Acylation of o-Tolualdehyde Cyclohexylimines with N-Methoxy-N-methylamides (Weinreb's Amides). A New Synthesis of Isoquinolines†

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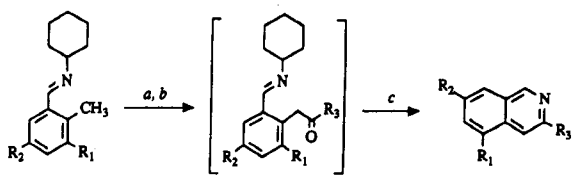
The classical methods for isoquinoline synthesis (Pictet–Spengler,[1] Bischler–Napieralski,[2] and Pomeranz–Fritsch[3] procedures) depend on electrophilic cyclization reactions to form the heteroatom-containing ring; consequently, these widely used methods are subject to limitations arising from steric and electronic effects on cyclization regioselectivity and a general dependence on electron-rich aromatic substrates to ensure reasonable yields of the cyclized products. The Pomeranz–Fritsch procedure gives isoquinolines directly; however, the Pictet–Spengler and Bischler–Napieralski methods afford tetrahydro- and dihydroisoquinolines, respectively, which must be dehydrogenated in a subsequent step if isoquinoline products are required. Only a few scattered reports[4] of distinctly novel isoquinoline syntheses which are unrelated to the classical methods have appeared. In one such report, Fields[4a] showed that indene could be ozonized in the presence of ammonia to give isoquinoline. Woodward and Hoye[4c] later employed an OsO_4–$NaIO_4$ oxidation/NH_4-OAc cyclization sequence in the transformation of a functionalized indene into the naturally occuring isoquinoline, illudinine. At about the same time, Miller and Frincke[4d] elaborated Fields' observation into a general two-step method for the synthesis of isoquinolines from indenes. They reported that ozonolysis of substituted indenes followed by reductive workup and treatment of the intermediate 1,5-dicarbonyl compounds with NH_4-OH gave isoquinolines in 60–90% yield. Nevertheless, this method has not been widely exploited for the synthesis of isoquinolines undoubtedly because the requisite indenes are themselves sometimes difficultly accessible.

We have recently demonstrated that o-tolualdehyde cyclohexylimine and some of its derivatives can be efficiently metalated on the C(2)-methyl group by the use of lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF solution; the intermediate 2-(lithiomethyl) aldimines react with alkyl halides or CO_2 to provide a straightforward route to various C(2)-substituted benzaldehydes.[5] In this paper we report that 2-(lithiomethyl)benzaldehyde cyclohexylimines react smoothly with N-methoxy-N-methylcarboxamides (Weinreb's amides)[6] or N,N-dimethylformamide to give a corresponding acylated or formylated tolualdehyde imine; treatment of these crude intermediates with refluxing aqueous NH_4OH–NH_4OAc affords isoquinolines in good yield (Scheme I).

Scheme I[a]



Aldimines

1: R_1=R_2=H

2: R_1=Me, R_2=H

3: R_1=H, R_2=Me

4: R_1=MeO, R_2=H

Isoquinolines (% yield)

5: R_1=R_2=H, R_3=n-Bu (82 %)

6: R_1=Me, R_2=R_3=H (57 %)

7: R_1=R_2=H, R_3=i-Bu (84 %)

8: R_1=H, R_2=Me, R_3=c-Pr (72 %)

9: R_1=MeO, R_2=H, R_3=c-Pr (75 %)

[a] Key: (a) 2 equiv of LTMP (THF, −15 → 0 °C); (b) $R_3CON(OMe)Me$ or Me_2CHO; (c) NH_4OH–NH_4OAc.

