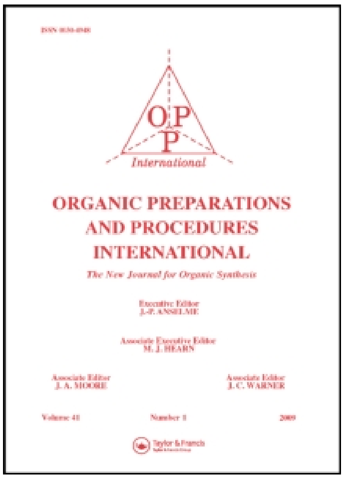

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AN IMPROVED SYNTHESIS OF KETIMINES

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AN IMPROVED SYNTHESIS OF KETIMINES

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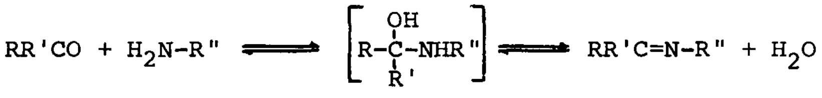

$$RR'CO + H_2N\text{-}R'' \rightleftharpoons \left[R\text{-}\overset{\overset{OH}{|}}{\underset{\underset{R'}{|}}{C}}\text{-}NHR'' \right] \rightleftharpoons RR'C{=}N\text{-}R'' + H_2O$$

I

I a. $R=R'=CH_3$, $R''=C_6H_5$ d. $R=R''=CH_3$, $R'=C_6H_5$

b. " " " R"=2-Biphenylyl e. " " " R'=2-Biphenylyl

c. " " " R"=2-Phenylethyl f. " " " R'=2-Phenylethyl

The formation of imines from aldehydes or ketones and amines is a reversible reaction.[1] Ketimine formation is particularly sensitive to the presence of water and, in general, its removal is necessary in order to obtain appreciable yields of I. The most usual method has been azeotroping, which is not possible when the ketone or amine is quite volatile (*e.g.* acetone or methylamine).

Several methods of circumventing the problem have been used by previous workers when the starting ketone was acetone: 2,2-diethoxypropane and the amine were reacted in ethanol;[2,3] *N*-isopropylideneaniline (Ia) was prepared from acetone and aniline hydriodide *via* the silver iodide complex of the hydriodide of the ketimine;[4] and magnesium sulfate has been added to the reaction medium.[5] When methylamine was used, magnesium sulfate[2] and potassium hydroxide pellets[6] have served as drying agents. In all of the more recent syntheses, preparative gas chromatography was used to separate the ketimine from starting material. The majority of the methods described above were used in these laboratories to obtain ketimines derived either from acetone or methylamine with quite unsatisfactory results. The use of preparative gas chromatography resulted in low yields and the manipulations involved caused hydrolysis (1-5%) which, in several cases, could not be detected by infrared spectroscopy but was easily discernible by g.l.c.

This paper presents a simple, direct method of synthesis of six ketimines (Ia-f), which are derived either from acetone (Ia, b, c) or from methylamine (d, e, f). Molecular sieves are used as drying agents to shift the equilibrium almost completely to product. In most cases, ether was used as solvent and the imines were flash distilled under high vacuum. The tedious technique of preparative gas chromatography was thus avoided and yields were much improved over previous procedures. More important, however, was that all the ketimines were obtained pure to better than 99.3% (as indicated by g.l.c.).

The method may easily be extended to the synthesis of imines in which volatility of starting materials is not a problem. For example, pure (>99.7%) N-(α-methylbenzylidene)-α-methylbenzylamine was obtained in 65% yield using molecular sieves.

