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A Synthesis of Quinoline-5,8-quinones via the Benzannulation of 1,4-Dihydro-2-pyridyl Carbene Complexes.

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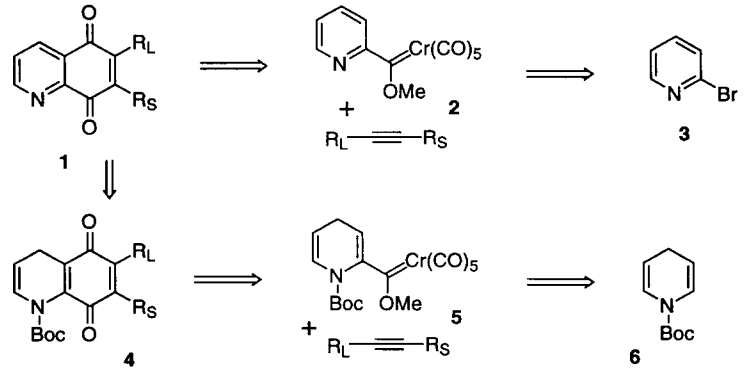
Abstract: A method for the preparation of quinoline-5,8-quinones is described with the key step the benzannulation of a dihydropyridyl Fischer carbene complex. The carbene complexes are generated by the standard Fischer method upon metallation of N-Boc protected 1,4-dihydropyridines and their reactions with alkynes to provide 1,4-dihydroquinolines. The latter are converted to quinoline,5,8-quinones by a two-step oxidation procedure involving ceric ammonium nitrate and trityl tetrafluoroborate.

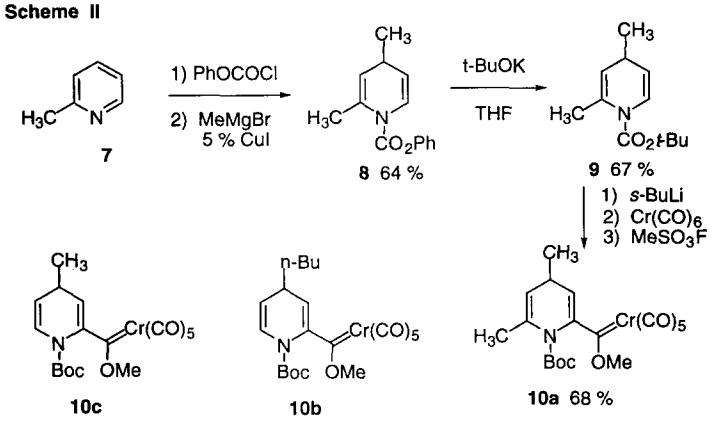
The quinoline-5,8-quinone unit **1** occurs in a variety of biological active compounds.[1] A simple and straightforward preparation of this class of molecules would be the benzannulation reaction of pyridyl carbene complexes with alkynes.[2] We have not been able to prepare pyridyl carbene complexes by the standard Fischer method, and a search of the literature reveals that the only example of this type of compound is the 4-fluoro-3-pyridyl complex.[3] Given this limitation, an alternative approach to this class of compounds outlined in Scheme I involving the benzannulation reaction of dihydropyridyl carbene complexes appeared too appealing to resist. The success of this method would rely on the synthesis of the dihydropyridyl carbene complexes from the organolithium generated from deprotonation of the N-Boc protected 1,4-dihydropyridine by the method of Comins.[4] We report herein the synthesis of dihydropyridyl complexes of the type **5** by this method and the realization of this overall strategy for the preparation of quinoline quinones.

