

ORGANOBISCUPRATES.

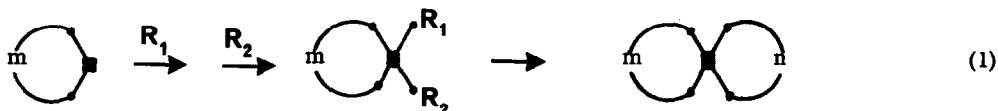
A SINGLE-STEP SPIROANNELATION METHOD

Paul A. Wender* and Stephen L. Eck

Department of Chemistry, Harvard University, Cambridge, MA 02138 U.S.A.

(Received in UK 30 November 1976; received in UK for publication 23 February 1977)

In recent years numerous synthetic methods have been developed which allow for the transformation of a functionalized secondary carbon center into a quaternary center,¹ an integral process in the synthesis of spiro compounds² (eq 1). However, the adaptations of these methods to the elaboration of such ring



systems, particularly the spiro[4.5]decane (1) and spiro[5.5]undecane (2) subunits common to various natural products,³ frequently require multi-step sequences which, consequently, attenuate the applicability



1



2

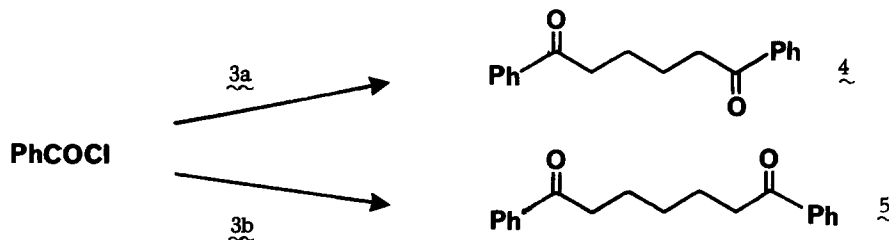


- 3
- a n = 4, L = SPh
 - b n = 5, L = SPh
 - c n = 4, L = \equiv -Pr

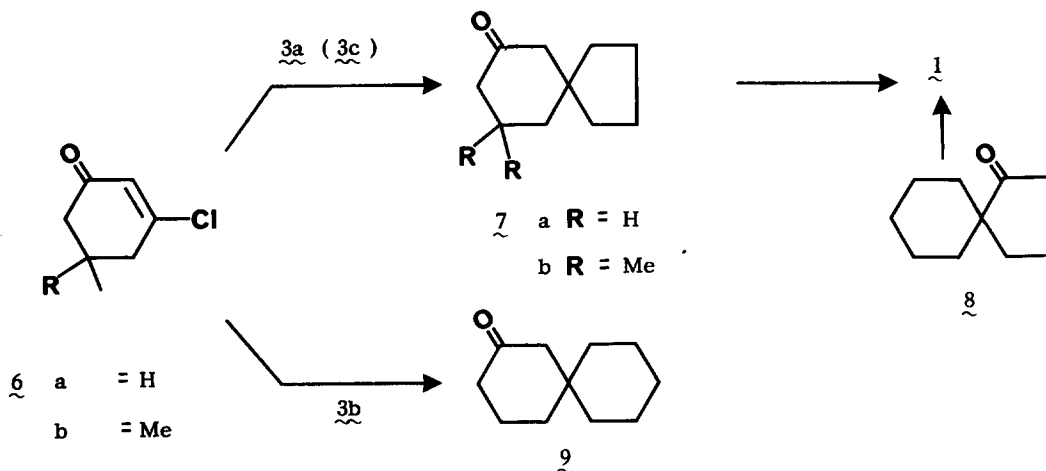
of these strategies. The recent finding⁴ that 3-acetoxycyclohex-2-enone is converted upon reaction with lithium dimethylcuprate into 3,3-dimethylcyclohexanone suggests that the reaction of these and related 3-substituted enones with cuprate reagents of the type 3⁵ would serve as a convenient single-step method for the synthesis of spiroalkanes. This communication describes the preliminary results of studies on the preparation of this new type of cuprate reagent and its use as a spiroannelating agent.

