Selective Reactions of *trans*-1,6-Dimethylbicyclo[4.3.0]nonane-2,7-dione, an Intermediate for Triterpene Synthesis

Jerrold L. Martin, Jacob S. Tou, and William Reusch*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

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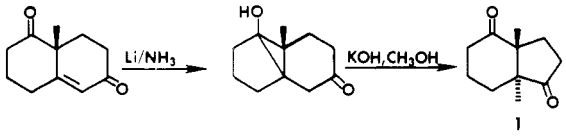
The six-membered carbonyl function of the title compound (1) is more reactive in nucleophilic addition reactions than the five-membered ketone. Reduction, ketalization, organolithium addition, and sulfur ylide condensation all proceed selectively at that site. If the six-membered ketone is blocked (e.g., 7), reactions at the five-membered carbonyl group are found to be very sluggish. In a study of more than a dozen strong nucleophiles only DIBAL and allylic Grignard reagents added to this function. Lithium ethoxyacetylide reacts with 7 in an anomolous fashion. The enolate anion formed by proton transfer from 7 to the acetylide base adds to the carbon–carbon triple bond, giving 19 in high yield. Trideuterio analogues of 1, 2, 7, 9, and 10 have been prepared so that the angular methyl resonance signals from these compounds can be assigned. Chemical shift increments derived from steroids can be applied to derivatives of 1. Both carbonyl functions in 1 generate enolate anions which may be trapped as silyl ether derivatives or condensed with benzaldehyde. One equivalent of strong base generates the six-membered ring enolate under equilibrating conditions, and this was trapped as silyl ether 23. Unexpectedly, condensation of 1 with 1 equiv of benzaldehyde gave the five-membered ring benzylidene product 27 under equilibrating conditions.

In a recent paper,[1] we reported an efficient two-step synthesis of *trans*-1,6-dimethylbicyclo[4.3.0]nonane-2,7-dione (1) from the Wieland–Miescher ketone (eq 1).

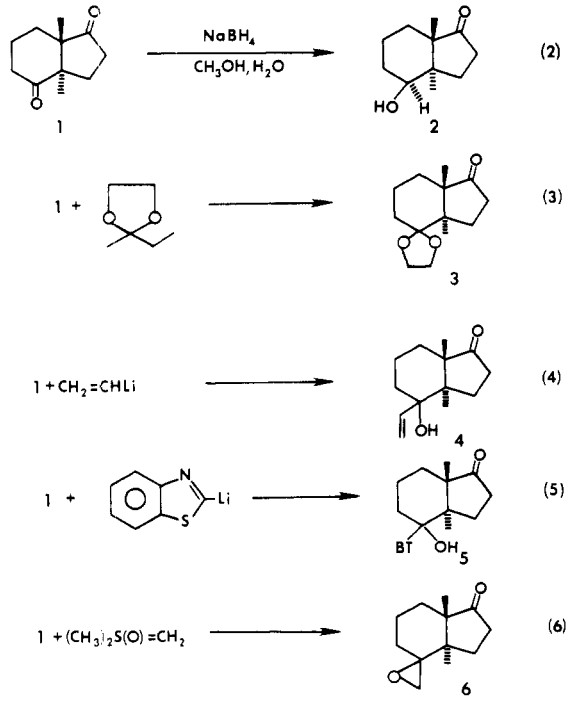


(1)

1

Since 1 is a potentially useful intermediate in terpene synthesis, we considered it important to establish the relative reactivities of the two carbonyl functions. Indeed, if 1 is to serve as a C/D synthon in a synthesis of lanostane and euphane triterpenes, it will be necessary to conduct selective annulation reactions at the six-membered ketone and introduce a branched alkyl group at the five-membered ketone.

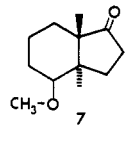
A high selectivity favoring addition reactions to the six-membered carbonyl group of 1 has been observed. Thus selective reduction (eq 2), ketalization (eq 3), vinyl lithium addition (eq 4), benzothiazole addition (eq 5), and dimethyloxosulfonium methylide condensation (eq 6) can be effected in good to excellent yields without protecting the five-membered carbonyl group.



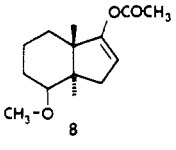
The peak width of the carbinol proton resonance in the ^{1}H NMR spectrum of 2 suggested an axial orientation for the hydroxyl group. This was later confirmed by an X-ray structure determination of derivative 19.

The selectivity displayed in reactions 2–6 is noteworthy, inasmuch as Dreiding models show little difference in the steric hindrance at each carbonyl function. Indeed, if the two rings in 1 were of equal size, these functions would have an enantiotopic relationship. An important factor in this functional discrimination is the I-strain effect described by H. C. Brown 25 years ago to account for the lower reactivity of cyclopentanone compared with cyclohexanone.[2]

When we seek to effect reactions at the five-membered carbonyl function, the same factors that favored addition reactions at the six-membered cyclic ketone work against us. This was dramatically demonstrated by the failure of many common organometallic reagents, ylides, and enolate salts to add to 7, prepared by methylation of 2. Methyllithium, vinyllithium, and vinylmagnesium chloride in ether or THF solution do not give addition products with 7, even in the presence of TMEDA and HMPA. (Triphenylphosphine)carboethoxymethylene,[3] the sodium salt of diethyl cyclohexyliminovinylphosphonate,[4] and dimethyloxosulfonium methylide[5] likewise fail to add to 7.



7



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It is noteworthy that the latter two reagents are reported to give addition products with 17-ketosteroids.[4,6] Furthermore, 7 does not undergo the Reformatsky reaction[7]

(1) W. Reusch, K. Grimm, J. Karoglan, J. Martin, K. P. Subrahamanian, P. S. Venkataramani, and J. D. Yordy, *J. Am. Chem. Soc.*, **99**, 1958 (1977).

(2) (a) H. C. Brown, J. H. Brewster, and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954); (b) H. C. Brown and K. Ishikawa, *Tetrahedron*, 1, 221 (1957).

(3) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963). Cf. A. Scettri, E. Castaguina, and G. Pinancatelli, *Gazz. Chim. Ital.*, **104**, 437 (1974).

(4) W. Nagata and Y. Hayase, *J. Chem. Soc. C*, 460 (1969).

(5) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **84**, 867 (1962).

(6) D. N. Kirk and M. A. Wilson, *J. Chem. Soc. C*, 414 (1971).

