(br s, 4 H), 3.83 (s, 3 H), 5.69 (br s, 2 H).

Anal. Calcd for $C_8H_9O_2N$: C, 63.56; H, 6.00. Found: C, 63.34; H, 6.04.

3-Cyclopentene-1,1-dicarbonitrile (5b).[7] To a stirred solution of 2.64 g (40.0 mmol) of malononitrile in 60 mL of dry DMF at 0 °C under nitrogen was added 0.77 g (96 mmol) of lithium hydride. After the evolution of hydrogen ceased (2 h), 4.8 mL (5.7 g, 46 mmol) of *cis*-1,4-dichloro-2-butene was added and the reaction mixture was allowed to warm to room temperature. After 60 h, the mixture was diluted with 50% ether in hexane and poured into cold water. The usual workup followed by distillation under reduced pressure gave 3.87 g (82%) of pure **5b**:[7] bp 66–68 °C (1 mm); IR 3070, 2250, 1620 cm^{-1}; ^1H NMR δ 3.19 (s, 4 H), 5.81 (s, 2 H).

Anal. Calcd for $C_7H_6N_2$: C, 71.16; H, 5.12. Found: C, 70.89; H, 5.21.

Methyl 1-Acetyl-3-cyclopentenecarboxylate (6a). Typical Procedure. To a stirred solution of 5.80 g (50.0 mmol) of methyl acetoacetate in 93 mL of dry 1,2-dimethoxyethane and 7 mL of dry hexamethylphosphoric triamide at 0 °C under nitrogen was added 0.960 g (120 mmol) of lithium hydride. After the evolution of hydrogen ceased (1 h), 6.0 mL (7.1 g, 57 mmol) of *cis*-1,4-dichloro-2-butene was added and the mixture was heated in an oil bath at 65 °C for 72 h. The resulting mixture was then cooled, diluted with 25% ether in hexane, and poured into water. The usual workup followed by distillation under reduced pressure afforded 5.50 g (65%) of **6a**, containing 3% of the corresponding vinylcyclopropane isomers **7a** and **8a**. Compound **6a**: bp 74–76 °C (1 mm); IR 3060, 1740, 1715, 1625 cm^{-1}; ^1H NMR δ 2.09 (s, 3 H), 2.97 (s, 4 H), 3.71 (s, 3 H), 5.53 (br s, 2 H).

Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.43.

Acknowledgment. We thank Professor A. Rassat and Dr. J.-L. Luche for their interest in this work, Mr. J. Revah for technical assistance, and the CNRS (LA 332 and PIRMED) for financial support.

Registry No. **1a**, 108-59-8; **1b**, 105-53-3; **2a**, 84646-68-4; **2b**, 21622-00-4; **2c**, 88326-51-6; **3**, 7686-77-3; **4a**, 17447-60-8; **4b**, 7686-78-4; **5a**, 88326-52-7; **5b**, 58920-81-3; **6a**, 88326-53-8; **6b**, 33626-80-1; **7a**, 88326-54-9; **7b**, 74379-81-0; **8a**, 88326-55-0; **8b**, 74379-82-1; **9a**, 88326-56-1; **9b**, 33626-83-4; I (Y = Z = CO_2-*t*-C_4H_9), 541-16-2; I (Y = CN, Z = CO_2CH_3), 105-34-0; I (Y = Z = CN), 109-77-3; II (Y = Z = CO_2-*t*-C_4H_9), 88326-57-2; III (Y = Z = CO_2-*t*-C_4H_9), 88326-58-3; III (Y = CN, Z = CO_2CH_3), 88326-59-4; methyl acetoacetate, 105-45-3; *cis*-1,4-dichloro-2-butene, 1476-11-5.

Efficient Syntheses of (±)-β-Cuparenone. Conjugate Addition of Organozinc Reagents

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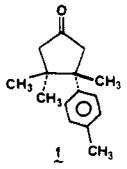
β-Cuparenone (**1**), isolated with α-cuparenone (**2**) from "mayur pankhi",[1] has been synthesized numerous times.[2]



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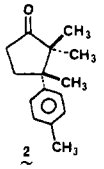
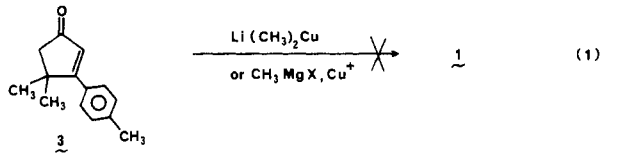


