Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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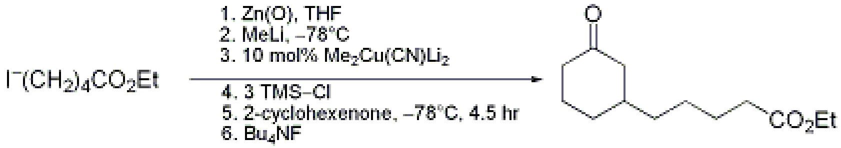
COPPER-CATALYZED CONJUGATE ADDITION OF FUNCTIONALIZED ORGANOZINC REAGENTS TO α,β-UNSATURATED KETONES: ETHYL 5-(3-OXOCYCLOHEXYL) PENTANOATE

[Pentanoic acid, 5-(3-oxocyclohexyl)-, ethyl ester]



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Checked by Ying Huang and David J. Hart.

1. Procedure

Ethyl 5-(3-oxocyclohexyl)pentanoate . A 50-mL, round-bottomed flask equipped with a magnetic stir bar and a septum, is cooled under a stream of argon (Note 1), and charged with 3.0 g of zinc powder (46 mmol , (Note 2)), followed by 16 mL of tetrahydrofuran (THF) (Note 3). To this mixture is added 155 µL of 1,2-dibromoethane (338 mg, 1.8 mmol, (Note 4)), and the stirred slurry is heated to ca. 65°C (Note 5) for 1 min using a heat gun. The flask is then placed in a water bath (ca. 23°C) with continued magnetic stirring. After one minute, 155 µL of chlorotrimethylsilane (TMS-Cl) (133 mg, 1.2 mmol, (Note 6)) is added, and the slurry is stirred for 15 min (Note 7). The flask is wrapped in aluminum foil and 6.7 mL of neat ethyl 5-iodovalerate (10.24 g, 40.0 mmol, (Note 8)) is slowly added dropwise over 10 min. The flask is placed in a 35°C oil bath and stirred overnight. Initially, the reaction is very exothermic, and THF can be seen slowly refluxing around the neck of the round-bottomed flask. Dry Ice is used to cool the neck of the flask to avoid leaching the septum with THF. Twelve hours later (overnight, (Note 9)), when the reaction is judged complete by TLC (Note 10), the aluminum foil and the oil bath are removed. The presence of a white "dust" that never quite settles is noted. The reaction is allowed to cool to room temperature and 20 mL of THF is added to the stirred slurry. Stirring is stopped, the solids are allowed to settle as much as possible (*vida supra*), and the THF solution of the alkylzinc iodide is transferred via canula to a clean, dry 250-mL, round-bottomed flask equipped with a stir bar and a septum. Two additional washes of the remaining excess zinc with THF (29 mL each) are carried out to ensure complete transfer and proper dilution of the alkylzinc iodide (0.38 M). The solution is cooled to −78°C, and methyllithium (MeLi) in ether (26 mL, 36 mmol, (Note 11)) is added dropwise over 15 min.

