Synthesis of Sterically Hindered Imines

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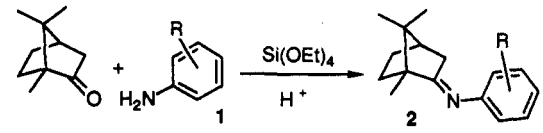
As part of a project directed toward the synthesis of camphor-based chiral heterocycles, we required the preparation of several imines derived from the condensation of camphor with aromatic amines. While traditional methods[1-3] were successful in some instances, in many others long reaction times (on the order of several days) were necessary in order to achieve reasonable yields of the desired imines. We sought to facilitate product formation by the addition of a dehydration agent. While $TiCl_4$ is commonly employed for this purpose,[3,4] it requires the use of a large excess of amine, owing to the formation of HCl as a byproduct. Furthermore, such reactions have been found to be quite sensitive to the substrate and reaction conditions employed.[4] We reasoned that a dehydration agent which produced a nonacidic byproduct would not require an excess of amine and chose to investigate the use of tetraethyl orthosilicate for this purpose.

Heating a mixture of the amine, camphor, tetraethyl orthosilicate, and a catalytic amount of concentrated H_2SO_4 generated ethanol, which was continuously removed from the reaction mixture by distillation. Typically, product formation was nearly complete after 4 h of heating at 160 °C, although allowing the reaction to run overnight would often improve isolated yields by about 10%. The imines **2** were purified by kugelrohr distillation, and as can be seen from Scheme I, yields were generally quite good.[5] In contrast to the $TiCl_4$-promoted method, only a slight excess of the amine was used (1.1 equiv), making this method particularly advantageous for use with less readily available amines. Frequently small amounts of hexaethoxydisiloxane and other oligomeric siloxanes were found to contaminate the products. These contaminants could be removed either by recrystallization of the product or by treatment of the mixture with ethanolic KOH (see Experimental Section), incurring only minimal loss of product.

Analogous reactions were conducted using two different hindered alkyl amines, with similar results (Scheme II). Imine **3a** has previously been reported, though it was obtained in only 45% yield after heating camphor and α-methylbenzylamine at 120 °C for 5 days in the presence of camphorsulfonic acid and 3-Å molecular sieves.[6]

Having successfully prepared a number of camphor imines, attention was turned to the application of this method to the preparation of other sterically hindered imines. Strekowski recently reported a novel method of

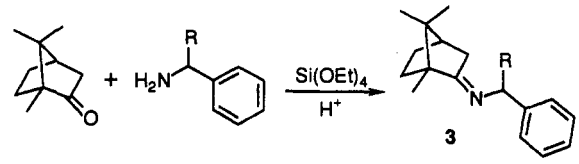
Scheme I



1 2

Compound	R	Yield(%)
2 a	H	74
2 b	2-Me	82
2 c	2-CN	90
2 d	2-Ph	82
2 e	2-CO_2Et	76
2 f	2-CF_3	87
2 g	4-OMe	69

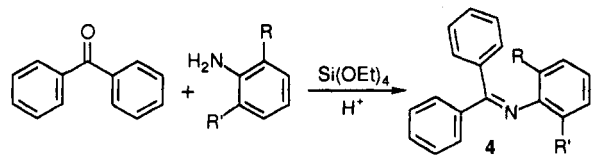
Scheme II



3

Compound	R	Yield(%)
3 a	Me	78
3 b	Ph	72

Scheme III



4

Compound	R	R'	Yield(%)
4 a	CN	H	93
4 b	Me	Me	75
4 c	Me	H	86
4 d	Ph	H	62
4 e	CF_3	H	98

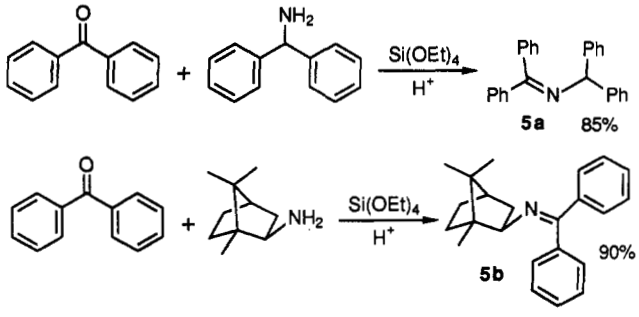
preparing sterically hindered benzophenone *N*-arylimines, a number of which had been reported to be unavailable by "traditional" methods.[7] We attempted the preparation of two such imines, *N*-(diphenylmethylene)-2-cyanoaniline (**4a**) and *N*-(diphenylmethylene)-2,6-dimethylaniline (**4b**), utilizing our method, and found both were obtained in good yield (Scheme III), although prolonged reaction times were required for the synthesis of **4b**.