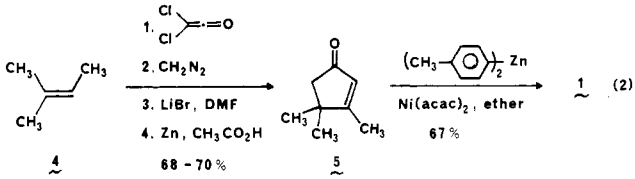
2

Successful conjugate addition-based approaches to β-cuparenone, however, have yet to be reported, which is not too surprising in light of the vicinal quaternary centers present in this molecule. In fact, Casares and Maldonado[2d] have reported 4,4-dimethyl-3-*p*-tolylcyclopentenone (**3**) to be "inert both to lithium dimethylcuprate and copper catalyzed methyl Grignard 1,4 additions", while others[3] have noted exclusive 1,2-addition in similar attempts to convert this enone to **1** (eq 1). This apparent impasse has



led to several alternative approaches; each of these, however, suffers from poor yields, a lack of selectivity, a large number of steps, or the need for difficultly accessible reagents.[2a-g] In this note we describe two straightforward and efficient conjugate addition-based syntheses of β-cuparenone that illustrate the largely unrecognized potency of organozinc reagents in this type of reaction.[4]

The known trimethylcyclopentenone **5**[5] could be easily obtained in improved overall yield through three-carbon annelation[6] of inexpensive β-isoamylene (**4**), as outlined in eq 2. The overall yield of pure **5** was reproducibly



68–70% and only a final chromatographic purification was necessary. While this enone as expected[2d,3] proved quite resistant to several copper-assisted conjugate addition techniques[4] for the introduction of a *p*-tolyl group, nickel acetylacetonate catalyzed conjugate addition of readily prepared di-*p*-tolylzinc (Li, C_7H_7Br, $ZnBr_2$, ether, ultrasonic irradiation)[4,7] was found to proceed smoothly *and produce in 67% yield (46% overall from* **4***) pure* (±)-β-*cuparenone* (**1**). Only a trace amount, if any, of the corresponding 1,2-addition product was formed in this reaction.

A second high-yield synthesis of β-cuparenone illustrates a similar application of another organozinc reagent (eq 3). Enone **3**, available in 50–60% yield from *p*-tolualdehyde,[2d,8]

(1) Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, 73. For structurally related natural products, see: Erdtman, H.; Norin, T. *Fortschr. Chem. Org. Naturst.* **1966**, *24*, 206. Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1972; pp 126–127.

(2) (a) Lansbury, P. T.; Hilfiker, F. R. *Chem. Commun.* **1969**, 619. (b) Mane, R. B.; Rao, G. S. K. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1806. (c) Leriverend, P. *Bull. Soc. Chim. Fr.* **1973**, 3498. Leriverend, M. L.; Leriverend, P. *C. R. Acad. Sci., Ser. C* **1975**, *280*, 791. See also: Leriverend, M. L.; Vazeux, M. *J. Chem. Soc., Chem. Commun.* **1982**, 866. (d) Casares, A.; Maldonado, L. A. *Synth. Commun.* **1976**, *6*, 11. (e) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *J. Org. Chem.* **1980**, *45*, 3017. (f) Jung, M. E.; Radcliffe, C. D. *Tetrahedron Lett.* **1980**, 4397. (g) Halazy, S.; Zutterman, F.; Krief, A. *Ibid.* **1982**, 4385. For syntheses of α-cuparenone, see: Greene, A. E.; Lansard, J. P.; Luche, J. L.; Petrier, C. *J. Org. Chem.* **1983**, *48*, 4763 and references cited therein.

(3) Parker, W.; Ramage, R.; Raphael, R. A. *J. Chem. Soc.* **1962**, 1558.

(4) For earlier work in this area and for related methods, see: Luche, J. L.; Petrier, C.; Lansard, J. P.; Greene, A. E. *J. Org. Chem.* **1983**, *48*, 3837 and references cited therein.

(5) (a) Sargent, H. *J. Org. Chem.* **1942**, *7*, 154. (b) Conia, J. M.; Leriverend, M. L. *Bull. Soc. Chim. Fr.* **1970**, 2981. (c) Smith, A. B., III; Toder, B. H.; Branca, S. J.; Dieter, R. K. *J. Am. Chem. Soc.* **1981**, *103*, 1996.

(6) Greene, A. E.; Deprês, J. P. *J. Am. Chem. Soc.* **1979**, *101*, 4003. Deprês, J. P.; Greene, A. E. *J. Org. Chem.* **1980**, *45*, 2036.

