

2,4-Di-*tert*-butyl-5,6-dialkylpyrimidines: easily prepared alternative to non-nucleophilic hindered bases

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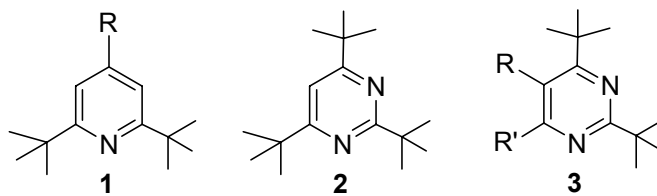
Abstract

2,4-Di-*tert*-butyl-5,6-dialkylpyrimidines were easily obtained in a one-step reaction from dialkyl ketones and pivalonitrile in the presence of triflic anhydride. pKa values determined show that these compounds can be used as highly sterically non-nucleophilic bases. It was applied to the synthesis of vinyl triflates in which the strong TfOH acid is formed. The results were compared with the obtained using commercially available 2,4,6-tri-*tert*-butylpyrimidine (TTBP).

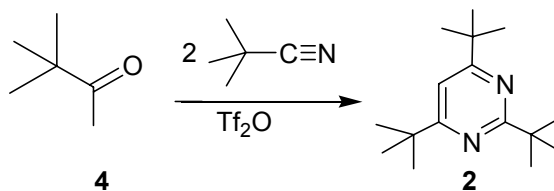
Keywords: Non-nucleophilic bases, pyrimidines, vinyl triflates

Introduction

Bases are a very important class of reagents for synthetic organic chemistry, as in a large amount of reactions the deprotonation is a key step in the synthesis of new structures. Different applications and reaction conditions often require the use of specific bases. Due to this, a broad range of organic bases have been developed and commonly used. These bases are differentiated by strength, nucleophilicity, steric hindrance or solubility. Many efforts have been made in optimizing the basicity and reducing the nucleophilic character of organic bases. Thus, steric hindered aliphatic amines, anilines and *N*-heterocycles have been widely applied and shown a couple of useful applications as i.e. in Dieckmann cyclization,¹ polymerizations² or metalation reactions.³ In this regard, 2,6-di-*tert*-butyl-4-alkyl-pyridines (**1**) were introduced by Brown and Kanner⁴ as a non-nucleophilic mild bases (Figure 1).

**Figure 1**

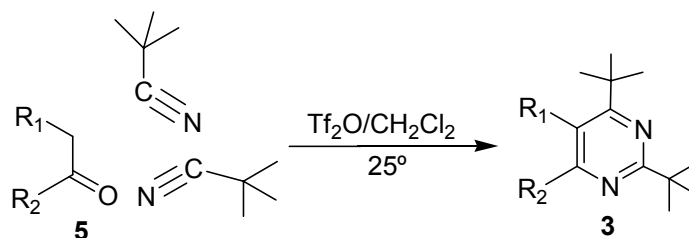
Compounds (**1**) have been extensively employed in a broad variety of contexts^{5,6} mainly the formation of vinyl triflates^{7,8} in spite of their multi-step preparation. More recently Crich *et al.*⁹ reported that 2,4,6-tri-*tert*-butylpyrimidine (TTBP, **2**) serves as an “admirable” replacement for (**1**) in the mentioned reactions. Additionally high amounts of **2** can be easily obtained following the improved procedure developed by us,¹⁰ which permits the synthesis of a large number of tetraalkyl-, tetraaryl- and alkyl-arylpurimidines in high yield. Thus, the synthesis of (**2**) involves the condensation of pinacolone (**4**) with two equivalents of pivalonitrile, promoted by one equivalent of trifluoromethanesulfonic anhydride (triflic anhydride, Tf₂O). The reaction was carried out at 25°C in dichloromethane as solvent. Unpolar solvents such as *n*-pentane or carbon tetrachloride can also be used (Scheme 1).¹⁰

**Scheme 1**

We now report the synthesis of new substituted 2,4-di-*tert*-butyl-5,6-dialkylpyrimidines (**3**) following the general procedure developed by us.¹⁰ Its pK_a values were determined and its application as non-nucleophilic bases in the formation of vinyl triflates studied.

