Regioselective Addition of Organozinc Reagents to 5,6-Dihydropyridinium Ions and Synthetic Equivalents. Factors Effecting 1,2- versus 1,4-Selectivity

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Summary: Organozinc reagents undergo nucleophilic addition to 5,6-dihydropyridinium ions with 1,2-versus 1,4-regioselectivity depending on the structure of the organic group and the presence of magnesium salts. Addition of organozinc reagents to 2-cyano-5,6-dihydropyridines, which are synthetic equivalents of 5,6-dihydropyridinium ions, gives exclusively 1,2-addition products.

5,6-Dihydropyridinium ions are readily prepared from tetrahydropyridine N-oxides using trifluoroacetic anhydride by a Polonovsky elimination reaction.[1] These compounds are notoriously unstable and direct nucleophilic additions are possible only with a limited number reagents, generally in low yields.[2] This is due, at least in part, to a tendency for the dihydropyridine to disproportionate.[3] One approach to solving this problem is the use of cyanide ion adducts as synthetic equivalents. In particular, Grierson, Harris, and Husson demonstrated that Grignard reagents could replace the cyanide to effect overall 1,2-addition.[4] In this report, we demonstrate that 5,6-dihydropyridinium ions can react with organozinc reagents in fair to good yield. Both 1,2- and 1,4-addition can occur and some of the factors controlling regioselectivity have been identified. The reaction of organozinc reagents with the 2-cyano and 4-phenylthio adducts of the dihydropyridinium ions were also explored as were some reactions with organocuprate reagents. Most of the studies were done with the 1-benzyl-3-ethyl-5,6-dihydropyridinium ion 1a and the corresponding adducts 2a and 3a.
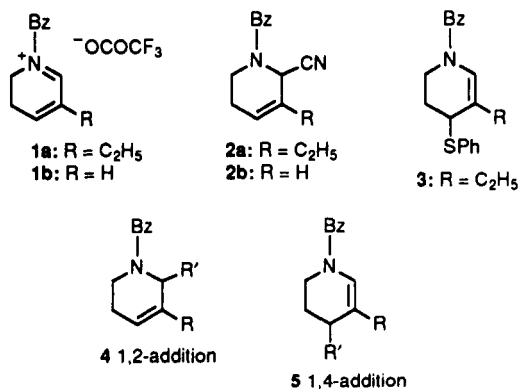
The initial studies were carried out with commercially available diethylzinc. A good yield (67%) of the 1,4 adduct was obtained (Table I, entry 1). Extension of this reaction

Table I. Yields and Regioselectivity of Addition Reactions

entries	reagents	yield,[a] % C2	C4
1	1a, Et$_2$Zn		67
2	1a, Ph$_2$Zn/dioxane		65
3	1a, Me$_2$Zn/dioxane	17	43
4	1a, Et$_2$Zn/MgBr$_2$	51	17
5	1a, Ph$_2$Zn/MgBr$_2$	50	10
6	1a, Me$_2$Zn/MgBr$_2$	73	
7	1a, Ph$_2$Zn/LiBr		58
8	1a, (CH$_2$=CH)$_2$Zn	75	
9	1a, (CH$_2$=CHCH$_2$)$_2$Zn	79	
10	1a, (PHC≡C)$_2$Zn	60	
11	1a, (MeOCH$_2$C≡C)$_2$Zn	67	
12	1a, (MeO$_2$CC≡C)$_2$Zn	65	
13	1a, [(MeO$_2$C)$_2$CH]$_2$Zn		70
14	1a, Me$_2$CuLi		74
15	1a, Ph$_2$CuLi		67
16	1a, (PhC≡C)$_2$CuLi	49	
17	1b, Et$_2$Zn		54
18	2a, Et$_2$Zn	92	
19	2a, Ph$_2$Zn	58	
20	2a, Me$_2$Zn	63	
21	2a, (CH$_2$=CH)$_2$Zn	58	
22	2a, Me$_2$CuLi		76
23	2a, Ph$_2$CuLi		82
24	2b, Et$_2$Zn	69	
25	2b, Ph$_2$Zn	55	
26	3a, Et$_2$Zn	68	
27	3a, Ph$_2$Zn	59	

[a] Product ratio was determined by ^{1}H NMR on crude product. Yields are by isolation after rapid purification through basic alumina.

to dimethylzinc and diphenylzinc, both of which were prepared in situ from zinc bromide and the corresponding Grignard reagent, gave predominantly the C2 addition products (entries 5 and 6). This interesting reversal of regioselectivity, apparently caused by the alternative mode of preparation of the zinc reagent, prompted further examination of the reaction.[5]

A modified preparation of dimethylzinc and diphenylzinc, which uses dioxane as cosolvent and leads to precipitation of a dioxane complex of MgBr$_2$,[6] resulted in predominantly C4 addition (entries 2 and 3). Conversely addition of MgBr$_2$ to the pure diethylzinc reagent resulted

(1) Ahond, A.; Cavé, A.; Kan-Fan, C.; Husson, H.-P.; de Rostolan, J.; Potier, P. *J. Am. Chem. Soc.* 1968, 90, 5622–5623. Chevolot, L.; Husson, A.; Kan-Fan, C.; Husson, H.-P.; Potier, P. *Bull. Soc. Chim. Fr.* 1976, 1222–1226.

