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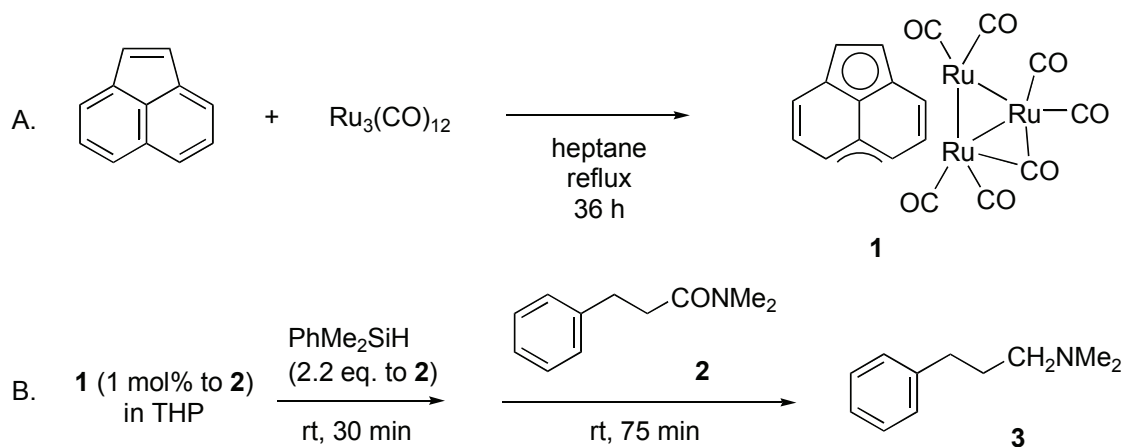
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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CATALYTIC REDUCTION OF AMIDES TO AMINES WITH HYDROSILANES USING A TRIRUTHENIUM CARBONYL CLUSTER AS THE CATALYST



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Checked by Joshua G. Pierce and Peter Wipf.

1. Procedure

Caution! Since reaction intermediates are potentially unstable to air and moisture, preparation of the ruthenium cluster should be carried out under an inert gas atmosphere.

A. ($\mu_3, \eta^2: \eta^3: \eta^5$ -Acenaphthylene) $Ru_3(CO)_7$ (**1**). A two-necked, 200-mL round-bottomed flask is equipped with a magnetic stir bar, a reflux condenser, and a stopcock. The top of the condenser is fitted with a three-way stopcock, of which one way is connected to an argon flow line and the other is connected to a vacuum line. The apparatus is flame-dried while under vacuum, and allowed to cool to room temperature under an argon purge. The stopcock is removed, and the flask is charged with $Ru_3(CO)_{12}$ (Note 1) (639 mg, 1 mmol), acenaphthylene (Note 2) (182 mg, 1.2 mmol), and heptane (Note 3) (75 mL) under an argon stream. The stopcock is again placed on the flask, and the mixture is heated under reflux. At the initial stage, the solution contains a yellow supernatant and an undissolved orange solid of $Ru_3(CO)_{12}$. The color of the solution gradually turns to red and all of the solid materials are dissolved after 30 min (Note 4).

After 36 h, a dark red solution and some red precipitates have formed. The mixture is cooled to room temperature under an argon atmosphere. From this stage, subsequent work can be performed in the air. The precipitates are collected on a glass filter, washed with *n*-hexane (30 mL), and dissolved in dichloromethane (20 mL) (Note 5). Celite[®] (*ca.* 3 g) (Note 6) is added to this solution and stirred for 1 min, then the solvent is removed under reduced pressure. The crude ruthenium complex adsorbed to Celite[®] is applied to a pre-packed silica gel column (20 mm x 100 mm) (Note 7), then sea sand (10 mm) (Note 8) is loaded onto the top of the Celite[®] for preventing the powder from diffusing into the eluent. The silica gel is first washed with 80 mL of *n*-hexane to remove a small amount of unreacted acenaphthylene (yellow band), then the product (red-brown band) is eluted with 2.5 L of 2:1 ether:*n*-hexane (Note 9, 10) to afford 620 mg (95%) of ($\mu_3, \eta^2: \eta^3: \eta^5$ -acenaphthylene)Ru₃(CO)₇ (**1**) (Note 11), which can be used for reduction of amides without further purification. Dark red crystals of **1** are obtained by recrystallization of the product obtained as above from a mixture of dichloromethane and *n*-hexane at -30 °C (Note 12).