Results and Discussion

The reaction of symmetric ketones (**5**) with 2 equivalents of pivalonitrile (Scheme 2) at 25°C in dichloromethane as solvent affords substituted pyrimidines (**3**) as the unique reaction product (Scheme 2). Symmetric ketones were chosen as starting products since only one regioisomer can be produced. Good yields were obtained (Table 1).



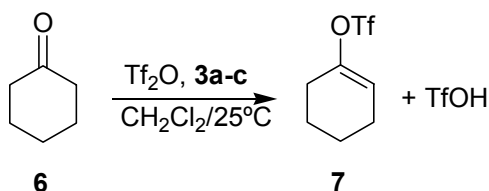
Scheme 2

Table 1. 2,4-Di-*tert*-butyl-5,6-dialkylpyrimidines (**3**) prepared

| Ketone 5 | Compound | Yield (%) ^a |
|---|-----------|------------------------|
| a R ¹ = Me, R ² = Et | 3a | 73 |
| b R ¹ = Et, R ² = Pr | 3b | 77 |
| c R ¹ = Pr, R ² = Bu | 3c | 70 |

^a Yield of isolated product.

2,4-Di-*tert*-butyl-5,6-dialkylpyrimidines (**3a-c**) were tested as non-nucleophilic bases by means of their use in the synthesis of the cyclohexenyl triflate (**7**), where triflic acid is generated as byproduct (Scheme 3). In comparison with 2,4,6-tri-*tert*-butylpyrimidine (**2**) slightly higher yields were obtained. pK_a values of new 2,4-di-*tert*-butylpyrimidines **3a-c** were determined using Differential Pulse Polarography (DPP) and compared with **2**.



Scheme 3

As shown in Table 2, pK_a values of new 2,4-di-*tert*-butyl-5,6-dialkylpyrimidines (**3a-c**) are higher than this from 2,4,6-tri-*tert*-butylpyrimidine (**2**). Although new bases (**3a-c**) are milder than (**2**), its basicity is sufficient to neutralize triflic acid, the byproduct originated in enol triflate formation and in a couple of reactions for which triflic anhydride is used as reagent. The absence of water in the reaction media avoids the total dissociation of TfOH.¹¹ However it is necessary to trap the formed acid because its presence provokes a partial decomposition of final products.

Table 2. pKa of pyrimidines (**2**, **3a-c**) and yield of vinyl triflate **7** obtained

| Compound | pKa | Yield (%) |
|-----------|------|-----------|
| 2 | 1.07 | 62 |
| 3a | 1.95 | 64 |
| 3b | 1.68 | 67 |
| 3c | 1.61 | 71 |

In comparison with the already known 2,4,6-tri-*tert*-butylpyrimidine (**2**), the preparation of 2,4-di-*tert*-butyl-5,6-dialkylpyrimidines (**3a-c**) is easier and the costs are lower. The above shown results obtained in the synthesis of cyclohexenyl triflate (**7**) are slight better. In summary we propose that 2,4-di-*tert*-butyl-5,6-dialkylpyrimidines (**3a-c**) easily synthesized in a one-step reaction from symmetric ketones offers new base-candidates to be used as non-nucleophilic bases replacing 2,4,6-tri-*tert*-butylpyrimidine (TTBP) (**2**).

