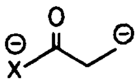
Tetrahedron Letters,Vol.23,No.14,pp 1463-1466,1982   0040-4039/82/141463-04$03.00/0
Printed in Great Britain

HOMOENOLATE DIANIONS OF SECONDARY AMIDES VIA TIN/LITHIUM EXCHANGE

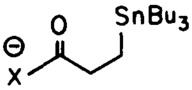
Ramanuj Goswami* and Daniel E. Corcoran
Research Laboratories, Eastman Kodak Company, Rochester, New York 14650

Abstract: Treatment of N-phenyl- as well as N-methyl-3-(tri-*n*-butylstannyl)-propionamide with 2 equiv of *n*-butyllithium in the presence of 1,4-diazabicyclo[2.2.2]octane at -78°C in tetrahydrofuran produced the corresponding dilithio derivatives (homoenolate dianions) **4** and **8** respectively. Reaction with various electrophiles (1 equiv) gave the terminally substituted amides in good yields.

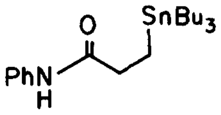
As a continuation[1] of our efforts to generate homoenolate dianion synthons **1** via tin/lithium exchange of the enolates **2**, we report here the successful generation of such dianions of secondary amides **1** (X = NR).



1

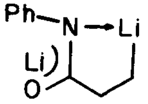


2

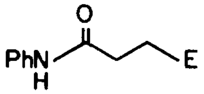


3

Addition of 2 equiv of *n*-butyllithium to a mixture of N-phenyl-3-(tri-*n*-butylstannyl)propionamide **3** and 1,4-diazabicyclo[2.2.2]octane (DABCO) in tetrahydrofuran at -78°C caused a facile tin/lithium exchange to generate the dilithio derivative **4**. Best results were obtained when there was a few minutes wait after the first equivalent of *n*-butyllithium was added. If both equivalents of *n*-butyllithium were added simultaneously, about 20% of N-phenylpropionamide (**3**, $SnBu_3$ = H) was isolated as a byproduct. This presumably resulted from the generation of dilithio derivative **4** in the presence of unreacted **3** under these reaction conditions.[2] DABCO was not essential for this tin/lithium exchange but its presence gave a cleaner reaction. Reaction of **4** with 1 equiv of various electrophiles gave β-substituted amides **5** after the usual workup (Table 1).

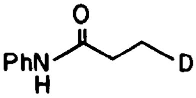
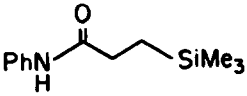
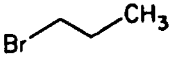
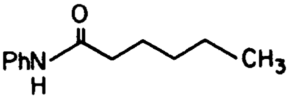
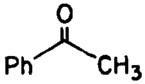
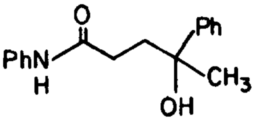
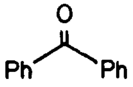
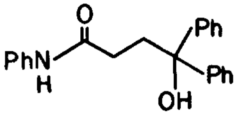


4



5

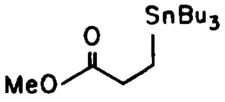
REACTIONS OF DILITHIO DERIVATIVE **4** WITH 1 EQUIV[a] OF VARIOUS ELECTROPHILES

Electrophile	Product	Yield, %[b]
CH_3OD		90 (78 d_1)
Me_3SiCl[a]		66
		66
		68
		80

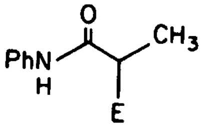
---

[a] 2 equiv of chlorotrimethylsilane was used. During workup the organic layer was washed with 2.5 M aqueous sodium hydroxide.

[b] Yields refer to isolated pure product.