Caution! The cluster 1 is first treated with excess hydrosilane for activation. Treatment of the activated catalyst with amides in the presence of excess hydrosilane is exothermic. The reaction apparatus should be equipped with an efficient reflux condenser, and the amide should be added carefully to avoid overheating of the reaction mixture.

B. N,N-Dimethyl-3-phenylpropylamine (3). A 200-mL, two-necked round-bottomed flask is equipped with an efficient reflux condenser and a septum. The top of the reflux condenser is fitted with a three-way stopcock, of which one way is connected to an argon flow line and the other is connected to a vacuum line. The apparatus is flame-dried *in vacuo*, and allowed to cool to room temperature under an argon purge. The septum is removed, and the flask is charged with **1** (365 mg, 0.557 mmol, 1 mol% based on *N,N*-dimethyl-3-phenylpropionamide (**2**) (Note 13)) under an argon flow. The septum is again placed on the flask, and tetrahydropyran (THP) (Note 14, 15) (4.5 mL) is added to dissolve the catalyst. Phenyltrimethylsilane (Note 16) (19 mL, 123 mmol) is charged *via* syringe through the septum, and the mixture is stirred for 30 min at room temperature. At this point, the initial dark-orange color of the catalyst solution changed to light orange. *N,N*-Dimethyl-3-phenylpropionamide (**2**) (10 mL, 56 mmol) (Note 17) is added drop wise over a period of 75 min *via*

syringe (Note 18). *Caution! The reaction is exothermic* (Note 19). The solution is stirred for an additional 75 min, resulting in consumption of the amide as determined by TLC analysis (Note 20). The solvent is removed by rotary evaporator at room temperature (70 Torr) and the residue is poured into a 500 mL Erlenmeyer flask containing conc. HCl (84 mL, 12 M) at 0 °C. The reaction flask is rinsed with ether (3 x 84 mL), and the liquid is added to the Erlenmeyer flask. The mixture is moved to a separatory funnel and shaken well. The resulting aqueous solution is washed three times with 84 mL of ether (totally 252 mL). All ether layers are discarded and the aqueous phase is moved to a 500 mL Erlenmeyer flask, cooled in an ice bath, and basified with KOH pellets (84 g) with stirring to form white solids. Ether (164 mL) is added to the mixture, stirred for 20 min, and the organic layer is separated. This ether extraction is repeated four times (84 mL each) (Note 21). The combined organic phases are dried over anhydrous Na₂SO₄ and concentrated under reduced pressure at room temperature (50 Torr). Distillation of the crude product at 57 °C (2.1 Torr) gives *N,N*-dimethyl-3-phenylpropylamine (**3**) as a colorless oil (Note 22, 23) (8.32 g, 91%).

2. Notes

1. Ru₃(CO)₁₂ (99%) is commercially available from Aldrich Chemical Company, Inc., although the submitters have prepared it according to a reported procedure.²

2. Acenaphthylene was purchased from Aldrich Chemical Company, Inc. (99+%) or Tokyo Kasei Kogyo Company, Ltd. (99+%) and used as received.

3. Heptane (99+%) was purchased from Kanto Chemical Company, Inc. and distilled from calcium hydride before use. Checkers purchased heptane from Aldrich Chemical Company.

4. The progress of the reaction was followed by TLC analysis (Merck Art No. 5715 : Silica gel 60 F₂₅₄, 0.25 mm thickness) with 2:1 ether:*n*-hexane as eluent and visualization with a UV lamp at 254 nm. The acenaphthylene and Ru₃(CO)₁₂ starting materials have an R_f = 0.89 and 0.95, respectively, and the complex **1** has an R_f = 0.42.

5. *n*-Hexane (96%) and dichloromethane (99%) were purchased from Kishida Chemical Co., Ltd. (submitters) or VWR (checkers), and used as received.

6. Celite 545 was purchased from Kishida Chemical Company, Ltd. (submitters) or Fisher Scientific (checkers), and used as received.

7. Silica gel 60 (70-230 mesh) (Merck Art No. 7734) was purchased from Merck (submitters) or Sorbent Technologies (checkers), and used as received.

8. Sea sand (425-850 μm ; 20-35 mesh) was purchased from Wako Pure Chemical Industries, Ltd. (submitters) or Aldrich (checkers), and used as received.