Experimental Section

General Procedures. All reagents were commercial grade and were used as received unless otherwise indicated. Triflic anhydride was prepared from TfOH and redistilled twice prior to use.^{12,13} Solvents were distilled from an appropriate drying agent before use. Reactions were monitored by thin-layer chromatography. Column chromatography was performed using silica gel 60. IR, NMR, Mass spectra and Elemental Analysis were carried out in the CAIs of the UCM. The IR spectra were measured with a Shimadzu FTIR 8300 instrument. NMR spectra were recorded on a Bruker DPX 300 and Bruker Avance AV 500 at 300 MHz for ¹H and 75.47 MHz for ¹³C and 500 MHz for ¹H and 125.72 MHz for ¹³C respectively. Chemical shifts are given in δ units (ppm) to residual CHCl₃ (7.26 and 77.0 respectively). *J* values are given in Hz. Mass spectra (EI) were recorded on a HP 5989A quadrupole instrument at 70 eV with a source temperature of 200 °C. Elemental analyses were performed with a Perkin-Elmer 2400 CHN apparatus.

General procedure for the synthesis of 2,4-di-*tert*-butyl-5,6-dialkyl substituted pyrimidines

To a well-stirred solution of triflic anhydride (6.4 g, 22.8 mmol) and pivalonitrile (3.0 g, 42 mmol) in anhydrous CH₂Cl₂ (20 mL) was added slowly a solution of the ketone **5** (20 mmol) in anhydrous CH₂Cl₂ (10 mL). The red-brown mixture was magnetically stirred for 24h at room temperature. Saturated NaHCO₃ solution (50 mL) was carefully added, and the organic phase was washed with brine (2x50 mL) and dried over MgSO₄. The solvent was removed *in vacuo*, and the crude product was purified by column chromatography over silica gel 60 (Merck) using hexane/ethyl acetate (9:1) as the eluent.

2,4-Di-*tert*-butyl-6-ethyl-5-methylpyrimidine (3a). Bp 100-101 °C (0.4 Torr); IR (CHCl₃) ν : 2956, 2871, 1541, 1448, 1012, 923 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.30 (t, *J* = 7.5 Hz, 3H, CH₃),

1.39 (s, 9H, 3CH₃), 1.44 (s, 9H, 3CH₃), 2.37 (s, 3H, CH₃), 2.76 (q, $J = 7.5$ Hz, 2H, CH₂); ¹³C NMR (CDCl₃) δ : 12.03, 15.10, 28.40, 29.69, 29.70, 39.14, 112.59, 169.15, 171.44, 171.81 ppm; MS (EI, 70 eV) m/z (%B): 234 (M⁺, 4), 233 (4), 219 (11), 205 (5), 192 (28), 102 (13), 97 (15), 71 (35), 57 (100), 44 (99); ; Anal. Calcd for C₁₅H₂₆N₂, C 76.87% H 11.18% N 11.95%. Found C 78.81% H 10.90 N 11.57%.

2,4-Di-*tert*-butyl-5-ethyl-6-propylpyrimidine (3b). Bp 120-121 °C (0.6 Torr); IR (CHCl₃) ν : 2958, 2927, 1537, 1479, 1055 cm⁻¹; ¹H NMR (CDCl₃) δ : 1.01 (t, $J = 7.3$ Hz, 3H, CH₃), 1.18 (t, $J = 7.3$ Hz, 3H, CH₃), 1.36 (s, 9H, 3CH₃), 1.42 (s, 9H, 3CH₃), 1.81 (sext, $J = 7.3$ Hz, 2H, CH₂), 2.71 (t, $J = 7.3$ Hz, 2H, CH₂), 2.85 (q, $J = 7.3$ Hz, 2H, CH₂); ¹³C NMR (CDCl₃) δ : 14.35, 15.25, 21.17, 22.15, 29.77, 30.68, 35.99, 39.17, 39.77, 128.28, 168.64, 171.49, 171.73 ppm; MS (EI, 70 eV) m/z (%B): 262 (M⁺, 4), 245 (62), 219 (7), 205 (27), 191 (14), 71 (19), 57 (61), 44 (100) ; Anal. Calcd for C₁₇H₃₀N₂, C 77.80% H 11.52% N 10.67%. Found C 77.71% H 11.65 N 10.34%.