While the alkylzinc is being formed, a 25-mL, round-bottomed flask, equipped with a stir bar and septum is cooled under argon, and charged with 178.9 mg of copper(I) cyanide (CuCN) (2.0 mmol, (Note 12)), followed by 10 mL of THF . The mixture is cooled to −78°C and MeLi in ether (2.86 mL, 4.0 mmol, (Note 11)) is added slowly over 10 min. When the addition of MeLi is complete, the slurry is gently warmed until the reaction mixture becomes homogeneous at which point it is recooled to −78°C. With both solutions at −78°C, the higher-order dimethylcyanocuprate is transferred via canula to the alkylzinc reagent. After 5 min at −78°C, 7.77 mL of neat TMS-Cl (6.65 g, 61.3 mmol, (Note 6)) is added dropwise over 10 min, followed by 10 min of stirring. Finally, 2.02 mL of neat 2-cyclohexen-1-one (2.01 g, 20.9 mmol, (Note 13)) is added dropwise over 15 min via syringe. After 4.5 hr, the reaction is complete as determined by TLC (Note 14) and it is quenched by pouring the reaction mixture into 200 mL of pH 7 buffer (Note 15) and 200 mL of diethyl ether (Et$_2$O) in a 1-L separatory funnel. An additional 25 mL of ether is used to complete the transfer of the reaction mixture to the separatory funnel. The aqueous layer is further extracted with an additional 50 mL of ether . The combined organic layers are shaken for 5 min with 50 mL of 1 M tetrabutylammonium fluoride (TBAF) in THF (Note 16), followed by three washes with 100 mL of brine . The combined organic phases are dried over anhydrous magnesium sulfate ($MgSO_4$). Gravity filtration, concentration under reduced pressure, and flash chromatography on silica gel (Note 17) using 10:1 (petroleum ether : ethyl acetate) affords 4.02 g of slightly contaminated product (Note 18). Warming this material at 50°C on a Kugelrohr apparatus for 2 hr at 0.5 mm affords 3.46 g (73%) of pure 5-(3-oxocyclohexyl)pentanoate as a pale-yellow liquid (Note 19).

2. Notes

1. All reactions are carried out under an inert atmosphere of argon (Linde prepurified grade) using oven-dried glassware, syringes, needles and canulas (at least 8 hr, in an oven at 120°C), employing standard syringe/septa techniques. After dry solids are added to reaction flasks by briefly removing the septum, argon is passed through the flask to purge it of atmospheric gases for ca. 15 min.
2. Zinc, powder, −100 mesh, 99.998%, was purchased from the Aldrich Chemical Company, Inc. , and quickly weighed out on a bench-top balance.
3. Tetrahydrofuran is freshly distilled from sodium benzophenone ketyl under a nitrogen atmosphere.
4. 1,2-Dibromoethane, 99+%, purchased from the Aldrich Chemical Company, Inc. , was used as received.
5. Gentle refluxing is seen on the sides of the round-bottomed flask, at which time the hot air of the heat gun is directed away from the flask, until the refluxing stops.
6. Chlorotrimethylsilane, redistilled, 99+%, was purchased from the Aldrich Chemical Company, Inc. , distilled from calcium hydride (CaH_2) under argon, and stored under a Teflon-taped polyethylene cap.
7. Gas evolution is occasionally observed at this point.
8. Ethyl 5-iodovalerate is prepared from commercially available ethyl 5-bromovalerate (Aldrich Chemical Company, Inc.) through a Finkelstein reaction in acetone with sodium iodide . To 12.5 g (59.5 mmol) of ethyl 5-bromovalerate in 150 mL of dry acetone is added a total of 44.8 g (299 mmol) of solid sodium iodide in three equal portions. The solution is warmed under reflux (oil bath temperature of 67° C) for 40 hr and then cooled to room temperature. The mixture is partitioned between 200 mL of diethyl ether and 200 mL of water. The aqueous phase is extracted with three 100-mL portions of ether . The combined organic phases are washed with 50 mL of 10% aqueous sodium bisulfite , 50 mL of brine , dried ($MgSO_4$), and concentrated under reduced pressure. The residual oil is distilled (170-180°C/0.5 mm) to give 14.3 g (94%) of the iodide: ^1H NMR ($CDCl_3$) δ: 1.24 (t, 3 H, J = 7), 1.72 (m, 2 H), 1.85 (m, 2 H), 2.31 (t, 2 H, J = 7), 3.17 (t, 2 H, J = 7), 4.12 (q, 2 H, J = 7) . The product is stored over freshly cut pieces of copper wire to ensure dryness and long-term purity.
9. The reaction time for complete zinc insertion is significantly less than 12 hr (usually 1-4 hr), but additional time at 35°C did not diminish the quality of the zinc reagent (unless the zinc reagent contained an enolizable ketone group). An overnight reaction time, for the zinc oxidative insertion, was used solely for convenience.
10. The starting iodide is no longer seen by TLC under UV-light, $R_f = 0.70$ in 10:1 petroleum ether : ethyl acetate on pre-coated silica gel 60 F_{254} plates (EMx Science), 0.25-mm layer thickness. Further evidence of complete zinc insertion is seen in the clumping of the excess zinc into small, shiny metallic balls.
11. MeLi in ether (1.4 M, low halide) was purchased from the Aldrich Chemical Company, Inc. and titered against distilled 2-pentanol , with 1,10-phenanthroline as indicator.
12. Copper(I) cyanide, 99%, purchased from the Aldrich Chemical Company, Inc. , was used as received and stored in an Abderhalden desiccator over potassium hydroxide . It is quickly weighed out on a bench-top balance.
13. 2-Cyclohexen-1-one, 95+%, was purchased from the Aldrich Chemical Company, Inc. and distilled prior to use.
14. Only a trace of 2-cyclohexen-1-one, ($R_f = 0.16$ in 10:1 petroleum ether : ethyl acetate) could be seen (see (Note 10) for type of TLC plates used). A new spot at $R_f = 0.50$ appeared corresponding to the TMS enol ether product if the TLC plate was eluted immediately after spotting. If, however, the TLC plate was not eluted for minutes after spotting, significant cleavage of the TMS enol ether occurred on the silica gel, allowing observation of the final ketone product at $R_f = 0.11$.
15. Aqueous pH 7 buffer was purchased from Fisher Scientific Company. An acidic workup should be avoided so as to prevent the formation of HCN.
16. 1 M TBAF in THF (5% water) was purchased from the Aldrich Chemical Company, Inc. , and used as received.

