Notes

Synthesis of 2-Acyl-1,4-diketones via the Diacylation of α,β-Unsaturated Ketones

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Received April 22, 1998

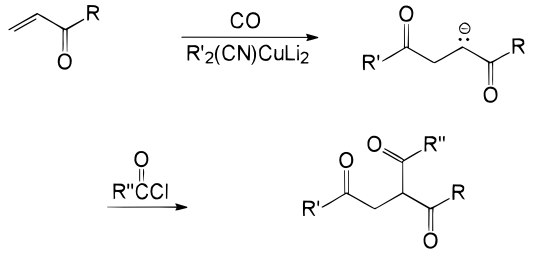
Summary: The first example of a diacylation of the carbon−carbon double bond in α,β-unsaturated ketones is described. The reaction of acylcyanocuprate reagents with α,β-unsaturated ketones, followed by C-acylation, produces 2-acyl-1,4-diketones in good yields (50−89%).

Introduction

The introduction of two carbonyl groups to the carbon−carbon double bond of α,β-unsaturated carbonyl compound provides an effective route to 2-acyl-1,4-diketones, which are useful reaction intermediates in the syntheses of cyclopentenone systems[1] as well as heterocyclic compounds.[2] It has been reported that some simple 2-acyl-1,4-diketones can be prepared by the thiazolium-salt-catalyzed addition of aldehydes to 2-acyl-conjugated enones[2a] or by the reaction of 1,3-diketones with α-haloketones,[3] 1-nitroalkenes,[1] or enamines.[2c] The scope of these reactions is limited by the fact that the structure of the product 2-acyl-1,4-diketones depends on the starting materials, 1,3-diketones.

The nucleophilic 1,4-addition of an acyl anion to conjugated enones has been of interest to organic chemists. Acyl anion intermediates generated by the addition of an organolithium or Grignard reagent to transition-metal carbon monoxide complexes such as nickel carbonyl,[4] iron carbonyl,[5] or cobalt carbonyl[6] react with α,β-unsaturated ketones to give 1,4-diketones. The acyl anion generated by reaction of an alkyl halide with $Na_2Fe(CO)_4$ also reacts with α,β-unsaturated ketones to produce 1,4-diketones.[7] Seyferth reported an efficient method for generating acyllithium by reacting alkyllithium reagents with carbon monoxide at low (−100 to −135 °C) temperature. The acyllithium generated by this method can react in situ with various electrophiles to afford acylated products.[8] The reagent reacts with conjugated enones to give the 1,2-addition product predominately.[9a] Seyferth also reported the direct nucleophilic 1,4-acylation of α,β-unsaturated carbonyl compounds using acylcuprate reagents prepared via the carbonylation of alkylcyanocuprates with carbon monoxide.[9] Lipshutz reported the 1,4-acylation of conjugated enones by allylic cuprates in the presence of carbon monoxide.[10] The 1,4-addition of organocuprate reagents to conjugated enones, followed by trapping of the enolate intermediates with various electrophiles, is one of the most useful synthetic reactions.[11−13] However, to the best of our knowledge, 1,4-acylation followed by trapping of the enolate intermediates with acid chloride has not been reported.

Scheme 1



Results and Discussion

In a continuation of our studies focused on acyl anion chemistry,[14] we found that the intermediates generated in the reaction of acylcyanocuprates with conjugated

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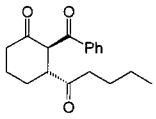
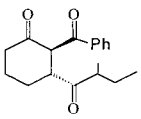
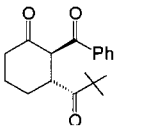
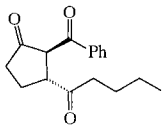
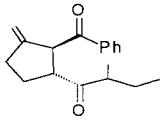
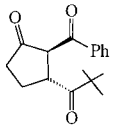
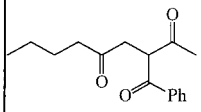
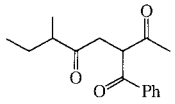
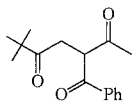
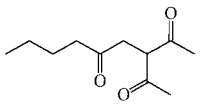
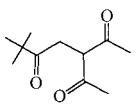
(13) The ratio of *C*- and *O*-acylated products was reported to be dependent on both the solvent and the acylating agent. See ref 12d.

