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Diastereoselectivity in the Formation of Quaternary Centers with Aryllead(IV) Tricarboxylates

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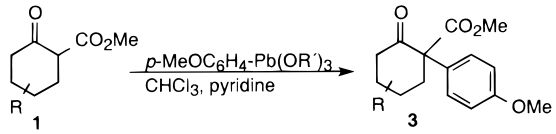
ABSTRACT



The formation of quaternary centers utilizing the reaction of aryllead(IV) tricarboxylates with β-ketoesters has been investigated. A series of substituted methyl 2-oxo-1-cyclohexanecarboxylates served as substrates for the evaluation of diastereoselectivity in the sp^2–sp^3 bond forming reaction with *p*-methoxyphenyllead tricarboxylates. Selectivities ranged from poor to excellent depending on the substituent. A comparison to iodonium salts is discussed.

Quaternary center formation[1] continues to provide challenges to the synthetic organic chemist, and many ingenious solutions to this problem have emerged. As part of our total synthesis of the marine natural product diazonamide A,[2] we have explored the chemistry of aryllead(IV) tricarboxylates as effective arylation reagents for the formation of sp^2-sp^3 bonds with carbon acids. Herein, we report our investigations on the effects of variations in the substituents, temperature, and base employed in the diastereoselective aryllead tricarboxylate reaction with substituted methyl 2-oxo-1-cyclohexanecarboxylates.

Arylation reactions mediated by organolead reagents have been extensively studied by Pinhey.[3] We found the reagents particularly attractive for our total synthesis venture for a number of reasons. First, they are easily prepared and the available synthetic methods allow for the widest range of substitutions on the aromatic nucleus. Second, these reagents contain only one aryl group (i.e., $ArPb(OC(O)R)_3$) that is transferred efficiently to the active methylene component. Thus, the lead-based reagents are quite economical, especially if a more elaborate and/or expensive aryl group is required. Third, aryllead tricarboxylates afford C-arylation products only.[4] Finally, the mechanism of aryllead tricarboxylate arylation reactions has been shown to not involve radicals.[5]

The stereochemistry of aryllead reactions has not been extensively investigated. Pinhey et al. have reported diastereoselectivity for the arylation of two compounds,[6] and Moloney et al. have done the same for a single compound.[7] We began our studies with the reaction of 5-substituted methyl 2-oxo-

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(1) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388−401. (b) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−66. (c) Martin, S. F. *Tetrahedron* **1980**, *36*, 419−60.

(2) (a) Konopelski, J. P.; Hottenroth, J. M.; Mónzo-Oltra, H.; Véliz, E. A.; Yang, Z.-C. *Synlett* **1996**, 609−11. (b) Hang, H. C.; Drotleff, E.; Elliott, G. I.; Ritsema, T. A.; Konopelski, J. P. *Synthesis* **1999**, 398−400.

(3) Pinhey, J. T. *Aust. J. Chem.* **1991**, *44*, 1353−82.

(4) *N*-Arylation afforded by copper catalysis. See: (a) López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **1996**, *61*, 5865−70. (b) López-Alvarado, P.; Avendaño, C.; Menéndez, J. C. *J. Org. Chem.* **1995**, *60*, 5678−82. (c) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J.-P.; Guiry, P. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2095−02.

(5) Morgan, J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1673−6.

(6) (a) Pinhey, J. T.; Rowe, B. A. *Aust. J. Chem.* **1980**, *33*, 113−20. Our sample of **3b** was spectroscopically identical to that described by Pinhey in this article. (b) Morgan, J.; Pinhey, J. T.; Rowe, B. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1005−8.

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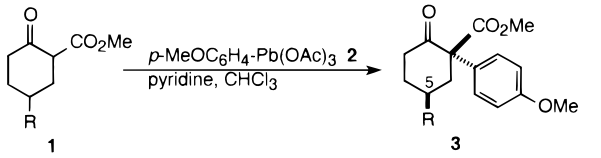
1-cyclohexanecarboxylates **1a**−**d**[8] with *p*-methoxyphenyllead triacetate **2**[9] (Table 1). Excellent isolated yields are obtained

Table 1. Arylation Results for 5-Substituted β-Ketoesters **1**[a]



entry	R	% yield **3**	diastereomer ratio
a	Me	98	7:1
b	*tert*-butyl	96	9:1
c	OTBDMS	97	20:1
d		92	3:2