9. Ether (99.5%) was purchased from Kishida Chemical Co., Ltd. (submitters) or VWR (checkers), and used as received.

10. Although the submitters prefer ether to dichloromethane for environmental reasons, a 1:1 mixture of dichloromethane:*n*-hexane (600 mL) can alternatively be used as the eluent for collection of a second red-brown band. Use of dichloromethane instead of ether can reduce the total amounts of eluent. TLC analysis (Merck Art No. 5715 : Silica gel 60 F₂₅₄, 0.25 mm thickness) was performed with 50% dichloromethane-hexane as eluent and visualization with UV lamp at 254 nm. The acenaphthylene and Ru₃(CO)₁₂ starting materials have $R_f = 0.86$ and 0.91 , and the complex **1** has $R_f = 0.22$.

11. The product exhibits the following physical and spectral properties: mp 231.2-232.1 °C (dec). ¹H NMR (500 MHz, CDCl₃) δ : 6.48 (d, 1 H, $J = 6.3$ Hz), 6.25 (dd, 1 H, $J = 9.2, 6.1$ Hz), 6.01 (d, 1 H, $J = 2.5$ Hz), 5.81 (d, 1 H, $J = 9.2$ Hz), 5.58 (t, 1 H, $J = 6.3$ Hz), 5.48 (d, 1 H, $J = 6.0$ Hz), 4.90 (d, 1 H, $J = 2.5$ Hz), 2.52 (d, 1 H, $J = 6.1$ Hz). ¹³C NMR (76 MHz, THF-*d*₈, -60 °C) δ : 265.9 (μ -CO), 207.4 (CO), 204.7 (CO), 204.0 (CO), 195.7 (CO), 192.2 (CO), 188.7 (CO), 130.4, 116.1, 99.1, 88.3, 84.8, 82.2, 80.1, 78.5, 69.0, 67.0, 66.1, 37.7. IR (KBr) cm^{-1} ν_{CO} 2039 (s), 2028 (s), 2012 (s), 1996 (s), 1986 (s), 1946 (s), 1768 (m: μ -CO). The purity (>98%) was determined by ¹H NMR and mp.

12. The complex (624 mg) is dissolved in 30 mL of dichloromethane at 40 °C, then cooled at room temperature. To this solution, 70 mL of *n*-hexane is carefully added and the two-phase solution is stored at -37 °C overnight. Orange crystals are collected by suction filtration on a Buchner funnel, washed three times with 20 mL of *n*-hexane (total of 60 mL), and

then transferred to a 20 mL, round-bottomed flask and dried for 4 h at 0.01 Torr to provide 497 mg (80%) of **1** as orange microcrystals, which can be stored in the air for years without decomposition.

13. At lower catalyst concentration, formation of an unidentified byproduct decreases the yield of the product. For example, use of 0.1 mol% of the catalyst to **2** affords the desired amine in about 60% yield.

14. Tetrahydropyran (THP) (98+%) was purchased from Kanto Chemical Company, Inc. (submitters) or Aldrich (checkers), and distilled from benzophenone ketyl before use. Anhydrous toluene, diethyl ether, and 1,4-dioxane (a cancer suspected reagent) can alternatively be used as the solvent.

15. The ruthenium cluster activated by hydrosilane is an efficient catalyst for conversion of hydrosilanes to silanols and siloxanes. The reduction should be performed in anhydrous THP under an inert gas atmosphere to avoid contact with moisture.

16. Phenyltrimethylsilane (98+%) was purchased from Aldrich Chemical Company, Inc. and distilled before use.

17. *N,N*-Dimethyl-3-phenylpropionamide is commercially available in milligram quantities (TimTec Overseas Stock, Ambinter Screening Library, MicroChemistry Screening Collection), but it can be prepared from dihydrocinnamoyl chloride (95+%) (purchased from Tokyo Kasei Kogyo Company, Ltd. (submitters) or Aldrich (checkers)) and dimethylamine (99+%) (purchased from Aldrich Chemical Company, Inc.) by application of a standard method and distilled before use (bp 108 °C / 2 Torr). The purity (>99%) was determined by ¹H NMR, and the submitters also used capillary GLC with a TC-WAX column (0.25 mm x 30 m) (oven temperature: 230 °C; head pressure: 60 kPa; retention time: 11.8 min).

18. Although a syringe was used for the addition of amide **2**, a syringe pump or an addition funnel can also be used.

19. Although the submitters controlled the exothermic reaction by the addition rate of the amide, a water bath can also be used to cool the reaction mixture.

20. The progress of the reaction was followed by TLC analysis (Merck Art No. 5715: Silica gel 60 F₂₅₄, 0.25 mm thickness) with ethyl acetate as eluent and visualization with UV lamp at 254 nm. The amide starting material has an R_f = 0.48 and the amine product has an R_f = 0.19.

