$ showed any complexation with **4**, which behaved with LSR just like DTBP and its 4-methyl derivative.

DTBP or its 4-methyl-derivative can be quaternized by reacting with methyl fluorosulfate only at high pressure;[36] other *N*-alkyldi-*tert*-butyl derivatives are not formed from the corresponding pyrylium salts with alkylamines. However, it should be mentioned that DTBP and its 4-methyl-derivative can readily afford *N*-amino derivatives[37] and that the corresponding *N*-oxides can also be prepared[38] via the reaction of hydroxylamine with the respective pyrylium salts, which had been described earlier.[7a,39,4039−40]

Analogously, hexasubstituted *N*-methyl- or *N*-ethylpyridinium salts (as hexafluorophosphates, **6** and **7**, respectively) can be obtained in high yield from **3** and methylamine or ethylamine at normal pressure, indicating that the steric shielding caused by the Janus effect can be overcome provided that the reaction has a high driving force.

Cationic Polymerization of IB in the Presence of Pyridine 4. The cationic polymerization of IB was carried out with the 2-chloro-2,4,4-trimethylpentane (TMPCl)/titanium tetrachloride ($TiCl_4$) initiating system in a hexanes (Hex)/methyl chloride (MeCl) (60:40, v/v) solvent mixture at −80 °C without (denoted as "no DTBP") and with the following proton traps: DTBP, 2,6-diisopropyl-4-methylpyridine (H-1), and compound **4** (H-2). The first-order plot of $\ln([M]_0/[M])$ versus time for the cationic polymerization of IB is presented in Figure 4. According to the first-order plot, termination cannot be detected during the polymerization of up to ∼80% monomer conversions. The slope of the $\ln([M]_0/[M])$ versus time plot gives the apparent rate constants of polymerization (k_{app}). The k_{app} values are similar in the [proton trap] = 0.004−0.008 mol/L concentration range, while in the absence of DTBP, the polymerization rate is significantly higher because of the initiation from protic impurities.

The M_n and M_w/M_n versus conversion plots are shown in Figures 5 and 6, respectively. The molecular weights follow the theoretical M_n−conversion line, indicating the absence of the chain transfer during the polymerization. The polydispersity index (PDI) decreases for all three proton traps with increasing conversion because of the

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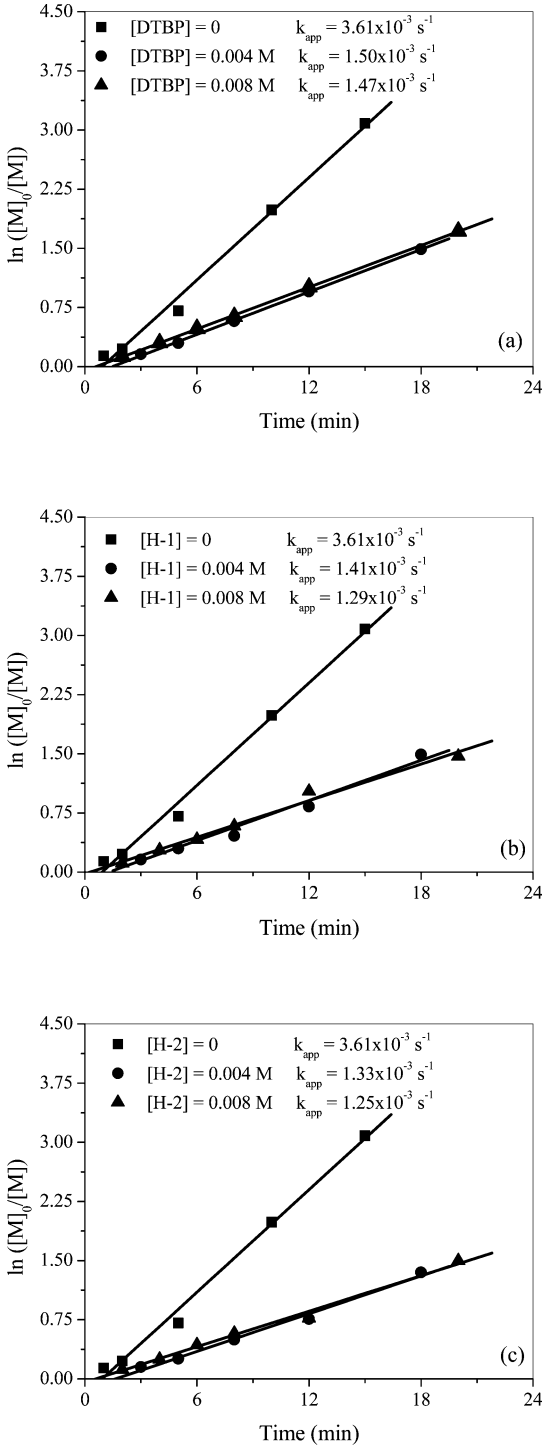