Other imines of benzophenone were also prepared, as shown in Schemes III and IV. Three of these imines have been reported previously. Imine **4c** was prepared in 63% yield from *o*-toluidine and dichlorodiphenylmethane, the authors stating that use of dichlorodiphenylmethane gave better yields than "other methods".[8] Imine **4d** has been prepared in 25% yield by heating benzophenone, 2-aminobiphenyl, and a catalytic amount of hydrobromic acid in the absence of solvent at 180 °C for 3.5 h.[9] Finally, imine **5a** was prepared in 95% yield from benzophenone

(1) Dayagi, S.; Degani, Y. In *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; John Wiley and Sons: New York, 1970; p 61.
(2) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570.
(3) Whitesell, J. K. In *Comprehensive Organic Synthesis*, Winterfeldt, E., Ed.; Pergamon Press: Oxford, 1991; Vol. 6 p 705.
(4) Carlson, R.; Larsson, U.; Hansson, L. *Acta Chem. Scand.* **1992**, *46*, 1211.
(5) Yields given are isolated yields of product obtained after kugelrohr distillation. Imines **4d**, **4e**, **5a**, and **5b** were not subjected to distillation, but were instead purified by recrystallization from ethanol.
(6) Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1990**, *46*, 523.
(7) Strekowski, L.; Cegla, M. T.; Harden, D. B.; Kong, S.-B. *J. Org. Chem.* **1989**, *54*, 2464.
(8) Seno, M.; Shiraishi, S.; Suzuki, Y.; Asahara, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1413.
(9) Abramovitch, R. A.; Kyba, E. P. *J. Am. Chem. Soc.* **1974**, *96*, 480.

0022-3263/93/1958-5556$04.00/0

Scheme IV



and aminodiphenylmethane, but required heating at reflux in toluene for 15 days.[10] We believe in all three cases our method is superior in either yield and/or simplicity of procedure.

While Strekowski's method provides imines in good overall yield, three synthetic transformations are nevertheless required, as compared to only one step in our method. Further, Strekowski's method is not compatible with the presence of alkyl groups on either the imine carbon or nitrogen, while our method suffers from neither of these limitations. Further applications of this methodology are currently under investigation.

Experimental Section

General Procedure. Camphor (15 mmol) and the amine (16.5 mmol) were combined and treated with one drop of concd H_2SO_4. The $Si(OEt)_4$ (16.5 mmol) was added and the mixture placed in a flask equipped with a still head. The solution was heated at 160 °C under nitrogen overnight (typically 16 h). The distillate (EtOH) was discarded and the residue was dissolved in Et_2O (50 mL) and washed with saturated $NaHCO_3$ solution and H_2O (25 mL each). The Et_2O solution was dried ($MgSO_4$) and solvent removed under reduced pressure. Crude products were purified by kugelrohr distillation. In those instances where siloxane impurities were found in the distillate, the imine (2 g) was dissolved in 10 mL of 95% EtOH and treated with 2 mL of 1 M KOH in EtOH. The solution was stirred for 15 min then filtered, and the precipitate washed with Et_2O. The filtrate was washed with H_2O (2 × 20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the purified imine.

***N*-(Bornan-2-ylidene)aniline (2a)**: ^1H NMR spectral data are consistent with those reported previously:[2] ^{13}C NMR δ 11.2, 19.0, 19.5, 27.4, 32.0, 36.1, 43.7, 47.1, 53.8, 119.3, 122.9, 128.8, 152.2, 184.6.

***N*-(Bornan-2-ylidene)-2-methylaniline (2b)**: ^1H NMR δ 0.87 (s, 3H), 0.97 (s, 3H), 1.12 (s, 3H), 1.2–1.3 (m, 1H), 1.5–2.0 (m, 5H), 2.08 (s, 3H), 2.1–2.2 (m, 1H), 6.58 (d, J = 7.6 Hz, 1H), 6.93 (t, J = 7.4 Hz, 1H), 7.1–7.2 (m, 2H); ^{13}C NMR δ 11.1, 17.4, 19.0, 19.6, 27.4, 32.2, 36.7, 43.7, 47.2, 54.0, 118.5, 122.9, 126.3, 127.2, 130.2, 150.6, 183.9; HRMS calcd for $C_{17}H_{23}N$ 241.1830, found 241.1831.

