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# Synthesis of Camphor-Based Chiral Quinolines

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# SYNTHESIS OF CAMPHOR-BASED CHIRAL QUINOLINES

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**Abstract:** Several chiral quinolines are prepared by the cyclization of imines derived from camphor.

Chiral aromatic nitrogen heterocycles are finding many applications in organic synthesis, particularly as ligands in the preparation of chiral metal complexes.[2] As part of a project directed toward the synthesis of new chiral oxidants and reductants, we required the preparation of a series of chiral quinoline derivatives. Since camphor-based chiral auxiliaries are known to be especially effective,[3] we have focused on the preparation of quinolines fused to the camphor skeleton (**1**).

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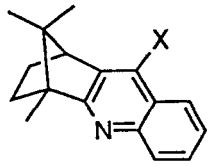
A number of aromatic nitrogen heterocycles fused to the camphor skeleton have been reported, including pyridines,[4] pyrazoles,[5] 1,2,3-triazines,[6] and quinolines.[7]

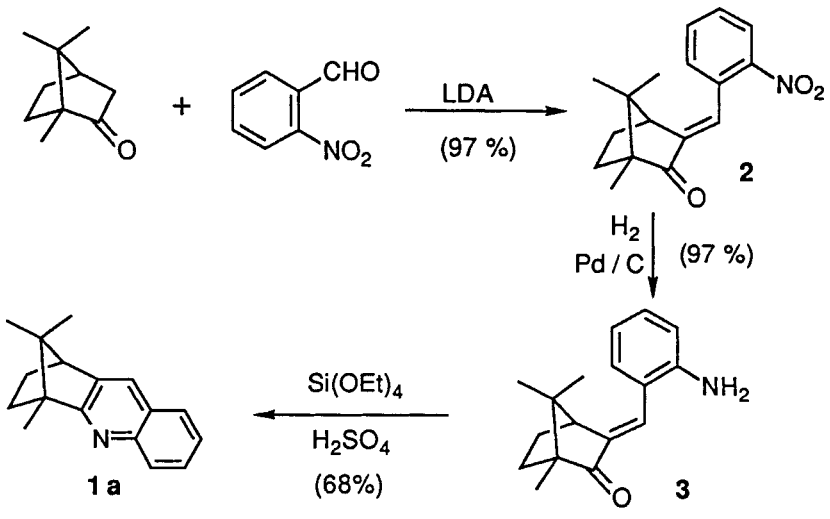



1

| | X |
|---|---|
| a | H |
| b | $OC(CH_3)_3$ |
| c | OH |
| d | $NH_2$ |
| e | N |

Quinoline (**1a**) was prepared (Figure 1) by condensing camphor with o-nitrobenzaldehyde to give (**2**).[8] Only one geometric isomer was observed, which is known to be the E isomer shown.[8] The nitro group in (**2**) was reduced by catalytic hydrogenation to give primary amine (**3**). Previously we have shown that camphor imines can be prepared in high yield by reacting camphor with primary amines in the presence of tetraethyl orthosilicate and a catalytic amount of $H_2SO_4$,[9] and these conditions were used to convert (**3**) into (**1a**). The conversion of (**3**) to (**1a**) is remarkable though, in that it

FIG. 1




requires isomerization of (**3**) to the less stable Z isomer prior to cyclization. We assume this isomerization takes place as shown in Figure 2.

Our preparation of amino-substituted quinolines (**1d**) and (**1e**) was patterned after the work of Strekowski.[7a, 10, 11] Camphor was treated with anthranilonitrile (**4a**) and tetraethyl orthosilicate in the presence of a catalytic amount of $H_2SO_4$[9] to produce (**5a**) in 90% yield (Figure 3). Treatment of (**5a**) with LDA at -78 °C gave (**1d**) in 75% yield. Imine (**5b**) (prepared from camphor and 2-aminobenzotrifluoride in 87% yield)[9] was

