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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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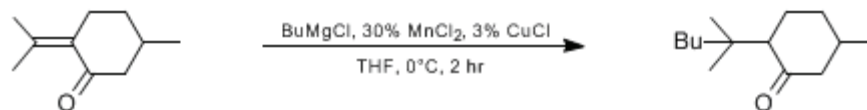
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Organic Syntheses, Coll. Vol. 9, p.328 (1998); Vol. 72, p.135 (1995).

MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMAGNESIUM REAGENTS TO α,β -ETHYLENIC KETONES: 2-(1,1-DIMETHYLPENTYL)-5-METHYLCYCLOHEXANONE FROM PULEGONE

[Cyclohexanone, 2-(1,1-dimethylpentyl)-5-methyl-]



Submitted by S. Marquais, M. Alami, and G. Cahiez¹.

Checked by Todd Gane and Stephen F. Martin.

1. Procedure

A 500-mL, three-necked, round-bottomed flask is equipped with a mechanical stirrer, 100-mL, pressure-equalizing dropping funnel, and a Claisen head fitted with a low-temperature thermometer and a nitrogen inlet (Note 1). The flask is charged with 80 mL of anhydrous tetrahydrofuran (THF, (Note 2)), 1.9 g (15 mmol) of anhydrous manganese chloride (Note 3), 0.15 g (1.5 mmol) of cuprous chloride (Note 4), 1.28 g (30 mmol) of lithium chloride (Note 5), and 7.61 g (50 mmol) of (R)-(+)-pulegone (Note 6). The mixture is stirred at room temperature until dissolution of the salts is complete (1 to 2 hr) (Note 7), then a solution of butylmagnesium chloride (58 mmol) in THF (Note 8) is added dropwise at 0°C over a 25–30 min period. Stirring is continued for 1.5 hr at 0°C. The reaction mixture is hydrolyzed by dropwise addition of 2 M hydrochloric acid (HCl, 100 mL). After addition of 80 mL of petroleum ether (35–60°C) and decantation (Note 9), the aqueous layer is extracted three times with 100-mL portions of petroleum ether (35–65°C). The combined organic layers are successively washed with 50 mL of 1 M HCl, 50 mL of a diluted ammonium chloride/ammonium hydroxide (NH₄Cl/NH₄OH) solution and 50 mL of a saturated sodium bicarbonate solution, then dried over magnesium sulfate. After filtration, the solvents are removed with a rotary evaporator (20 mm, room temperature). The product is obtained in crude form in almost quantitative yield as a 61.5:38.5 mixture of diastereoisomers, purity > 96% (Note 10). Distillation under reduced pressure affords 9.85 g of pure 2-(dimethylpentyl)-5-methylcyclohexanone (94%, (Note 12)), bp 101–105°C (3 mm).

2. Notes

1. The apparatus is flame-dried under a stream of dry nitrogen or argon. Later a slight positive nitrogen pressure is maintained with an oil bubbler throughout the reaction.
2. THF is freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere.
3. Manganese chloride, 98%, was purchased from Aldrich Chemical Company, Inc., or from Janssen Chimica. It must be finely pulverized, then dried by heating at 180°–200°C (0.1 mm to 0.01 mm) for 6 hr (for example, in a vacuum oven) prior to use. The anhydrous salt is very hygroscopic and must be protected against moisture (a well-closed bottle is convenient). It can, however, be handled *very quickly* without any special precaution.
4. Pulverized cuprous chloride purchased from Aldrich Chemical Company, Inc., was used.
5. Anhydrous lithium chloride purchased from Aldrich Chemical Company, Inc., was used. It is finely pulverized, then dried by heating at 200°C (0.1 mm to 0.01 mm) for 6 hr (vacuum oven) before use. The salt is hygroscopic and must be handled *very quickly*. The reaction can be achieved by using only 1.2 equiv of lithium chloride (18 mmol) instead of 2 equiv.
6. (R)-(+)-Pulegone available from Fluka AG (puriss; 99%), was distilled before use.
7. Generally a green-brown solution is obtained; this color is primarily due to the presence of the copper salt. However, the rate of dissolution (formation of the ate-complex MnCl₄Li₂) is very dependent on both the grain size of the two salts (MnCl₂ and LiCl) and on their purity. When unpulverized Aldrich or

Janssen material is used it is necessary to stir for at least 4 hr to obtain complete dissolution. On the other hand, with finely pulverized anhydrous manganese chloride obtained by drying an analytical grade manganese chloride tetrahydrate (e.g., manganese chloride tetrahydrate p.a., Janssen Chimica), it is possible to obtain complete dissolution after only 5 to 10 min. Moreover, formation of the ate-complex is exothermic.