(7) The reagent obtained by using magnesium in place of lithium also gave **1** but in slightly lower yield.

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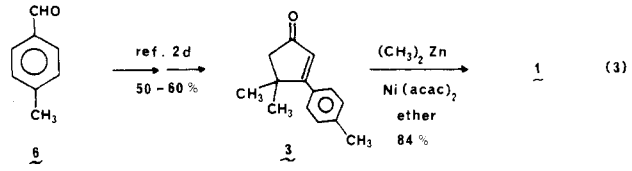

in the presence of easily prepared dimethylzinc (Li, CH_3I, $ZnBr_2$, ether, ultrasonic irradiation)[4,7] and a catalytic amount of nickel acetylacetonate also underwent smooth 1,4-conjugate addition (compare with eq 1) *to give* (±)-β-*cuparenone* (1) *in a remarkable 84% yield (42–50% overall from* 6). Again, no appreciable amount of the 1,2-addition product was formed.

These syntheses of β-cuparenone, undoubtedly the simplest and most efficient ones reported to date, indicate clearly that the nickel-catalyzed conjugate addition reaction of organozinc reagents has considerable potential in organic synthesis.

Experimental Section

Solvents were generally distilled prior to use. Ether was distilled from sodium hydride–lithium aluminum hydride, and dimethylformamide was distilled under reduced pressure from calcium hydride. Phosphorus oxychloride was distilled from potassium carbonate. Reactions were generally stirred under a nitrogen or argon atmosphere. Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdophosphoric acid in ethanol. Merck 230 silica gel 60 was employed for column chromatography. A Perkin-Elmer Model 298 or 397 spectrophotometer was used to record the IR spectra (as neat liquid films). A JEOL PMX-60 spectrometer was employed for the ^1H NMR spectra (Me_4Si as the internal reference in CCl_4 solutions). Microanalyses were performed by the Central Service of the CNRS.

2,2-Dichloro-3,3,4-trimethylcyclobutanone.[9] To a mixture of 10.0 g (ca. 155 mmol) of zinc–copper couple and 5.96 g (85.0 mmol) of 2-methyl-2-butene (4) in 75 mL of dry ether, stirred under argon at room temperature, was added over 45 min a solution of 24.44 g (134.4 g mmol) of trichloroacetyl chloride and 20.56 g (134.1 mmol) of phosphorus oxychloride in 75 mL of dry ether. The mixture was stirred overnight, after which the ether solution was separated from the excess couple and added to hexane, and the resulting mixture was partially concentrated under reduced pressure in order to precipitate the zinc chloride. The supernatant was decanted and washed successively with a cold aqueous solution of sodium bicarbonate, water, and brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure followed by distillation of the residue gave 13.35 g (87%) of known[9] 2,2-dichloro-3,3,4-trimethylcyclobutanone: bp 75 °C (2 torr); IR 1805, 1460, 1375, 1180, 870, 805, 745, 685 cm^{-1}; ^1H NMR δ 1.13 (d, J = 7 Hz, 3 H), 1.18 (s, 3 H), 1.50 (s, 3 H), 3.45 (q, J = 7 Hz, 1 H).

3,4,4-Trimethyl-2-cyclopenten-1-one (5).[5] A 2.65-g (14.6 mmol) sample of the above dichlorocyclobutanone was treated with a solution of ca. 1 g of diazomethane in 70 mL of ether and 1.5 mL of methanol at room temperature.[6] After 35 min, a small amount of acetic acid was added to consume the excess diazomethane, and the solvents were removed under reduced pressure to give 2.82 g of the crude dichlorocyclopentanone (IR 1765 cm^{-1}). A mixture of 600 mg (ca 3.1 mmol) of this material and 2.60 g (29.9 mmol) of lithium bromide in 10 mL of dimethylformamide was heated at 100 °C under argon for 2.5 h. The resultant crude monochloro ketone (IR 3070, 1715, 1615) was isolated with ether in the usual manner and then immediately stirred at 35 °C with 1.00 g (15.3 mmol) of zinc in 4.0 mL of acetic acid. After 2 h, the crude product was isolated with ether and purified by dry silica gel chromatography with ether in pentane to yield 305 mg (79%) of the known[5] enone 5: IR 3060, 1715–1685, 1620, 1270, 1240, 845 cm^{-1}; ^1H NMR δ 1.22 (s, 6 H), 2.03 (d, J = 1 Hz, 3 H), 2.16 (s, 2 H), 5.67 (m, 1 H). These values are in good agreement with those reported in the literature.[5b,c]