(2) Eisner, U.; Kuthan, J. *Chem. Rev.* 1972, 72, 1–42. Stout, D. M.; Meyers, A. I. *Chem. Rev.* 1982, 82, 223–243.

(3) Sundberg, R. J.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* 1984, 49, 2400–2404. Lasne, M.-C.; Ripoll, J.-L.; Guillemin, J.-C.; Denis, J.-M. *Tetrahedron Lett.* 1984, 25, 3847–3848.

(4) Grierson, D. S.; Harris, M.; Husson, H.-P. *J. Am. Chem. Soc.* 1980, 102, 1064–1082.

(5) **General Procedure.** The 5,6-hydropyridinium ions were prepared by treating the amine oxide with TFAA (3 equiv) in CH$_2$Cl$_2$. The solution was then evacuated (~1 Torr) at 0 °C for 15 min. The residue was dissolved in THF and cooled to 0 °C. A solution of the organozinc reagent (2.5–3 equiv) was added slowly by syringe. After 3 h the reaction solution was diluted with 2 volumes of CH$_2$Cl$_2$ and shaken with an aqueous buffer of pH 7.5 made from equal volumes of saturated NaCl, saturated NaHCO$_3$, and saturated NH$_4$Cl. The aqueous layer was extracted again with CH$_2$Cl$_2$ and the combined extracts were dried over Na$_2$SO$_4$. The product ratio was determined from the ^{1}H NMR at this point. The product was then purified by rapid passage through activity II/III basic alumina and yields are based on the purified product. The purified products were characterized by ^{1}H and ^{13}C NMR and a unit resolution CI-MS [M + 1]$^+$ ion. The 1,2-adducts are stable to normal conditions but the 1,4-adducts, being enamines, are unstable in solution and to acid, but can be stored neat for some time in a freezer.

(6) von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* 1992, 48, 5719–5730.

in primarily C2 addition (entry 4). These results demonstrate that the presence of $MgBr_2$ causes the dialkyl and diarylzinc reagents to add 1,2. No comparable effect was noted with lithium bromide was present as the result of preparation of diphenylzinc from phenyllithium (entry 7).

The study was extended to divinylzinc and diallylzinc, both of which were prepared by the dioxane-precipitation method.[6] These reagents both added 1,2 (entries 8 and 9). Similarly, (phenylethynyl)zinc, which was prepared directly from phenylacetylene and diethylzinc,[7] also gave only a 1,2-addition product (entry 10). These results indicate that allyl-, vinyl-, and alkynylzinc reagents give 1,2-addition, even in the absence of $MgBr_2$.

The cyanide adduct **2a** reacted with dimethyl-, diethyl-, diphenyl-, and divinylzinc, under conditions where $MgBr_2$ is absent, to give exclusively 1,2-addition (entries 18–21). Similarly 1,2-addition occurred with the phenylthio adduct **3a** with both diethyl- and diphenylzinc (entries 26 and 27).

We also examined the reactivity of both the dihydropyridinium ion **1a** and the cyanide adduct **2a** with dimethylcuprate and diphenylcuprate. Good yields of the C4 addition product was obtained in each case (entries 14, 15, 22, and 23). Thus the organocuprates exhibit the expected preference, for 1,4-addition.[8] An exception was bis(phenylethynyl)cuprate which added 1,2 (entry 16).[9]

Since organozinc reagents offer the potential for introduction of functionally,[10a] several functionalized zinc reagents were examined. The zinc enolate of dimethyl malonate gave the C4 adduct in good yield (entry 13). Bis(3-methoxypropynyl)zinc and bis(2-carbomethoxyethynyl)zinc gave good yields of 1,2 adducts[11] (entries 11 and 12).

The unsubstituted dihydropyridinium ion **1b** and its synthetic equivalent **2b** were examined briefly. The dihydropyridinium ion reacted with diethylzinc to give a 1,4-addition product in 54% yield. However, no product could be isolated from diphenylzinc and the yield with dimethylcuprate was poor. The cyanide equivalent **2b** gave satisfactory yields of the 1,2-addition product with both diethyl- and diphenylzinc (entries 24 and 25).

These results provide new methodology for preparation of substituted tetrahydropyridines by demonstrating that dihydropyridinium ions can be used *directly* in reactions with both organozinc reagents and organocuprate reagents. Furthermore, by choice of organometallic reagent or reaction conditions it is possible to control 1,2- versus 1,4-regioselectivity. Since both organozinc and organocopper reagents can be prepared with functional groups present,[10] the procedures may permit introduction of functionalized substituents on to tetrahydropyridine rings.

The results also present an intriguing mechanistic pattern for the organozinc reagents. The regioselectivity of addition to dihydropyridinium ions is normally attributed to the hard/soft dichotomy, with harder nucleophiles preferring C2 additon. The previous results with Grignard reagents[4] and the present results with organocuprate reagents fit this pattern. The organozinc reagents appear to be poised at a selectivity borderline and therefore very sensitive to reaction variables. Our results indicate exclusive C2 addition for allyl-, alkynyl-, and vinylzinc reagents, but condition-dependent regioselectivity for alkyl and phenyl reagents.