4-Butyl-2,4-di-*tert*-butyl-5-propylpyrimidine (3c). Bp 150-151 °C (0.6 Torr); IR (CHCl₃) ν : 2958, 2929, 1533, 1402, 1215, 1089, 908 cm⁻¹; ¹H NMR (CDCl₃) δ : 0.96 (t, $J = 7.3$ Hz, 3H, CH₃), 1.05 (t, $J = 7.3$ Hz, 3H, CH₃), 1.35 (s, 9H, 3CH₃), 1.41 (s, 9H, 3CH₃), 1.64 (m, 6H, 3CH₂), 2.71 (m, 4H, 2CH₂); ¹³C NMR (CDCl₃) δ : 14.06, 14.63, 22.82, 24.19, 29.62, 30.51, 30.71, 31.04, 33.70, 39.02, 39.64, 126.84, 168.77, 171.37, 171.56 ppm; MS (EI, 70 eV) m/z (%B): 290 (M⁺, 3), 289 (4), 276 (16), 275 (86), 261 (30), 247 (68), 233 (40), 219 (19), 206 (20), 191 (22), 178 (10), 97 (17), 81 (16), 71 (39), 69 (39), 57 (100), 42 (44); Anal. Calcd for C₁₉H₃₄N₂, C 78.56% H 11.80% N 9.64%. Found C 78.51% H 11.90 N 9.57%.

Synthesis of cyclohexenyl triflate (7) in the presence of 4-butyl-2,4-di-*tert*-butyl-5-propylpyrimidine (3c)

To a stirred solution of cyclohexanone (6) (2 g, 20.4 mmol) and pyrimidine (3c) (6.67 g, 23 mmol) in anhydrous CH₂Cl₂ (20 mL) was added dropwise a solution of triflic anhydride (6.31 g, 22.4 mmol) in anhydrous CH₂Cl₂ (20 mL) at 0°C. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed *in vacuo* and the residue extracted with hexane (3x50 mL). The hexane extract was washed with 1.5 M aqueous hydrochloric acid (2x50 mL), saturated with sodium hydrogen carbonate solution (2x50 mL) and saturated brine (2x50 mL). The organic layer was dried with magnesium sulfate and the solvent removed under vacuum. The residue was purified by column chromatography using hexane as the eluent. 3.3 g (71%) of triflate (7) were obtained.¹³

Determination of pKa values

Electrodes and electrochemical cell

The electrochemical cell consisted of a multimode Metrohm 6.1246.020 Hg electrode equipped with a Metrohm 6.1226.030 capillary tube and operated in the DME mode, a Metrohm 6.0728.000 Ag/AgCl/3 mol L⁻¹ KCl reference electrode, and a Metrohm 6.1247.000 auxiliary glassy carbon electrode, in a Metrohm 6.1415.0210 vessel.

A Metrohm AG-9100 combined electrode was used for pH measurements.

Reagents and solutions: Procedure

DP polarograms were recorded in 1.0×10^{-5} mol L⁻¹ solutions of each compound in a Britton-Robinson buffer solution containing each component acid at 0.2 mol L⁻¹ (pH range 0.5-4.0) and with a 6% content in ethanol. The prepared solutions (25 mL) were transferred into the electrochemical cell and deoxygenated by passing an argon stream through them for 15 min. Polarograms were recorded at 25 ± 1 °C keeping an inert atmosphere in the cell, with $\Delta E = -50$ mV, $v = 10$ mV s⁻¹, and $t_d = 1$ s.

DPP allows the achievement of polarograms (current-potential plots at the dropping mercury electrode) when a pulse train of constant amplitude is superimposed to a steadily varying with the time potential program, in the buffer solution containing the sample. The peak potential decreased only slightly between pH 0.5-2.0 in all cases, while a strongly pH dependence between pH 2.0-4.0 was found (Fig. not shown). A plot of the influence of pH on the peak potentials obtained, gives various linear regions whose intersection points can be associated to the pKa value of each studied compound. The RSDs values for each measured compound were lower than 5% in all cases.

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