(7) M. W. Rathke, *Org. React.*, **22**, 438 (1975).

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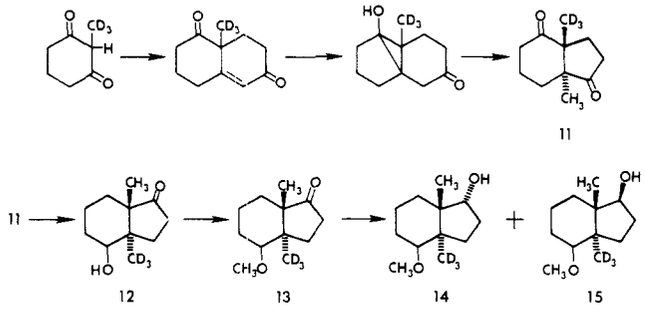
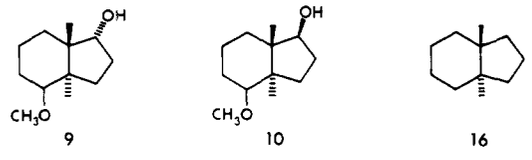
Scheme I



and does not add ester enolate reagents derived from ethyl acetate,[8] *tert*-butyl acetate,[9] or *tert*-butyl (trimethylsilyl)acetate.[10]

When reactions of **7** with vinyllithium and lithium *tert*-butyl acetate were worked up by quenching with acetic anhydride, significant yields of enol acetate **8** were obtained. The relative inertness of **7** to nucleophilic addition reactions can therefore be attributed *in part* to facile enolization by strong bases.

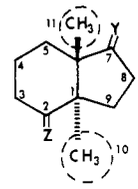
Since steric hindrance at the carbonyl function is severe, we turned our attention to the action of small but highly nucleophilic species such as hydride and acetylide on **7**. Treatment of **7** with excess lithium aluminum hydride in refluxing ether slowly reduced the carbonyl group; however, this reduction was best accomplished by the action of diisobutylaluminum hydride at −5 °C. A mixture of epimeric alcohols **9** and **10** was obtained in essentially



quantitative yield, and each component was isolated by preparative TLC. Assignment of configurations **9** and **10** to the major (60%) and minor (40%) epimers respectively was made on the strength of characteristic ^{1}H NMR shifts of the angular methyl substituents in these compounds. In order to distinguish these methyl groups beyond question, we prepared the tris(deuterio) derivatives **11** through **15** by the reactions outlined in Scheme I.

Since the ^{1}H NMR spectra of these deuteriomethyl compounds allowed a clear assignment of the angular methyl signals in **1**, **2**, **7**, **9**, and **10**, we decided to analyze these signals by the chemical shift additivity principle suggested by Shoolery and Rogers[11] for steroid angular methyl groups. The unknown parent hydrocarbon **16** for these rigid bicyclic compounds provides a useful reference in our argument, because the chemical shifts of the homotopic angular methyl groups therein would be the same. Introduction of functional groups into either ring would in most cases destroy the C_2 symmetry of **16**, causing the angular methyl groups to have different chemical shifts. Substituent effects on steroid angular methyl chemical shifts have been tabulated[12] and may be used to calculate the separation of methyl ^{1}H NMR signals in compounds

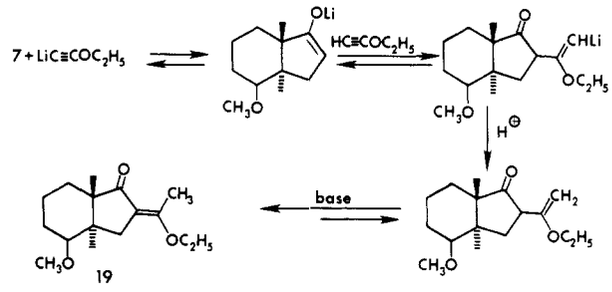
Table I. Calculated and Observed $\Delta(\delta_{11} - \delta_{10})$ Values for **1**, **2**, **7**, **9**, **10**, and **17**[a]



compd	δ_{10}[b]	δ_{11}[b]	Δ_{obsd}	Δ_{calcd}
1	1.15	0.85	−0.30	−0.32
2	0.90	1.25	0.35	0.32
7	0.85	1.15	0.30	0.32
9	1.00	0.90	−0.10	−0.05
10	1.00	1.20	0.20	0.23
17	0.93	1.05	0.12	0.09

[a] **1**, Y = Z = O. **2**, Y = O; Z = β-OH, α-H. **7**, Y = O; Z = β-OCH_3, α-H. **9**, Y = α-OH, β-H; Z = β-OCH_3, α-H. **10**, Y = α-H, β-OH; Z = β-OCH_3, α-H. **17**, Y = O; Z = H_2. [b] δ values are ppm from Me_4Si at 60 MHz and are accurate to ±0.02.

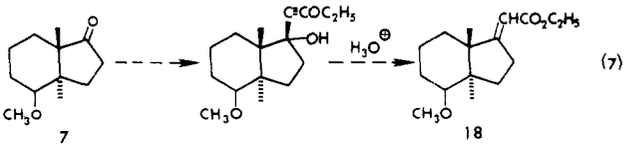
Scheme II



1, **2**, **7**, **9**, **10**, and **17**. For example, the single carbonyl function in **17** (see Table I) will perturb the C-11 methyl signal in approximately the same way that a 17-keto function affects the C-18 methyl of a steroid. Likewise, the C-10 methyl in **17** is subject to a carbonyl effect similar to that experienced by the C-18 methyl of a 15-keto steroid. The appropriate steroid substituent values predict a difference in chemical shifts for the methyl groups in **17** of almost 0.1 ppm, and the observed value is 0.12. Clearly, the sign of such chemical shift differences is as important as their magnitude, and both are listed in Table I.

The effect of lanthanide shift reagents on epimers **9** and **10** proved to be similar. The 11-methyl resonance underwent a significant downfield shift, but the 10-methyl resonance was only slightly perturbed.