21. The submitters reported the reduction gave a single product

(determined by ^1H NMR) in an earlier paper,³ but isolated yields were somewhat lower (75%). This can be attributed to a loss of the product during the chromatographic removal of siloxane byproducts. In the improved procedure reported herein, separation of the silane products from the desired amine is achieved by simple extraction, which contributes to an improvement in the yield of the product.

22. The product **3**⁴ exhibits the following physical and spectral properties: ^1H NMR (500 MHz, CDCl_3) δ : 7.32-7.27 (m, 2 H), 7.22-7.18 (m, 3 H), 2.65 (t, 2 H, $J = 7.7$ Hz), 2.31 (t, 2 H, $J = 7.3$ Hz), 2.24 (s, 6 H), 1.45-1.78 (m, 2 H). ^{13}C NMR (76 MHz, CDCl_3) δ : 142.2, 128.3, 128.2, 125.6, 59.2, 45.4, 33.5, 29.4. IR (neat) cm^{-1} 3062, 3026, 2942, 2764, 1603, 1496, 1454, 1265, 1030. EIMS m/z 163 (M^+ , 40), 91 (60), 84 (65), 74 (60), 59 (100), 58 (90); HRMS (EI) m/z calcd for $\text{C}_{11}\text{H}_{17}\text{N}$ 163.1376, found 163.1361. The purity (>99%) was determined by ^1H NMR, and the submitters also used capillary GLC with a TC-WAX column (0.25 mm x 30 m) (oven temperature: 120 °C; head pressure: 60 kPa; retention time: 16.1 min).

23. The submitters measured the amount of residual ruthenium species in the product by ICP-MS to be less than *ca.* 3 ppm.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The reduction of amides has been generally accomplished by aluminum hydrides such as LiAlH_4 in THF or Et_2O , DIBAL-H, and Red-Al in benzene at room temperature.^{5,6} Alanes, AlH_3 in Et_2O and $\text{AlH}_3 \cdot \text{Et}_3\text{N}$, or boranes, $\text{BH}_3 \cdot \text{THF}$ and $\text{BH}_3 \cdot \text{SMe}_2$ are also useful.⁶ However, these reagents are air- and moisture sensitive, and careful handling is required. It is also well known that separation of the product from aluminum or boron wastes is often troublesome. Alkali borohydrides are rather stable and their handling is easy; however, reduction of amides with NaBH_4 requires application of high temperatures or addition of activators. For example, reduction of

amides is achieved by NaBH₄ in the presence of Lewis acids such as TiCl₄ and ZrCl₄.⁵ Activation of amides is an alternative method for successful borohydride reduction; a two step procedure consisting of iminium salt formation from amides by treatment with Et₃OBF₄ or POCl₃ followed by reduction with NaBH₄ is reported.⁷

Hydrosilanes are stable reducing agents and their handling is easy. Although a number of catalytic hydrosilylations of ketones and aldehydes have been reported, in which addition of the H-Si bond to the C=O moiety is catalyzed by transition metal salts or complexes, there have been few reports for the reduction of amides. The RhCl(PPh₃)₃-catalyzed reduction of amides has recently been reported by Ito and coworkers; the reaction requires the use of dihydrosilanes or trihydrosilanes.⁸ Removal of the silicon waste from the reaction mixture is not easy. Fuchikami reported the reduction of amides with trialkylsilanes, which are rather convenient to manipulate compared to dihydrosilanes or trihydrosilanes, in the presence of several ruthenium catalysts; however, the reaction proceeds under drastic conditions.⁹ Thus, the procedure using trialkylsilanes, which are stable and easy to work with, deserves further attention, especially when the reduction of amides can be achieved under mild conditions.

The ruthenium complex **1**¹⁰ is a useful catalyst for hydrosilylation of ketones and aldehydes,¹⁰ reduction of carboxylic acids, esters, and amides with hydrosilanes,³ and reduction of acetals and cyclic ethers with hydrosilanes.¹¹ It is also a good catalyst for silane-induced ring-opening polymerization of cyclic ethers,¹¹ cyclic siloxanes,¹² and vinyl ethers.¹³ Treatment of **1** with molecular hydrogen followed by treatment with carbon monoxide provides 4,5-dihydroacenaphthylene, which has never been synthesized by other methods.¹⁴

The amide reduction is accomplished under mild conditions by the use of **1** as the catalyst. Phenyl dimethylsilane as the reducing reagent has the advantage of stability towards air and moisture, and it is easy to handle. It is known that the siloxane byproducts are sometimes difficult to separate in many silane-mediated reductions of carbonyl compounds. In the present procedure, the siloxane byproducts are easily removed by extraction. Thus, the present method is an easy way to synthesize amines from amides.