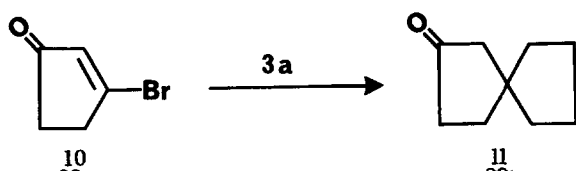
Reagent 3a was prepared by the addition (5 min) of 1,4-dilithiobutane⁶ (1 equiv, 0.24 M ether) to a vigorously stirred suspension of copper (I) thiophenoxide⁷ [CuSPh₃ (2 equiv)] in tetrahydrofuran-hexane

maintained at -78° , followed by warming to -30° (5 min) and recooling to -78° . The formation of a copper based reagent of the type 3a in this preparation was determined by a trapping experiment using benzoyl chloride (2.1 equiv) which afforded upon standard work-up diketone 4⁸ in 60% yield. As such, the reaction of 3a with benzoyl chloride parallels that found for the related alkyl(hetero)cuprates⁷ and is contrasted by the reaction of 1,4-dithiobutane with benzoyl chloride (conducted under the above conditions in the absence of CuSPh) which provided a complex mixture of products containing less than 5% of diketone 4. The preparation and reactivity of reagent 3b followed that found for 3a. Thus, addition of 1,5-dithiopentane⁶ (1 equiv) to a suspension of CuSPh (2 equiv) in tetrahydrofuran-hexane (-78°) followed (30 min) by quenching with benzoyl chloride (2.2 equiv) provided diketone 5⁸ in 55% yield.



The suitability of the above reagents in the aforementioned spiroannellation strategy was initially examined using 3-acetoxycyclohex-2-enone. In striking contrast to the reaction of this substrate with dialkylcuprates, its reaction with reagent 3a proceeded with cleavage of the oxygen-acetyl bond to provide mainly cyclohexan-1,3-dione rather than the expected spiro compound. However, screening of other 3-substituted enones eventually led to the finding that the readily available 3-chloroenones⁹ serve as suitable substrates for the desired spiroannellation process. Thus, chloroenone 6a (0.5 equiv, 1 M ether) was added (30 min) to reagent 3a (1.2 equiv, suspension in tetrahydrofuran-hexane at -78°) and the resulting mixture stirred for 2 hr at -78° and subsequently allowed to warm slowly to ambient temperature. Standard work-up gave the spiroketone 7a¹⁰ in 60% yield. The structure of 7a was confirmed by its





conversion¹¹ to 1, an authentic sample of which was prepared from a similar reduction of ketone 8.

Analogous to the spiroannellation of 6a, compound 6b reacted with reagent 3a to give the substituted spiro[4.5]decanone 7b in 55% yield. The spiro[5.5]undecanone 9 was obtained in 40% yield from the annellation of 6a with reagent 3b. Since the procedure used for these spiroannellations was not optimized for the individual cases, the lower yield found in the formation of 9 relative to 7a and 7b presumably reflects the relative rates of closure to the six- and five-membered rings.

The mixed alkynyl cuprate 3c, prepared¹² from the reaction of 1,4-dithiobutane with pentynyl-copper, was also found to be effective in the above spiroannellations. However, the yields of 7a and 7b obtained with this biscuprate (3c) were approximately 15% lower than the yields found using the thiophenoxy reagent 3a. Finally, the spiroannellation strategy is readily extended to bromoenones as evidenced by the formation of the spiro[4.4]nonanone 11 in 60% yield from the reaction of 10 with the biscuprate 3a.

