Generation of *N*-Acylpyridinium Ions from Pivaloyl Chloride and Pyridine Derivatives by Means of Silyl Triflates†

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The addition of a carbon nucleophile to an *N*-acyliminium ion represents a powerful and versatile carbon−carbon bond-forming reaction. Therefore, a multitude of different methods for the generation of *N*-acyliminium ions have emerged.[1] In a simple and frequently used approach, *N*-acyliminium ions are generated by acylation of an appropriate azaaromatic with a suitable acid halide. A major drawback of this approach arises from the fact that these reactions are equilibrium reactions and that depending on the nature of the reactants the position of such equilibria may more or less reside on the side of the educts. Though also for equilibria with an unfavorable position trapping reactions of the *N*-acyliminium ions may proceed smoothly such trapping reactions are only reasonably successful if the reaction of the nucleophile with the *N*-acyliminium ion is more favorable as compared to the reaction with the acid halide.[2] Thus, methods that would allow the shift of such equilibria toward the side of the *N*-acyliminium ion would be certainly of high value as they should broaden the scope of the *N*-acyliminium ion chemistry.

Recently, Yamaguchi et al.[3] reported that the reactivity of *N*-acyliminium ions generated from quinoline and chloroformates may be severely increased by means of certain additives such as AgOTf, NaOTf, LiOTf, $AgBF_4$, and Me_3SiOTf. This increase in reactivity became evident, as in the presence of these additives even the less nucleophilic allyltrimethylsilanes could be smoothly added to the *N*-acylquinolinium ions whereas in their absence only allyltributylstannanes appeared to be sufficiently reactive to add to the *N*-acyliminium ions.

According to a proposal of the authors these additives, that had been applied in catalytic amounts, give rise to the formation of a *N*-acyliminium salt wherein the chloride ion resulting from the chloroformate ester is replaced by the anion provided by the additive. The lower nucleophilicity of the new counterion was thought to increase the electrophilicity of the *N*-acyliminium ion thus promoting the addition reactions.

It appeared to us that at least for some of the abovementioned additives the observed effect might result from a shift of the position of the equilibrium from the side of the educts toward the *N*-acyliminium ions associated with an increase of the reaction rates for the subsequent addition reactions.

The present study was performed to uncover whether silyl triflates might indeed effect the position of such *N*-acyliminium ion equilibria. It was thought that this phenomenon might be best investigated by ^{1}H NMR spectroscopy. In addition, also the effects of these additives on the yields of subsequent trapping reactions appeared to be of interest and should be determined. For the generation of the *N*-acyliminium ions the pyridine derivatives **2a**−**c**[4] were selected (Scheme 1). These compounds are the basis for some ongoing synthetic programs, and they are, which appeared more important, significantly different in their nucleophilicities. Chiral *N*-acyliminium ions provided with an α-quaternary acyl residue acting as a chiral auxiliary play the key role in an efficient method that we have developed for the asymmetric construction of α-substituted nitrogen heterocycles.[5] Therefore, we employed pivaloyl chloride (**3**) as the second component. The steric requirements of **3** are close to those of the aforementioned chiral auxiliary, and as the bulkiness of **3** should inhibit the *N*-acyliminium ion formation, this might help that the effects resulting from the additives such as silyl triflate might become even more apparent.

In a first series of experiments, the extent of the *N*-acyliminium ion formation in the absence of additives was determined. To this end, the respective pyridines **2a**−**c** and pivaloyl chloride (**3**) were dissolved in CD_2Cl_2 (see series A in Table 1) to give 0.1 M solutions that, after they had been allowed to equilibrate for 1 h, were measured by ^{1}H NMR spectroscopy. With one exception no signals other than those for the starting materials **2a**−**c** and **3** were detected, when a range of temperatures from room temperature to −78 °C was checked (by ^{1}H NMR). For 4-methoxypyridine **2c**, however, at −78 °C an additional set of signals with an intensity of 40% occurred that was assigned to the *N*-acylpyridinium ion **1c**. Obviously, only **2c** of the three pyridines **2a**−**c** exhibits a sufficient nucleophilicity so that a significant amount of the respective *N*-acyliminium ion **1c** is formed.

When the same set of experiments was performed in the presence of 1.0 equiv[6] of trimethylsilyl triflate a significant shift toward the formation of the *N*-acylimin-

† Dedicated to F. Eiden with best wishes on the occasion of his 75th birthday.

