Tetrahedron Letters Vol. 21, pp 3151 - 3154
©Pergamon Press Ltd. 1980. Printed in Great Britain

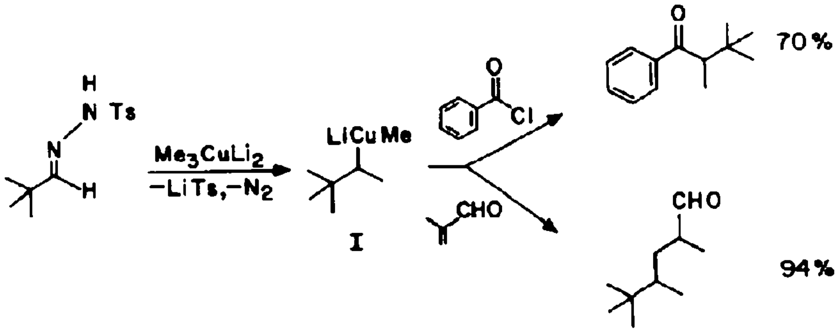
0040-4039/80/0808-3151$02.00/0

THE PREPARATION OF HINDERED CUPRATES FROM ALDEHYDE TOSYLHYDRAZONES

by
Steven H. Bertz
Bell Laboratories
Murray Hill, New Jersey 07974

Abstract: Copper reagents react with secondary and tertiary aldehyde tosylhydrazones to give unique, hindered cuprates which are alkylated in a one-flask procedure.

Aldehyde tosylhydrazones are more prone to addition than ketone tosylhydrazones[1] when treated with lithium reagents, the corresponding "reductive alkylation" products having been isolated in 20-54% yields.[2] Except in the case of fluorenone tosylhydrazone, the intermediate carbanion has not been trapped by an external electrophile other than a proton.[3] It has been discovered in this laboratory that by including copper (I) in the reaction mixture, the addition is facilitated due to the activation of the carbon-nitrogen double bond by cuprous ion;[4] and the intermediate cuprate can be efficiently coupled to an electrophile.



For example pivaldehyde tosylhydrazone and dilithium trimethylcuprate give a quantitative yield of an intermediate (conjectured to be I above) which undergoes typical cuprate reactions with alkyl halides[5] (97-99% by gc, see Table), methacrolein[6] (99% by NMR, 94% isolated product), and benzoyl chloride. 2,2-Dimethyl-3-lithiobutane has been prepared in only 50% yield;[7] the lithium reagents corresponding to the other intermediate cuprates prepared in this study are presently unknown.

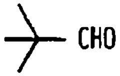
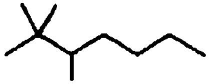
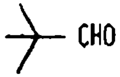
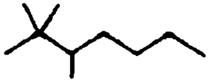
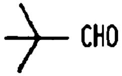
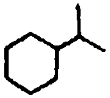
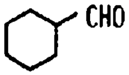
The additional examples in the Table reveal a number of salient features of this new method The bromomagnesium salts of the tosylhydrazones (Method A) give the highest yields with methyllithium (entries 1,2,4 and 7); with the other alkyllithiums used the lithiotosylhydrazones (Method B) give better results (entries 3,6,8 and 9). In Method A five equivalents of lithium reagent are required to one of copper; if only four are used, virtually no product is formed. I the reagent prepared from four equivalents of MeLi, one of MeMgBr, and one of CuI is added to th lithium salt of cyclohexane carboxaldehyde tosylhydrazone (1), a 90% yield of isopropylcyclohex results. Within experimental uncertainty this is the same as the yield by Method A (94%), in which the reagent prepared from five equivalents of MeLi and one of CuI is added to the bromomagnesium salt of 1. It is therefore likely that a magnesiocuprate[8] is the actual reagent.