8. THF solutions of butylmagnesium chloride purchased from Aldrich Chemical Company, Inc., or, preferably, freshly prepared from butyl chloride and magnesium under a nitrogen atmosphere (Note 11), were used. They were standardized immediately before use according to the titration procedure of Watson and Eastham² (see also (Note 6), Gall, M.; House, H. O. *Org. Synth., Coll. Vol. VI* 1988, 121). During addition of the butylmagnesium chloride solution (about 1.5 M) a brownish color appears, indicating the formation of the intermediate organomanganese reagent. Magnesium-manganese exchange occurs instantaneously.

9. Metallic copper can be filtered off (on Celite) before decantation.

10. Purity was determined by capillary GC analysis, OV-1, 25 m × 0.33 mm i.d., 0.5 μm film thickness.

11. To prepare a THF solution of butylmagnesium chloride from butyl chloride, the procedure described by Olah and Arvanaghi (Olah, G. A.; Arvanaghi, M. *Org. Synth., Coll. Vol. VII* 1990, 451) for the preparation of 2-phenylethylmagnesium chloride (PhCH₂CH₂MgCl) is convenient. However one should adjust the addition rate of the THF solution of butyl chloride to keep the temperature of the reaction mixture between 40°C to 45°C, then stir for 6 hr at this temperature.

12. Yields of 92 to 95% were obtained on several runs. The spectra are as follows: ¹³C NMR (CDCl₃) δ (the values separated by a slash correspond to the diastereoisomers): 14.20, 19.45/22.40, 23.60, 24.60/24.95, 25.05/25.25, 26.05, 24.15/28.25, 31.50/34.05, 34.60/34.90, 32.35/36.45, 40.35/40.55, 50.50/52.55, 57.25/57.30, 212.25/213.20; IR (neat) cm⁻¹: 1710.

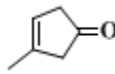
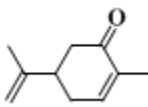
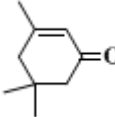
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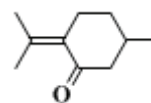
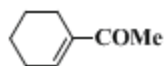
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Manganese-copper-catalyzed conjugate addition of organomagnesium reagents to α,β-enones is a general synthetic method. Table I shows that the reaction can be successfully performed even with enones of low reactivity. 30% Manganese chloride is necessary to obtain good yields. In most cases, however, 0.1% cuprous chloride is sufficient.³

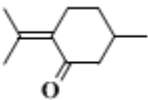
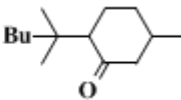
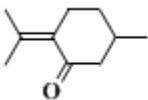
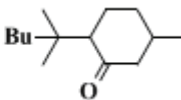
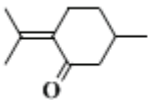
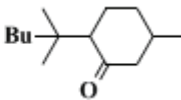
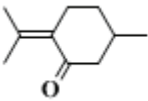
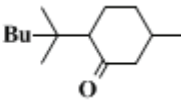
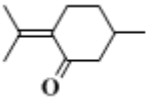
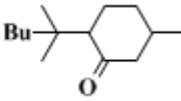
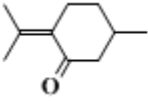
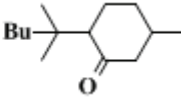
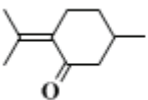
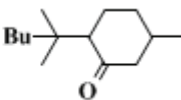
TABLE I
MANGANESE-COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMAGNESIUM CHLORIDES TO α,β-ETHYLENIC KETONES IN THF AT 0°C

