MODEL STUDIES TOWARD THE SYNTHESIS OF N_α-ACETYL-N_β-METHYLPHLEGMARINE: ADDITION OF CYCLOHEXYLMETHYL ORGANOMETALLICS TO 1-ACYLPYRIDINIUM SALTS

Daniel L. Comins,* Chris J. Foti, and Adam H. Libby

Department of Chemistry
North Carolina State University, Raleigh, NC 27695-8204, USA

Abstract- *Addition of various cyclohexylmethyl organometallics to a chiral 1-acylpyridinium salt was investigated as a model study toward the asymmetric synthesis of the Lycopodium alkaloid, phlegmarine (1d).*

The *Lycopodium* alkaloids are plentiful, contain various structural types, and provide challenging targets for total synthesis.[1] In 1978, Nyembo and coworkers reported the isolation of the alkaloid phlegmarine (**1a**) and several of its congeners (**1b-d**).[2] The phlegmarine skeleton was proposed to be a key intermediate in the biosynthesis of several *Lycopodium* alkaloids. Unlike most other *Lycopodium* alkaloids containing a decahydroquinoline ring system, the phlegmarines were shown to possess a *trans*-decahydroquinoline unit in their skeleton rather than the usual cis arrangement.[3]
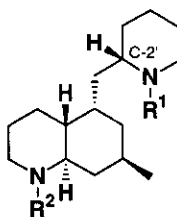

1a,　R^1 = H, R^2 = H　　　phlegmarine
　b,　R^1 = H, R^2 = Me　　$N\beta$-methylphlegmarine
　c,　R^1 = Me, R^2 = H　　$N\alpha$-methylphlegmarine
　d,　R^1 = COMe, R^2 = Me　$N\alpha$-acetyl-$N\beta$–methylphlegmarine

We have been studying an approach to the asymmetric synthesis of phlegmarine (**1d**). Our synthetic plan calls for the preparation of enantiopure *trans*-decahydroquinoline fragment (**2**), conversion of this halide to an organometallic, and subsequent addition of the organometallic to chiral 1-acylpyridinium salt (**3**) to give intermediate dihydropyridone (**4**). If successful, this route will allow the incorporation of the stereocenter

at C-2′ with a high degree of stereocontrol. Conversion of **4** to phlegmarine (**1d**) will be accomplished in approximately 4 steps, based on previous results from our laboratories.[5]

Preliminary model studies have indicated that the preparation of intermediate amino halide (**2**) can be carried out in a stereoselective fashion.[5] The key step in the total synthesis, however, is the organometallic preparation from halide (**2**) and its addition to chiral 1-acylpyridinium salt (**3**). This paper reports model studies designed to develop conditions for carrying out this crucial transformation. Two potential problems had to be addressed: (1) the conversion of an amino halide to an organometallic species on a small scale, and (2) the addition of that organometallic to 1-acylpyridinium salt (**3**) with good yield and stereoselectivity.