On treatment with sodium or lithium acetylide in ether or THF solution, **7** failed to give an adduct. Unexpectedly, the corresponding reaction with lithium ethoxyacetylide, followed by a 4 N hydrochloric acid wash, gave a crystalline product (composition $C_{16}H_{26}O_3$) in excellent yield. This result agreed with our initial goal to effect the transformations outlined in eq 7.[13] However, the absence of an



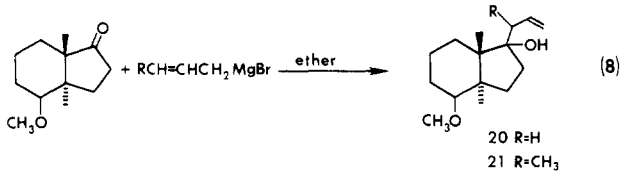
(7)

olefinic proton signal in the δ 4.0 to 7.0 region of the ^{1}H NMR spectrum together with a pronounced UV absorption at λ_{max} 272 nm (ε 990) provided compelling evidence that the compound in hand was not **18**.

(8) S. Shiotani, *J. Org. Chem.*, **40**, 2033 (1975).
(9) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973).
(10) S. Hartzell, D. F. Sullivan, and M. W. Rathke, *Tetrahedron Lett.*, 1403 (1974).
(11) J. N. Shoolery and M. T. Rogers, *J. Am Chem. Soc.*, **80**, 5121 (1958).
(12) (a) R. F. Zurcher, *Helv. Chim. Acta*, **44**, 1380 (1961); **46**, 2054 (1963); (b) A. I. Cohen and S. Rock, *Steroids*, **3**, 243 (1964); (c) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964.
(13) J. Arens, *Adv. Org. Chem.*, **2**, 117 (1960).

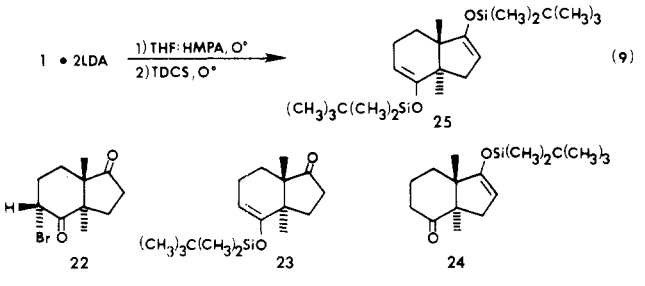
Spectroscopic data outlined in the Experimental Section suggested structure **19** for the crystalline adduct. This remarkable transformation can be viewed as proceeding by proton exchange followed by addition of the ketone enolate to the ethoxyacetylene triple bond (Scheme II). Although heteronucleophiles are known to add to alkoxyacetylenes,[13,14] this appears to be the first example of an intermolecular addition of a carbon nucleophile. Because of the unprecedented nature of this proposal, an X-ray structure determination of **19** was undertaken, and this confirmed the structure given here.[15]

The introduction of a branched alkyl group at the five-membered carbonyl function in **7** was finally accomplished by the action of allylic Grignard reagents. Benkeser has shown that hindered ketones react readily with such reagents,[16] the kinetically favored product being that formed by an allylic rearrangement. We find that this reaction (eq 8) proceeds better in ether than in THF solution and confirm the allylic rearrangement of the side chain (as in **21**).



(8)

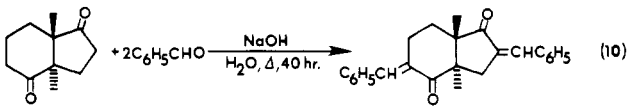
The usefulness of diketone **1** as an intermediate in synthesis would be further enhanced if selective enolate formation could be achieved. Since bromination of **1** with 1 equiv of 2-pyrrolidone hydrotribromide (PHT) gave monobromide **22** in high yield,[17] the prospects for such selectivity appeared good.



(9)

Both carbonyl functions in **1** are readily converted to enolate species, as demonstrated by formation of the bis(silyl) ether **25** under mild conditions (eq 9). At reaction temperatures ranging from 0 to 65 °C, **1** reacted with 1 equiv of lithium diisopropylamide (LDA) to give the six-membered enolate base, trapped as silyl ether **23** by reaction with *tert*-butyldimethylchlorosilane (TDCS). Since this result did not change on extending the reaction time, we assume that **23** represents the thermodynamically favored monoenolate derived from **1**. The low solubility of enolate salts from **1** in THF:HMPA solutions at temperatures below −10 °C complicated our efforts to trap the kinetically favored enolate. Heterogeneous reactions of monoenolate salt suspensions with TDCS gave bis(silyl) ether **25** and both mono ethers **23** and **24** in varying proportion.

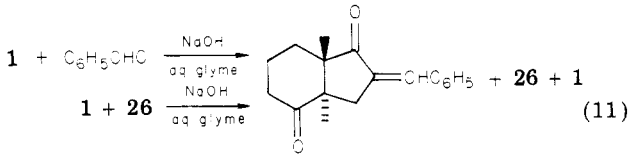
Condensation reactions of **1** with benzaldehyde took an unexpected course. The biscondensation shown in eq 10 demonstrated that both α-methylene groups were able to



(10)

1 **26**

serve as enolate donors. However, a 1:1 reaction of **1** with benzaldehyde gave a mixture of the five-membered monoadduct **27**, the bisadduct **26**, and **1**, without any detectable amount of the six-membered monoadduct (eq 11).



(11)

27

(**27**–**26** 2:1)

Since a 1:1 mixture of **1** and **26** gave the same products under identical reaction conditions, equilibrium product control is operating here. Reaction of **1** with 0.5 equiv of benzaldehyde gave **27** as the sole condensation product.

We regard the formation of enol derivative **23** (thermodynamic favoring of the six-membered enolate) as a reflection of angle strain in the trans-fused five-membered ring. This view, however, appears to be inconsistent with the exclusive formation of the five-membered benzlidene product **27** noted above. A possible rationalization of this anomaly may be found in π-conjugation differences in the benzylidene adducts. Molecular models (Dreiding) show a substantial dihedral angle (ca. 35°) between a six-membered carbonyl group and an α-benzylidene grouping, whereas the two functions are essentially coplanar when on a five-membered ring. Indeed, α-benzylidenecyclohexanones have molar extinction coefficients ($\epsilon \approx 16\,000$) roughly 70% that of acyclic or five-membered analogues ($\epsilon \approx 24\,000$).[18]

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Proton magnetic resonance spectra were taken in a deuteriochlorform solution with a Varian T-60 spectrometer and are calibrated in parts per million (δ) downfield from tetramethylsilane as an internal standard. Ultraviolet spectra were recorded on a Unicam SP-800 spectrophotometer. Mass spectra were obtained with a Hitachi RMU-6 mass spectrometer. Melting points were taken on either a Hoover-Thomas apparatus (capillary tubes) or on a hot-stage microscope and are uncorrected.