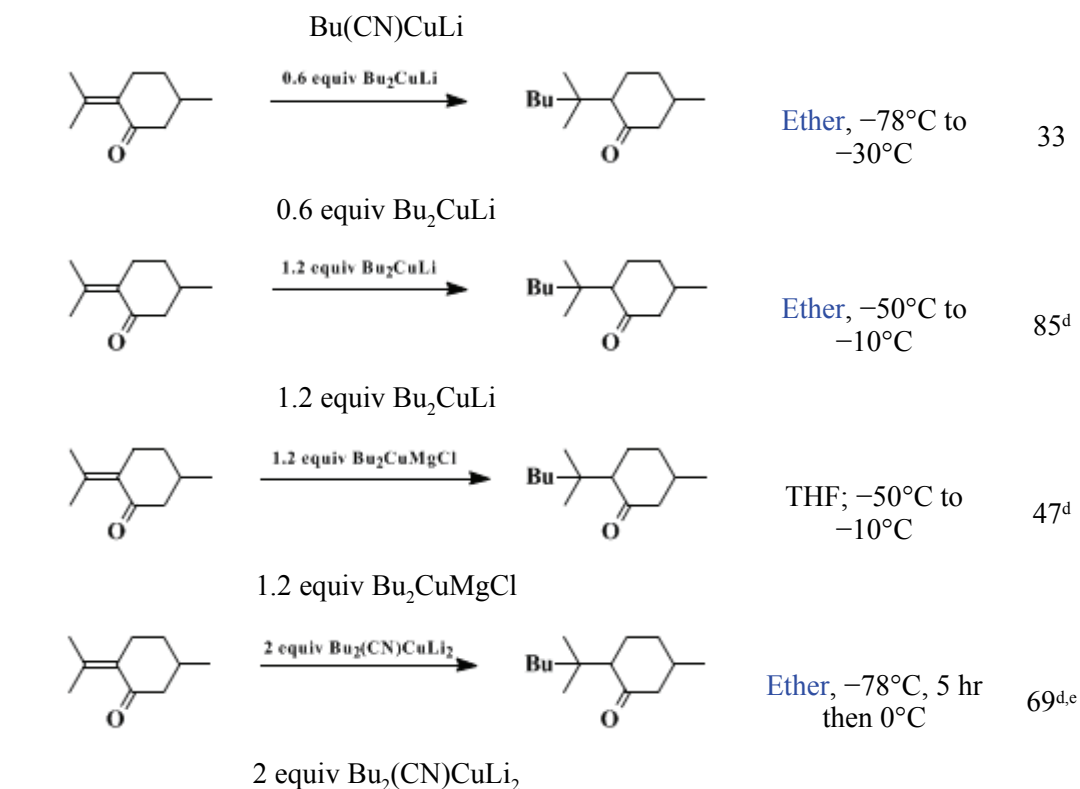
$\begin{array}{c} R^1 \\ \diagdown \\ C=C \\ \diagup \\ R^2 \end{array} \begin{array}{c} CO-R^4 \\ \diagdown \\ C \\ \diagup \\ R^3 \end{array}$ α-Enone	$\xrightarrow[\text{THF, 0°C, 30 min to 2 hr}]{\text{BuMgCl, 30\% MnCl}_2, 3\% \text{ CuCl}}$ $\begin{array}{c} R^1 \\ \diagdown \\ C \\ \diagup \\ R^2 \end{array} \begin{array}{c} CO-R^4 \\ \diagdown \\ C \\ \diagup \\ R^3 \end{array}$	Isolated Yield %	α-Enone	Isolated Yield %
Me ₂ C=CHCOMe		94		81
		87		93
		87		94



This manganese-copper-catalyzed conjugate addition reaction compares favorably with the classical copper-catalyzed reaction. The two reactions are easily and similarly carried out under mild conditions, but the first one gives higher yields. This difference, already observed in the case of β -monosubstituted α,β -ethylenic ketones, is especially noticeable with β,β -disubstituted or α,β,β -trisubstituted α,β -ethylenic ketones which are known to be less reactive.⁴ Thus, in the case of the title compound, the manganese-copper catalyzed reaction is clearly superior (see Table II).