The current method for isoquinoline synthesis is simple, it utilizes readily available starting materials, and it appears to be complementary to the extant methodology for isoquinoline synthesis. For example, the most widely used isoquinoline synthesis, the Pommeranz–Fritsch method, generally fails to give adequate yields of isoquinolines unless the aromatic ring of the starting material is activated with one or more alkoxy substituents; furthermore, the incorporation of a C(3) substituent into the product isoquinolines is lengthy using this procedure.[3] On the other hand, the method described in this paper does not suffer from the intrinsic regiochemical and electronic limitations of an electrophilic cyclization process and it is especially well-suited to the incorporation of a variety of C(3) functional groups into the product isoquinolines.

Experimental Section

General. The aromatic aldimines used in this study have been previously described.[5] N-Methoxy-N-methylcarboxamides were prepared by the method of Weinreb[6] and isolated by fractional distillation at reduced pressure. N,N-Dimethylformamide was distilled from barium oxide and stored over activated 4-Å molecular sieves. 2,2,6,6-Tetramethylpiperidine was distilled from CaH_2 and stored under a nitrogen atmosphere. Tetrahydrofuran was distilled from sodium–benzophenone under a nitrogen atmosphere immediately before use. ^1H NMR and ^{13}C NMR spectra were recorded on $CDCl_3$ solutions with an FT instrument operating at 300 MHz and 100 MHz, respectively.

The following procedure is typical.

3-Butylisoquinoline, 5. In a three-neck round-bottom flask equipped with a magnetic stirrer, internal thermometer, and a nitrogen inlet was placed 3.00 g (21.0 mmol) of 2,2,6,6-tetramethylpiperidine in 50 mL of dry THF. The solution was cooled to −15 °C, and 16.0 mL of 1.3 M s-BuLi (cyclohexane solution) was added over 5 min. After 15 min, 2.00 g (10.0 mmol) of imine 1 was added dropwise over 5 min to give a deep purple-colored solution. The solution was allowed to warm to 0 °C over 20 min, and 1.90 g (13.0 mmol) of N-methoxy-N-methylvaleramide was

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added in one portion. The reaction mixture was allowed to stand at room temperature for 30 min, poured into saturated NH_4Cl solution, and extracted with ether. The ether solution was washed with additional saturated NH_4Cl and water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 2.76 g of a yellow oil; concentrated aqueous NH_4OH (50 mL) and glacial AcOH (3 mL) were added to the crude oily product, and the mixture was refluxed for 4 h. The reaction mixture was allowed to cool to room temperature, diluted with 100 mL of water, and extracted with ether. The ether extracts were washed with several portions of water, dried ($MgSO_4$), filtered, and concentrated with a rotary evaporator to give 2.03 g of a brown residue. The crude material was distilled with a Kugelrohr apparatus to give 1.52 g (82%) of a colorless oil: bp (0.6 Torr) = 90–100 °C; ^{1}H NMR δ 9.20 (s, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.74 (d, J = 8.0 Hz, 1 H), 7.63 (td, J = 6.5, 1.0 Hz, 1 H), 7.51 (td, J = 8.0, 1.0 Hz, 1 H), 7.46 (s, 1 H), 2.94 (t, J = 7.7 Hz, 2 H), 1.80 (m, 2 H), 1.42 (sextet, J = 7.6 Hz, 2 H), 0.96 (t, J = 7.5 Hz, 3 H). ^{13}C NMR: δ 155.7, 151.9, 136.4, 130.0, 127.3, 126.9, 126.1, 125.9, 117.8, 37.7, 32.0, 22.4, 13.9.

Picrate: mp = 172–173 °C (ethanol).

Anal. (picrate) Calcd for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38; N, 13.52. Found: C, 55.18; H, 4.36; N, 13.59.

5-Methylisoquinoline, 6.[4d] Prepared from imine **2** and *N*,*N*-dimethylformamide in 57% yield: bp (1.0 Torr) = 80–90 °C; mp = 38–39 °C (hexane); ^{1}H NMR δ 9.23 (s, 1 H), 8.55 (d, J = 6.0 Hz, 1 H), 7.81 (dd, J = 7.0, 2.0 Hz, 1 H), 7.75 (d, J = 6.0 Hz, 1 H), 7.75 (d, J = 6.0 Hz, 1 H), 7.51 (s, 1 H), 7.49 (t, J = 7.0 Hz, 1 H), 2.67 (s, 3 H); ^{13}C NMR δ 152.8, 142.8, 135.1, 133.4, 130.4, 128.6, 126.8, 125.6, 116.9, 18.3.