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(6) In the case of **2b** also the extent of the formation of **6b** was examined when only 0.2 equiv of trimethylsilyl triflate was applied. Under these conditions, 19% *N*-acylpyridinium ion **6b** was present independent from the temperature.

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Scheme 1

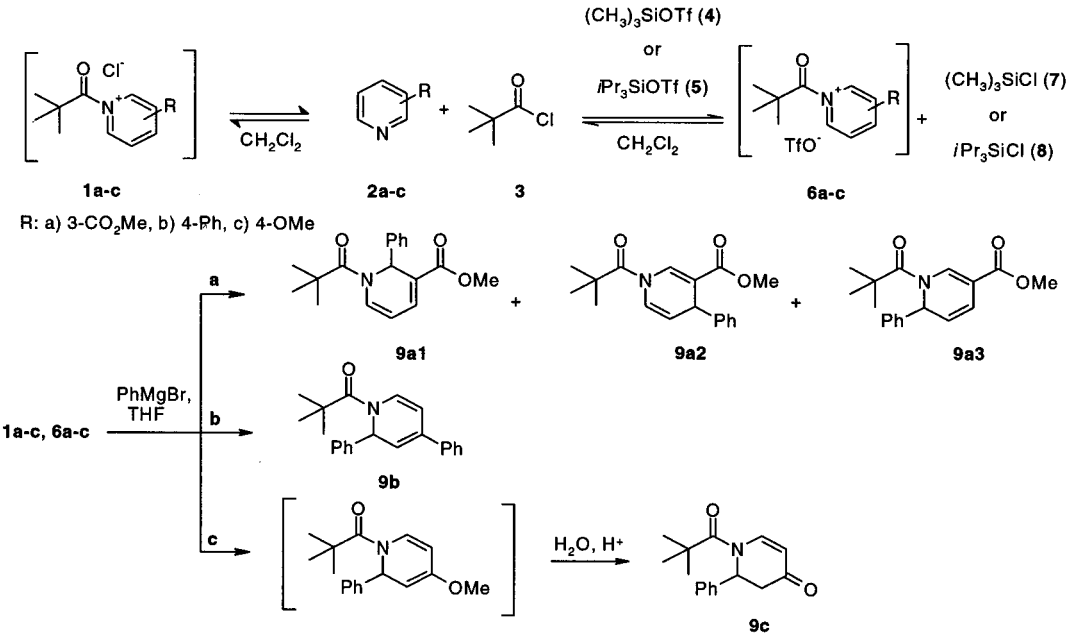
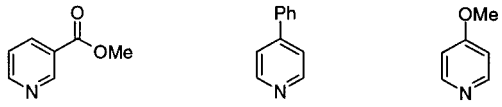


Table 1. Reaction of 2a−c and 3 in the Absence (A) and in the Presence of $(CH_3)_3SiOTf$ (B)[a]



T (°C)	A 1a (9a)	B 6a (9a)	A 1b (9b)	B 6b (9b)	A 1c (9c)	B 6c (9c)
rt	0	35[b]	0	78[b]	0	86[b]
0	0	43[b]	0	81[b]		83[b]
−30	0	57	0 (77%)	81 (87%)	0 (84%)	84 (83%)
−78	0 (21%)[c]	61 (44%)[d]	0 (54%)	80[e] (81%)	40 (65%)	− (68%)[f]

[a] Concentration for all reactions: 0.1 M in CH_2Cl_2 or CD_2Cl_2. [b] As the ^{1}H NMR signals were broadened due to coalescence, the integrals could not be exactly determined. [c] Regioselecitivity determined by ^{1}H NMR: **9a1**/**9a2**/**9a3** = 3/21/76. [d] Regioselecitivity determined by ^{1}H NMR: **9a1**/**9a2**/**9a3** = 14/30/56. [e] Measurement carried out after 10 min at −78 °C to avoid precipitation of **6b**. [f] As the reaction mixture was heterogeneous, the yield is less meaningful.

ium ions **6a**−**c** was observed. For the methyl nicotinate **2a**, 35% of **6a** was found at room temperature, and this part increased to 61% at −78 °C. Finally for 4-phenylpyridine and 4-methoxypyridine even 80−85% of the *N*-acyliminium ions **6b** and **6c** were formed[7] with the position of the equilibrium being only insignificantly effected by the temperature (see B in Table 1). The increasing amount of **6** in the order **6a** < **6b** < **6c** may be accounted by the increasing nucleophilicity of the pyridines **2a**−**c** that parallels the former.