All reactions in which strongly basic reagents were used were conducted under nitrogen or argon.

Microanalyses of carbon and hydrogen were performed by Spang Microanalytical Laboratories, Eagle Harbor Mich., and in all cases were within 0.2% of the calculated values.

Preparation of Ketol 2 from 1. To a solution of 27.0 g (0.15 mol) of 1^1 in 1350 mL of ethanol (cooled to 0 °C) was added dropwise a solution of 23.2 g (0.58 mol) of sodium hydroxide and 6.45 g (0.17 mol) of sodium borohydride in 100 mL of ethanol and 50 mL of water. This addition was effected over a 30-min period with vigorous stirring. After 3.5 h at 0 °C, GLC (130 °C, 4% SE-30) showed that **1** had been totally consumed. The ethanol was removed from the reaction mixture, and the residue was dissolved in water and ether. The aqueous phase was extracted with ether, and the combined ether extract was washed se-

(14) L. Brandsma, H. Bos, and J. Arens, "Chemistry of Acetylenes", H. Viehe, Ed., Marcel Dekker, New York, 1969, p 788.
(15) D. Ward and J. Martin, *Acta Crystallogr., Sect. B*, **32**, 2871 (1976).
(16) R. A. Benkeser, *Synthesis*, 347 (1971).
(17) J. D. Yordy and M. A. Neuman, *J. Cryst. Mol. Struct.*, **4**, 121 (1974).
(18) (a) H. O. House and R. L. Wasson, *J. Am. Chem. Soc.*, **78**, 4394 (1956); (b) W. S. Johnson, E. Rogier, and J. Ackerman, *ibid.*, 6322 (1956); (c) A. StAndre, H. MacPhillamy, J. Nelson, A. Shabica, and C. Scholz, *ibid.*, **74**, 5506 (1952).

quentially with water and brine. After the solvent was dried and removed, 26.57 g (97.5%) of essentially pure **2** was obtained. An analytical sample displayed the following properties: mp 173–175 °C (sealed tube); IR ($CDCl_3$) 3590, 3450, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (s, 3 H), 1.25 (s, 3 H), 1.3–2.7 (m, 11 H), 3.8 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 182 (41), 167 (15), 154 (5), 149 (8), 138 (10), 122 (40), 111 (100), 109 (85), 96 (64), 81 (58), 67 (45), 55 (62), 41 (80).

Preparation of Ketal 3 from 1. A solution of 0.18 g (1.0 mmol) of **1** in 25 mL of 2-methyl-2-ethyl-1,3-dioxolane containing 10 mg of *p*-toluenesulfonic acid was heated at reflux with slow distillation over a 2-h period. Most of the solvent was then removed by distillation, and the residual material was chromatographed on silica gel. The crude monoketal was obtained by chloroform elution in 85% yield. Crystallization at low temperature gave material having the following properties: mp 42–45 °C; IR (neat) 2850–3000, 1730, 1160, 1115, 1050–1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.1 (s, 3 H), 1.3–1.6 (m, 6 H), 1.8–2.2 (m, 4 H), 3.7–3.9 (s, 4 H); MS (70 eV), *m/e* (rel intensity) 224 (5), 209 (20), 140 (18), 113 (45), 112 (95), 86 (100), 55 (30).

Preparation of Vinylcarbinol 4 from 1. To a solution of 5.4 g (0.03 mol) of **1** in 300 mL of THF at room temperature was added 50 mL of 2.0 M vinyllithium in THF (Ventron) in one portion, and the resulting solution was stirred for 3 days. The reaction mixture was poured into saturated ammonium chloride solution and extracted with ether. The ether extracts were washed with water and brine and dried; they yielded 5.0 g of light yellow amorphous solid after removal of the solvent. This solid was recrystallized from ethyl acetate–petroleum ether with a 4.3 g (70%) yield of **4**: mp 111–112 °C; IR 3410, 1725, 1630, 990, 930 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (s, 3 H), 1.3 (s, 3 H), 1.35–3.7 (m, 11 H), 5.1 (m, 2 H), 5.9 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 208 (8), 193 (20), 190 (11), 175 (9), 133 (25), 111 (100), 96 (36), 82 (27), 67 (25), 55 (48), 41 (43).

Preparation of the Benzothiazole Adduct 5 from 1. To a cold (−78 °C) solution of 0.5 mL (1.2 mmol) of 2.42 M *n*-butyllithium (hexane solution) in 15 mL of dry ether was added 0.135 g (1.2 mmol) of benzothiazole. After 20 min, a solution of 0.18 g (1.0 mmol) of **1** in 15 mL of ether was added dropwise with stirring, and the reaction mixture was then warmed to room temperature. Following a 1-h reaction period, the mixture was quenched with water and extracted with ether. The combined ether extracts were washed, dried, and condensed, yielding 0.22 g (70%) of the adduct **5**. Recrystallization from ether gave a pure sample: mp 193–194.5 °C; IR ($CHCl_3$) 3555, 3400, 2925, and 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 1.4 (s, 3 H), 1.5–2.8 (m, 11 H), 3.2 (s, 1 H), 7.0–7.4 (m, 2 H), 7.5–8.0 (m, 2 H); MS (70 eV), *m/e* (rel intensity) 315 (50), 300 (17), 204 (37), 178 (64), 149 (100), 136 (45).

Preparation of Ketoepoxide 6. To 300 mL of dry Me_2SO was added 2.66 g (0.111 mol) of oil-free sodium hydride, and this mixture was heated with stirring at 70 °C until a yellow solution formed. After this solution was cooled to 15 °C, 24.40 g (0.111 mol) of trimethyloxosulfonium iodide was added in one portion. Stirring this mixture 30 min at room temperature gave a solution to which 8.00 g (0.0455 mol) of **1** in 100 mL of Me_2SO was added. After seven days at room temperature, the reaction mixture was poured into 400 mL of ice water, and the resulting mixture was extracted with five, 200-mL portions of ether. The combined ether extract was washed sequentially with water and brine and then dried. Removal of the solvent gave 7.33 g (83%) of **6** as a white solid. An analytical sample of **6** displayed the following properties: mp 159–161 °C (petroleum ether); IR 1735 cm^{-1}; ^1H NMR (CCl_4) 1.0 (s, 3 h), 1.1 (s, 3 H), 1.15–2.2 (m, 10 H), 2.3 (m, 2 H); MS (70 eV), *m/e* (rel intensity) 194 (28), 179 (13), 166 (17), 151 (17), 136 (44), 122 (46), 107 (100), 93 (58), 79 (45), 67 (37), 55 (42), 41 (72).