R* = (-)- *trans*-2-(α-cumyl)cyclohexyl (TCC)[7]
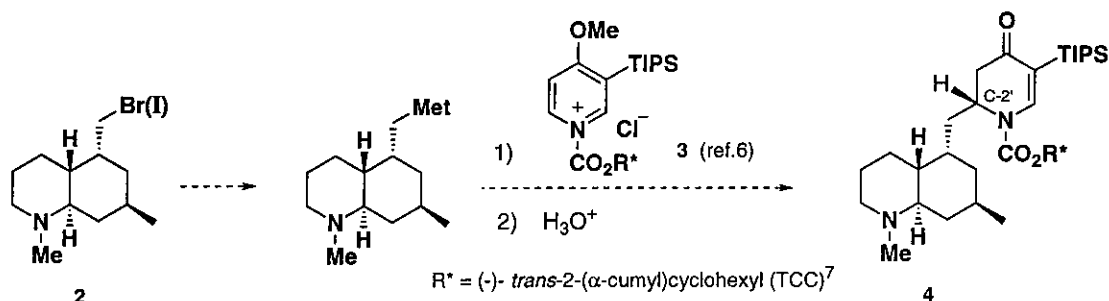
A Grignard reagent has been the organometallic most used in the asymmetric 1-acylpyridinium salt addition reaction.[6] Generally, the yields of dihydropyridones are excellent and the de's range from 85-95%. Preparation of a Grignard reaction on a very small scale can be problematical, however, and the effect of a tertiary amine added more uncertainty. Our initial model reaction involved the use of cyclohexylmethyl bromide (**5**) as the Grignard precursor. An equivalent of TEA was added to mimic the tertiary amine functionality in halide (**2**). The Grignard of **5** was prepared in THF using Rieke's magnesium[8] on a small scale (0.13-0.17 mmol). Although we were successful in forming the Grignard reagent in this way, the reaction was found to be very sensitive to air, moisture and the batch of freshly prepared Rieke's magnesium. The most consistent results were obtained using commercially available Rieke's magnesium.[9] After considerable effort, we were able to use this method to obtain a 68% yield of dihydropyridone (**7**) from pyridinium salt (**3**) and bromide (**5**). This result was somewhat disappointing for the yield of this reaction is 20-25% lower than that usually obtained using most primary Grignard reagents including isobutylmagnesium bromide.[6a] The next step was to use a more appropriate model halide. The bromomethyl moiety of **2** is in the axial orientation, so *cis*-1-bromo-4-*tert*-butylcyclohexane (**6**)[10] was chosen for further study. The Grignard of (**6**), prepared using Rieke's magnesium (~0.15 mmol), was added to pyridinium salt (**3**) (toluene/THF, 4:1, -78 °C).[6] Unfortunately, the yield of **8** from this reaction was only 22%.
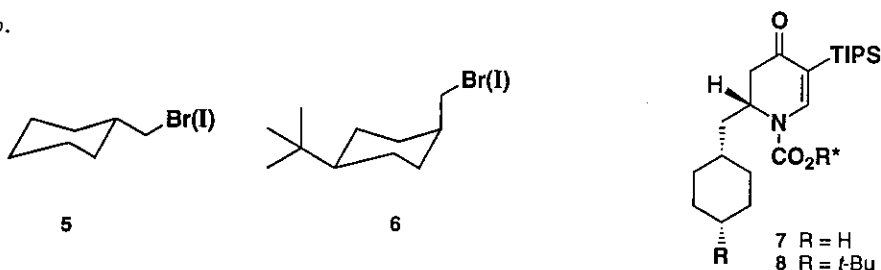
Due to the low yield obtained using **6** , and the difficulty of using Rieke's magnesium on the required small scale, other organometallics were investigated as shown in Table 1. Organocopper reagents were prepared from **5** and **6** by treatment with *tert*-BuLi[11] or LiDBB[12] followed by a copper salt. These organocopper reagents added to 1-acylpyridinium salt (**3**) in variable yields (entries c-f). Reagents prepared from halide (**5**) provided moderate yields of dihydropyridone (**7**), and those derived from halide (**6**) gave low yields of **8** . The simplicity of converting a halide to an organolithium species led us to evaluate the use of alkyllithiums as nucleophiles with pyridinium salt (**3**). Generally, alkyllithiums do not work well in the 1-acylpyridinium salt reaction, as the 1-acyl carbonyl group is attacked.[13] Fortunately, the chiral pyridinium salt (**3**) has a hindered carbonyl, which allows alkyllithiums to preferentially attack the pyridinium ring as shown in Table 1.

Table 1. Addition of organometallics to 1-acylpyridinium salt (**3**).

entry[a]	alkyl halide	conditions	dihydropyridone	yield,[c,d] %
a	**5** (Br)	Rieke's Mg, THF	7	68
b	**6** (Br)	Rieke's Mg, THF	8	22
c	**5** (Br)	1) *tert*-BuLi, Et$_2$O 2) ThCu(CN)Li[b]	7	60
d	**6** (Br)	1) *tert*-BuLi, Et$_2$O 2) ThCu(CN)Li	8	24
e	**5** (Br)	1) LiDBB, THF 2) CuCN•2LiBr	7	43
f	**6** (Br)	1) LiDBB, THF 2) CuCN•2LiBr	8	35
g	**5** (Br)	*tert*-BuLi, Et$_2$O	7	30
h	**6** (Br)	*tert*-BuLi, Et$_2$O	8	23
i	**5** (Br)	LiDBB, THF	7	32
j	**6** (Br)	LiDBB, THF	8	27
k	**5** (I)	*tert*-BuLi, Et$_2$O	7	68
l	**6** (I)	*tert*-BuLi, Et$_2$O	8	46

[a]The reactions were performed on a 0.13-0.17 mmol scale in the presence of 1 equivalent of TEA. [b] Lithium 2-thienylcyanocuprate in THF was purchased from Aldrich Chemical Co. [c] The yield is of the major diastereomer isolated from radial PLC. The de's were estimated to be in the 80-90% range by ^{1}H NMR analysis of the crude products. [d]Satisfactory IR, ^{1}H and ^{13}C NMR, and microanalysis data were obtained for all new products.