The formation of trimethylsilyl chloride from trimethylsilyl triflate is thought to be the driving force that gives rise to the observed shift of the position of the above equilibria. In support of this assumption in the ^{1}H NMR spectra of the reaction mixtures the signals (Me) expected for TMSCl were found.

To further verify the structures of the *N*-acyliminium ions **6a**−**c** that were already evident from the ^{1}H NMR spectra in which data were in good accord with those in the literature,[8] some NOE-experiments were performed. In each case (**6a**−**c**) irradiation of the *tert*-butyl group of **6a**−**c** gave rise to a significant NO effect for H-2 and H-6 of the pyridine nucleus in support of the *N*-acyliminium ion structure.

Next, the reaction mixtures of series A (reaction in the absence of trimethylsilyl triflate) and series B (reaction in the presence of trimethylsilyl triflate) were used for trapping reactions. These were carried out at −78 °C and at −30 °C using phenylmagnesium bromide as a nucleophile. In each case the respective addition products **9a**−**c** were formed. Overall the yields were reasonable to good. For the reactions at −78 °C of series A the yields increased with the nucleophilicity of the pyridine (**9a**, 21%; **9b**, 54%; **9c**, 65%) and were higher at −30 °C than those at −78 °C. Obviously, even for mixtures wherein according to ^{1}H NMR spectroscopy no significant (or detectable) quantities of the *N*-acyliminium are present, reasonable yields for the trapping reactions are obtained. However, it must be emphasized that in most cases the yields obtained from the reactions performed according to series B were higher than those from series A. Interestingly, these differences in the yields between series A and series B were more pronounced for the reactions carried out at −78 °C than for those performed at −30 °C (see Table 1). This might indicate that the *N*-acyliminium ion formation for series A has become much slower at −78 °C as compared to the rate of the subsequent trapping reaction, thus lowering the yields of the addition products.

(7) According to ^{1}H NMR data the compounds present in addition to **6** are the *N*-silylpyridinium salts and in some cases unchanged **2** and hydropyridinium salts.

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Table 2. Formation of 6a−c in the Presence of (i-Pr)$_3$SiOTf and Yields of Trapping Reactions Leading to 9b and 9c

	2a		2b		2c	
T (°C)	c = 0.1 M **6a**	c = 0.2 M **6a**	c = 0.1 M **6b**	c = 0.2 M **6b** (**9b**)	c = 0.1 M **6c**	c = 0.2 M **6c** (**9c**)
rt	0	12[a]	82[a]	94	89[a]	95[a]
0	2	15[a]		94		95[a]
−30	3	19[a]	78	94 (91%)	88[a]	93[a] (87%)

[a] As the ^{1}H NMR signals were broadened due to coalescence, the integrals could not be exactly determined.

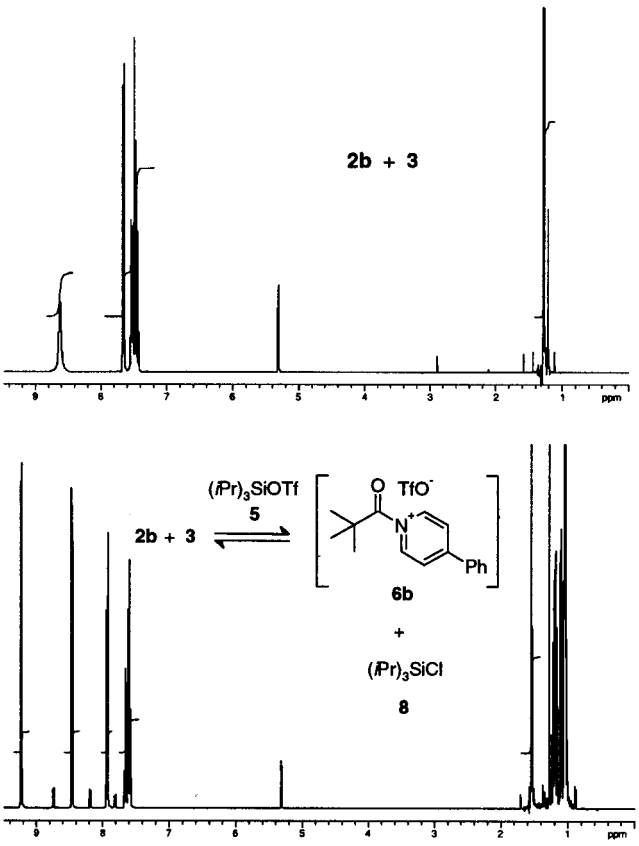

Figure 1. ^{1}H NMR in CD_2Cl_2 at −30 °C.