Preparation of Methoxy Ketone 7 from 2. A solution of dimsylsodium (90 mmol in 250 mL of Me_2SO) was cooled to room temperature, and 8.20 g (45 mmol) of **2** was added in one portion. The solid quickly dissolved, and the resulting solution was stirred for 1 h at room temperature, followed by the addition of 9.58 g (67.5 mmol) of methyl iodide in one portion. After this reaction mixture had been stirred for 19 h at room temperature, it was poured into 250 mL of water, and the resulting aqueous mixture was extracted with benzene. The benzene extract was washed with water and brine and then dried. After removal of the solvent, 8.54 g of yellow oil was recovered. This oil was distilled at 0.005 torr, and 6.50 g (73.7%) of **7** was collected (bp 51–53 °C). An analytical sample displayed the following properties: IR (neat) 1735 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (s, 3 H), 1.15 (s, 3 H), 1.20–2.70 (m, 10 H), 3.3 (s, 3 H); MS (70 eV), *m/e* (rel intensity) 196 (5), 125 (8), 120 (9), 109 (8), 105 (11), 91 (9), 85 (9), 78 (93), 71 (13), 63 (100), 61 (15), 55 (11).

Reduction of 7 to Epimeric Alcohols 9 and 10. To a solution of 3.92 g (20 mmol) of **7** in 100 mL of THF at 0 °C was added 43 mL of a 20% solution of diisobutylaluminum hydride in hexane (Ventron). The reaction was kept at 5 °C for 2 days and was then poured into cold 4 N hydrochloric acid and extracted with ether. The ether extracts were washed sequentially with 4 N hydrochloric acid, water, and brine and then dried. Removal of the solvent gave 3.91 g (98.7%) of a clear oil which proved to be a mixture of the epimeric alcohols **9** and **10**. Analysis by GLC (160 °C, 4% QF-1) showed that **7** had been completely consumed and that the two epimeric alcohols were present in the ratio of 1.4:1 (α:β). An analytical sample of each of the alcohols was obtained by preparative thin-layer chromatography (20% ethyl acetate in cyclohexane) of 0.1583 g of the epimeric mixture. The higher band on the plate yielded 0.0665 g of one epimer which corresponded to the shorter rentention component on GLC. It was assigned configuration **9** and displayed the following properties: mp 84–85 °C; IR (CCl_4) 3610, 3480 cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (s, 3 H), 1.0 (s, 3 H), 1.1–2.6 (m, 11 H), 3.05 (m, 1 H), 3.20 (s, 3 H), 3.6 (m, 1 H); MS (15 eV, ion source 100 °C), *m/e* (rel intensity) 198 (8), 180 (34), 166 (34), 154 (24), 148 (63), 133 (19), 122 (100), 112 (12), 93 (16), 84 (50), 71 (20).

The lower band on the plate yielded 0.0533 g of the other epimer which corresponded to the longer retention component on the GLC. It was assigned configuration **10** and displayed the following properties: mp 106–108 °C; IR (CCl_4) 3615, 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 (s, 3 H), 1.0 (s, 3 H), 1.1–2.6 (m, 11 H), 3.0 (m, 1 H), 3.2 (s, 3 H), 3.8 (m, 1 H); MS (15 eV, source 100 °C), *m/e* (rel intensity) 198 (10), 180 (4), 166 (35), 154 (25), 148 (39), 133 (8), 122 (100), 112 (38), 93 (8), 84 (33), 71 (16).

Preparation of Deuterium-Labeled Compounds 11, 12, 13, 14, and 15. A solution of 6.0 g (47 mmol) of 2-methyl-d_3-cyclohexane-1,3-dione (prepared by alkylation of dihydroresorcinol with iodomethane-d_3) in ethyl acetate (30 mL) containing 10 mL of triethylamine and 6.0 mL of methyl vinyl ketone was refluxed for 6 h. The reaction mixture was cooled, filtered, and evaporated, and the resulting residue was dissolved in toluene (200 mL) containing a little pyrrolidine (0.17 mL) and acetic acid (0.11 mL). Following a 12-h reflux, this mixture was cooled, diluted with ether (200 mL), and extracted with 4 N hydrochloric acid. The organic layer was then washed with sodium bicarbonate solution and after workup yielded 5.84 g (69%) of d_3-Wieland-Miescher ketone.

A solution of 5.75 g (32 mmol) of the labeled Wieland-Miescher ketone was reduced by lithium in ammonia, following the published procedure,[1] and yielded 5.18 g (89%) of the corresponding cyclopropanol. This on treatment with a solution of KOH (1.75g) in 60 mL of aqueous methanol (50:50) gave 2.65 g of a yellow solid, which was crystallized from ether–petroleum ether to give 1.30 g (25%) of *trans*-1-methyl-d_3-6-methylbicyclo[4.3.0]nona-2,7-dione (**11**). The following properties were observed for **11**: mp 158–160 °C; IR (CCl_4) 2200, 1725, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.4–2.7 (m, 12 H); MS (70 eV), *m/3* (rel intensity) 183 (64), 168 (9), 165 (56), 141 (21), 137 (23), 128 (50), 113 (100), 99 (63), 85 (60), 69 (30), 55 (31), 41 (49).

Transformation of **11** into the labeled compounds **12**, **13**, **14**, and **15** was effected in the same manner as the preparations of **2**, **7**, **9**, and **10** described earlier in this section.

12: mp 176–177 °C; IR ($CHCl_3$) 3600, 3450, 2200, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (s, 3 H), 1.3–2.6 (m, 11 H), 3.8 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 185 (55), 170 (10), 167 (10), 125 (42), 114 (78), 112 (100), 99 (80), 81 (57), 69 (53), 55 (28), 43 (33), 41 (45).

13: oil; IR ($CHCl_3$) 2215, 2200, 2050, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (s, 3 H), 1.2–2.6 (m, 10 H), 3.15 (m, 1 H), 3.25 (s, 3 H); MS (70 eV), *m/e* (rel intensity) 199 (44), 184 (4), 181 (4), 167 (9), 143 (11), 139 (12), 128 (40), 125 (55, 115 (60), 71 (100).