S0276-7333(98)00303-3 CCC: $15.00
Publication on Web 07/18/1998

Table 1. Preparation of 2-Acyl-1,4-diketones

R′[a]	α,β-unsaturated ketones	acid chloride	reaction time[b] (h)	product[c]	yields (%)[d]
n-Bu			2		81
s-Bu			2		89
t-Bu			2		89
n-Bu			2		88
s-Bu			1		87
t-Bu			1.5		88
n-Bu			1.5		58
s-Bu			2		68
t-Bu			2		76
n-Bu[e]			2		64
t-Bu[f]			2		50

[a] R′ is the alkyl in the dialkylcyanocuprate [$R'_2(CN)CuLi_2$]. [b] Time required for 1,4-addition reaction. [c] All products characterized by ^1H NMR, ^{13}C NMR and elemental analyses. [d] Isolated yields. [e] A small quantity of the *O*-acylation product is also isolated.[13] [f] *t*-$BuC(O)CH_2CH{=}C(CH_3)OC(O)CH_3$ is formed in 40% yield.[13]

enones can be trapped by acyl chlorides to give 2-acyl-1,4-diketones. The reaction provides the first example of a diacylation of a carbon−carbon double bond of conjugated enones, Scheme 1.

Acylcyanocuprate reagents were prepared in situ via the carbonylation of dialkylcyanocuprate with carbon monoxide at −110 °C in a mixed-solvent system[9a] and then reacted with α,β-unsaturated ketones at −110 °C, followed by warming to −78 °C for 1−2 h. Subsequent reaction with acyl chlorides at −78 °C for 30 min generated the 2-acyl-1,4-diketones in good yields (50−89%). The results of the reactions of various acylcuprate reagents with α,β-unsaturated ketones and acid chlorides are summarized in Table 1. As shown, the intermediate generated by reaction of acylcuprates with acyclic enones can be trapped by either benzoyl chloride or acetyl chloride to give the corresponding triketones in good yields (50−76%). Intermediates from reactions of acylcuprate reagents with cyclic enones are trapped by benzoyl chloride to give the corresponding triketones in excellent yields. However, these intermediates react with acetyl chloride to give complex reaction mixtures. β-Substituted acyclic enones such as 4-hexen-3-one and 4-phenyl-3-buten-2-one also failed to generate the desired diacylated product, presumably due to steric interactions.

The 1,4-acylation of intermediates generated by reaction of 2-cyclohexenone with monoalkylcyanocuprates such as *s*-butylcyanocuprate and *tert*-butylcyanocuprate[9b] can also be trapped by benzoyl chloride to give the corresponding triketones. In these cases, the reaction is incomplete. This may be a consequence of the lower reactivity of monoalkylcyanocuprates compared to dialkylcyanocuprates.

The products listed in Table 1 exist predominately as triketones, although trace quantities of the corresponding enols are found in some cases. The configuration of the two acyl groups on the cyclohexyl ring is trans based on the analysis of ^{1}H NMR data. The stereochemistry of the cyclopentyl products is presumably also trans based on previously reported 1,4-addition reactions involving organocuprate reagents in which acyl halides were utilized to trap the reaction intermediates.[12c]

Conclusion

The reaction described in this paper provides a useful method for adding two carbonyl groups to the carbon−carbon double bond of α,β-unsaturated ketones. It provides an alternative synthesis for 2-acyl-1,4-diketones which might not be easily prepared from 1,3-diketones.[1−3] The reactive intermediates described in this report may also react with electrophiles such as methyl chloroformate, *N*,*N*-dialkyl chloroformate, aldehydes, and active alkyl halides. We are currently investigating these possibilities.

Experimental Section

All reagents and solvents were transferred using techniques designed to eliminate contact with air. All glassware and syringes were oven-dried for 24 h prior to use. THF and diethyl ether were distilled over sodium benzophenone ketyl. Pentane was dried and distilled over calcium hydride. *n*-Butyllithium (1.6 M in hexane), *s*-butyllithium (1.3 M in cyclohexane), *tert*-butyllithium (1.7 M in pentane), copper(I) cyanide, enones, and carboxylic acid chlorides were purchased from Aldrich Chemical Co. Copper(I) cyanide was dried under vacuum at 150 °C. Enones and carboxylic acid chlorides were purified by distillation. ^{1}H NMR and ^{13}C NMR spectra were obtained using a Bruker AC-250 (250 MHz) NMR spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