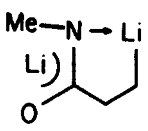
6



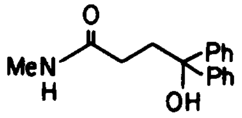
7

N-Phenyl-3-(tri-*n*-butylstannyl)propionamide **3** was prepared easily in 90% yield by treating dilithioaniline[3] with methyl 3-tri-*n*-butylstannylpropionate **6**[4] at room temperature for 15 min. Compound **3** was also prepared in 70% yield by reaction of **6** with aniline and sodium hydride in dimethyl sulfoxide[5] and in 70% yield from 3-tri-*n*-butylstannylpropionic acid via the corresponding acid chloride.[6]

It is apparent that, to generate a species such as **4**[7] under the prescribed reaction conditions (THF, *n*-BuLi, -78°C), the tin/lithium exchange of **2** (X = NPh) must be faster than proton abstraction. The absence of **7** in the products indicates that the proton transfer is very slow under the reaction conditions used.



8



9

It is also possible to generate an analogous dilithio derivative such as N-methylamide 8 using similar reaction conditions. Reaction of 8 with benzophenone produced the desired product 9 in 50% yield after recrystallization.[8]

The following experimental procedure is representative of the general method developed for the generation of the dilithio derivative 4 and its subsequent reactions with electrophiles. Any variations in conditions are given in Table 1.

In a dry 50-ml flask, equipped with a rubber septum and an argon inlet, were placed 1.31 g (3.0 mmol) of the N-phenylamide 3 and 700 mg (6.25 mmol) of 1,4-diazabicyclo[2.2.2]octane (DABCO). About 25 ml of freshly distilled dry THF was added, and the flask was flushed with argon; a positive pressure of argon was maintained during the reaction. This THF solution was cooled to -78°C, and 3.0 mmol (1.5 ml of a 2.0 M hexane solution) of *n*-butyllithium was added. The resulting mixture was stirred at -78°C for 8 min, and 3.2 mmol (1.6 ml of a 2.0 M hexane solution) more of *n*-butyllithium was then added. The reaction mixture was stirred at -78°C for 15 min. Then 3.2 mmol of the electrophile in about 5 ml of THF was added to this slightly yellow solution. The reaction mixture was stirred at -78°C for 5 min and allowed to warm to room temperature over 15 min. Dilute HCl was added, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous sodium sulfate. After evaporation under reduced pressure, the residue was partitioned between 50 ml of hexanes and 50 ml of acetonitrile.[9] The acetonitrile layer was evaporated under reduced pressure. The residue was usually recrystallized from a mixture of ethyl acetate and hexane to give the pure product. The crude residue could also be purified by modified flash chromatography[10] on silica gel eluted with hexane/ethyl acetate.

REFERENCES and NOTES

1. Successful generation of an analogous homoenolate dianion derived from a β-ketophosphonate ester has been reported: Goswami, R. *J. Am. Chem. Soc.* **1980**, *102*, 5973-5974.

2. Even though the subsequent tin/lithium exchange was slower than the proton abstraction, it was competitive to the extent of at least 20%. An example of bromine/lithium exchange being faster than proton abstraction from carboxylic acid was reported by Stein, A.; Morton, T. H. *Tetrahedron Lett.* **1973**, 4933-4936.

3. Kaiser, E. M.; Yun, H. H. *J. Org. Chem.* **1970**, *35*, 1348.

4. VanDerKerk, G. J. M.; Noltes, J. G.; Luijten, J. G. A. *J. Appl. Chem.* **1957**, *7*, 356. We prefer to purify **6** by chromatography on silica gel rather than by distillation. On thin-layer plates **6** can be easily visualized by using iodine vapor.

5. Singh, B. *Tetrahedron Lett.* **1971**, 321.

6. Alkaline hydrolysis of **6** in aqueous ethanol followed by the usual workup with dil. HCl gave the corresponding acid in good yield. The corresponding acid chloride, pure enough for the next step, was prepared by allowing the acid to react with oxalyl chloride in hexane.

7. Gay, R. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1967**, *89*, 1647-1651.

8. The yield of this reaction was not optimized.

9. Berge, J. M.; Roberts, S. M. *Synthesis* **1979**, 471.

10. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(Received in USA 18 December 1981)