FIGURE 4. First-order plot of ln([M]$_0$/[M]) versus time for the cationic polymerization of IB initiated by TMPCl/$TiCl_4$ in Hex/MeCl (60:40, v/v) at −80 °C. [TMPCl] = 0.002 M, [IB] = 2.0 M, and [$TiCl_4$] = 0.036 M with (a) DTBP, (b) H-1 and (c) H-2.

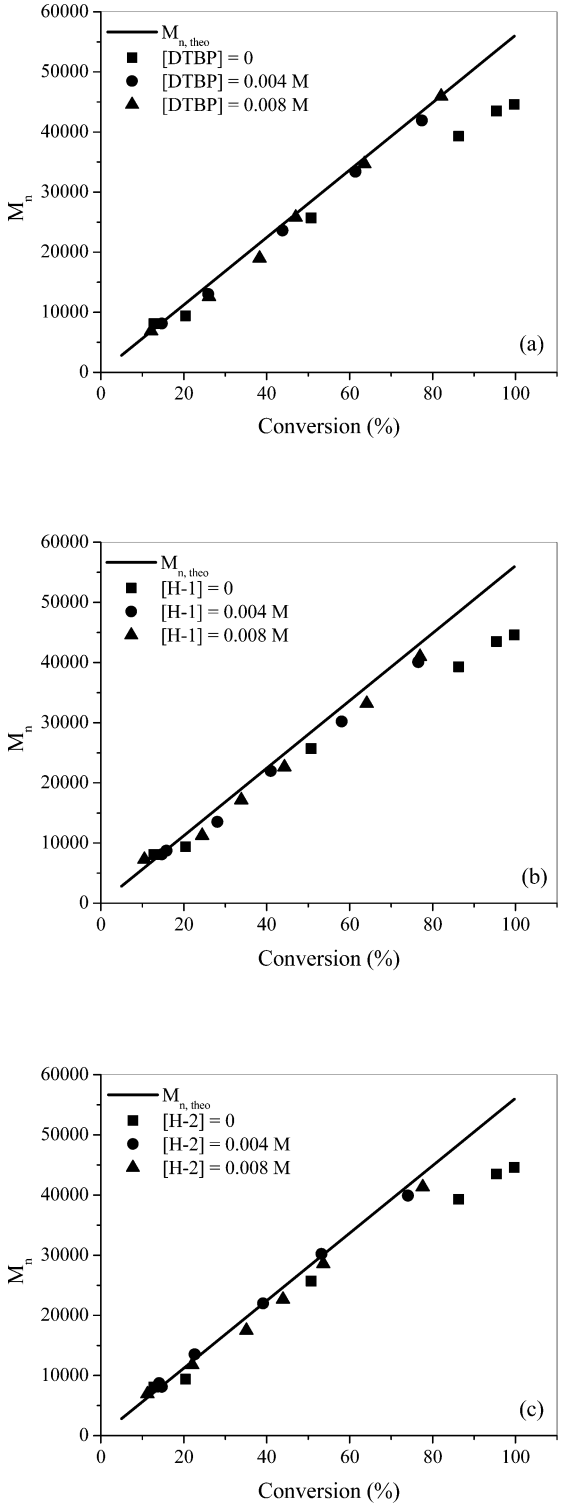

FIGURE 5. Variation of M_n with the conversion for (a) DTBP, (b) H-1, and (c) H-2. Reaction conditions are the same as those in Figure 4.

dynamic exchange between the dormant and living centers during polymerization. In conclusion, all three proton traps efficiently trap adventitious protons. This was a rather expected finding, because even the nonsubstituted pyridine can be used as a proton scavenger. In this case, however, the pyridine/$TiCl_4$ complex is the active proton scavenging species. Because of this complex formation, polymerization is absent when the concentration of the unhindered pyridines is equal to or higher than that of $TiCl_4$.