***N*-(Bornan-2-ylidene)-2-cyanoaniline (2c)**: ^1H NMR δ 0.92 (s, 3H), 0.99 (s, 3H), 1.12 (s, 3H), 1.3–1.4 (m, 1H), 1.6–2.0 (m, 5H), 2.1–2.2 (m, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.4–7.6 (m, 2H); ^{13}C NMR δ 10.8, 18.9, 19.5, 27.0, 31.9, 36.5, 43.7, 47.4, 54.6, 102.8, 117.0, 119.9, 123.1, 132.7, 133.4, 155.3, 188.1; mp 58–60 °C; HRMS calcd for $C_{17}H_{20}N_2$ 252.1626, found 252.1625.

***N*-(Bornan-2-ylidene)-2-phenylaniline (2d)**: ^1H NMR δ 0.39 (s, 3H), 0.7–0.9 (m, 1H), 0.82 (s, 3H), 0.9–1.1 (m, 1H), 0.99 (s, 3H), 1.37 (d, J = 17.5 Hz, 1H) 1.4–1.8 (m, 3H), 1.8–1.9 (m, 1H), 6.74 (d, J = 7.7 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 7.2–7.4 (m, 5H), 7.4–7.5 (m, 2H); ^{13}C NMR δ 11.0, 18.89, 18.92, 27.1, 31.3, 37.6, 43.6, 47.0, 53.8, 119.6, 123.4, 126.5, 127.8, 128.0, 129.4, 130.1, 132.0, 140.1, 150.0, 183.8; mp 58–62 °C; HRMS calcd for $C_{22}H_{25}N$ 303.1987, found 303.1993.

***N*-(Bornan-2-ylidene)-2-carbethoxyaniline (2e)**: ^1H NMR δ 0.91 (s, 3H), 0.97 (s, 3H), 1.12 (s, 3H), 1.2–1.3 (m, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.6–2.0 (m, 5H), 2.1–2.2 (m, 1H), 4.28 (q, J = 7.1 Hz, 2H), 6.65 (d, J = 7.9 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 7.37 (t; J = 7.6 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 10.9, 14.3, 18.9, 19.5, 27.2, 31.3, 36.3, 43.7, 47.3, 53.9, 60.3, 120.5, 120.8, 122.4, 130.8, 132.5, 152.9, 166.2, 183.4; HRMS calcd for $C_{19}H_{25}NO_2$ 299.1885, found 299.1891.

***N*-(Bornan-2-ylidene)-2-(trifluoromethyl)aniline (2f)**: ^1H NMR spectral data are consistent with those reported previously;[11] ^{13}C NMR δ 10.9, 19.0, 19.4, 27.2, 31.6, 36.3, 43.8, 47.3, 54.4, 120.4, 122.6, 126.3 (q, J = 5.2 Hz), 132.5, 150.7, 186.2.

***N*-(Bornan-2-ylidene)-4-methoxyaniline (2g)**: ^1H NMR δ 0.85 (s, 3H), 0.96 (s, 3H), 1.08 (s, 3H), 1.2–1.3 (m, 1H), 1.5–1.6 (m, 1H), 1.7–2.0 (m, 4H), 2.2–2.3 (m, 1H), 3.76 (s, 3H), 6.68 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H); ^{13}C NMR δ 11.1, 18.9, 19.4, 27.3, 31.9, 36.2, 43.7, 46.9, 53.8, 55.2, 114.0, 120.5, 145.2, 155.6, 184.7; HRMS calcd for $C_{17}H_{23}NO$ 257.1780, found 257.1782.

***N*-(1-Phenylethyl)-2-bornanimine (3a)**. A mixture of diastereomers was obtained. ^1H and ^{13}C NMR spectral data are consistent with those reported previously.[6] HRMS calcd for $C_{18}H_{25}N$ 255.1987, found 255.1987.

***N*-(Diphenylmethyl)-2-bornanimine (3b)**: ^1H NMR δ 0.63 (s, 3H), 0.91 (s, 3H), 1.07 (s, 3H), 1.1–1.2 (m, 1H), 1.3–1.4 (m, 1H), 1.6–2.0 (m, 4H), 2.3–2.4 (m, 1H), 5.44 (s, 1H), 7.1–7.4 (m, 10H); ^{13}C NMR δ 11.5, 19.0, 19.5, 27.5, 32.0, 35.9, 44.0, 47.1, 54.0, 68.2, 126.40, 126.43, 127.47, 127.53, 128.1, 128.2, 144.9, 145.0, 181.6; mp 77.0–77.5 °C; HRMS calcd for $C_{23}H_{27}N$ 317.2144, found 317.2133.

***N*-(Diphenylmethylene)-2-cyanoaniline (4a)**: 4 h of heating were employed instead of 16 h. ^1H NMR spectral data are consistent with those reported previously:[12] ^{13}C NMR δ 103.7, 117.5, 121.2, 123.0, 128.0, 128.2, 129.0, 129.1, 129.7, 131.5, 132.6, 132.8, 135.5, 138.3; mp 114–117 °C (lit.[7] mp 118–119 °C).