FIG. 2

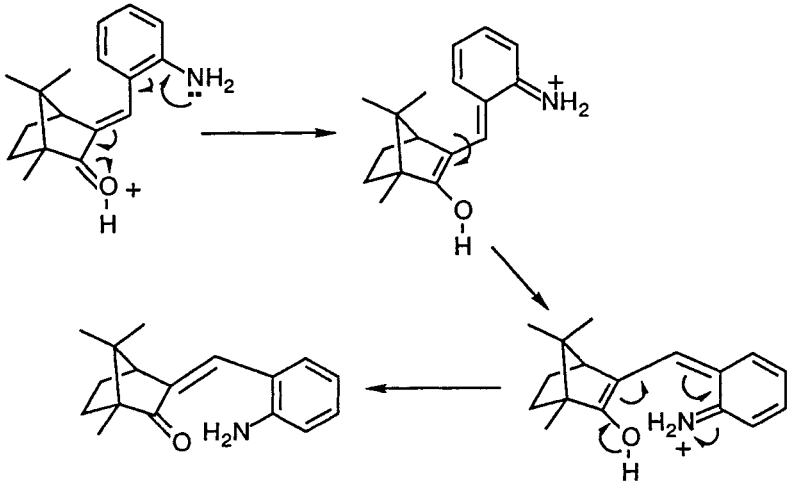
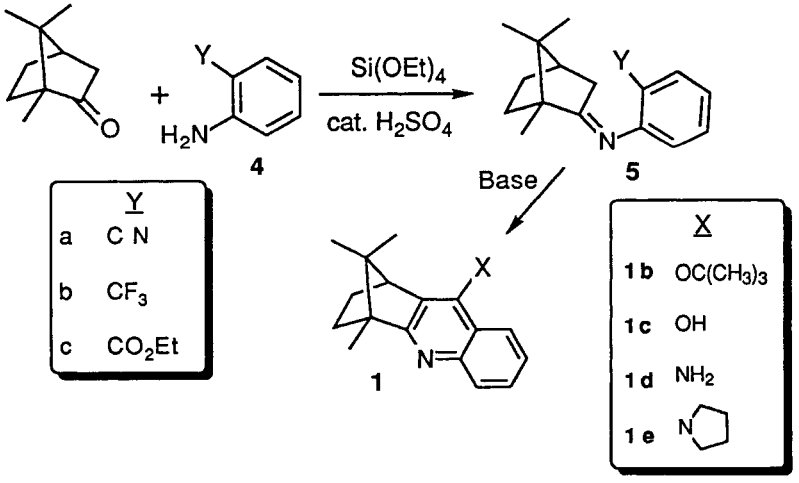


FIG. 3



treated with the lithium salt of pyrrolidine to give quinoline (**1e**) in 95% yield.[12]

We utilized another procedure reported by Strekowski[11,13] for our preparation of oxygen-substituted quinolines (**1b**) and (**1c**). Imine (**5b**) was treated with potassium t-butoxide in THF to give (**1b**) in 83% crude yield. Quinoline (**1b**) was then heated in a mixture of p-dioxane and 6 M HCl to produce quinoline (**1c**) in 89% yield.

An alternate route to (**1c**) was also investigated, in which imine (**5c**) was first prepared from camphor and ethyl 2-aminobenzoate in 76% yield. Treatment of (**5c**) with potassium t-butoxide in THF also lead to the formation of (**1c**), though purification proved more difficult than in the previous approach, and the purified product was obtained in only 24% yield. Thus, the former synthesis, proceeding through quinoline (**1b**), though involving an additional step, is the preferred approach to (**1c**).

In summary, a series of camphor-based chiral quinolines have been prepared. Both the synthesis of optically active analogues of these compounds and a study of their use in the preparation of chiral oxidants and reductants are in progress.

## EXPERIMENTAL

General: THF was freshly distilled from sodium/benzophenone ketyl prior to use. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC 250 instrument operating at 250 MHz and 62.9 MHz, respectively. "Standard isolation procedures" implies the organic phase was dried ($MgSO_4$), and the solvent removed by rotary evaporator, followed by high vacuum.

**3-(2-Nitrophenyl)methylene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (2)**

Camphor (3.00 g, 19.7 mmol) in THF (10 mL) was added dropwise over 10 min to 1.1 eq. of LDA at -78 °C under dry $N_2$. The solution was stirred for 1 hr, then 2-nitrobenzaldehyde (2.98 g, 19.7 mmol) in THF was added dropwise over 10 min. The solution was stirred at -78 °C for 2 hrs, then allowed to warm to room temperature overnight. The solution was neutralized with 1M HCl and extracted with ether, followed by standard isolation procedures to give 5.70 g (97%) of a yellow solid. A small portion was recrystallized from petroleum ether to give compound of m.p. 118 °C. $^{1}H$ NMR($CDCl_3$) 0.85 (s, 3H), 0.97 (s, 3H), 1.04 (s, 3H), 1.5-1.6 (m, 2H), 1.79 (t, J = 8 Hz, 1H), 2.0-2.2 (m, 1H), 2.73 (d, J = 4.2 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H),

7.5-7.6 (m, 1H), 7.6-7.7 (m, 1H), 8.08 (d, J = 7.0 Hz, 1H); $^{13}C$ NMR($CDCl_3$) 9.2, 18.1, 20.6, 26.2, 30.3, 46.5, 48.6, 57.6, 123.3, 124.8, 128.9, 130.9, 131.7, 133.0, 144.9, 148.7, 206.7.