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Appendix

Chemical Abstract Nomenclature; (Registry Number)

Acenaphthylene; (208-96-8)

Ru₃(CO)₁₂: Ruthenium, dodecacarbonyltri-, triangulo; (15243-33-1)

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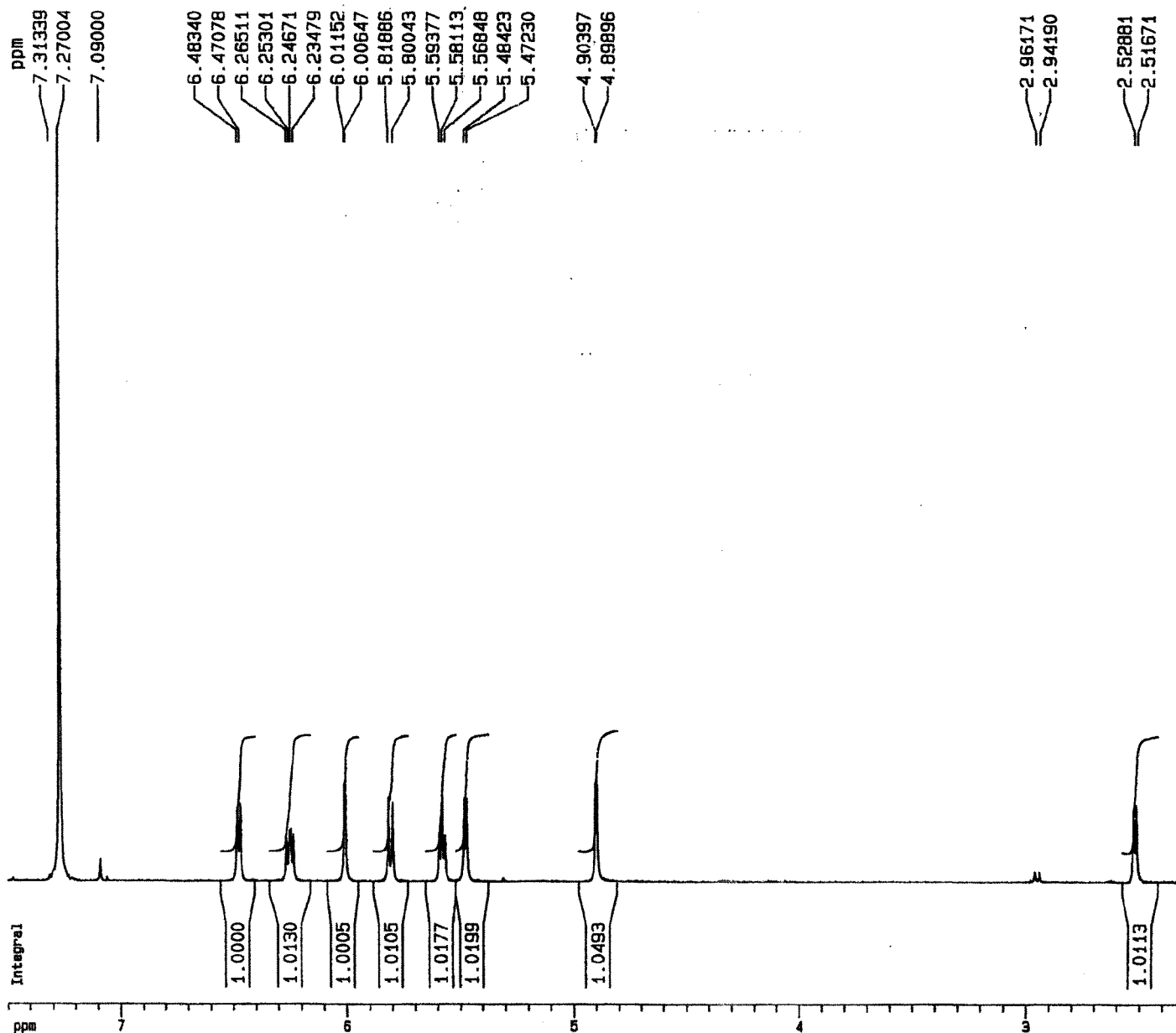
[μ_3 -[(1,2,2a,8a,8b- η^3 :3,4- η^5 :5a,6- η^2)-acenaphthylene]]- μ -carbonyl-hexacarbonyltri-, triangulo; (151364-75-9)