If the lithium salt of the tosylhydrazone is the substrate (Method B), two equivalents of RLi per CuI are sufficient to induce a good yield. For example, a 75% yield of isopropylcyclohexane results when the lithium salt of 1 is treated with Me$_2$CuLi; however, the maximum yield (88%) also is reached with "Me$_5$CuLi$_4$". In this case 11% ethylcyclohexane was observed versus 5 with Method A. Thus the magnesium protects the intermediate carbanion from protonation by the medium. It is well known that Grignard reagents are less basic than the corresponding alkyllithiums. Intentional protonation gives a 99% yield of ethylcyclohexane. When MeLi (2-4 equivalents) alone is added to 1, 27-28% of ethylcyclohexane, but no isopropylcyclohexane, resu after quenching with MeI. Therefore, the presence of Cu(I) is essential for coupling the intermediate carbanion to an alkyl halide as well as to promote addition to the carbon-nitrogen double bond. Since the isopropyl group is a common appendage of many terpenoids, this efficien new method for its construction is certain to be useful.

While the tosylhydrazones of secondary and tertiary aldehydes give good to excellent yield (entries 1-4 and 9) of *gem*-alkylated products, the unbranched *n*-heptaldehyde tosylhydrazone giv unusably small yields with both MeLi and *n*-BuLi. Intermediate yields are obtained from the β-branched 3-methylpentanal tosylhydrazone. Thus the polypropylene model compound 3,5,7-trimethy nonane[9] is formed in ~20% yield using either MeLi (Method A) and 1-bromo-2-methylbutane or 2-methylbutyllithium (Method B) and MeI. However, it is formed in 71% yield by the addition of lithium di-*sec*-butylcuprate[10] to the lithium salt of 2,4-dimethylhexanal tosylhydrazone (entrie 7-9). Increasing the amount of *sec*-BuLi to five equivalents lowers the yield (63%). Diethyl ether (containing only that hydrocarbon present in the lithium reagent) is the best solvent for these reactions. The use of hexane or tetrahydrofuran lowers the yield. For example repeating entry 7 in hexane gave an 11% yield; in THF it was only 6%. The failure of primary aldehyde tosylhydrazones is not a serious limitation because the corresponding lithium reagents are easi prepared by standard methods. Benzaldehyde tosylhydrazone gave no cumene, and the starting material was recovered when treated with Me$_3$CuLi$_2$ and MeI, thus selective reactions should be possible.

In summary the lithium and magnesium salts of secondary and tertiary aldehyde tosylhydrazones[11] react with copper reagents to give new highly hindered cuprates which cannot be formed other methods. These intermediates are alkylated to give good to excellent yields of branched hydrocarbons. The example of 3,5,7-trimethylnonane illustrates the flexibility inherent in the method: since there are many retrosynthetic analyses possible for any given branched hydrocarbo the aldehyde component may be chosen from a number of candidates. One of the reagents is nucleophilic and the other one electrophilic, thus the alkyl groups need not be identical and m be chosen in either of two ways for a particular aldehyde. The experimental simplicity of this procedure[12] coupled with its conceptual flexibility should make it a valuable addition to synthetic methodology.

Acknowledgements: I thank C. W. Wilkins, Jr. for his advice and A. M. Mujsce for GC-MS.

ENTRY	PRODUCT	STARTING MATERIALS			YIELDS(%)^A	
		Tosylhydrazone of	RLi	Halide	Method A^B	Method B^C
1			MeLi	MeI	97(6h)	89(6h)
2			MeLi	nBuBr	99(6h)	83(1h)
3			nBuLi	MeI	68(1h)	86(0.5h)
4			MeLi	MeI	94(2h)	75(2h)
5			MeLi	MeI	<1(2h)	<1(2h)
6			nBuLi	HCl	1(1h)	4(1h)
7			MeLi		22(1h)	<1(1h)
8				MeI	11(0.5h)	23(0.5h)
9				HCl	D	71(0.5h)

(A) Measured by GC calibrated against an internal standard.