***trans*-2-Benzoyl-3-pentanoylcyclohexanone. Typical Procedure.** Di-*n*-butylcyanocuprate (2.5 mmol) was prepared under an argon atmosphere by addition of *n*-BuLi (5.0 mmol, 3.1 mL of a 1.6 M solution in hexane) to copper(I) cyanide (2.5 mmol, 0.23 g) in THF (5 mL) at −78 °C. The mixture was warmed briefly to obtain a clear solution and then maintained at −78 °C under argon.[9a] A 4:4:1 mixture of THF, diethyl ether, and pentane (75 mL) was placed in a separate three-necked, 100 mL, round-bottomed flask equipped with a magnetic stirrer, glass-enclosed thermocouple, and a fritted-glass gas dispersion tube. The mixture was cooled to −110 °C, and carbon monoxide was then bubbled through the mixture for 20 min at −110 °C. The cooled *n*-Bu_2(CN)CuLi (2.5 mmol) solution was then added slowly to the solvent mixture (by cannula) while the CO stream was continued. The resulting solution was kept at −110 °C for 20 min under a CO atmosphere, and then 2-cyclohexenone (2.5 mmol, 0.24 mL) was added via syringe. The deep orange solution was warmed to −78 °C and stirred for 2 h while maintaining a CO atmosphere. Benzoyl chloride (3.0 mmol, 0.35 mL) was then added to the reaction mixture at −78 °C. After stirring at −78 °C for 30 min under a CO atmosphere, the mixture was warmed to 0 °C and treated with 20 mL of a 1:10, by volume, mixture of concentrated NH_4OH and saturated aqueous NH_4-Cl. The product was extracted into ether (3 × 20 mL), and the combined ether layers were dried and concentrated under reduced pressure. *trans*-2-Benzoyl-3-pentanoylcyclo-hexanone (0.58 g, 81% yield) was isolated by silica gel chromotography using hexane/ethyl acetate = 8/2 (v/v) as the eluant. ^{1}H NMR ($CDCl_3$/TMS): δ 7.90−7.80 (m, 2H), 7.59−7.49 (m, 1H), 7.49−7.34 (m, 2H), 4.80 (d, 1H, J = 11 Hz), 3.65−3.50 (dt, 1H, J_1 = 3.5, J_2 = 11 Hz), 2.65−1.19 (m, 12H), 0.89 (t, 3H, J = 7.2 Hz). ^{13}C NMR($CDCl_3$): δ 210.5, 208.1, 197.7, 137.3, 133.1, 128.5, 128.3, 59.4, 52.9, 41.9, 41.3, 27.7, 26.2, 25.5, 22.3, 13.8. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.31; H, 7.82.

All other 2-acyl-1,4-diketones were prepared via the procedure outlined for *trans*-2-benzoyl-3-pentanoylcyclohexanone. The reaction time for 1,4-addition and yields of products are indicated in Table 1. The spectral characteristics and elemental analyses of these compounds are as follows.

***trans*-2-Benzoyl-3-(2-methylbutanoyl)cyclohexanone.** The ratio of diastereomers was 54:46 based on the ^{1}H NMR and ^{13}C NMR data. ^{1}H NMR ($CDCl_3$/TMS): δ 7.87 (d, 2H, J = 7.6 Hz), 7.55−7.34 (m, 3H), 4.84 (d, 0.54H, J = 11 Hz), 4.81 (d, 0.46H, J = 11 Hz), 3.74−3.56 (m, 1H), 2.81−2.61 (m, 1H), 2.56−1.16 (m, 8H), 1.08 (d, 1.6H, J = 7.1 Hz), 1.03 (d, 1.4H, J = 6.8 Hz), 0.92−0.76 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 213.5, 213.3, 208.1, 208.0, 197.5 (197.5), 137.1 (137.1), 132.7 (132.7), 128.2 (128.2), 127.9 (127.9), 58.7 (58.7), 52.6, 51.9, 46.2, 45.3, 41.4 (41.4), 27.2, 26.9, 26.0, 25.8 (25.8), 25.0, 16.5, 15.0, 11.7, 11.0. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.42; H, 7.76.

***trans*-2-Benzoyl-3-(2,2-dimethylpropanoyl)cyclohexanone.** ^{1}H NMR ($CDCl_3$/TMS): δ 7.89−7.78 (m, 2H), 7.57−7.48 (m, 1H), 7.48−7.36 (m, 2H), 4.90 (d, 1H, J = 11 Hz), 3.94 (dt, 1H, J_1 = 3.4, J_2 = 11 Hz), 2.57−1.53 (m, 6H), 1.20 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 216.0, 208.3, 197.8, 137.4, 133.1, 128.5, 128.2, 60.1, 48.2, 44.4, 41.8, 28.8, 27.1, 26.0. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.53; H, 7.81.

***trans*-2-Benzoyl-3-pentanoylcyclopentanone.** ^{1}H NMR ($CDCl_3$/TMS): δ 8.01−7.95 (m, 2H), 7.65−7.35 (m, 3H), 4.71

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(d, 1H, J = 9.4 Hz), 4.18−3.96 (m, 1H), 2.72−1.18 (m, 10H), 0.89 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$/TMS): δ 209.8, 209.6, 194.3, 136.2, 133.5, 129.5, 128.4, 59.1, 51.0, 41.2, 38.7, 25.4, 24.2, 22.1, 13.6 δ. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 75.08; H, 7.51.