***N*-(Diphenylmethylene)-2,6-dimethylaniline (4b)**: 75 h of heating were employed instead of 16 h. ^1H NMR spectral data are consistent with those reported previously:[7] ^{13}C NMR δ 18.4, 122.6, 125.6, 127.5, 127.6, 128.0, 128.3, 128.9, 129.2, 130.4, 136.7, 139.6, 148.8, 166.9.

***N*-(Diphenylmethylene)-2-methylaniline (4c)**: ^1H NMR δ 2.17 (s, 3H), 6.44 (d, J = 7.5 Hz, 1H), 6.8–7.0 (m, 2H), 7.0–7.2 (m, 3H), 7.2–7.3 (m, 3H), 7.3–7.5 (m, 3H), 7.79 (d, J = 6.5 Hz, 2H); ^{13}C NMR δ 18.2, 119.4, 123.0, 125.8, 127.8, 128.1, 128.5, 128.8, 129.2, 129.8, 130.5, 136.3, 139.4, 150.0, 167.2; mp 50–51 °C (lit.[8] mp 50–51 °C); HRMS calcd for $C_{20}H_{17}N$ 271.1361, found 271.1365.

***N*-(Diphenylmethylene)-2-phenylaniline (4d)**: ^1H NMR δ 6.62 (d, J = 7.3 Hz, 2H), 6.91 (d, J = 7.7 Hz, 1H), 6.9–7.3 (m, 11H), 7.3–7.4 (m, 3H), 7.63 (d, J = 7.1 Hz, 2H); ^{13}C NMR δ 121.7, 123.6, 126.3, 127.39, 127.43, 127.8, 128.0, 128.3, 128.8, 129.2, 129.4, 130.1, 130.4, 131.4, 136.3, 139.4, 139.9, 149.0, 167.7; mp 118–119 °C (lit.[9] mp 120–121 °C); HRMS calcd for $C_{25}H_{19}N$ 333.1517, found 333.1520.

***N*-(Diphenylmethylene)-2-(trifluoromethyl)aniline (4e)**: ^1H NMR δ 6.47 (d, J = 7.9 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.1–7.4 (m, 6H), 7.4–7.6 (m, 4H), 7.80 (d, J = 7.0 Hz, 2H); ^{13}C NMR δ 121.1, 122.7, 126.0 (q, J = 5.2 Hz), 127.9, 128.2, 128.7, 129.0, 129.5, 131.0, 131.8, 135.8, 138.9, 149.4, 168.6; mp 81.5–82.0 °C; HRMS calcd for $C_{20}H_{14}F_3N$ 325.1078, found 325.1079.

***N*-(Diphenylmethyl)diphenylmethanimine (5a)**: ^1H and ^{13}C NMR spectral data are consistent with those reported previously;[10] mp 153.5–155.5 °C (lit.[10] mp 150–152 °C); HRMS calcd for $C_{26}H_{21}N$ 347.1674, found 347.1673.

***exo*-*N*-(Diphenylmethylene)-2-bornanamine (5b)**: ^1H NMR δ 0.80 (s, 3H), 0.88 (s, 3H), 0.9–1.1 (m, 1H), 1.37 (s, 3H), 1.4–1.9 (m, 6H), 3.23 (dd, J = 4.5, 8.5 Hz, 1H), 7.1 (m, 2H), 7.2–7.3 (m, 3H), 7.3–7.5 (m, 3H), 7.6 (m, 2H); ^{13}C NMR δ 12.7, 20.5, 20.9, 27.5, 36.1, 39.7, 45.7, 47.6, 50.1, 69.8, 127.8, 127.9, 128.23, 128.26, 128.29, 129.4, 137.4, 140.5, 163.9; mp 140–141 °C; HRMS calcd for $C_{23}H_{27}N$ 317.2144, found 317.2142.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of imines (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) Armesto, D.; Gallego, M. G.; Horspool, W. H.; Perez-Ossorio, R. *J. Chem. Soc., Perkin Trans. 1* **1986**, 799.

(11) Strekowski, L.; Patterson, S. E.; Janda, L.; Wydra, R. L.; Harden, D. B.; Lipowska, M.; Cegla, M. T. *J. Org. Chem.* **1992**, *57*, 196.

(12) Strekowski, L.; Cegla, M. T.; Harden, D. B.; Mokrosz, J. L.; Mokrosz, M. J. *Tetrahedron Lett.* **1988**, *29*, 4265.