[a] All reactions consisted of 1 mmol of **1**, 1.4 mmol of **2**, and 3.3 mmol of pyridine at room temperature.

at the optimum reagent-to-substrate ratio of 1.4:1.0. Selectivities range from poor for ketal **1d** to excellent for protected alcohol **1c**.[10]

The stereochemistry of the final product was determined with the aid of a single-crystal X-ray structure determination of **3a** (Figure 1b).[11] This stereochemistry is the opposite of

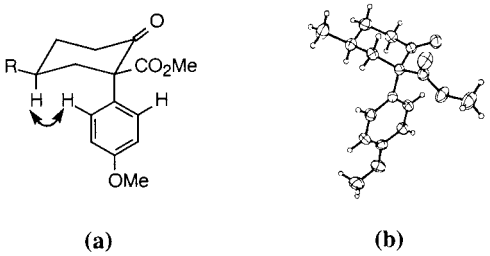
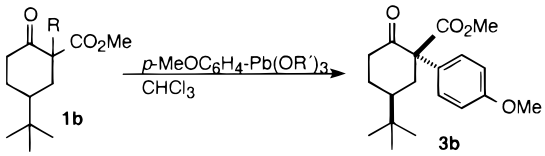


Figure 1. (a) Depiction of solution structures of **3b** (R = *tert*-butyl) and **3c** (R = OTBDMS), with NOE enhancement. (b) Solid-state structure of **3a** obtained from crystallography.

that proposed by Pinhey for **3b**.[6a] However, we were able to establish an NOE enhancement for the C5 proton of compounds **3b** and **3c** when the ortho protons of the *p*-methoxyphenyl group were irradiated and visa-versa (Figure 1a). This establishes the solution conformation of all three compounds to be identical to the solid-phase depiction of **3a**.

Temperature, counterion, and carboxylate variations are shown in Table 2. All reactions in this study were performed

Table 2. Arylation Results at Varying Conditions of **1b**[a]



entry	R	R′	temp, °C	base	% yield of **3b**	dr[e]
A[b]	H	$C(O)CH_3$	60	pyridine	61	6:1
B	H	$C(O)CH_3$	25	pyridine	66	9:1
C	H	$C(O)CH_3$	70	pyridine	59[c]	6:1
D	H	$C(O)CH_3$	4	pyridine	48[d]	10:1
E	H	$C(O)C_6H_5$	25	pyridine	62	9:1
F	H	$C(O)CHCl_2$	25	pyridine	65	9:1
G	Na	$C(O)CH_3$	25	none	60	9:1

[a] All reactions consisted of 1 mmol of **1b**, 1.1 mmol of **2**, and 3.3 mmol of pyridine. [b] Taken from ref 6a. [c] No starting material remained at the end of this reaction. [d] Starting material isolated (47%). [e] Diastereomer ratio.

with a reagent-to-substrate ratio of 1.1:1.0 so that the persistence of starting material and/or byproducts could be ascertained. In most cases reactions are quite clean, with unreacted starting material (15−20%) and desired product being the only identifiable materials in the mixture.[12] Pinhey has already reported that the formation of **3b** at 60 °C affords a diastereomeric ratio of 6:1 (entry A). The reaction at room temperature (entry B) yields a 9:1 ratio of isomers. Lower temperatures (entry D) afford a slightly greater selectivity at the expense of yield, with the remaining mass consisting of starting material. Conversely, higher temperatures (entry C) lead to a slightly decreased yield and decreased selectivity, with more byproduct formation and no recovered starting material. Substitution of benzoate ligands onto the lead for the kinetically labile acetates affords no stereochemical advantage, nor does use of the more electron withdrawing dichloroacetate ligand (entries E and F[13]). Finally, we were intrigued with Pinhey's results on the use of preformed anions of β-ketoesters (sodium or potassium salts) in a THF/pyridine mixed solvent system.[14] In our hands, however, the reaction proceeded in $CHCl_3$ without any loss of yield or diastereoselectivity with no added pyridine (entry G).

The major product of the preceding reactions is explained by the generally accepted mechanism for electrophilic

(7) Dyer, J.; Keeling, S.; Moloney, M. G. *Chem. Commun.* **1998**, 461−2.