When trimethylsilyl triflate was replaced by triisopropylsilyl triflate (Table 2), the reaction mixtures containing the pyridines **2b** and **2c** in a concentration of 0.1 M exhibited a similar shift toward the *N*-acyliminium ions **6b** and **6c** as observed before. Under these conditions for **2a**, however, only minimum amounts of the *N*-acyliminium ion **6a** were formed. At a concentration of 0.2 M the amount of **6a** increased, but remained still very low. This poor result, which is quite different from those obtained with **6b** and **6c**, is possibly due to the low nucleophilicity of **2a**. Most interestingly for **2b** and **2c**, the *N*-acyliminium ions **6b** and **6c** were formed almost quantitatively when the concentration was raised to 0.2 M, the *N*-acyliminium ions **6b** and **6c** being then present in about 95%. In Figure 1 the ^{1}H NMR spectra for the mixture of **2b** + **3** and of **6b** are given, which best exemplify the dramatic change of the composition of the reaction mixtures caused by the silyl additives. Besides also the trapping reactions of **6b** and **6c** performed at −30 °C proceeded quite smoothly and with excellent yields providing **9b** and **9c** in 91 and 87%, respectively.

In summary, we have found that the amount of *N*-acyliminium ions when formed by reaction of an azaaromatic with an acid chloride may significantly be raised by the addition of silyl triflates. Furthermore, it has been demonstrated that also the yields for subsequent trapping reactions of the *N*-acyliminium ions may be improved by this procedure.

Further studies to extend the scope of this method to different azaaromatics, imines, amines, acid halides, and chloroformates and to utilize it in the preparative isolation of *N*-acylpyridinium salts are in progress.

Experimental Section

General Methods. All reactions were carried out in vacuum-dried glassware sealed with rubber septa under nitrogen or argon atmosphere. All reagents were used as commercially available. The solvents were dried and distilled. CH_2Cl_2 and CD_2Cl_2 were freshly distilled from CaH_2 prior to use. Pivaloyl chloride was freshly distilled from quinoline. Melting points are uncorrected. The ^{1}H NMR spectra were recorded at 400 MHz.

General Procedure for the Examination of the Reaction Mixture by ^{1}H NMR (GP1). One equivalent of pivaloyl chloride was added to the pyridine (0.1 or 0.2 M in CD_2Cl_2) followed by 1 equiv of the trimethylsilyl triflate or triisopropylsilyl triflate after 5 min, when these additives were applied. After 1 h, the resulting reaction mixture was examined by ^{1}H NMR.

General Procedure for the Alkylation with Phenylmagnesium Bromide (GP2). One equivalent of pivaloyl chloride was added to the pyridine (0.1 or 0.2 M in CH_2Cl_2) followed by 1 equiv of the trimethylsilyl triflate or triisopropylsilyl triflate after 5 min, when these additives were applied. The solution was stirred for 1 h at room temperature. After the solution was cooled to alkylation temperature, 3 equiv of phenylmagnesium bromide (1 M in THF) was added. The reaction mixture was stirred for 1 h, quenched, and worked up as given.

1-(2,2-Dimethylpropionyl)-3-methyloxycarbonylpyridinium Trifluormethansulfonate (6a). According to GP1, from 27 mg (0.2 mmol) of pyridine **2a** in 2 mL of CD_2Cl_2, 25 mg (0.2 mmol) of pivaloyl chloride and 44 mg (0.2 mmol) of trimethylsilyl triflate: ^{1}H NMR (CD_2Cl_2, −30 °C) δ 1.46 (s, 9 H), 3.96 (s, 3 H), 8.40 (dd, 1 H, J = 8.0, 5.5 Hz), 9.12 (d, 1 H, J = 8.0 Hz), 9.50 (s, 1 H), 9.54 (d, 1 H, J = 5.5 Hz).