14: mp 76–78 °C; IR ($CHCl_3$) 3590, 3415, 2220, 2205, 2120 2030 cm^{-1}; ^1H NMR ($CDCl_3$) 0.95 (s, 3 H), 1.1–2.6 (m, 11 H), 3.15 (m, 1 H), 3.25 (s, 3 H), 3.75 (m, 1 H); MS (15 eV, 100 °C source), *m/e*

(rel intensity) 201 (11), 183 (12), 169 (38), 157 (35), 151 (37), 125 (100), 115 (9), 112 (9), 108 (10).

15: mp 107–109 °C; IR ($CHCl_3$) 3580, 3410, 2215, 2205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (s, 3 H), 1.1–2.6 (m, 11 H), 3.05 (m, 1 H), 3.25 (s, 3 H), 3.9 (m, 1 H); MS (15 eV, 100 °C source), *m/e* (rel intensity) 201 (12), 169 (42), 157 (32), 151 (38), 125 (100), 115 (34), 112 (8), 108 (12).

Isolation of Enol Acetate 8. To a solution of 3.33 mL of a 1.5 M stock solution (THF) of vinyllithium in 2.5 mL of tetramethylethylenediamine and 6.5 mL of THF was added dropwise a solution of 0.49 g (2.5 mmol) of **7** in 6.5 mL of THF. The resulting solution was refluxed for 24 h, cooled to room temperature, and then quenched by the addition of 1.08 g (10.6 mmol) of acetic anhydride. The cloudy, brown reaction mixture became translucent at this point and was poured into water and extracted with ether. The ether extracts were washed sequentially with water and brine and then dried. Removal of the solvent yielded 0.89 g of brown oil, which was chromatographed on 80 g of silica gel, eluting with 30% ether–pentane followed by 50% ether–pentane. The eluant fractions yielded 0.210 g (35.3%) of **27** and 0.326 g of **7**. The enol acetate **27** displayed the following properties: IR (neat) 1760, 1640, 895, 805 cm^{-1}; ^1H NMR (CCl_4) δ 1.1 (s, 3 H), 1.15 (m, 3 H), 1.2–2.8 (m, 8 H), 2.05 (s, 3 H), 3.15 (m, 1 H), 3.2 (s, 3 H), 5.2 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 238 (1), 196 (22), 181 (10), 178 (9), 164 (33), 149 (100), 135 (23), 131 (14), 121 (30), 119 (19), 117 (30), 107 (25), 93 (24), 91 (24), 79 (25), 73 (25), 73 (25), 71 (52), 67 (23), 55 (39), 45 (34), 43 (86), 41 (62).

Formation of 19 from 7. To a solution of 0.280 g (4.0 mmol) of ethoxyacetylene (Farchan) in 10 mL of ether was added 1.93 mL of 2.08 M *n*-butyllithium in hexane (Ventron), and the resulting cloudy solution was stirred for 10 min at room temperature. A solution of 0.434 g (2.2 mmol) of **7** in 10 mL of ether was then added in one portion, followed by 0.70 mL of HMPA. The reaction mixture was stirred for 12 h, poured into cold 4 N hydrochloric acid, and extracted with ether. The ether extract was washed sequentially with 4 N hydrochloric acid, water, and brine and then dried. After removal of the solvent, the residue was crystallized from petroleum ether–ethyl acetate to yield 0.579 g (98.3%) of light yellow, crystalline **19**. An analytical sample of **19** displayed the following properties: mp 132–134 °C; IR (CCl_4) 1700, 1630, 1265 cm^{-1}; ^1H NMR (CCl_4) δ 0.9 (s, 3 H), 1.05 (s, 3 H), 1.25 (t, 3 H), 1.4–2.9 (m, 11 H), 3.15 (m, 1 H), 3.25 (s, 3 H), 3.9 (q, 2 H); UV (95% ethanol) 272 nm (ϵ 992); MS (70 eV), *m/e* (rel intensity) 266 (53), 251 (4), 237 (4), 234 (60), 219 (26), 205 (50), 196 (65), 177 (35), 163 (45), 157 (45), 129 (55), 109 (58), 97 (100), 71 (60), 55 (86), 43 (95), 41 (87); ^{13}C NMR ($CDCl_3$) δ (Me_4Si) 13.57 (q), 15.32 (q), 17.08 (t), 20.08 (q), 23.67 (t), 24.08 (q), 25.73 (t), 33.10 (t), 42.03 (s), 52.44 (s), 57.70 (q), 62.26 (t), 83.58 (d), 113.03 (s), 163.46 (s), 182.69 (s).

Preparation of Allyl Adduct 21. A solution of 0.484 g (4.0 mmol) of allyl bromide in 15 mL of ether was stirred with 0.096 g (4.0 mmol) of magnesium turnings until all the magnesium had dissolved to form a clear solution (3 h). A solution of 0.196 g (1.0 mmol) of **7** in 5 mL of ether was added to the Grignard reagent, and this mixture was stirred for 12 h at room temperature, followed by a 2-h reflux. The reaction was cooled to room temperature, poured into saturated aqueous ammonium chloride, and extracted with ether. The ether extracts were washed sequentially with water and brine and then dried. After removal of the solvent, 0.212 g (89.1%) of **21** was obtained as a colorless oil. An analytical sample of **21** displayed the following properties: IR (neat) 3520, 3025, 1630, 985, 905 cm^{-1}; ^1H NMR (CCl_4) δ 1.0 (s, 3 H), 1.1 (s, 3 H), 1.2–2.4 (m, 13 H), 3.0 (m, 1 H), 3.15 (s, 3 H), 5.0 (m, 2 H), 5.7 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 238 (0.1), 220 (0.6), 206 (0.8), 197 (0.6), 188 (0.5), 179 (2), 165 (3), 147 (8), 122 (9), 107 (6), 93 (4), 81 (5), 71 (9), 58 (30), 43 (100).