(8) Compound **1d** has been described. See: Konopelski, J. P.; Deng, H.; Schiemann, K.; Keane, J. M.; Olmstead, M. M. *Synlett* **1998**, 1105−7. Compound **1c** has been fully characterized by infrared 500 MHz ^1H and ^{13}C spectra and elemental analysis.

(9) Kozyrod, R. P.; Pinhey, J. T. *Org. Synth.* **1984**, *62*, 24−30.

(10) **General Procedure for Arylations.** β-Ketoester (1 mmol) is stirred in $CHCl_3$ (5 mL) at room temperature. To this solution, pyridine (3.3 mmol) is added and the solution allowed to stir for 10 min. A solution of aryllead tricarboxylate (1.4 mmol) in $CHCl_3$ (5 mL) is added. The resulting solution is allowed to stir for 48 h at room temperature. The reaction is quenched with the addition of H_2SO_4 (2 M solution, 3 mL) and stirred for an addition 5 min. The reaction mixture is passed through Celite to remove solid material, the organic layer is separated, and the aqueous layer is extracted with $CHCl_3$ (3 × 5 mL). The organic layer is dried over sodium sulfate and concentrated in vacuo. Column chromatography affords the desired product. All new compounds have been fully characterized by infared and 500 MHz ^1H and ^{13}C spectra and elemental analysis.

addition to β-ketoester enolates.[15] The stabilized enolate allows for a more product-like transition state in which the differences between the possibilities ($A^{\ddagger}$ for axial arylation and $E^{\ddagger}$ for equatorial arylation) are accentuated. As shown in Figure 2, the transition state leading to ($A^{\ddagger}$) possesses a

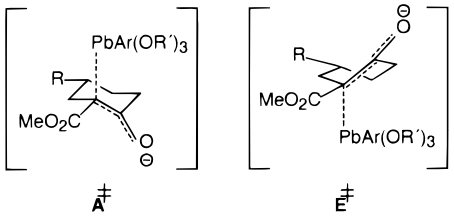


Figure 2. Transition states for axial and equatorial attack of the enolate of **1** on aryllead(IV) tricarboxylate reagent.

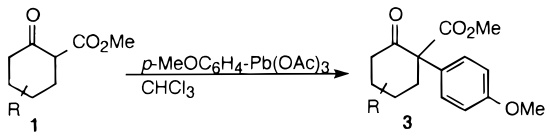
chairlike structure that minimizes torsional and eclipsing strain, whereas the transition state leading to $E^{\ddagger}$ possesses a twist-boat structure with significantly more eclipsing interactions between adjacent centers. Higher temperatures would be expected to minimize these differences, lower temperatures to accentuate them. Disubstitution at C5 negates any preferred conformation and gives poor stereoselectivity (Table 1, entry **3d**). Changes in the ligand system of the lead reagent or the method of carbocyclic anion formation seem to have little effect (Table 2, compare entries B, E, F, and G). Thus, to a first approximation, the aryllead reagent reacts as any other electrophile with the stabilized enolate of **1**.

However, this simple steric argument does not explain the high degree of selectivity exhibited in the formation of **3c**. Literature values for conformational energies[16] would suggest a much higher selectivity for the production of **3b** (R = *tert*-butyl) than for **3c** (R = OTBDMS). A final explanation for this result must await further mechanistic study.

Table 3 shows the results obtained when the 3-, 4-, 5-, and 6-methyl derivatives of methyl 2-oxo-1-cyclohexanecarboxylate are employed as substrates. The selectivities ranged from moderate to excellent, with the 3-methyl derivative giving the best selectivity (Table 3, entry **3e**). The yield of this reaction was poor, however, with no recovered starting material. We suggest that this lone example of poor mass recovery of a room-temperature reaction is due to over-oxidation at the C3 center, with concomitant formation of water-soluble materials. This side reaction may originate from an increase in acidity of the C3 proton due to complexation of the β-ketoester functionality with lead as a Lewis acid. The high diastereoselectivity may also arise through this mechanism; that is, by an equilibration of the final product under the reaction conditions. Alternatively, one diastereomer could oxidize more rapidly, resulting in a significant increase in the amount of that isomer relative to that of the least reactive isomer. These details also must await further mechanistic studies. By contrast, the yield of product **3g** is low, but starting material makes up the remainder of material isolated. This low yield is most likely attributed to enhanced steric interactions in that system.