The spiroannellation method described above compares favorably in regard to efficiency with current multistep methods (eq 1) for the preparation of spiro[4.4]nonanes, spiro[4.5]decanes, and spiro[5.5]undecanes. We are continuing to investigate the scope of this method, the properties of the above cuprate reagents and related metallocycles, and the preparation of analogous functionalized reagents.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

REFERENCES AND NOTES

- 1) A recent example of a geminal alkylation method cites references which reflect other types of strategies in this area: B. M. Trost and M. Preckel, *J. Am. Chem. Soc.*, 95, 7862 (1973).
- 2) Recent examples of synthetic work in this area contain references to earlier work: E. Piers, C. K. Lau, and I. Nagakura, *Tetrahedron Lett.*, 3233 (1976); E. Piers and I. Nagakura, *ibid.*, 3237 (1976); D. Caine, A. A. Boucugnani, and W. R. Pennington, *J. Org. Chem.*, 41, 3632 (1976); S. F. Martin, *ibid.*, 41, 3337 (1976); G. Büchi, D. Berthet, R. Decorzant, A. Brieder, and A. Hauser, *ibid.*, 41, 3208 (1976); D. Caine, A. Boucugnani, S. T. Chao, J. B. Dawson, and P. F. Ingwalson, *ibid.*, 41, 1539 (1976); W. G. Dauben and O. J. Hart, *J. Am. Chem. Soc.*, 97, 1622 (1975); D. Buddhsukk and P. Magnus, *J. Chem. Soc., Chem. Commun.*, 975 (1975); B. M. Trost, M. Preckel, and L. M. Leichter, *J. Am. Chem. Soc.*, 97, 2224 (1975); B. M.

- Trost, K. Hiroi, and N. Holy, ibid., 97, 5873 (1975); and J. D. White, S. Torii, and J. Nogami, Tetrahedron Lett., 2879 (1974).
- 3) For a review and examples of naturally occurring spiro compounds, see: J. A. Marshall, S. F. Brady, and N. H. Andersen, Fortschr. Chem. Org. Naturst., 31, 283 (1974) and T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds," Vol. II, Academic Press, New York, 1972.
 - 4) C. P. Casey, D. F. Marten, and R. A. Boggs, Tetrahedron Lett., 2071 (1973).
 - 5) Other work in this area includes the copper catalyzed addition of butane-1,4-di(magnesium bromide) to ethyl isopropylidenemalonate [R. M. Schila and W. C. Hammann, J. Org. Chem., 35, 3225 (1970)] and the reaction of a copper phosphine complex of 1,4-dilithiobutane with carbon monoxide [J. Schwartz, Tetrahedron Lett., 2803 (1972)].
 - 6) R. West and E. G. Rochow, J. Org. Chem., 18, 1739 (1953). The preparation of dilithioalkanes was modelled after the procedure given in the above reference with the following modifications: high sodium content (1-2%) lithium wire was used; after addition of the dibromoalkane the resulting mixture was allowed to stand at -10 - 0° for 16 hr then centrifuged; the supernatant was then transferred to a heavy-walled vial for storage and use. For more recent preparations of dilithioalkanes, see: G. Fraenkel and J. W. Cooper, J. Am. Chem. Soc., 93, 7228 (1971); and J. X. McDermott, M. E. Wilson, and G. M. Whitesides, ibid., 98, 6529 (1976).
 - 7) G. H. Posner, C. E. Whitten, and J. J. Sterling, J. Am. Chem. Soc., 95, 7788 (1973); and G. H. Posner, P. J. Brunelle, and L. Sinoway, Synthesis, 662 (1974).
 - 8) Authentic samples of the diketones 4 and 5 were prepared by the reaction of the appropriate dilithioalkane with benzaldehyde followed by Jones oxidation of the crude product.
 - 9) For the preparation of and cuprate additions to chloroenones, see: E. Piers and I. Nagakura, Synth. Commun., 5, 193 (1975); E. Piers and I. Nagakura, J. Org. Chem., 40, 2694 (1975); R. D. Clark and C. H. Heathcock, ibid., 41, 636 (1976); and J. P. Marino and L. J. Browne, ibid., 41, 3629 (1976).
 - 10) All new compounds gave satisfactory spectroscopic and elemental analyses.
 - 11) R. O. Hutchins, B. E. Maryanoff, and C. A. Milewski, J. Am. Chem. Soc., 93, 1793 (1971).
 - 12) The preparation of 3c was modelled after the procedure given for the preparation of the analogous alkynyl cuprates: E. J. Corey and D. J. Beames, J. Am. Chem. Soc., 94, 7210 (1972).