Preparation of Methyallyl Adduct 22. A mixture of 7.2 g (0.3 mol) of magnesium turnings, a small crystal of iodine, and 30 mL of ether was stirred while a solution of 13.5 g (0.1 mol) of crotyl bromide (Aldrich) in 70 mL of ether was added dropwise over 5 h at room temperature. After the addition was complete, the metallic gray solution was stirred a further 30 min, followed by addition of 10 g (0.051 mol) of **7** in 100 mL of ether over 1 h. The reaction was stirred for another hour and then poured into cold, saturated ammonium chloride. The aqueous mixture was extracted with ether, and the extracts were washed sequentially with water and brine and dried. Analysis by GLC (160 °C, 4% QF-1) indicated that **7** had been totally consumed. Removal of the solvent gave 12.40 g (96.5%) of **22** as a clear oil. An analytical sample of **22** displayed the following properties: IR (neat) 3520, 3025, 1630, 990, 905 cm^{-1}; ^1H NMR (CCl_4) δ 0.95 (d, 3 H), 1.1 (bs, 6 H), 1.15–2.6 (m, 12 H), 3.0 (m, 1 H), 3.15 (s, 3 H), 4.9 (m, 2 H), 5.8 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 252 (0.3), 234 (2), 224 (6), 220 (3), 210 (2), 202 (2), 197 (19), 165 (30), 147 (100), 125 (32), 122 (37), 105 (35), 91 (25), 81 (31), 71 (52), 55 (51), 41 (56).

Preparation of Bis(silyl) Ether 25. A solution of LDA was prepared by reacting 0.61 mL (4.4 mmol) of diisopropylamine in 10 mL of dry THF with 1.74 mL of 2.42 M *n*-butyllithium in hexane for 20 min at −78 °C. To this was added a solution of 0.36 g (2 mmol) of dione **1** in 10 mL of THF, and the resulting cloudy mixture was warmed to 0 °C following the addtiion of 0.5 mL of HMPA (hexamethylphosphoric triamide). After this enolate solution was quenched with *tert*-butyldimethylchlorosilane (0.63 g in 5 mL of THF), the resulting mixture was warmed to room temperature and worked up by addition to ice water and extraction with ether. The combined ether extracts were washed and dried (magnesium sulfate) before removal of the solvent. The resulting yellow oil was purified by distillation (110 °C, 10^{-3} torr), yielding 690 mg (85%) of a low-melting solid. Analysis of this product by GLC (4% QF1, 180 °C) and TLC showed it to be chiefly the bis adduct **25**, containing ca. 2% of the mono adduct **24**. A sample of **25** obtained by GLC (5% PDEAS, 160 °C) had the following properties: mp 57–59 °C; IR (CCl_4) 1645 and 1620 cm^{-1}; ^1H NMR (CCl_4) δ 0.15 (s, 12 H), 0.9 (br s, 21 H), 1.15 (s, 3 H), 1.2–2.6 (m, 6 H), 4.2 (m, 2 H); MS (70 eV), *m/e* (rel intensity) 408 (12), 393 (11), 351 (6), 277 (11), 75 (35), 73 (100), 69 (30), 61 (34).

A sample of **24** was also obtained by GLC and displayed the following properties: IR (CCl_4) 1720, 1620 cm^{-1}; ^1H NMR (CCl_4) δ 0.15 (s, 6 H), 0.9 (s, 12 H), 1.3 (s, 3 H), 1.4–2.8 (m, 8 H), 4.2–4.3 (m, 1 H); MS (70 eV), *m/e* (rel intensity) 294 (30), 279 (15), 251 (5), 237 (12), 223 (16), 75 (100), 73 (90).

Preparation of Monosilyl Ether 23. To a solution of LDA (1.1 mmol) in 10 mL of THF at −78 °C was added a solution of 180 mg of **1** (1.0 mmol) in 10 mL of THF. The resulting mixture was stirred for 20 min, warmed to 0 °C (the enolate salt precipitates), and then combined with 4 mL of HMPA to give a clear light-yellow solution. This enolate solution was quenched at 0 °C by addition of 243 mg of *tert*-butyldimethylchlorosilane (1.5 mmol) in 5 mL of THF. In a second experiment, the enolate solution was refluxed for 4 h prior to quenching, and the results were the same. Workup of the reaction mixture by the previously described procedure gave, after distillation (100 °C, 10^{-3} torr), 278 mg of a colorless solid (95%) which proved to be **23** contaminated with ca. 1% **24**. A sample of **23** obtained by GLC (5% PDEAS, 160 °C) had the following properties: mp 58–60 °C; IR (CCl_4) 1740, 1645 cm^{-1}; ^1H NMR (CCl_4) δ 0.15 (s, 6 H), 0.9–1.1 (overlapping s, 15 H), 1.2–1.5 (m, 8 H), 4.3 (t, 1 H); MS (70 eV), *m/e* (rel intensity) 294 (26), 279 (20), 237 (38), 145 (37), 75 (100), 73 (78), 60 (53).

Preparation of Benzylidene Adduct 26. A mixture of 180 mg **1** (1 mmol), 400 mg of benzaldehyde (2.5 mmol), and 40 mg of sodium hydroxide in 20 mL of 1:1 water–ethanol was refluxed for 40 h. The cooled reaction mixture was filtered and the solid product washed with aqueous ethanol. Recrystallization of the crude **26** from ethyl acetate–petroleum ether gave 300 mg (85%) of **26**: mp 163–166 °C; IR (CCl_4) 1720, 1695, 1630, and 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.2 (br s, 6 H), 1.4–3.6 (m, 6 H), 7.2–7.5 (m, 12 H); MS (70 eV), *m/e* (rel intensity) 356 (40), 341 (28), 314 (31), 313 (36), 226 (70), 199 (100), 116 (97).

Preparation of Benzylidene Adduct 27. A mixture of 144 mg of **1** (0.8 mmol), 96 mg of benzaldehyde (0.9 mmol), and 36 mg of sodium hydroxide in 25 mL of 2:3 water–glyme was refluxed for 45 h (the reaction mixture remains homogeneous throughout). After it was cooled, the reaction mixture was neutralized with aqueous hydrochloric acid and concentrated under reduced pressure. This concentrate was dissolved in a mixture of water and ether, and the aqueous portion was extracted with additional ether. The combined organic extracts were washed and dried in the usual fashion. Evaporation of the solvent gave a product mixture which was separated by preparative TLC (silica gel, 40% ethyl acetate–cyclohexane). The R_f 0.4 band yielded 58 mg (36%

based on benzaldehyde) of **26**. A band at R_f 0.28 yielded 87 mg (36%) of mono adduct **27**, and a weak band at R_f 0.17 proved to be 26 mg of recovered **1**. Compound **27** exhibited the following properties: mp 126–129 °C; IR ($CDCl_3$) 1715 and 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.15 (s, 3 H), 1.4–3.4 (m, 8 H), 7.0–7.5 (m, 6 H); MS (70 eV), m/e (rel intensity) 268 (35), 253 (12), 116 (100), 115 (35); λ_{max} (EtOH) 294 nm (ϵ 25 000).