Recently, the use of mixed diaryliodonium salts for the arylation of malonates has been reported.[17] This interesting methodology allows for the selective transfer of the most electron deficient aryl group in a mixed diaryliodonium reagent.[18] For example, Oh et al.[17] showed that phenyl transferred at a rate 10 times greater than that of *p*-methoxyphenyl to malonates and β-ketoesters when using the mixed iodonium salt to afford desired products in good yield. We elected to explore the limits of this reaction in comparison to our organolead chemistry by preparing the 4,4′-dimethoxydiphenyliodonium salts[19] and attempting the arylation of the β-ketoesters **3**. However, we were never able to isolate more than a few percent of desired material from the complex mixture that was formed under a variety of reaction conditions. Thus, it would appear that the organolead reagents are superior to the corresponding iodonium salts for the transfer of electron rich aryl groups. Finally, preliminary experiments using inductively coupled plasma mass spectrometry (ICP-MS[20]) indicate residual lead levels

Table 3. Arylation Results for Substituted β-Ketoesters **1**[a]



entry	R	% yield **3**	diastereomer ratio
e	3-Me	16[b]	15:1
f	4-Me	65	3:1
a	5-Me	74	7:1
g	6-Me	23	9:2

[a] All reactions consisted of 1 mmol of **1**, 1.1 mmol of **2**, and 3.3 mmol of pyridine at room temperature. [b] No starting material remained at the end of this reaction.

(11) Crystals of **3a** are triclinic, $a = 7.981(13)$, $b = 8.737(15)$, and $c = 12.26(2)$ Å, $\alpha = 80.61(2)$, $\beta = 73.49(2)$, and $\gamma = 66.55(2)°$, space group $P1$, $Z = 2$, $\rho = 1.223$ g/cm^3 for $C_{16}H_{20}O_4$. A total of 2897 independent reflections were measured with graphite-monochromated Mo Kα radiation at 297(2) K on a Bruker SMART diffractometer in the θ range of 1.74−26.00°. The structure was solved by using direct methods and refined to a final *R* value of 5.32%. The primary program used was SHELXS-97, 1997, by G. M. Sheldrick.

(12) Each entry in Table 1 was performed at the 1.1:1 ratio. Yields of desired product ranged from 66 to 74%, with the remaining mass consisting of starting material.

(13) Prepared as an intermediate in the synthesis of reagent **2**. See ref 9 for details.

(14) (a) Kopinski, R. P.; Pinhey, J. T.; Rowe, B. A. *Aust. J. Chem.* **1984**, *37*, 1245−54. (b) Morgan, J.; Pinhey, J. T.; Rowe, B. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1005−8.

(15) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 900−1.

(16) See ref 15, p 696.

(17) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338−40.

(18) (a) Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **1998**, *120*, 13523−24. (b) See ref 17.

(19) (a) Beringer, F. M.; Falk, R. A.; Karnol, M.; Lillien, I.; Masullo, G.; Mausner, M.; Sommer, E. *J. Am. Chem. Soc.* **1959**, *81*, 342−51. (b) Beringer, F. M.; Drexler, M.; Gindler, E. M.; Lumpkin, C. C. *J. Am. Chem. Soc.* **1953**, *75*, 2705−08.

(20) Gwiazda, R.; Woolard, D.; Smith, D. *J. Anal. Atom. Spectrom.* **1998**, *13*, 1233−38.

to be in the 40 ppm range for compounds **3a**, **3b**, and **3c** following our standard isolation procedure. Since no care was taken to minimize the ambient lead contamination, these results must be considered maximum levels in the samples and, in fact, could be much lower.

In conclusion, we have shown that aryllead tricarboxylates afford excellent yields of arylated products under mild conditions. Diastereoselectivities can be excellent in certain cases. These selectivities can be largely understood by invoking the accepted mechanism of reaction between cyclic β-ketoester enolates and electrophiles, although anomalies exist. The use of aryllead reagents is preferred for the introduction of electron rich aryl groups over the corresponding diaryliodonium salts, and lead contamination of the organic sample is minimal. Further studies of organolead reagents are ongoing in our laboratory and will be presented in due course.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org.

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