Tetrahedron Letters No. 52, pp 5167 - 5170.
© Pergamon Press Ltd. 1978. Printed in Great Britain.

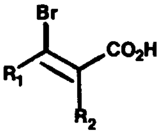
0040-4039/78/1222-5167$02.00/0

A DIRECT SYNTHESIS OF α,β-BUTENOLIDES BY REACTION OF LITHIUM β-LITHIOACRYLATES WITH CARBONYL COMPOUNDS

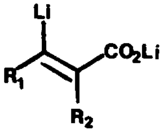
Drury Caine* and A. Stephen Frobese
School of Chemistry, Georgia Institute of Technology
Atlanta, Georgia 30332

A large number of biologically important natural products contain an α,β-butenolide ring.[1] Much of the recent methodology on the synthesis of α,β-butenolides which have the double bond unsubstituted or bearing alkyl substituents has been based upon the thermal fragmentation of α-seleninyl[2] and α-[3] or β-sulfinyl-γ-lactones.[4] Other methods have involved selective reductions of γ-hydroxy-α,β-acetylenic acids,[1a,5] intramolecular cyclizations of α-acetoxy methyl ketones,[6] heating of Z-4-bromo-2-butenoic acids,[7] electrolytic decarboxylations of γ-substituted paraconic acids,[8] pyrolysis of pyrazolines of γ-butyrolactones,[9a] and isomerizations of β-alkylidenebutyrolactones.[9b]

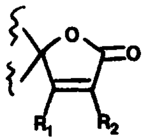
Recently, we reported a convenient synthesis of γ-butyrolactones (butanolides) by addition of lithium β-lithiopropionate to carbonyl compounds followed by lactonization.[10] We have now found that Z-β-bromoacrylic acid (1a),[11a] and its α-(1b)[11b] and β-methyl derivatives (1c)[11c] can be converted into the corresponding lithium β-lithioacrylates 2 and reacted with carbonyl compounds to give butenolides 3 in moderate yields.



1



2

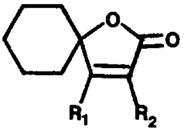


3

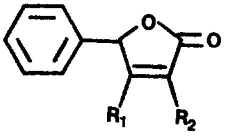
a. $R_1=R_2=H$
b. $R_1=H$, $R_2=CH_3$
c. $R_1=CH_3$, $R_2=H$

α-Lithio derivatives of α,β-unsaturated acid salts have been prepared from halogen-metal exchange of the corresponding α-bromo acids with n-butyllithium in tetrahydrofuran(THF)-ether-pentane (4:1:1) at -115°[12a] or in THF at -100°.[12b] However, to our knowledge, no examples of the preparation of β-lithiated α,β-unsaturated acid salts have been reported.[13] In view of the successful use of halogen-metal exchange reactions for the stereospecific preparations of Z-vinyllithium reagents having alkyl,[14] phenyl,[15] or heteroatom substituents[16] at the β-carbon, it appeared that bromides such as 1 might be convertible into the lithiated carboxylates 2 by reaction with alkyllithium reagents.

The best results were obtained when the halogen-metal exchange reactions were carried out by treating the bromoacids with two equivalents of *n*-butyllithium in diethyl ether at -78°. Addition of the carbonyl compound (cyclohexanone or benzaldehyde) and workup then gave the butenolides **4** or **5** in the yields indicated in the Table. The following procedure is illustrative. *n*-Butyllithium (26.8 ml, 60 mmol, of a 2.24 M solution in hexane) was added dropwise over 1.5 h to a rapidly stirred solution of 4.53 g (30 mmol) of bromoacid **1a** in 300 ml of anhydrous diethyl ether at -78° under nitrogen. The mixture was stirred for 1.5 h at -78° and 1.004 g (10.2 mmol) of cyclohexanone in 35 ml of anhydrous THF was added dropwise with stirring. The mixture was stirred for 2 h at -78°, allowed to warm to room temperature, and treated with 50 ml water. The layers were separated and the organic layer was extracted with an additional 50-ml portion of water. The aqueous basic solution was washed with ether, cooled to 0° and acidified with cold 5% hydrochloric acid. The mixture was allowed to stand for 1 h at 25°, saturated with sodium chloride and extracted with two 50-ml portions of ether. The combined ethereal extracts were washed with a saturated solution of sodium bicarbonate and dried over anhydrous magnesium sulfate. Removal of the solvent *in vacuo* gave 0.740 g (48%) of a pale yellow oil. Micro-Hickman distillation of the residue gave 0.637 g (41%) of butenolide **4a**, b.p. 109°(bath temperature)/ 0.6 mm; reported[8] 117-119°/2.0 mm.