Picrate: mp = 232–233 °C (ethanol).

Anal. (picrate) Calcd for $C_{16}H_{12}N_4O_7$: C, 51.62; H, 3.25; N, 15.05. Found: C, 51.52; H, 3.28; N, 14.99.

3-Isobutylisoquinoline, 7. Prepared from imine **1** and *N*-methoxy-*N*-methylisovaleramide in 84% yield: bp (0.9 Torr) = 110–115 °C; ^{1}H NMR δ 9.19 (s, 1 H), 7.92 (d, J = 8.2 Hz, 1 H), 7.74 (d, J = 8.2 Hz, 1 H), 7.63 (td, J = 6.6, 1.1 Hz, 1 H), 7.51 (td, J = 6.6, 1.1 Hz, 1 H), 7.43 (s, 1 H), 2.79 (d, J = 6.8 Hz, 2 H), 2.22 (9-line multiplet, J = 6.8 Hz, 1 H), 0.97 (d, J = 6.8 Hz, 6 H); ^{13}C NMR δ 154.8, 152.0, 136.4, 130.2, 127.5, 126.3, 126.1, 118.9, 47.4, 29.1, 22.5.

Picrate: mp = 151–152 °C (ethanol).

Anal. (picrate) Calcd for $C_{19}H_{18}N_4O_7$: C, 55.07; H, 4.38; N, 13.52. Found: C, 54.78; H, 4.25; N, 13.32.

3-Cyclopropyl-7-methylisoquinoline, 8. Prepared from imine **3** and *N*-methoxy-*N*-methylcyclopropylcarboxamide. Isoquinoline **8** was isolated by column chromatography (silica gel; 95:5 hexane–ethyl acetate) in 72% yield: mp = 100–101 °C; ^{1}H NMR δ 9.01 (s, 1 H), 7.63 (s, 1 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.43 (dd, J = 8.4, 1.7 Hz, 1 H), 7.40 (s, 1 H), 2.49 (s, 3 H), 2.16 (m, 1 H), 1.10–0.90 (m, 4 H); ^{13}C NMR δ 155.2, 151.5, 145.9, 135.6, 132.6, 127.3, 126.2, 125.5, 116.2, 21.7, 16.9, 9.1.

Picrate: mp = 214–215 °C (ethanol).

Anal. (picrate) Calcd for $C_{19}H_{16}N_4O_7$: C, 55.34; H, 3.91; N, 13.59. Found: C, 55.18; H, 4.14; N, 13.78.

3-Cyclopropyl-5-methoxyisoquinoline, 9. Prepared from imine **4** and *N*-methoxy-*N*-methylcyclopropylcarboxamide. Isoquinoline **9** was isolated as an oil by column chromatography (silica gel; 9:1 hexane–ethyl acetate) in 75% yield: ^{1}H NMR δ 9.09 (s, 1 H), 7.84 (s, 1 H), 7.48 (d, J = 8.2 Hz, 1 H), 7.39 (t, J = 8.1 Hz, 1 H), 6.94 (d, J = 7.6 Hz, 1 H), 4.01 (s, 3 H), 2.24 (m, 1 H), 1.15–1.00 (m, 4 H); ^{13}C NMR δ 155.8, 153.9, 151.4, 129.1, 127.7, 125.9, 119.3, 110.8, 107.4, 55.6, 17.2, 9.3.

Picrate: mp = 209–210 °C (ethanol).

Anal. (picrate) Calcd for $C_{19}H_{16}N_4O_8$: C, 53.28; H, 3.77; N, 13.08. Found: C, 53.63; H, 3.65; N, 13.17.