To elucidate the complex formation, polymerizations were also carried out at [$TiCl_4$] = [proton trap] = 0.036 mol/L, and in 12 min, 62.3, 9.1, and 26% of the monomer conversion was found for DTBP, H-1, and H-2, respectively. The conversion for DTBP is virtually identical with

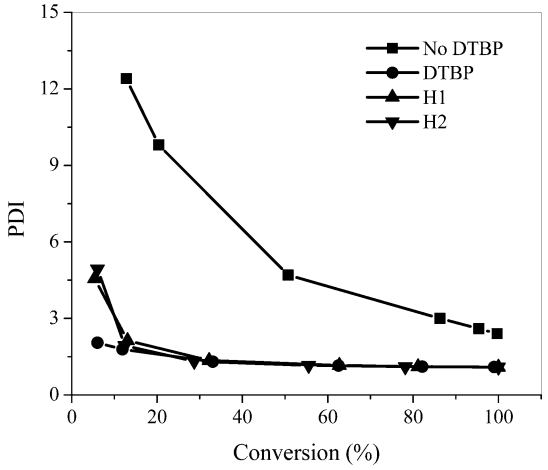

FIGURE 6. Variation of PDI with the conversion for the cationic polymerization of IB in Hex/MeCl (60:40, v/v) at −80 °C. [TMPCl] = 0.002 M, [IB] = 2.0 M, [$TiCl_4$] = 0.036 M, and [DTBP] = [H-1] = [H-2] = 0.004 M.

that obtained in the presence of [DTBP] = 0.004 and 0.008 M, indicating the absence of the complex formation between $TiCl_4$ and DTBP. For H-1 and H-2, the lowered conversions do suggest the complex formation for which the equilibrium constant is much higher for H-1 compared to H-2.

Conclusion

Triethylcarbinol reacts with isobutyric anhydride and Brønsted acids yielding a 4-ethyl-2,6-diisopropyl-3,5-dimethylpyrylium salt, which can be converted by ammonia into **4**. Owing to a double Janus effect, the isopropyl groups are shielding the heteroatom like *tert*-butyl groups, as shown by X-ray crystallography. Thus, pyridine **4** is a weakly nucleophilic base and can substitute 2,6-di-*tert*-butylpyridine or its 4-methyl derivative in its uses as a nonnucleophilic base.

Experimental Section

NMR spectra were recorded on a Varian Inova spectrometer equipped with a 5 mm indirect detection probe, operating at 500 MHz for ^{1}H and at 125 MHz for ^{13}C NMR. Chemical shifts are reported in parts per million relative to TMS. The ^{1}H and ^{13}C NMR chemical-shift assignments are based on the one-bond and long-range ^{1}H−^{13}C correlations seen in the ghmbc (gradient heteronuclear multiple-bond correlation) spectra.