17. Flash chromatography was performed on ICN BioMedical's, ICN Silica, 32-63, 60 Å, using ca. 150 g of silica in a 2-in diameter column.

18. Impurities consisted of a small amount of 2-cyclohexen-1-one and another impurity that displayed a triplet at δ 0.9 in its NMR spectrum. These volatile impurities could be removed by warming the crude product under reduced pressure for several hours.

19. The spectral data are as follows: ^{1}H NMR δ:1.22 (t, 3 H, J = 7, CH_3), 1.31 (m, 5 H), 1.54-2.04 (m, 6 H), 2.19-2.40 (m, 4 H), 2.24 (t, 2 H, J = 7, CH_2CO_2), 4.07 (q, 2 H, J = 7, OCH_2CH_3) ; ^{13}C NMR δ: 14.1 (q), 24.8 (t), 26.0 (t), 26.1 (t), 31.1 (t), 34.1 (t), 36.1 (t), 38.3 (d), 41.3 (t), 47.9 (t), 60.1 (t), 173.4 (s), 211.6 (s) ; IR (neat) cm^{-1}: 2933, 2861, 1734, 1188 ; MS (El), m/e (rel. intensity) 226 (M^+, 2), 181 (7), 135 (5), 101 (7), 98 (8), 97 (100), 82 (6), 81 (7), 67 (7), 55 (16) ; HRMS (El) calcd for [M^+, $C_{13}H_{22}O_3$] 226.1563; found: 226.1569 .