Phenyldimethylsilane: Silane, dimethylphenyl-; (766-77-8)

N,N-Dimethyl-3-phenylpropionamide: Benzenepropanamide, *N,N*-dimethyl-; (5830-31-9)

N,N-Dimethyl-3-phenylpropylamine: Benzenepropanamine, *N,N*-dimethyl-; (1199-99-1)

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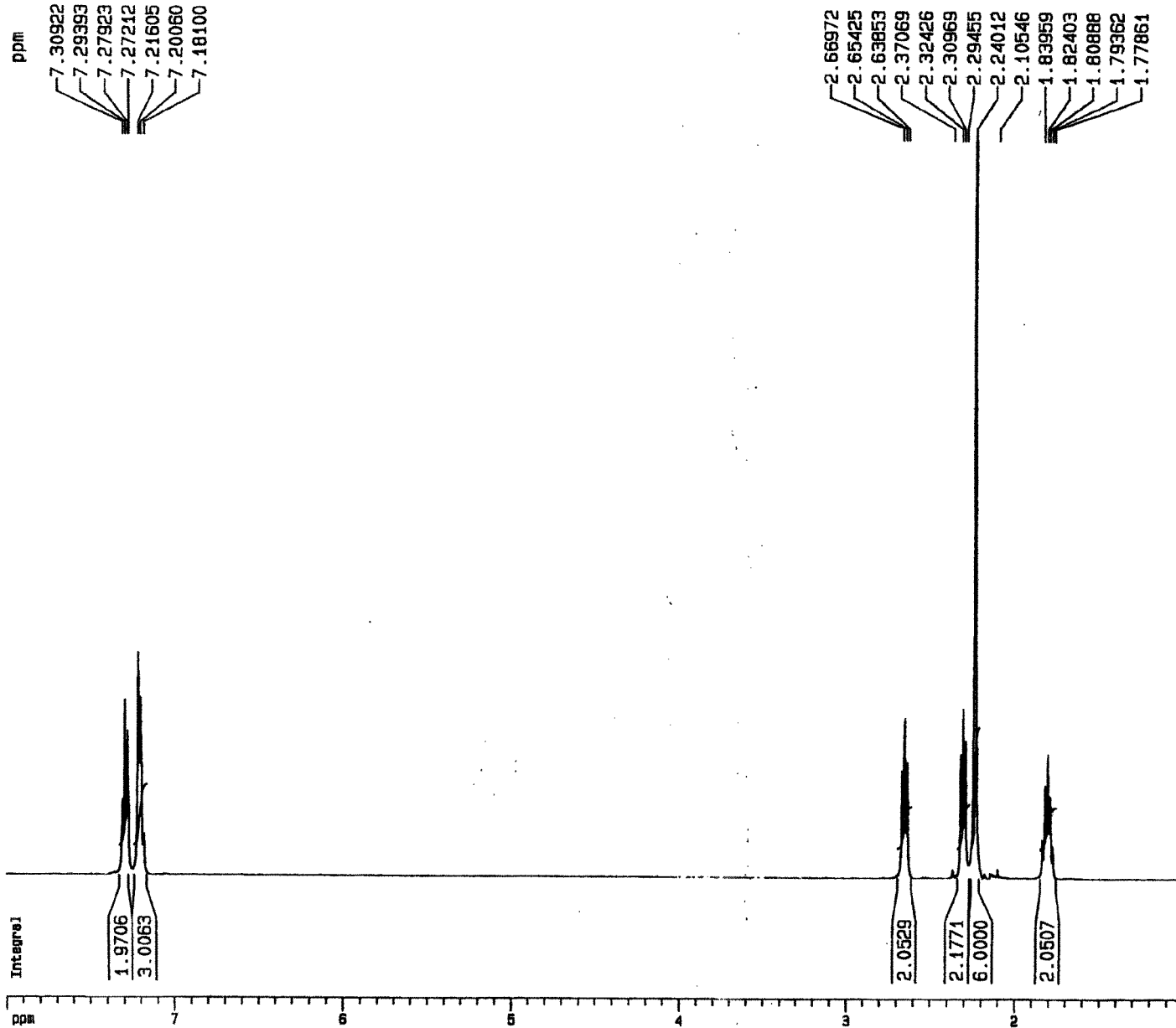
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jp_ORG_SYN_B 1H NMR 500 MHz CDC13 3/22/05



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