Scheme I



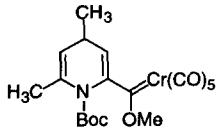
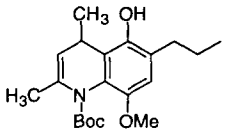
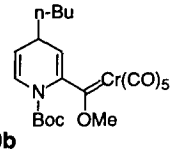
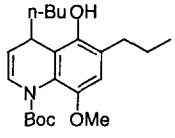
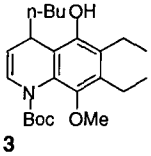
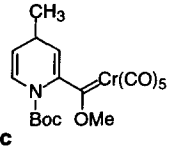
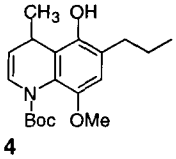
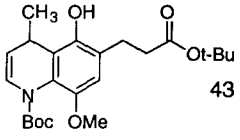
The 1,4-dihydropyridines were prepared in a selective fashion by the copper-catalyzed addition of Grignard reagents to N-carbamoylpyridinium salts according to the procedure of Comins and Abdullah [5] and this is illustrated in Scheme II for the synthesis of 4,6-dimethyl-1,4-dihydro-2-pyridyl carbene complex **10a**. Prior to conversion to the carbene complex, the phenyl carbamate **8** is convert to the *t*-butyl carbamate since the latter is more effective in heteroatom directed metallations.[4] The α-lithio-1,4-dihydropyridine generated from carbamate **9** and *s*-butyllithium was directly converted to the carbene complex **10a** by the Fischer method. A THF solution of the anion generated from **9** was transferred to a slurry of chromium hexacarbonyl in THF at -45 °C. The reaction mixture was allowed to warm to ambient temperature overnight and then was methylated by addition of one equivalent of methyl fluorosulfonate (or methyl triflate). The reaction was quenched after 30 minutes with aqueous sodium bicarbonate, and purification on silica gel with 10 % ethyl acetate in hexane gave the carbene complex **10a** as a red viscous oil in 68 % yield.[6] The carbene complexes **10b** and **10c** were prepared in a similar manner in 36 % and 33 % overall yields from pyridine, respectively.

Scheme II



The results of the benzannulation of carbene complexes **10a**, **10b** and **10c** with various alkynes are summarized in Table I. The reactions were carried out under an argon atmosphere in THF at 0.04 M in carbene complex with 1.5 equivalents of alkyne at 60 °C for 42 hours. The 1,4-dihydroquinoline products **11** - **15** were all isolated as yellow sticky oils that were somewhat air sensitive and which showed substantial decomposition if allowed to stand in solution in air for several hours. Nonetheless, satisfactory elemental analysis could be obtained for the representative structures **12** and **13** and each product could be obtained in a pure form by chromatography on silica gel.[7] The data in the Table reveals that the efficiency of the benzannulation reaction of dihydropyridine complexes is dependent on the nature of the alkyne. Terminal alkynes give moderate yields but internal alkynes are not efficient in producing the normal benzannulated product (reaction of **10c** with 3-hexyne gives a 13 % yield of the analog of **13**). The benzannulation reaction is sensitive to reaction conditions and to functionality patterns and has been shown to give a very broad range of structurally diverse side-products.[2] These reactions were screened only for the benzannulated product, and the mass balance of these reactions was not accounted for. For simple alkenyl carbene complexes, a difference is not seen between the yields of the benzannulation reactions with internal and internal alkynes. The yields for the reactions of simple alkenyl complexes with terminal alkynes are only slightly higher yields than observed here with dihydropyridine complexes.[2] However, a similar difference in the yields of benzannulated products from internal and terminal alkynes has recently been seen from the reactions of alkenyl carbene complexes that are stabilized with an amino group rather than a methoxyl group.[8] The source of the dependence of these reactions on the nature of the alkyne was not determined in that work and remains a mechanistic issue to be examined.

Table I. Dihydroquinolines from Dihydropyridine Carbene Complexes. [a]

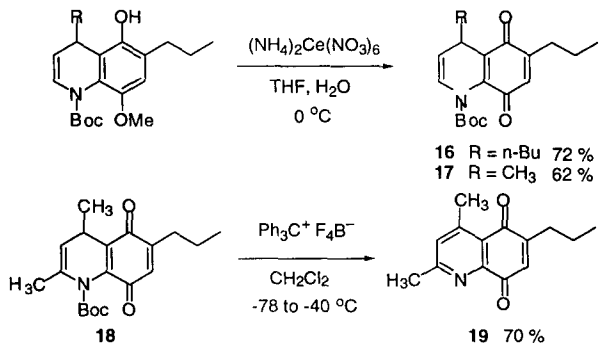
Dihydropyridyl Carbene Complex	Alkyne	Dihydroquinoline	Yield [b]
 **10a**	1-pentyne	 **11**	58 %
 **10b**	1-pentyne	 **12**	47 %
	3-Hexyne	 **13**	12 %
 **10c**	1-pentyne	 **14**	60 %
	t-Butyl-4-pentynoate	 **15**	43 %

[a]All reactions were carried out in THF at 0.04 M in carbene complex with 1.5 equivalents of the alkyne for 42 h at 60 °C. [b]Isolated yields after silica gel chromatography.