**3-(2-Aminophenyl)methylene-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one (3)**

To (2) (0.50 g, 1.75 mmol) in EtOH (10 mL) was added approx. 0.05 g 10% Pd/C and the mixture hydrogenated for 2 hrs (40 psi $H_2$). The catalyst was removed by filtration through celite, and the solvent removed from the filtrate under reduced presssure to give 0.44 g (97%) of a yellow solid. A small portion was recrystallized from ether to give compound of m.p. 132-133 °C. $^1H$ NMR($CDCl_3$) 0.82 (s, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 1.5-1.6 (m, 2H), 1.7-1.8 (m, 1H), 2.1-2.2 (m, 1H), 2.99 (d, J = 4.3 Hz, 1H), 3.87 (br s, 2H), 6.7-6.8 (m, 2H), 7.1-7.3 (m, 2H); $^{13}C$ NMR($CDCl_3$) 9.3, 18.3, 20.6, 26.3, 30.6, 46.5, 48.9, 57.5, 115.8, 118.2, 120.7, 122.2, 129.3, 129.9, 142.8, 145.8, 208.1.

**4-Methyl-1,2,3,4-tetrahydro-1,4-(dimethylmethano)-acridine (1a)**

To a mixture of (3) (0.88 g, 3.45 mmol) and $Si(OEt)_4$ (3.60 g, 17.25 mmol) were added 6 drops of conc. $H_2SO_4$. The flask

was equipped with a still head and heated at 150 °C under nitrogen overnight. The solution was then cooled to room temperature to give a two-phase system. The upper phase was treated with 1M HCl, and any undissolved material was discarded. The aqueous HCl solution was then basified and extracted with ether. Concurrently, the lower phase from the original product mixture was suspended in 1M NaOH and extracted with ether. The two ether extracts were combined, washed with $H_2O$, and subjected to standard isolation procedures to give 0.56 g (68%) of a yellow oil. $^1H$ NMR($CDCl_3$) 0.57 (s, 3H), 1.07 (s, 3H), 1.1-1.4 (m, 2H), 1.43 (s, 3H), 1.9-2.1 (m, 1H), 2.2-2.3 (m, 1H), 2.97 (d, J = 4.0 Hz, 1H), 7.4-7.5 (m, 1H), 7.5-7.7 (m, 1H), 7.71 (s, 1H), 7.72 (d, J = 6.7 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H); $^{13}C$ NMR($CDCl_3$) 10.6, 19.0, 20.2, 26.4, 31.9, 51.2, 54.1, 55.2, 125.1, 126.0, 127.4, 127.5, 127.9, 128.8, 140.1, 146.8, 172.1.

**4-Methyl-9-(1,1-dimethylethoxy)-1,2,3,4-tetrahydro-1,4-(dimethylmethano)acridine (1b)**

A solution of (**5b**) (1.50 g, 5.8 mmol) in THF was added dropwise under nitrogen to a solution of potassium t-butoxide

(3.2 g, 29 mmol) in THF which had been cooled to 0 °C. The solution was heated at reflux overnight, then cooled to room temperature and treated with 1M HCl to bring the pH to 7-8. The solution was extracted with petroleum ether and subjected to standard isolation procedures to give 1.30 g (83%) of a yellow oil which eventually solidified. A small sample was purified to give colorless crystals with m.p. 124.5-125.5 °C. $^1$H NMR($CDCl_3$) 0.62 (s, 3H), 1.06 (s, 3H), 1.3-1.6 (m, 2H), 1.41 (s, 3H), 1.47 (s, 9H), 1.9-2.1 (m, 1H), 2.2-2.3 (m, 1H), 3.25 (d, J = 4.1 Hz, 1H), 7.4-7.5 (m, 1H), 7.5-7.6 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H); $^{13}$C NMR($CDCl_3$) 10.8, 19.0, 20.4, 26.2, 29.8, 31.9, 49.6, 54.6, 55.3, 82.0, 123.4, 124.5, 127.1, 127.6, 128.5, 131.0, 148.7, 151.6, 173.9.