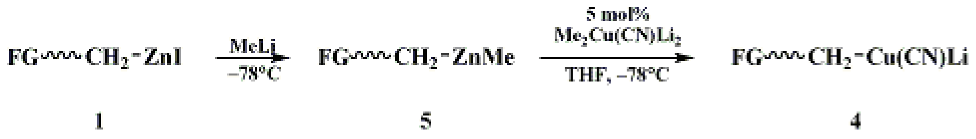
Waste Disposal Information

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

3. Discussion

Organocopper chemistry[2] has steadily evolved so that it now includes the preparation and coupling reactions of cuprates bearing ligands that contain electrophilic centers.[3,4,5] Functional groups (FG) such as esters, ketones, nitriles, and halides can be incorporated into lower order cyanocuprates, **2**, via metathesis between precursor organozinc halides **1** and CuCN.[3] Use of zinc in this scheme allows for generation of organometallics such as **1** that would otherwise be difficult to prepare in the corresponding lithiated form (**3**) en route to lithiocyanocuprates **4**.[6] The reactivity patterns of cuprates **2** reflect the importance of the gegenion in Michael-type additions, for while their lithio counterparts **4** react with most enones quickly at low temperatures,[2] zinc halide cuprates are relatively sluggish.[7] Most significantly, greater than stoichiometric amounts of copper are normally required. The procedure described here[8] addresses these shortcomings, as well as those of related procedures which, e.g., rely on excesses of hexamethyl phosphoramide (HMPA).[9]

The key feature that allows the cuprate-catalyzed procedure described is the facility with which ligands on zinc and copper undergo exchange.[8] Thus, when zinc halide **1** is converted to the mixed zinc species **5** and then exposed to 5 mol% $Me_2Cu(CN)Li_2$ at low temperatures, catalytic amounts of FG∼$CH_2Cu(CN)Li$ (**4**) are produced via transmetallation (along with Me_3ZnLi).[10] In the presence of TMS-Cl as an activating additive,[11] **4** delivers the functionalized ligand to the β-position of an enone (Scheme 1). The intermediate enolate is trapped by the Me_3SiCl present, the Si-O bond being cleaved on workup with fluoride ion to arrive at the product ketone. As anticipated from earlier studies,[12] **4** is the most reactive among several species in solution.[10] The overall process is made catalytic in Cu(I) by virtue of formation of a silyl enol ether, thereby releasing the metal for recycling.



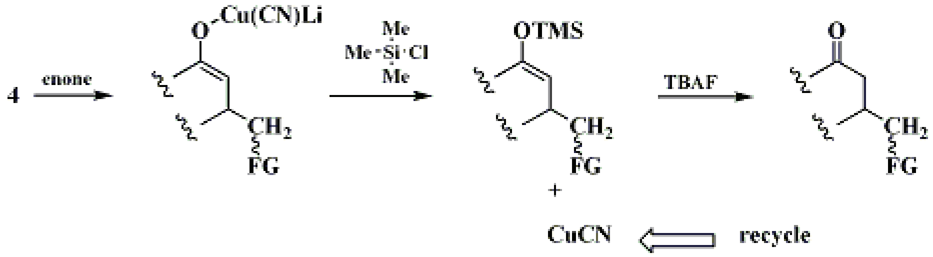
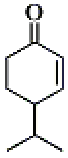
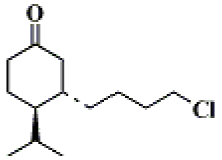
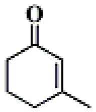
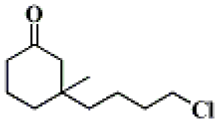
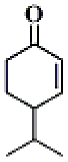
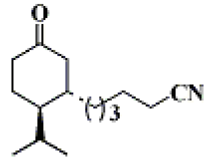
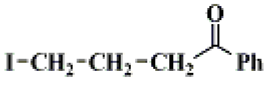
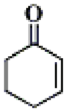
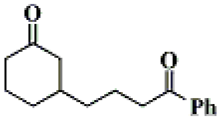
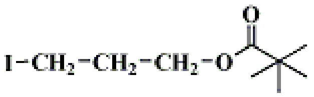
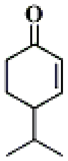
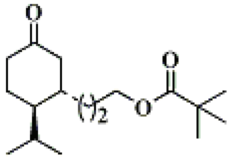
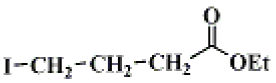
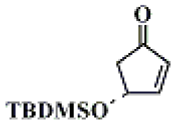
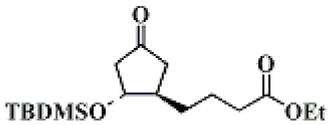
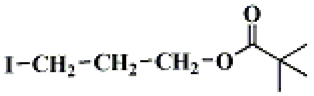
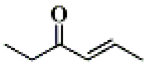
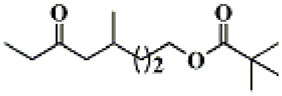
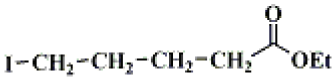
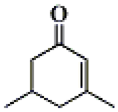
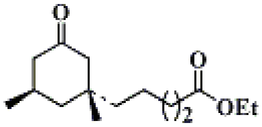
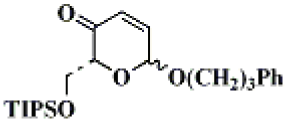
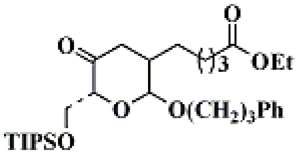
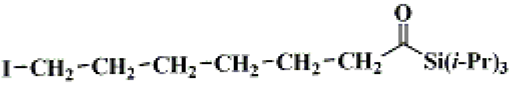
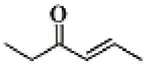
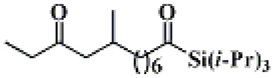