The 1,4-dihydroquinoline products obtained from the benzannulation reaction of dihydropyridyl carbene complexes can be oxidized in a stepwise fashion to quinoline-5,8-quinones as indicated in Scheme III. Treatment of the dihydroquinolines **12** and **14** with ceric ammonium nitrate leads to a rapid color change of yellow to red which signals the formation of the 1,4-dihydroquinoline-5,8-quinones **16** and **17**. The latter can be isolated in pure form by chromatography on silica gel as deep scarlet red oils and are somewhat air sensitive but are stable indefinitely under argon at -15 °C. The oxidation with cerium is complete within a few minutes, and if the dihydroquinoline quinones **16** and **17** are not isolated from the crude reaction mixture immediately, reduced yields are observed. Final oxidation to quinoline-5,8-quinones is illustrated for the dihydroquinoline quinone **18** which was obtained in 45 % yield from **11**. After screening several oxidants, it was found that efficient conversion to the quinoline-5,8-quinone **19** could be achieved with triphenylmethyl tetrafluoroborate (2 equivalents). The reagents were mixed at -78 °C but the reaction did not ensue until warming to -40 °C as indicated by a change in color from red to yellow. Upon consumption of starting material, the reaction was

quenched at -40 °C with sodium bicarbonate, and **19** was isolated by chromatography on silica gel as a yellow solid which slowly darkened in air at room temperatures over several hours.[9]

Scheme III



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4. a) Comins, D. L., *Tetrahedron Lett.* **1983**, *24*, 2807. b) Comins, D. L.; Weglarz, M. A., *J. Org. Chem.* **1988**, *53*, 4437.
5. Comins, D. L.; Abdullah, A. H., *J. Org. Chem.* **1982**, *47*, 4315.
6. Complex **10a** is a red oil: ^{1}H NMR ($CDCl_3$) δ 1.11 (d, 3 H, J = 7 Hz), 1.45 (s, 9 H), 2.25 (m, 1 H), 2.42 (s, 3 H), 4.69 (s, 3 H), 4.87 (brd s, 1 H), 5.03 (brd s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.6, 20.8, 27.7, 28.3, 66.4, 82.4, 112.8, 118.4, 135.3, 149.8, 151.7, 216.0, 223.0, 337.4; IR ($CHCl_3$) 2060, 1985, 1940 cm^{-1}; mass spectrum, calcd for $C_{19}H_{21}CrNO_8$ m/z 443.0672, measd 443.0727.
7. Dihydroquinoline **12** is a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.85 (m, 3 H), 1.00 (t, 3 H, J = 7 Hz), 1.28 (m, 4 H), 1.49 (s, 9 H), 1.55 (m, 4 H), 2.55 (t, 2 H, J = 7 Hz), 3.60 (m, 1 H), 3.78 (s, 3 H), 4.42 (s, 1 H), 5.42 (m, 1 H), 6.56 (s, 1 H), 6.96 (s, 1 H); IR ($CHCl_3$) 1710, 1660 cm^{-1}; mass spectrum, m/z (% rel intensity) 375 M+ (6). Anal calcd for $C_{22}H_{33}NO_4$: C, 70.36; H, 8.86; N, 3.73. Found : C, 70.15; H, 9.04; N, 3.59.
8. Wulff, W. D.; Gilbert, A. M.; Hsung, R. P.; Rahm, A., *J. Org. Chem.* **1995**, *60*, 4566.
9. Quinoline,5-8-quinone **20** is a yellow solid; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7 Hz), 1.58 (m, 2 H), 2.50 (t, 2 H, J = 7 Hz), 2.66 (s, 3 H), 2.71 (s, 3 H), 6.82 (s, 1 H), 7.24 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.9, 21.9, 24.5, 31.2, 125.4, 130.3, 148.0, 150.1, 151.9, 162.8, 183.8, 186.5; IR ($CHCl_3$) 1678, 1657 cm^{-1}; mass spectrum, calcd for $C_{14}H_{15}NO_2$ m/z 229.1103, measd 229.1103.

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