In a parallel experiment, a mixture of 90 mg of **1** (0.5 mmol), 214 mg of **26** (0.6 mmol), and 36 mg of sodium hydroxide in 25 mL of 2:3 water–glyme was refluxed for 42 h. Workup and separation as before gave 110 mg of **26** (0.3 mmol), 101 mg of **27** (0.4 mmol), and 20 mg of **1**.

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Registry No. **1**, 62617-74-7; **2**, 71277-26-4; **3**, 71277-27-5; **4**, 71277-28-6; **5**, 71277-29-7; **6**, 71277-30-0; **7**, 60975-75-9; **8**, 71277-31-1; **9**, 71277-32-2; **10**, 71277-33-3; **11**, 71277-34-4; **12**, 71277-35-5; **13**, 71277-36-6; **14**, 71277-37-7; **15**, 71277-38-8; **17**, 62617-82-7; **19**, 61024-41-7; **20**, 71277-39-9; **21**, 71277-40-2; **23**, 71277-41-3; **24**, 71277-42-4; **25**, 71277-43-5; **26**, 71277-44-6; **27**, 71277-45-7; 2-methyl-2-ethyl-1,3-dioxolane, 126-39-6; vinyllithium, 917-57-7; *n*-butyllithium, 109-72-8; benzothiazole, 95-16-9; trimethyloxosulfonium iodide, 1774-47-6; 2-methyl-d_3-cyclohexane-1,3-dione, 71277-46-8; ethoxyacetylene, 927-80-0; allyl bromide, 106-95-6; crotyl bromide, 4784-77-4; *tert*-butyldimethylchlorosilane, 18162-48-6; benzaldehyde, 100-52-7.

Selective Catalytic Hydrogenation of Aromatic Nitro Groups in the Presence of Acetylenes. Synthesis of (3-Aminophenyl)acetylene via Hydrogenation of (3-Nitrophenyl)acetylene over Cobalt Polysulfide and Ruthenium Sulfide Catalysts

Anatoli Onopchenko,* Edward T. Sabourin, and Charles M. Selwitz

Gulf Research & Development Company, Chemicals and Minerals Division, Pittsburgh, Pennsylvania 15230

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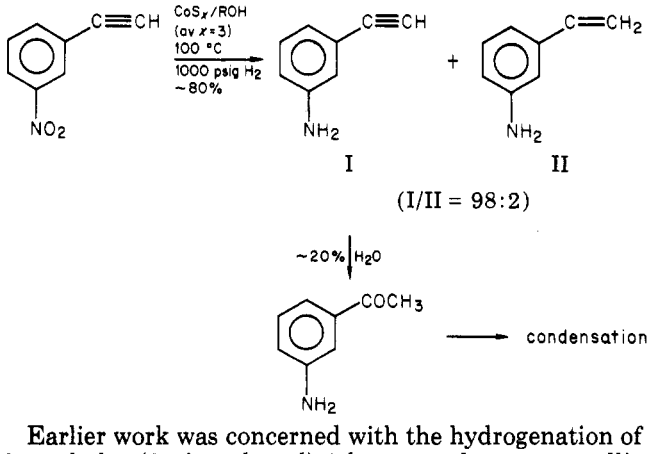
Cobalt polysulfide (CoS_x, av x = 3) and ruthenium(IV) sulfide were found to be selective for the preferential hydrogenation of aromatic nitro groups in the presence of acetylenes. Thus, (3-nitrophenyl)acetylene, 2-methyl-4-(3-nitrophenyl)-3-butyn-2-ol, and the propargyl and 3-methyl-1-hexyn-3-yl benzoates were converted to the corresponding amines in 75–85% yield. Typical reactions were carried out in isopropyl alcohol solvent at temperatures around 100 °C and hydrogen pressures of 25–70 atm. With the activated and unprotected (3-nitrophenyl)acetylene, hydration of the acetylene bond competes with the nitro group hydrogenation. Hydrogenation is interpreted to involve a chemical reduction with hydrogen sulfide, which is catalytically generated under the reaction conditions. Highly reactive substrates interfere with the regenerative cycle of the catalyst by removing sulfur species from the system, which leads to low turnover frequency. Cobalt maintains the 2^+ valency throughout its regenerative cycle, while ruthenium changes from the 4^+ to the 2^+ valency state.

In view of the interest shown in (aminophenyl)acetylenes as end-capping agents for the preparation of polyimide resins stable at high temperatures,[1-3] we wish to report on the catalytic hydrogenation of (3-nitrophenyl)acetylene and related substrates to the corresponding amines over cobalt polysulfide and ruthenium sulfide catalysts.



Earlier work was concerned with the hydrogenation of 2-methyl-4-(3-nitrophenyl)-3-butyn-2-ol over metallic ruthenium to give 2-methyl-4-(3-aminophenyl)-3-butyn-2-ol in essentially quantitative yields, which on treatment with caustic produced (3-aminophenyl)acetylene and acetone.[4] Direct hydrogenation of unprotected (3-nitrophenyl)acetylene over metallic ruthenium failed as this substrate was strongly adsorbed to the catalyst surface and led to poisoning. Recently, we succeeded in hydrogenating (3-nitrophenyl)acetylene to amine using a heterogeneous cobalt polysulfide or ruthenium sulfide catalysts.

Results and Discussion

Cobalt Polysulfide. Our work with sulfides was initiated when during catalyst screening it was observed that sulfided commercial 2.25% Ni, 1.25% Co, and 11.0% Mo on alumina catalyst reduced (3-nitrophenyl)acetylene selectively to the amine (100 °C, 1000 psig H_2) in 3% conversion. This result led us to investigate cobalt, nickel, molybdenum, and iron sulfides in more detail. On a 5–10-g scale, all of the above sulfides reduced the nitro group selectively, although conversions were less than ~12%. Spent catalysts were completely inactive on recycle. These results were rationalized by assuming that sulfides probably represent the inactive form of the catalyst and that the limited reaction observed came from impurities such as the polysulfides. A search of the literature indeed

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