4



5

a. $R_1=R_2=H$
b. $R_1=H$, $R_2=CH_3$
c. $R_1=CH_3$, $R_2=H$

Table. Preparation of Butenolides by Reaction of Lithium β-Lithioacrylates with Carbonyl Compounds.

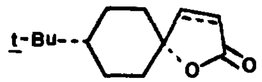
Organolithium Reagent	Carbonyl Compound	Equiv Carbonyl Compound	Butenolide	% Yield	Ref.
2a	cyclohexanone	0.33	**4a**	48[a] (41)[b]	8
2a	benzaldehyde	0.33	**5a**	49[a] (38)[c]	3c
2b	cyclohexanone	0.50	**4b**	71[a] (66)[b]	17
2b	benzaldehyde	0.50	**5b**	70[a] (61)[b]	18
2c	cyclohexanone	0.33	**4c**	57[a] (51)[b]	6
2c	benzaldehyde	0.33	**5c**	52[a] (47)[b]	17

a. Isolated yield of product which was homogeneous by nmr and glc. b. Yield of distilled product. c. Distillation in a micro-Hickman still gave a *ca*. 2:1 mixture of butenolide **5a** and the corresponding β,γ-isomer.[3c]

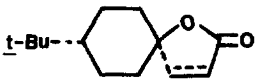
When the above workup conditions were employed in the runs in which **4b** or **4c** were produced, the butenolides were found to be distributed between the ether fraction extracted from the aqueous basic solution and the neutral fraction obtained after acidification. In these cases, it appeared that the γ-alkoxy carboxylate adduct underwent partial cyclization prior to the addition of water. For these runs, it was found to be experimentally convenient to acidify the reaction mixture prior to ether extraction and to separate the butenolide from the other neutral materials by chromatography on silica gel.

Competition between elimination to an acetylenic carboxylate and halogen-metal exchange was an important factor which contributed to the lower yields in the runs involving reagents 2a and 2c. For example, when 1c was lithiated as described above and the mixture quenched with wet THF, spectroscopic evidence indicated that a *ca.* 7:2:1 mixture of *trans*-crotonic acid, 2-butynoic acid, and the starting acid 1c was produced. Attempts to reduce the extent of elimination proved fruitless. For example, treatment of 1c with 2 equiv of *n*-butyllithium in THF-ether-pentane (4:1:1) at approximately -110° or in THF at -78° followed by protonation led to even greater amounts of the acetylenic acid than when ether was used as the solvent. There was no improvement when 1c was converted to its calcium salt (by reaction with calcium hydride in THF at room temperature) prior to treatment with 1 equiv of *n*-butyl or *t*-butyllithium in THF at -78° or THF-ether-pentane at -110°. Likewise, poorer results were obtained when halogen-metal exchange reactions on 1a or its calcium salt with *n*-butyl- or *t*-butyllithium were attempted in solvents other than diethyl ether.

The stereochemical outcome of the addition of the vinyllithium reagent 2a to 4-*t*-butylcyclohexanone was also investigated. GLC analysis (carbowax column) indicated that a 58:42 mixture (48% yield) of the syn and anti isomers, 6a and 7a, derived from equatorial and axial attack, respectively, of the carbanionic reagent on the carbonyl group was produced. This butenolide mixture was not separated, but was converted to a *ca.* 60:40 mixture of the corresponding butanolides, 6b and 7b,[10,19] by catalytic hydrogenation using palladium-on-carbon. Thus a somewhat greater proportion of axial attack on the carbonyl group was observed in the case of 2a than when lithium β-lithiopropionate was reacted with 4-*t*-butylcyclohexanone.[10] The smaller size of the vinyl carbanion apparently accounts for this.[20]



6



7

a. Unsaturated Lactone
b. Saturated Lactone

Reactions of vinyllithium reagents such as 2 with electrophilic reagents provide potentially useful routes to a variety of α,β-unsaturated acids with a Z configuration. Some of these reactions are being explored.

References and Notes

1. (a) Y. S. Rao, *Chem. Rev.*, *76*, 625 (1976); (b) R. C. Larock, B. Riefling, and C. A. Fellows, *J. Org. Chem.*, *43*, 131 (1978); (c) A. A. Avetisyan and M. T. Dangyan, *Russ. Chem. Rev.*, *46*, 643 (1977).