Experimental

All chemicals used were commercially available reagent grade with the exception of the known[7] 2-acetylbiphenyl, which was prepared by reacting 2-biphenylylcarboxylic acid with methyllithium.[8] All chemicals were distilled prior to use with the exception of 2-aminobiphenyl, which was recrystallized from petroleum ether (b.p. 30-60°). Methylamine was generated from a 40% aqueous solution by distillation through two 6 in. double surface condensers leading to a 1 ft. potassium hydroxide pellet drying tube and finally into a pressure tube immersed in a acetone-dry ice bath. Molecular sieves [Davison (Fisher Scientific Co.), type 4A, grade 514, 8-12 mesh, effective pore size 4Å] were activated by heating at 350° for 3 hr. and cooling in a vacuum dessicator. The pressure tube (120 ml. capacity) Fisher-Porter combustion tube vessel with an aluminum and Teflon sealing disc and standard pipe coupling.

N-Isopropylideneaniline (Ia). To a solution of aniline (4.72 g., 50.7 mmole) in dry ether (50 ml.) in the presence of molecular sieves (30 g.), was added in one portion a solution of acetone (5.64 g., 97.0 mmole) in dry ether[a] (33 ml.). The resulting mixture was allowed to stand for 10 hr. at 0°,[b] warmed to room temperature, the molecular sieves were filtered and another portion of molecular sieves (20 g.) was added. After standing for an additional 20 hr.[c] at 0°, the molecular sieves were filtered and the solvent was evaporated.[d] The

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[a] Although the ketimine is formed using acetone in large excess, i.e. as the solvent as well as the reactant, much aldol condensation occurred to give 4-hydroxy-4-methylpentan-2-one and 4-methylpent-3-en-2-one. By diluting the reactants and running the reaction at room temperature or below, this side reaction was almost completely eliminated.

[b] The low temperature was necessary to suppress the formation of an unidentified high molecular weight product, which could be detected by g.l.c.

[c] All the reactions were followed by g.l.c. and the reaction time reported represents the minimum time required for $>99.7\%$ of the starting material to have reacted. Good separation from starting material could be obtained for all the ketimines reported, using a 6' x 3/16" column packed with SE 30 (20%) on Gas Chrom Q (60-100 mesh), and a helium flow rate of 60 ml./min. The oven temperature was adjusted such that the elution time of the ketimine was approximately 15 min.

[d] In all cases, molecular sieves (ca. 1g.) were used as boiling chips to remove the solvent. All glassware was dried at 160° for 12 hr. and stored in a vacuum dessicator. Care was taken to exclude moisture from the distillation apparatus.

residue was distilled under vacuum to give Ia as a colorless liquid (3.94 g., 59%), b.p. 37-40°/20 μ (lit.[2] b.p. 121-133°/15 mm.); ir (liquid film) 1660 cm.$^{-1}$ (C=N); M.W. (mass spec., 70eV): m/e 133 (M^+), Calcd. for $C_9H_{11}N$: 133.

N-<u>Isopropylidene-2-aminobiphenyl</u> (Ib). A mixture of 2-aminobiphenyl (5.50 g., 32.5 mmole), acetone[e] (47.3 g., 800 mmole) and molecular sieves (30 g.) in a pressure tube was heated in a steam bath for 6 hr. The molecular sieves were filtered and a second portion (20 g.) was added. After heating for an additional 6 hr., the molecular sieves were filtered and the acetone was evaporated. The residue was distilled under vacuum to give Ib as a colorless viscous liquid (3.25 g., 48%), b.p. 75-78°/10 μ; ir (liquid film) 1665 cm.$^{-1}$ (C=N); M.W. (mass spec., 70 eV) m/e 209 (M^+). Calcd. for $C_{15}H_{15}N$: 209. <u>Anal</u>. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22 Found: C, 85.91; H, 7.38.