***trans*-2-Benzoyl-3-(2-methylbutanoyl)cyclopentanone.** The ratio of diastereomers was 50:50 based on the ^{1}H and ^{13}C NMR data. ^{1}H NMR ($CDCl_3$/TMS): δ 8.01−7.95 (m, 2H), 7.62−7.35 (m, 3H), 4.74 (d, 1H, J = 9.4 Hz), 4.27−4.04 (m, 1H), 2.78−1.29 (m, 7H), 1.09 (d, ∼1.5 H, J = 6.8 Hz), 1.08 (d, ∼1.5 H, J = 7.0 Hz), 0.95−0.75 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 213.52, 213.46, 209.7 (209.7), 194.42, 194.36, 136.3 (136.3), 133.5 (133.5), 129.5 (129.5), 128.4 (128.4.), 59.4, 59.3, 50.3, 49.6, 47.1, 46.3, 38.7, 38.6, 26.0, 25.0, 24.5, 24.3, 16.2, 15.1, 11.7, 11.3. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.86; H, 7.41.

***trans*-2-Benzoyl-3-(2,2-dimethylpropanoyl)cyclopentanone.** ^{1}H NMR ($CDCl_3$/TMS): δ 8.02−7.93 (m, 2H), 7.65−7.54 (m, 1H), 7.53−7.36 (m, 2H), 4.77 (d, 1H, J = 9.6 Hz), 4.51−4.30 (m, 1H), 2.68−1.51 (m, 4H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 216.1, 210.2, 194.8, 136.5, 133.7, 129.5, 128.6, 61.1, 45.8, 44.5, 38.8, 26.5, 26.0. Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.87; H, 7.49.

3-Benzoyl-2,5-nonanedione. ^{1}H NMR ($CDCl_3$/TMS): δ 8.07−7.96 (m, 2H), 7.67−7.56 (m, 1H), 7.56−7.43 (m, 2H), 5.10 (t, 1H, J = 6.7 Hz), 3.24−2.94 (m, 2H), 2.49 (t, 2H, J = 7.6 Hz), 2.17 (s, 3H), 1.64−1.47 (m, 2H), 1.40−1.21 (m, 2H), 0.89 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 207.8, 202.3, 196.2, 135.9, 133.7, 128.9, 128.7, 56.7, 42.3, 41.2, 29.2, 25.7, 22.1, 13.7. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.60; H, 7.99.

3-Benzoyl-6-methyl-2,5-octanedione. ^{1}H NMR ($CDCl_3$/TMS): δ 8.02 (d, 2H, J = 7.6 Hz), 7.67−7.56 (m, 1H), 7.56−7.45 (m, 2H), 5.10 (t, 1H, J = 6.7 Hz), 3.30−2.97 (m, 2H), 2.62−2.46 (m, 1H), 2.18 (s, 3H), 1.80−1.31 (m, 2H), 1.15−1.04 (m, 3H), 0.94−0.81 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 211.4, 202.3, 196.2, 136.0, 133.7, 128.8, 128.7, 56.6, 47.5, 40.0, 29.3, 25.8, 15.6, 11.4. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.67; H, 7.70.

3-Benzoyl-6,6-dimethyl-2,5-heptanedione. ^{1}H NMR ($CDCl_3$/TMS): δ 8.02 (d, 2H, J = 7.8 Hz), 7.62 (t, 1H, J = 7.3 Hz), 7.57−7.46 (m, 2H), 5.09 (t, 1H, J = 6.7 Hz), 3.35−3.01 (m, 2H), 2.18 (s, 3H), 1.18 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 213.1, 202.5, 196.4, 136.1, 133.8, 128.9, 128.8, 56.8, 44.0, 36.4, 29.5, 26.5. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.56; H, 7.79.

3-Acetyl-2,5-nonanedione. ^{1}H NMR ($CDCl_3$/TMS): δ 4.19 (t, 1H, J = 7.0 Hz), 2.99 (d, 2H, J = 7.0 Hz), 2.54−2.41 (m, 2H), 2.27 (s, 6H), 1.65−1.48 (m, 2H), 1.41−1.20 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 207.9, 202.9, 62.2, 42.1, 40.9, 29.7, 25.7, 22.1, 13.7. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.1 Found: C, 66.47; H, 9.24.

3-Acetyl-6,6-dimethyl-2,5-heptanedione. ^{1}H NMR ($CDCl_3$/TMS): δ 4.18 (t, 1H, J = 7.0 Hz), 3.10 (d, 2H, J = 7.0 Hz), 2.27 (s, 6H), 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 213.1, 203.1, 62.4, 43.8, 36.0, 29.8, 26.4. Anal. Calcd for $C_{16}H_{20}O_3$: C, 66.64; H, 9.15. Found: C, 66.76. H, 9.12.

Acknowledgment. We wish to thank the Department of Energy and the Robert H. Cole Foundation for their support of this research.

OM980303Q