(B) Treatment of the MgBr salt with "R_5CuLi_4".

(C) Treatment of the Li salt with R_2CuLi.

(D) Not determined due to interfering peaks.

REFERENCES AND NOTES

1. Shapiro, R. H., "Organic Reactions", Vol. 23, Dauben, W. G., Ed., John Wiley & Sons, Inc., New York, 1976, p 411.
2. Vedejs, E. and Stolle, W. T., Tetrahedron Lett., 1977, 135-8.
3. Shapiro, R. H. and Gadek, T., J. Org. Chem., 1974, 39, 3418-9.
4. Bertz, S. H., J. Org. Chem., 1979, 44, 4967-9.
5. The scope of the coupling reaction of cuprates with alkyl halides has been determined: Whitesides, G. M., Fischer, W. F., San Filippo, Jr., J., Bashe, R. W. and House, H. O., J. Am. Chem. Soc., 1969, 91, 4871-82.
6. Few examples of cuprate additions to α,β-unsaturated aldehydes are known: Posner, G. H., "Organic Reactions", Vol. 19, Dauben, W. G., Ed., John Wiley & Sons, Inc., 1972, p 24.
7. Screttas, C. G. and Micha-Screttas, M., J. Org. Chem., 1979, 44, 713-9.
8. Whitesides, G. M. and Bergbreiter, D. E., J. Org. Chem., 1975, 40, 779-82; Bergbreiter, D. E. and Killough, J. M., J. Org. Chem., 1976, 41, 2750-3; Drouin, J., Leyendecker, F. and Conia, J. M., Nouv. J. Chim., 1978, 2, 267-70.
9. Previously prepared by a "multistage synthesis": Ritter, W., Möller, M. and Cantow, H.-J., Makromol. Chem., 1978, 179, 823-7.
10. Schwartz, R. H. and San Filippo, Jr., J., J. Org. Chem., 1979, 44, 2705-12.
11. Tosylhydrazones were prepared by standard methods. See e.g. Jiricny, J., Orere, D. M. and Reese, C. B., Synthesis, 1978, 919-21; Kaufman, G. M., Smith, J. A., Vander Stouw, G. G., and Shechter, H., J. Am. Chem. Soc., 1965, 87, 935-7.
12. Typical Experimental Procedure: Pivaldehyde tosylhydrazone (5.08 g, 20 mmol) dissolved in ether (50 mL, dist. benzophenone ketyl) was cooled to -70° (dry ice-isopropanol) under Ar and treated dropwise with the reagent prepared from 4.18 g (22 mmol) of CuI (Alfa ultrapure) and 50.0 mL of 1.33 M MeLi·LiBr (66 mmol, Aldrich). The homogenous tan solution was allowed to warm slowly to 25°, resulting in vigorous bubbling and the precipitation of a white solid. After 6 h the reaction mixture was cooled to -70°, and 3.3 g (47 mmol) of methacrolein in 50 mL of dry ether was added over 15 min with vigorous stirring. It was allowed to warm to 0° for 15 min and then poured into 35 mL of 2 M HCl. The layers were separated and the water was extracted with 100 mL more ether. The combined ether layers were extracted with 20 mL of M NaOH and dried over $MgSO_4$. The ether was evaporated at 20° under reduced pressure (>40 torr) and the residue was distilled at 70°/10 torr to yield 2.89 g (94%) of 2,4,5,5-tetramethylhexanal. IR (neat) 2810 (w), 2710 (w), 1725 (s) cm^{-1}. ^1H-NMR ($CDCl_3$) δ 0.87 (s, 12 H), 1.15 (d, J = 7 Hz, 3 H), 1.3-2.6 (m, 4 H), 9.6 (d, J = 3 Hz, 1 H); in some preparations a second diasteriomer was present: δ 1.18 (d, J = 7 Hz, 3 H), 9.7 (d, J = 2 Hz).

(Received in USA 13 December 1979)