Table I[8] highlights several other examples that demonstrate the scope of the coupling process. Cases of simple ethyl esters (entries 1-3), pivaloates (entries 4,5), chlorides (entries 6,7), a nitrile (entry 8), and a ketone (entry 9), all participate readily. Note the transfer of an acyl silane[13] (entry 10), and the fact that these couplings are effected under very mild conditions and afford good isolated yields.

Table I. Cuprate-Catalyzed 1,4-Additions of Organozinc Reagents[8]

Entry	Iodide	Enone	Functionalized Product
1	$I\text{-}(CH_2)_4Cl$		
2	$I\text{-}(CH_2)_4Cl$		
3	$I\text{-}(CH_2)_5CN$		
4	 $I{-}CH_2{-}CH_2{-}CH_2{-}C(=O)Ph$ "		
5			
6	 $I{-}CH_2{-}CH_2{-}CH_2{-}C(=O)OEt$		
7			

8	 $I-CH_2-CH_2-CH_2-CH_2-C(O)OEt$		
9	 $I-CH_2-CH_2-CH_2-CH_2-C(O)OEt$		
10	 $I-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-C(O)Si(i\text{-}Pr)_3$		

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

Zinc (8,9); (7440-66-6)

1,2-Dibromoethane:
Ethane, 1,2-dibromo- (8,9); (106-93-4)

Chlorotrimethylsilane:
Silane, chlorotrimethyl- (8,9); (75-77-4)

Ethyl 5-iodovalerate:
Pentanoic acid, 5-iodo-, ethyl ester (9); (41302-32-3)

Methyllithium:
Lithium, methyl- (8,9); (917-54-4)

Copper(I) cyanide:
Copper cyanide (8,9); (544-92-3)

2-Cyclohexen-1-one HIGHLY TOXIC: (8,9); (930-68-7)

Tetrabutylammonium fluoride:
Ammonium, tetrabutyl-, fluoride (8);
1-Butanaminium, N,N,N-tributyl-, fluoride (9); (429-41-4)

Ethyl 5-bromovalerate:
Valeric acid, 5-bromo-, ethyl ester (8);
Pentanoic acid, 5-bromo-, ethyl ester (9); (14660-52-7)

Sodium iodide (8,9); (7681-82-5)

2-Pentanol (8,9); (6032-29-7)

1,10-Phenanthroline (8,9); (66-71-7)