Synthesis of the Pyrylium Salt 3. A mixture of 11.6 g (12.1 mL, 0.1 mol) of triethylcarbinol and 101 g (106 mL, 0.64 mol) of isobutyric anhydride was placed in a three-necked flask equipped with an efficient stirrer (at the end of the reaction, the crystal slurry is quite thick), immersed thermometer, dropping funnel, and reflux condenser. Then about one-third from 25 g (15 mL, 0.1 mol) of 60% hexafluorophosphoric acid (which contains 5.4 mol of water per mole of HPF_6) was added dropwise, allowing the temperature to rise fairly rapidly to about 90 °C (otherwise the product crystallizes, and the mixing becomes difficult), and the remaining acid was added at such a rate as to allow the temperature to stay in the range of 90−100 °C. When the addition was complete, the mixture was cooled to room temperature. A total of 100 mL of ethyl ether was added to the mixture, and the crystallized off-white product was filtered off and washed thoroughly with ether on the filter. It contained as an impurity the hexafluorophosphate of the unsaturated ketonic monoacylation product. Recrystallization from 120 mL of ethanol or a smaller volume of acetic acid followed by washing of the product on the filter with ethyl ether afforded white crystals with mp 235 °C. The yield was around 50%. HRMS: calcd for $C_{15}H_{25}O^+PF_6^-$, 221.1905; found, 221.1903. Fragments at m/z = 220, 205 (base peak), 197, 192, 177, 155, 135, 107, 91, 77, 65, 55, and 43. ^{1}H NMR in DMSO (δ, ppm; J, Hz): 1.16 (3H, t, J = 7.6, 4-Me), 1.35 (12 H, d, J = 7.0, 2,6-Me_4), 2.44 (6H, s, 3,5-Me_2), 2.95 (2H, q, J = 7.6, 4-CH_2), 3.71 (2H, septet, J = 7.0, 2,6-CH). ^{13}C NMR in DMSO (δ, ppm): 11.6 (4-Me), 13.0 (3,5-Me_2), 19.8 (2,6-Me_4), 25.3 (4-CH_2), 31.8 (2,6-CH), 129.9 (C-3,5), 175.1 (C-4), 178.9 (C-2,6). The corresponding perchlorate (from 70% perchloric acid, which contains 2.4 mol of water per mole of $HClO_4$) was obtained in 55% yield and had mp 142−143 °C. Anal. Calcd for $C_{15}H_{25}ClO_5$: C, 56.16; H, 7.85. Found: C, 56.25; H, 7.81.

Synthesis of 4. The above pyrylium salt **3** was heated to boiling with 30 mL of ethanol and an excess of concentrated aqueous ammonia. The conversion into **4** was complete in a few minutes. The cooled solution was diluted with an equal volume of water and extracted three times with ethyl ether. The base from the combined extracts was extracted with an excess of 10% hydrochloric acid, and the aqueous acid layer was treated with an excess of aqueous sodium hydroxide for regenerating the base. After three extractions with ethyl ether, the combined organic layer was dried over powdered potassium hydroxide, and the solvent was evaporated under reduced pressure. The liquid product **4** was distilled in a vacuum, bp 104 °C/4 Torr, mp 37−38 °C. The yield of the reaction was 85−90%. Anal. Calcd for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.39. Found: C, 81.79; H, 11.13; N, 6.41. HRMS: calcd for $C_{15}H_{25}N$, 219.1987; found, 219.1983. Fragments at m/z = 218, 204 (base peak), 191, 188, 176, 171, 163, 143, 131, 97, 83, 71, 69, 55, and 43. ^{1}H NMR in DMSO (δ, ppm; J, Hz): 1.02 (3H, t, J = 6.8, 4-Me), 1.14 (12 H, d, J = 7.7, 2,6-Me_4), 2.18 (6H, s, 3,5-Me_2), 2.59 (2H, q, J = 6.8, 4-CH_2), 3.19 (2H, h, J = 7.7, 2,6-CH). ^{13}C NMR in DMSO (δ, ppm): 19.8 (4-Me), 13.5 (3,5-Me_2), 22.5 (4-CH_2 and 2,6-Me_4), 31.4 (2,6-CH), 124.5 (C-3,5), 149.2 (C-4), 159.9 (C-2,6). For preparing enol esters, in particular cholesta-3,5-dien-3-yl trifluoromethanesulfonate[41] when a nonnucleophilic base is needed,[32,41] this pyridine served exactly as well as 2,6-di-*tert*-butylpyridine. Picrate **5** of **4**, mp from ethanol 150 °C. Anal. Calcd for $C_{21}H_{28}N_4O_7$: C, 56.24; H, 6.29; N, 12.49. Found: C, 56.41; H, 6.33; N, 12.69.