Methyl 1-(2,2-Dimethylpropionyl)-2-phenyl-1,2-dihydropyridine-3-carboxylate (9a1), Methyl 1-(2,2-Dimethylpropionyl)-4-phenyl-1,4-dihydropyridine-3-carboxylate, and Methyl 1-(2,2-Dimethylpropionyl)-6-phenyl-1,6-dihydropyridine-3-carboxylate (9a2 and 9a3). (A) According to GP2, from 69 mg (0.5 mmol) of pyridine **2a** in 5 mL of CH_2Cl_2, 61 mg (0.5 mmol) of pivaloyl chloride, and 1.5 mL (1.5 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −78 °C; quenching at −78 °C with phosphate buffer (pH = 7, c = 1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (*n*-heptane/ethyl acetate = 80:20) and separation of the regioisomers by preparative HPLC (*n*-heptane/ethyl acetate = 87:13, 9.0 mL/min; **9a2**, **9a3**: t_R = 20.06 min; **9a1**: t_R = 25.26 min) yielded 1.5 mg (1%) of **9a1** and 30 mg (20%) of a mixture of **9a2** and **9a3** (20/80).

9a1: colorless crystals; mp 142 °C; TLC R_f = 0.28 (*n*-heptane/ethyl acetate = 80:20); ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 9 H), 3.73 (s, 3 H), 5.51 (dd, 1H, J = 7.7, 5.9 Hz), 6.74 (s, 1 H), 7.19−7.28 (m, 5 H), 7.34−7.39 (m, 2 H); IR (KBr) 1701, 1648 cm^{-1}; MS (70 eV) m/z 299 (11) [M$^+$]. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.33; H, 7.16; N, 4.48.

9a2, 9a3: colorless oil; TLC R_f = 0.34 (*n*-heptane/ethyl acetate = 80:20); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 7.2 H), 1.42 (s, 1.8 H), 3.65 (s, 0.6 H), 3.81 (s, 2.4 H), 4.46 (d, 0.2 H, J = 4.7 Hz), 5.23 (dd, 0.2 H, J = 8.1, 4.7 Hz), 5.77 (dd, 0.8 H, J = 10.0, 5.4 Hz), 6.07 (d, 0.8 H, J = 5.4 Hz), 6.49 (d, 0.8 H, J = 10.0 Hz), 7.14 (d, 0.2 H, J = 8.1 Hz), 7.15−7.36 (m, 5 H), 8.13 (s, 0.8 H), 8.30 (s, 0.2 H); IR (film) 1655, 1607 cm^{-1}; MS (70 eV) m/z 299 (8) [M$^+$]. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 72.23; H, 7.20; N, 4.54.

(B) According to GP2, from 69 mg (0.5 mmol) of pyridine **2a** in 5 mL of CH_2Cl_2, 61 mg (0.5 mmol) of pivaloyl chloride, 111 mg (0.5 mmol) of trimethylsilyl triflate, and 1.5 mL (1.5 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −78 °C; quenching at −78 °C with phosphate buffer (pH = 7, c = 1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (*n*-heptane/ethyl acetate = 80:20) and separation of the regioisomers by preparative HPLC (*n*-heptane/ethyl acetate = 87:13, 9.0 mL/min; **9a2**, **9a3**: t_R = 20.06 min; **9a1**: t_R = 25.26 min) yielded 9 mg (6%) of **9a1** and 57 mg (38%) of a mixture of **9a2** and **9a3** (30/70).

1-(2,2-Dimethylpropionyl)-4-phenylpyridinium Trifluoromethansulfonate (6b). According to GP1 from 31 mg (0.2 mmol) of pyridine **2b** in 2 mL of CD_2Cl_2, 25 mg (0.2 mmol) of pivaloyl chloride and 44 mg (0.2 mmol) of trimethylsilyl triflate: ^{1}H NMR (CD_2Cl_2, −30 °C) δ 1.54 (s, 9 H), 7.56−7.69 (m, 3 H), 7.96−7.99 (m, 2 H), 8.44−8.49 (m, 2 H), 9.21−9.26 (m, 2 H).

1-(2,2-Dimethylpropionyl)-2,4-diphenyl-1,2-dihydropyridine (9b). (A) According to GP2, from 155 mg (1 mmol) of pyridine **2b** in 10 mL of CH_2Cl_2, 121 mg (1 mmol) of pivaloyl chloride, and 3 mL (3 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −30 °C; quenching at −30 °C with phosphate buffer (pH = 7, c = 1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (*n*-heptane/ethyl acetate = 90:10) yielded 247 mg (77%) of **9b**.