**4-Methyl-1,2,3,4-tetrahydro-1,4-(dimethylmethano)-acridin-9-one (1c)**

To (**1b**) (1.30 g, 4.4 mmol) in p-dioxane (5 mL) was added 6M HCl (2 mL), and the solution heated at reflux for 3 hrs. The solution was cooled to room temperature, neutralized with satd. $NaHCO_3$, and extracted with $CH_2Cl_2$. The organic layer was washed with $NaHCO_3$ and $H_2O$ and subjected to

standard isolation procedures to give 0.99 g (89%) of a pale yellow solid. A small portion was recrystallized from $CH_2Cl_2$ to give a white solid with m.p. 291-292 °C. $^1H$ NMR($CDCl_3$) 0.76 (s, 3H), 0.91 (s, 3H), 1.2-1.4 (m, 2H), 1.32 (s, 3H), 1.8-1.9 (m, 1H), 2.0-2.1 (m, 1H), 3.18 (br s, 1H), 7.2-7.4 (m, 1H), 7.4-7.6 (m, 1H), 7.68 (d, J = 8.1 Hz, 1H), 8.44 (d, J = 7.9 Hz, 1H), 10.88 (br s, 1H); $^{13}C$ NMR(DMSO-*d6*) 10.1, 18.8, 19.6, 25.9, 32.3, 46.8, 54.2, 55.9, 118.3, 122.3, 122.5, 124.9, 126.5, 129.9, 139.4, 159.9, 171.1.

**4-Methyl-1,2,3,4-tetrahydro-1,4-(dimethylmethano)-acridin-9-amine (1d)**

To a solution of LDA (5.6 mmol) in THF (10 mL) cooled to -78 °C was added (**5a**) (1.20 g, 4.8 mmol) in THF (10 mL) dropwise over 15 min. The solution was allowed to come to room temperature over 20 min, then heated at reflux for 3 hrs. After cooling to room temperature the solution was diluted with 50 mL ether and 25 mL $H_2O$. The aqueous layer was discarded and the organic layer extracted with 1M HCl (3 x 25 mL). The combined HCl layers were washed with ether then basified with 3M NaOH. The solution was extracted with

$CH_2Cl_2$ and subjected to standard isolation procedures to give 0.90 g (75%) of a yellow solid. Purification by column chromatography gave a white solid with melting point 172-174 °C. $^1H$ NMR($CDCl_3$) 0.63 (s, 3H), 1.05 (s, 3H), 1.1-1.4 (m, 2H), 1.40 (s, 3H), 1.8-2.0 (m, 1H), 2.1-2.2 (m, 1H), 2.92 (d, J = 3.9 Hz, 1H), 4.39 (br s, 2H), 7.40 (dd, J = 6.9, 8.3 Hz, 1H), 7.56 (dd, J = 6.9, 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H); $^{13}C$ NMR($CDCl_3$) 10.6, 19.0, 20.0, 25.5, 32.4, 47.3, 54.3, 55.1, 119.3, 119.4, 120.0, 123.6, 127.5, 129.1, 140.7, 147.5, 172.0.

**4-Methyl-9-pyrrolidino-1,2,3,4-tetrahydro-1,4-(dimethylmethano)acridine (1e)**

Pyrrolidine (2.08 g, 29.3 mmol) was dissolved in dry ether, cooled to -10 °C under nitrogen and treated with t-BuLi (1 eq.). After 20 min, a solution of (**5b**) (2.16 g, 17.3 mmol) in ether was added dropwise over 10 min. The solution was stirred at -10 °C for 1 hr, then allowed to come to room temperature overnight. The pH was adjusted to 8 with 1M HCl, and the solution extracted with ether. The combined ether extracts were washed with $H_2O$ and subjected to standard isolation procedures to give 2.13 g (95%) of a yellow solid.

Recrystallization from petroleum ether gave a white solid with melting point 126-126.5 °C. $^{1}H$ NMR($CDCl_3$) 0.60 (s, 3H), 1.03 (s, 3H), 1.2-1.3 (m, 2H), 1.40 (s, 3H), 1.8-2.2 (m, 6H), 3.34 (d, J = 4.1 Hz, 1H), 3.4-3.6 (m, 4H), 7.36 (t, J = 8.2 Hz, 1H), 7.53 (t, J = 8.3 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 8.07 (d, J = 8.5 Hz, 1H); $^{13}C$ NMR($CDCl_3$) 11.0, 19.1, 20.3, 25.3, 27.0, 32.0, 51.7, 53.0, 53.4, 53.9, 123.6, 124.7, 124.8, 127.2, 127.3, 128.7, 146.6, 148.1, 173.1.



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