TABLE II
CONJUGATE ADDITION OF BU-METAL COMPOUNDS TO PULEGONE

	$\xrightarrow{\text{Bu-Metal}}$		Reaction Conditions	Isolated Yield (%) ^a
	Bu-Metal			
	$\xrightarrow{\text{BuMgCl}}$		30% MnCl ₂ -3% CuCl THF, 0°C, 2 hr	94
	BuMgCl			
	$\xrightarrow{\text{BuMnCl}}$		3% CuCl; THF, 0°C, 1 hr	95
	BuMnCl			
	$\xrightarrow{\text{BuMgCl}}$		5% CuCl; THF, 0°C	51 ^b
	BuMgCl			
	$\xrightarrow{\text{BuCu}}$		Ether-Me ₂ S, -50°C to -10°C	43 ^c
	BuCu			
	$\xrightarrow{\text{BuCu}}$		1.1 equiv Me ₃ SiCl; ether, -10°C	70 ^c
	BuCu			
	$\xrightarrow{\text{Bu(CN)CuLi}}$		Ether, -50°C to -10°C	13



(a) All reactions have been performed on a 30-mmol scale. (b) Conjugate addition of copper-catalyzed butylmagnesium halide to [pulegone](#) gives a better yield in THF than in [ether](#). (c) BuCu from CuBr-Me₂S. (d) Yield based on the starting enone. (e) There is some 1,2-addition.

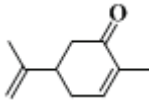
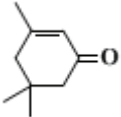
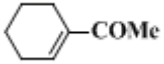
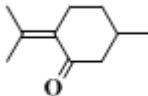
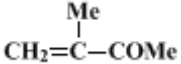
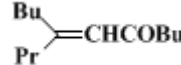
A comparison with various organocopper or cuprate reagents is also favorable since the procedure described here gives higher yields. In addition, the reaction is simpler and more economic, since it is performed at 0°C, using only 1 equiv of organometallic reagent, and no special additive such as HMPA, Bu₃P, BF₃-Et₂O or Me₃SiCl is required. (See ref. ³ for a comparison with the case of the [mesityl oxide](#).)

[Manganese chloride](#) is inexpensive and the work-up is easier with [manganese](#) than with [copper](#). This is an advantage, especially for large-scale preparations.

The procedure described here is a variant of the copper-catalyzed conjugate-addition of organomanganese reagents to α,β -ethylenic ketones. Thus, alkyl, alkenyl, or arylmanganese [chloride](#) reagents react with a vast array of α,β -ethylenic ketones in THF³ and in the presence of [copper chloride](#) to give 1,4-addition products in high yields (see Table III).

Table III
COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMANGANESE CHLORIDES,^a RMnCl
ETHYLENIC KETONES IN THF AT 0°C

	$\xrightarrow[\text{THF, } 0^\circ\text{C, 2 to 4 hr}]{\text{RMnCl, 5\% CuCl}}$		R	Isolated Yield %	
α -Enone					
			Bu	95	

Ph Me ₂ C=CH	94 92	Bu	90
	Bu	98	
 CH ₂ =CHCOMe	Bu	86 ^b	 Me ₂ C=CHCOC ₇ H ₁₅
 C ₇ H ₁₅ PrCH=CH	Bu	94	
Bu	90		Ph
PentCH=CHCOMe Me ₂ C=CH	Me 81	85	Bu

(a) Unless otherwise stated 1.05 equiv of RMnCl was used. Organomanganese reagents RMnCl were prepared from RLi or RMgX (X = Cl, Br, I). (b) 1.5 equiv of BuMnCl was used. With 1.05 equiv of BuMnCl the yield drops to 77%. (c) The reaction was performed in the presence of 1.2 equiv of Me to trap the intermediate enolate to prevent its addition to the starting methyl vinyl ketone (Michael or aldol condensation). A mixture THF/AcOEt 50:50 was used as solvent. (d) A mixture THF/AcOI 50:50 was used as solvent (an 82% yield was obtained in THF alone).