2. K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, 95, 6137 (1973).
3. (a) B. M. Trost, T. N. Salzmann, and K. Hiroi, *ibid.*, 98, 4887 (1976); (b) P. A. Grieco and J. J. Reap, *Tetrahedron Lett.*, 1097 (1974); (c) K. Iwai, H. Kosugi, H. Uda, and M. Kawai, *Bull. Chem. Soc. Jpn*, 50, 242 (1977).
4. (a) P. A. Bartlett, *J. Am. Chem. Soc.*, 98, 3305 (1976); (b) P. A. Grieco and M. Miyashita, *J. Org. Chem.*, 40, 1181 (1975); (c) K. Iwai, H. Kosugi, A. Miyazaki, and H. Uda, *Synth. Comm.*, 6, 357 (1976); (d) P. Brownbridge and S. Warren, *J. Chem. Soc. Chem. Commun.*, 465 (1977).
5. A. A. Jakubowski, F. S. Guziec, Jr., and M. Tishler, *Tetrahedron Lett.*, 2399 (1977).
6. H. G. Lehmann, *Angew. Chem. Int. Ed. Engl.*, 4, 783 (1965).
7. A. Löffler, F. Norris, W. Taub, K. L. Svanholt, and A. S. Dreiding, *Helv. Chem. Acta*, 53, 403 (1970).
8. S. Torii, T. Okamoto, and H. Tanaka, *J. Org. Chem.*, 39, 2486 (1974).
9. (a) S. W. Pelletier, Z. Djarmati, S. D. Lajšić, I. V. Mićović, and D. T. C. Yang, *Tetrahedron*, 31, 1659 (1975); (b) J. E. McMurry and S. F. Donovan, *Tetrahedron Lett.*, 2869 (1977)
10. D. Caine and A. S. Frobese, *Tetrahedron Lett.*, 883 (1978).
11. (a) C. Rappe, *Acta. Chem. Scand.*, 19, 31 (1965); (b) Rappe and coworkers (ref. 11c) have reported that E-3-bromo-2-butenoic acid is the major product of tribromination of methyl ethyl ketone followed by Favorski rearrangement. However, we have found that this compound is actually Z-3-bromo-2-methylpropenoic acid (**1b**). The ^{13}C nmr spectrum of **1b** was the same as that previously reported (ref. 11d). Additional evidence to support this structural assignment will be presented later in a full paper; (c) C. Rappe, T. Nilson, G. Carlson, and K. Andersson, *Arkiv. Kemi*, 24, 95 (1965); (d) C. Rappe, E. Lippmaa, T. Pehk, and K. Andersson, *Acta. Chem. Scand.*, 23, 1447 (1969).
12. (a) H. L. Elbe and G. Kobrich, *Tetrahedron Lett.*, 2557 (1974); (b) W. E. Parham and D. W. Boykin, *J. Org. Chem.*, 42, 260 (1977).
13. Preparations of β-lithiated functionalized acrylic acid derivatives such as N,N-diethyl-E-β-(1-pyrrolidinyl)acrylamide (R. R. Schmidt and J. Talbiersky, *Angew. Chem. Int. Ed. Engl.*, 15, 171 (1976)), E-β-(1-pyrrolidinyl)acrylonitrile (R. R. Schmidt and J. Talbiersky, *ibid.*, 16, 853 (1977)), or ethyl E-β-(1-pyrrolidinyl)acrylate (*ibid*, 17, 204 (1978)) by deprotonation with *t*-butyllithium or lithium diisopropylamide have been reported.
14. G. Cahiez, D. Bernard, and J. F. Normant, *Synthesis*, 245 (1976).
15. H. Neumann and D. Seebach, *Tetrahedron Lett.*, 4839 (1976).
16. K. S. Y. Lau and M. Schlosser, *J. Org. Chem.*, 43, 1595 (1978).
17. **4b**: IR ($CC\ell_4$) 1765, 1667 cm^{-1}; NMR ($CC\ell_4$) δ 1.63 (bs, 10H), 1.82 (d, J = 1.6 Hz, 3H), 7.02 (q, J = 1.6 Hz, 1H); MS Calcd for $C_{10}H_{14}O_2$: 166.0994; Found: 166.0990. **5c**: IR ($CHCl_3$) 1798, 1761, 1647 cm^{-1}; NMR ($CDCl_3$) δ 1.87 (m, 3H), 5.72 (bs, 1H), 5.92 (m, 1H), 7.34 (m, 5H); MS Calcd for $C_{11}H_{10}O_2$: 174.0681; Found: 174.0637.
18. S.A.M.T. Hussain, W. D. Ollis, C. Smith, and J. F. Stoddart, *J. Chem. Soc. Perkin I*, 1480 (1975).
19. B. M. Trost and M. J. Bogdanowicz, *J. Am. Chem. Soc.*, 95, 5321 (1973).
20. E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, 75, 521 (1975).

(Received in USA 24 October 1978)