Although the yields are low with the alkyl bromides (entries g,h), we were able to obtain a good reaction (46%) with iodide (**6**) using the *tert*-BuLi procedure (entry l).[14] The lithium-halogen exchange of iodide (**6**) with *tert*-BuLi was shown to be efficient by trapping the alkyllithium with DMF to give the corresponding aldehyde in 91% yield. Given this result, and the ease of carrying out the transformation on a small scale, it is anticipated that these conditions will be effective for preparing phlegmarine (**1d**) from iodide (**2**) *via* intermediate dihydropyridone (**4**). Efforts toward this goal will be reported in due course.

The use of cyclohexylmethylmagnesium bromide as a nucleophile is well established in the literature.[15] Although reduction of benzophenones and certain other ketones has been reported with cyclohexylmethyl Grignards,[15] no dihydropyridone product resulting from an analogous reduction of pyridinium salt (3) was isolated or detected by ^{1}H NMR analysis. At this time we do not know what side reactions are responsible for the low to moderate yields obtained on addition of cyclohexylmethyl organometallics to 3 . This model study has (1) revealed an anomaly in the asymmetric Grignard/1-acylpyridinium salt reaction, (2) shown that organocuprates and certain alkyllithiums can be effective nucleophiles in this asymmetric reaction, and (3) demonstrated the reaction's tolerance for tertiary amine groups, a versatility which should prove useful in alkaloid synthesis.

ACKNOWLEDGEMENT

REFERENCES AND NOTES

1.   (a) W. A. Ayer and L. S. Trifonov, 'The Alkaloids,' Vol. 45, ed. by G. A. Cordell and A. Brossi, Academic Press, Inc., San Diego, 1994, pp. 233-274. (b) T. A. Blumenkopf and C. H. Heathcock, 'Alkaloids: Chemical and Biological Perspectives,' Vol. 3, ed. by S. W. Pelletier, Wiley, New York, 1985, pp. 185-240. (c) D. Schumann and A. Naumann, *Liebigs Ann. Chem.*, 1984, 1519. (d) J. Szychowski and D. B. MacLean, *Can. J. Chem.*, 1979, **57**, 1631.

2.   L. Nyembo, A. Goffin, C. Hootele, and J. -C. Braekman, *Can. J. Chem.*, 1978, **56**, 851.

3.   (a) A. Leniewski, J. Szychowski, and D. B. MacLean, *Can. J. Chem.*, 1981, **59**, 2479. (b) A. Leniewski, D. B. MacLean, and J. K. Saunders, *Can. J. Chem.*, 1981, **59**, 2695.

4.   D. L. Comins and S. P. Joseph, 'Advances in Nitrogen Heterocycles,' Vol. 2, ed. by C. J. Moody, JAI Press, Inc., Greenwich, CT, pp. 251-294.

5.   D. L. Comins and R. S. Al-awar, *J. Org. Chem.*, 1995, **60**, 711.

6.   (a) D. L. Comins, S. P. Joseph, and R. R. Goehring, *J. Am. Chem. Soc.* 1994, **116**, 4719. (b) D. L. Comins and L. Guerra-Weltzien, *Tetrahedron Lett.*, 1996, **37**, 3807 and reference cited therein. (c) D. L. Comins, X. Chen, and L. A. Morgan, *J. Org. Chem.*, 1997, **62**, 7435.

7.   (a) D. L. Comins and J. M. Salvador, *Tetrahedron Lett.*, 1993, **34**, 801. (b) D. L. Comins and J. M. Salvador, *J. Org. Chem.*, 1993, **58**, 4656.

8.   R. D. Rieke, *Acc. Chem. Res.*, 1977, **10**, 301.

9.   Rieke Metals, Inc., Lincoln, NE.

10.   For the preparation of *cis*-1-(bromomethyl)-4-*tert*-butylcyclohexane, see (a) M. Tichy, J. Jonas, and J. Sicher, *Collection Czech. Chem. Commun.*, 1959, **24**, 3434. (b) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *J. Am. Chem. Soc.*, 1968, **90**, 5793.

11.   E. R. Punzalan and W. F. Bailey, *J. Org. Chem.*, 1990, **55**, 5404.

12.   P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924.

13.   K. Akiba, Y. Iseki, and M. Wada, *Tetrahedron Lett.*, 1982, **23**, 429.

14.   Alkyl bromides occasionally give lower yield than the corresponding iodides in the lithium-halogen exchange reaction using *tert*-BuLi, see reference 11.

15.   (a) A. Habashi, W. Tadros, and H. Z. Shams, *Indian J. Chem.*, 1980, **19B**, 659. (b) M. Falorni, L. Lardicci, G. Uccello-Barretta, and G. Giacomelli, *Gazz. Chim. Ital.*, 1988, **118**, 495.