N-<u>Isopropylidene-2-phenylethylamine</u> (Ic). To a solution of 2-phenylethylamine (4.13 g., 34.1 mmole) in dry ether (50 ml.) was added acetone (9.8 g., 167 mmole) and molecular sieves (35 g.). The mixture was allowed to stand at room temperature for 2 hr., the molecular sieves were filtered and

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[e] Since this ketimine was quite high boiling, separation of the acetone aldol condensation products and ketimine was easily effected by pumping under high vacuum at a bath temperature of 50-60°. No ether was used.

the solvent was evaporated. The residue was distilled under vacuum to give Ic as a colorless liquid (3.37 g., 61%), b.p. 50-52°/20 μ; ir (liquid film) 1660 cm.$^{-1}$ (C=N); M.W. (mass spec., 70eV) m/e 161 (M^+). Calcd. for $C_{11}H_{15}N$: 161. Anal. Calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.67; H, 9.44.

N-(α-Methylbenzylidene)methylamine (Id). A mixture of acetophenone (5.16 g., 43.0 mmole), methylamine (5 g., 160 mmole) and molecular sieves (30 g.) in dry ether (40 ml.) in a pressure tube was heated in a steam bath for 10 hr. The molecular sieves were filtered and the solvent was evaporated. The residue was distilled under vacuum to give Id as a colorless liquid (3.47 g., 61%), b.p. 35°/10 μ (lit.[9] b.p. 96°/10 mm.); ir (liquid film) 1630 cm.$^{-1}$ (C=N); M.W. (mass spec., 70eV) m/e 133 (M^+). Calcd. for $C_9H_{11}N$: 133.

N-[α-(2-Biphenylyl)ethylidene]methylamine (Ie). A mixture of 2-acetylbiphenyl (2.06 g., 10.5 mmole), methylamine (2 g., 65 mmole) and molecular sieves (30 g.) in methanol[f] (60 ml.) in a pressure tube was heated in a steam bath for 5 hr. After allowing it to stand at room temperature for 15 hr.

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[f] This was the only ketimine which was stable enough to withstand the temperature necessary for removal of methanol and prolonged contact with the atmosphere without significant amounts of hydrolysis.

the molecular sieves were filtered and the reaction mixture was concentrated on a rotary evaporator. The residue was distilled under vacuum to give Ie as a colorless viscous liquid (1.28 g., 58%), b.p. 87-90°/15 μ; ir (liquid film) 1650 cm.$^{-1}$ (C=N); M.W. (mass spec., 70eV) m/e 209 (M^+). Calcd. for $C_{15}H_{15}N$: 209. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22. Found: C, 86.02; H, 7.36.

N-[<u>2-(4-Phenyl)butylidene</u>]<u>methylamine</u> (If). A mixture of 4-phenylbutan-2-one (5.02 g., 33.9 mmole), methylamine (5 g., 160 mmole), molecular sieves (25 g.) and dry ether (50 ml.) in a pressure tube was heated in a steam bath for 2 hr. The molecular sieves were filtered and the solvent was evaporated. The residue was distilled under vacuum to give If as a colorless liquid (3.53 g., 65%), b.p. 50°/20 μ; ir (liquid film) 1655 cm.$^{-1}$ (C=N); M.W. (mass spec., 70eV) m/e 161 (M^+). Calcd. for $C_{11}H_{15}N$: 161. <u>Anal</u>. Calcd. for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.67; H, 9.27.

N-(<u>α-Methylbenzylidene)-α-methylbenzylamine</u>. A mixture of <u>α</u>-methylbenzylamine (2.02 g., 16.7 mmole), acetophenone (2.01 g., 16.7 mmole) and molecular sieves (20 g.) in benzene was boiled under reflux for 5 hr. The reaction mixture was filtered and concentrated on a rotary evaporator. The residue was distilled under vacuum to give the ketimine as a colorless liquid (2.47 g., 66%),[g] b.p. 102-104°/15 μ (lit.[10] b.p. 106°/

0.2 mm.); ir (liquid film) 1630 cm.$^{-1}$ (C=N); M.W. (mass spec., 70eV) m/e 223 (M^+). Calcd. for $C_{16}H_{17}N$: 223.

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[g] This reaction was run only once and no attempt was made to maximize the yield.

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