3,3,4-Trimethyl-4-(4-methylphenyl)cyclopentanone [(±)-β-Cuparenone, 1].[1,2] **From Enone 5.** A mixture of 347 mg (2.03 mmol) of *p*-bromotoluene, 225 mg (1.00 mmol) of zinc bromide, and 28 mg (4.0 mmol) of lithium[7] wire in 6 mL of dry ether under argon at room temperature was sonicated for 15 min.[4] A mixture of 62 mg (0.50 mmol) of enone 5 and 3 mg (0.01 mmol) of nickel acetylacetonate in 2 mL of ether was then added and the resulting mixture was magnetically stirred for 20 h at room temperature. The mixture was then added to aqueous ammonium chloride–ether and the crude product was isolated with ether in the usual manner and purified by dry silica gel chromatography with 3% ethyl acetate in hexane to give 72 mg (67%) of pure (±)-β-cuparenone (1).[1,2]

From Enone 3. A mixture of 426 mg (3.00 mmol) of methyl iodide, 338 mg (1.50 mmol) of zinc bromide, and 42 mg (6.0 mmol) of lithium[7] wire in 6 mL of dry ether under argon at room temperature was sonicated for 30 min.[4] A mixture of 100 mg (0.50 mmol) of enone 3[2d,8] and 3 mg (0.01 mmol) of nickel acetylacetonate in 2 mL of ether was then added dropwise to the mixture at 0 °C and the resulting mixture was magnetically stirred for 20 h at room temperature. The mixture was then added to aqueous ammonium chloride–ether and the crude product was isolated with ether and purified as before to afford 91 mg (84%) of pure (±)-β-cuparenone (1), identical with that prepared above. (±)-β-Cuparenone:[1,2] IR 1740, 1405, 1380, 1290, 1210, 1020, 820 cm^{-1}; ^1H NMR δ 0.70 (s, 3 H), 1.20 (s, 3 H), 1.40 (s, 3 H), 2.16 (s, 2 H), 2.30 (s, 3 H), 2.58 (AB q, J = 18 Hz, $\Delta\nu_{AB}$ = 49 Hz, 2 H), 7.16 (m, 4 H). These values are in excellent agreement with those given in the literature.[1,2] Anal. Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.56; H, 9.37.

Acknowledgment. We thank Prof. Rassat for his interest in this work and the CNRS (LA 332, ATP Chimie Fine) for financial support.

Registry No. (±)-1, 28152-91-2; 3, 58812-72-9; 4, 513-35-9; 5, 30434-65-2; (±)-2,2-dichloro-3,3,4-trimethylcyclobutanone, 88303-76-8; $Ni(acac)_2$, 3264-82-2; di-*p*-tolylzinc, 15106-88-4; dimethylzinc, 544-97-8; dichloroketene, 4591-28-0; diazomethane, 334-88-3.

(8) We are most grateful to Dr. L. A. Maldonado (UNAM, Mexico) for the spectra and a sample of enone 3. Three-carbon annelation[6] of 2-methyl-1-*p*-tolylpropene also produced 3 but in lower overall yield. For other preparations of 3, see ref 2e–f and 3.

(9) Bak, D. A.; Brady, W. T. *J. Org. Chem.* **1979**, *44*, 107.

Reactions of Nitroimidazoles with Hydrazine[1]

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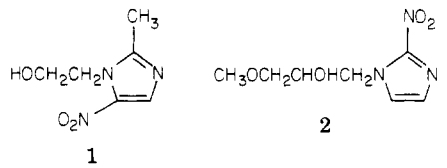
Nitroimidazoles have significant biological activity as mutagens, tumorigens, radiosensitizers, and clinically useful antiparasitic and bactericidal agents.[4] For example, metronidazole (1, 2-methyl-5-nitro-1*H*-imidazole-1-ethanol)



is effective against trichomoniasis, various forms of

(1) Presented in part at the 65th Conference of the Canadian Institute of Chemists, Toronto, June 2, 1982.

(2) Harvard Medical School; present address, Harvard School of Public Health, Boston, MA 02215.

(3) Université de Montréal.

(4) For a review of the biological activity of nitroheteroaromatic compounds, see: Grunberg, E.; Titsworth, E. H. *Annu. Rev. Microbiol.* **1973**, *27*, 317–346.

0022-3263/84/1949-0932$01.50/0