9b: colorless crystals; mp 111−113 °C; TLC R_f = 0.23 (*n*-heptane/ethyl acetate = 90:10); ^{1}H NMR (CD_2Cl_2) δ 1.34 (s, 9 H), 5.73 (dd, 1 H, J = 8.0, 1.9 Hz), 6.11 (ddd, 1 H, J = 6.4, 1.9, 1.0 Hz), 6.27 (d, 1 H, J = 6.4 Hz), 7.13 (dt, 1 H, J = 8.0, 1.0 Hz), 7.20−7.47 (m, 10 H); IR (KBr) 1649, 1634 cm^{-1}; MS (CI) m/z 318 (100) [M$^+$+ 1]. Anal. Calcd for $C_{22}H_{18}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.17; H, 7.46; N, 4.35.

(B) According to GP2 from 155 mg (1 mmol) of pyridine **2b** in 10 mL of CH_2Cl_2, 121 mg (1 mmol) of pivaloyl chloride, 223 mg (1 mmol) of trimethylsilyl triflate, and 3 mL (3 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −30 °C; workup and purification as described under method A; yield 277 mg (87%) of **9b**.

(C) According to GP2, from 155 mg (1 mmol) of 4-phenylpyridine in 10 mL of CH_2Cl_2, 121 mg (1 mmol) of pivaloyl chloride, 306 mg (1 mmol) of triisopropylsilyl triflate, and 3 mL (3 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −30 °C; workup and purification as described under method A; yield 289 mg (91%) of **9b**.

1-(2,2-Dimethylpropionyl)-4-methoxypyridinium Trifluoromethansulfonate (6c). According to GP1, from 22 mg (0.2 mmol) of pyridine **2c** in 2 mL of CD_2Cl_2, 25 mg (0.2 mmol) of pivaloyl chloride and 44 mg (0.2 mmol) of trimethylsilyl triflate: ^{1}H NMR (CD_2Cl_2, −30 °C) δ 1.54 (s, 9 H), 4.19 (s, 3 H), 7.61 (d, 2 H, J = 5.9 Hz), 9.06 (d, 2 H, J = 5.8 Hz).

1-(2,2-Dimethylpropionyl)-2-phenyl-2,3-dihydropyridine-4(1*H*)-one (9c). (A) According to GP2, from 54 mg (0.5 mmol) of pyridine **2c** in 5 mL of CH_2Cl_2, 61 mg (0.5 mmol) of pivaloyl chloride, 1.5 mL (1.5 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −30 °C; quenching at −30 °C with 5 mL of 2 M HCl. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo. Purification by CC (diisopropyl ether/ethyl acetate = 80:20) yielded 108 mg (84%) of **9c**.

9c: colorless crystals; mp 112−114 °C; TLC R_f = 0.31 (diisopropyl ether/ethyl acetate = 80:20); ^{1}H NMR ($CDCl_3$) δ 1.39 (s, 9 H), 2.90 (d, 1 H, J = 16.7 Hz), 3.09 (dd, 1 H, J = 16.7, 6.9 Hz), 5.33 (d, 1 H, J = 8.4 Hz), 6.04 (d, 1 H, J = 6.9 Hz), 7.16−7.29 (m, 5 H), 7.99 (d, 1 H, J = 8.4 Hz); IR (KBr) 1663, 1590 cm^{-1}; MS (70 eV) m/z 257 (43) [M$^+$]. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.68; H, 7.47; N, 5.42.

(B) According to GP2, from 54 mg (0.5 mmol) of pyridine **2c** in 5 mL of CH_2Cl_2, 61 mg (0.5 mmol) of pivaloyl chloride, 111 mg (0.5 mmol) of trimethylsilyl triflate, and 1.5 mL (1.5 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −30 °C; workup and purification as described under A; yield 107 mg (83%) of **9c**.

(C) According to GP2, from 54 mg (0.5 mmol) of pyridine **2c** in 5 mL of CH_2Cl_2, 61 mg (0.5 mmol) of pivaloyl chloride, 153 mg (0.5 mmol) of triisopropylsilyl triflate and 1.5 mL (1.5 mmol) of phenylmagnesium bromide (1 M in THF); alkylation temperature −30 °C; workup and purification as described under A; yield 112 mg (87%) of **9c**.

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