The scope of the reaction has been successfully extended to α,β -ethylenic aldehydes,⁵ esters,⁶ and amides⁷ as well as to α,β -acetylenic ketones⁸ (see Table IV). With esters, the reaction must be performed in the presence of chlorotrimethylsilane (Me₃SiCl) to avoid the Claisen reaction by trapping the intermediate enolate. In most cases the organomanganese procedure is simpler and more efficient than the organocopper procedure.

TABLE IV
COPPER-CATALYZED CONJUGATE ADDITION OF ORGANOMANGANESE CHLORIDES, RMnCl, TO α,β -UNSATURATED CARBONYL SUBSTRATES IN THF

α,β -Unsaturated Carbonyl Substrates	RMnCl	Yield (%) of 1,4-Addition Product
Me ₂ C=CHCHO	C ₇ H ₁₅ MnCl	80 ^a
MeCH=CHCOOEt	i-PrMnCl	96 ^b
MeCH=CHCONEt ₂	BuMnCl	87 ^b
C ₅ H ₁₁ C \equiv CCOBu	BuMnCl	79 ^c
Me ₂ C=C(COOEt) ₂	PrCH=CH	92 ^d
Me ₂ C=C(COOEt) ₂	Ph	87 ^e

(a) 3% CuCl, 1.2 equiv Me₃SiCl, -30°C. (b) 3% CuCl, 1.2 equiv Me₃SiCl, 0°C. (c) 3% CuCl, -20°C. (d) 3% CuCl, 0°C to 20°C. (e) Without CuCl, 20°C.

Good yields of 1,4-addition products have also been obtained with alkylidene malonate esters which generally react with organomanganese reagents in the absence of copper salts⁹ (see Table IV).

In conclusion, copper-manganese-catalyzed organomagnesium reagents and copper-catalyzed organomanganese reagents are a simple, efficient, and economic alternative to copper-catalyzed organomagnesium reagents and especially to organocopper or cuprate reagents for conjugate addition reactions to α,β -unsaturated carbonyl compounds.

Organomanganese reagents have also been used to prepare numerous simple or functionalized ketones in high yields.¹⁰ They can be also used to carry out in high yields, at room temperature, various chemoselective 1,2-addition reactions, for example to keto aldehydes.¹¹

References and Notes

1. Ecole Supérieure de Chimie Organique et Minérale (ESCOM), Département de Chimie, 13, Boulevard de l'Hautil, F-95092 Cergy-Pontoise, France.
2. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.
3. Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 3541.
4. Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. *J. Org. Chem.* **1982**, *47*, 119.
5. Cahiez, G.; Alami, M. *Tetrahedron Lett.* **1989**, *30*, 7365.
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10. Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 7369 and references therein.
11. Cahiez, G.; Figadère, B. *Tetrahedron Lett.* **1986**, *27*, 4445.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

sodium benzophenone ketyl

hydrochloric acid,
HCl (7647-01-0)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

magnesium (7439-95-4)

nitrogen (7727-37-9)

copper (7440-50-8)

Butyl chloride (109-69-3)

cuprous chloride (7758-89-6)

copper chloride (7758-89-6)

ammonium hydroxide (1336-21-6)

Mesityl oxide (141-79-7)

chloride

magnesium sulfate (7487-88-9)

manganese (7439-96-5)

Tetrahydrofuran (109-99-9)

methyl vinyl ketone (78-94-4)

Lithium chloride (7447-41-8)

argon (7440-37-1)

CHLOROTRIMETHYLSILANE (75-77-4)

pulegone (89-82-7)

Butylmagnesium chloride (693-04-9)

2-(1,1-DIMETHYLPENTYL)-5-METHYL-CYCLOHEXANONE,
2-(dimethylpentyl)-5-methylcyclohexanone,
Cyclohexanone, 2-(1,1-dimethylpentyl)-5-methyl- (109539-17-5)

manganese chloride (7773-01-5)

(R)-(+)-pulegone

manganese chloride tetrahydrate

2-phenylethylmagnesium chloride