While the dihydropyridinium ion gives exclusive 1,4-addition with diethylzinc, the 2-cyano and 4-phenylthio adducts give exclusively 1,2-addition. Since these reactions must ostensibly proceed through the same dihydropyridinium ion intermediate, the cyanide and phenylthiolate species evidently direct organozinc addition to C2. This can be pictured as occurring through an ion pair formed by zinc-assisted elimination. The presence of soluble
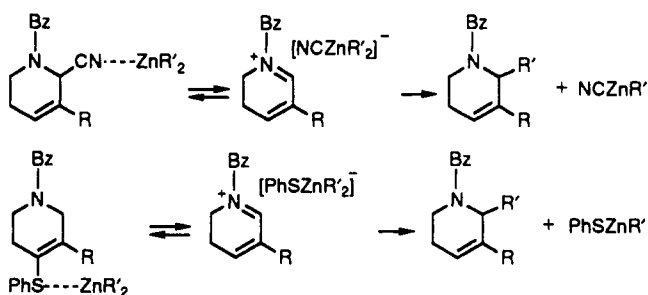
magnesium salts also must effect the detailed structure of the zinc reagent. This may involve a complex with $MgBr_2$ or a higher order cluster. The effect is evidently to increase the "hardness" of the organic substituent and thus favor 1,2-addition.
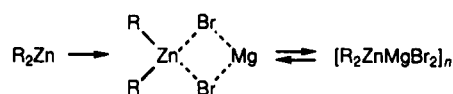
It is also clear that the regioselectivity of the zinc reagents depends on the structure of the organic residue with allyl, ethynyl, and vinyl groups having a preference for 1,2-addition (1,4-addition was not observed with these groups) while phenyl and alkyl groups are capable of either 1,2- or 1,4-addition, depending upon reaction variables. We considered two related characteristics of the organic groups which might influence regioselectivity. With reference to the hard/soft concept, one would expect that the oxidation potential of the reagents to be important.[12] There are examples in the reactivity of organozinc reagents with diimines and α-imino carbonyl compounds which indicate regioselectivity is correlated with oxidation potential.[13] The anionic character of the organic group should be correlated with the acidity of the parent hydrocarbon. The

(7) Okhlobystin, O. Y.; Zakharkin, L. I. *J. Organomet. Chem.* **1965**, *3*, 257–258. Niwa, S.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 937–943.

(8) Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; Wiley Interscience: New York, 1980; pp 4–8.

(9) A previous example of divergence in reactivity of this cuprate has been reported. It acts as a base rather than a nucleophile toward 4-bromo-2-sulfolene: Chou, T.; Hung, S. C.; Tso, H.-H. *J. Org. Chem.* **1987**, *52*, 3394–3399.

(10) (a) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418–4420. Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445–1453. (b) Ebert, G. W.; Rieke, R. D. *J. Org. Chem.* **1984**, *49*, 5280–5282. Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5056–5057. Wu, T.-C.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 5057–5059.

(11) The 1,2-adduct from bis(β-carbomethoxyethynyl)zinc rearranges on exposure to alumina to 1-benzyl-2-(β-carbomethoxyvinyl)-3-ethyl-5,6-dihydropyridine.

(12) Fehlner, T. P.; Ulman, J.; Nugent, W. A.; Kochi, J. K. *Inorg. Chem.* **1976**, *15*, 2544–2547. Wong, C. I.; Mochida, K.; Gin, A.; Weiner, M. A.; Kochi, J. K. *J. Org. Chem.* **1979**, *44*, 3979–3981. Lochynski, S.; Boduszek, B.; Shine, H. J. *J. Org. Chem.* **1991**, *56*, 914–920. Sugiyama, K.; Shine, H. J. *J. Org. Chem.* **1983**, *48*, 143–146.

(13) Jastrzebski, J. T. B. H.; Klerks, J. M.; van Koten, G.; Vrieze, K. *J. Organomet. Chem.* **1981**, *210*, C49–C53. van Vilet, M. R. P.; van Koten, G.; Modder, J. F.; van Beck, J. A. M.; Klarer, W. J.; Goubritz, K.; Stam, C. H. *J. Organomet. Chem.* **1987**, *319*, 285–301. van Vilet, M. R. P.; van Koten, G.; Buyshigh, P.; Jastrzebski, J. T. B. H.; Spek, A. L. *Organometallics* **1987**, *6*, 537–546.

order ethynyl > allyl > vinyl ≈ phenyl > alkyl is in general agreement with the trend from 1,2- to 1,4-addition. The apparently greater tendency for 1,4-addition with phenyl (as compared to vinyl) may reflect steric influences. As is consistent with expectation, both alkyl- and phenyl-cuprates added 1,4 to 5,6-dihydropyridinium ions and there was no change in regioselectivity with the 2-cyano adduct.

Supplementary Material Available: ^{13}C-NMR spectra (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.