Reaction of the Pyrylium Salt 3 with Methylamine. 4-Ethyl-2,6-diisopropyl-1,3,5-trimethylpyridinium hexafluorophosphate (**6**) was prepared in 88% yield from **3** by refluxing for 3 h in ethanol with a small excess of methylamine and with a small amount of acetic acid. Mp from ethanol: 248 °C. Anal. Calcd for $C_{16}H_{28}F_6NP$: C, 50.66; H, 7.44; N, 3.39. Found: C, 50.73; H, 7.15; N, 3.74. ^{1}H NMR in DMSO (δ, ppm, J, Hz): 1.12 (3H, t, J = 7.7, 4-Me), 1.44 (12H, d, J = 7.2, 2,6-Me_2), 2.83 (2H, q, J = 7.7, 4-CH_2), 2.46 (6H, s, 3,5-Me_2), 3.88 (2H, septet, J = 7.2, 2,6-CH), 4.11 (3H, s, 1-Me). ^{13}C NMR in DMSO (δ, ppm): 12.2 (4-Me), 16.2 (3,5-Me_2), 19.7 (2,6-Me_4), 24.3 (4-CH_2), 30.8 (2,6-CH), 43.5 (1-Me), 133.5 (C-3,5), 159.1 (C-2,6), 161.2 (C-4).

Reaction of 3 with Ethylamine. In a similar manner, the pyrylium salt **3** afforded 1,4-diethyl-2,6-diisopropyl-3,5-dimethylpyridinium hexafluorophosphate (**7**) with ethylamine with mp from ethanol 228 °C. Anal. Calcd for $C_{17}H_{30}F_6NP$: C, 51.90; H, 7.69; N, 3.56. Found: C, 52.11; H, 7.38; N, 3.57. ^{1}H NMR in DMSO (δ, ppm, J, Hz): 1.13 (3H, t, J = 7.6, 4-Me), 1.47 (12H, d, J = 7.2, 2,6-Me_2), 1.50 (3H, t, J = 6.7, 1-Me), 2.82 (2H, q, J = 7.6, 4-CH_2), 2.48 (6H, s, 3,5-Me_2), 4.52 (2H, q, J = 6.7, 1-CH_2), 3.85 (2H, septet, J = 7.2, 2,6-CH). ^{13}C NMR in DMSO (δ, ppm): 11.8 (4-Me), 16.3 (3,5-Me_2), 16.7 (1-Me), 20.3 (2,6-Me_4), 23.6 (4-CH_2), 30.6 (2,6-CH), 49.8 (1-CH_2), 134.1 (C-3,5), 158.4 (C-2,6), 162.1 (C-4).

Cationic Polymerizations of IB. Materials. MeCl and IB were dried in the gaseous state by passing them through

(41) Cacchi, S.; Morera, E.; Ortar, G. *Org. Synth.* **1990**, *68*, 138−147.

inline gas-purifier columns packed with BaO/Drierite. They were condensed in the cold bath of a glovebox prior to polymerization. $TiCl_4$ (Aldrich, 99.9%) and DTBP (Aldrich, 97%) were used as received. The synthesis of TMPCl and purification of Hex and methanol have been published elsewhere.[15]

Polymerizations. All polymerizations were carried out under a dry nitrogen atmosphere in an MBraun 150-M glovebox (Innovative Technology Inc., Newburyport, MA). Large (75 mL) culture tubes were used as the polymerization reactors. The total volume of the reaction mixture was 10 mL. The polymerization was quenched with excess prechilled methanol. The polymer was recovered and purified by reprecipitation from Hex/methanol. Monomer conversions were determined by gravimetric analysis.

Characterization of Polymers. Molecular weights were measured with a Waters HPLC system equipped with a model 510 HPLC pump, model 410 differential refractometer, model 441 absorbance detector, online multiangle laser light scattering detector (MiniDawn, Wyatt Technology Inc. Santa Barbara, CA), model 712 sample processor, and five Ultrastyragel GPC columns connected in the following series: 500, 10^3, 10^4, 10^5, and 100 Å. THF was used as a carrier solvent with a flow rate of 1 mL/min.

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Supporting Information Available: Crystal data for **3**−**5** and ghmbc NMR spectra for **3**, **4**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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