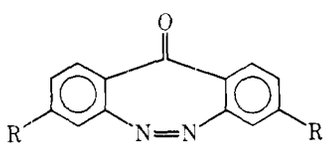
Communications

Synthesis of Biheteroaryls by Facile Decarbonylation of Electron-Poor Heteroaromatic Ketones[1]

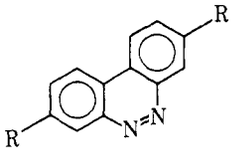
Summary: Substituted di(2-pyridyl) ketones undergo mild decarbonylation upon treatment with base in xylene to give the corresponding bipyridyl.

Sir: Although aldehydes undergo relatively easy decarbonylation under a variety of reaction conditions,[2] decarbonylation of ketones has been achieved primarily via photolytic[3] or drastic pyrolytic (>500 °C)[3,4] conditions. Generally, these photolytic reactions occur by radical pathways,[2] whereas pyrolytic decarbonylations proceed by either radical[4a-e] or retro-ene[4f] mechanisms.

Chemical decarbonylations are best demonstrated for α-diketones (benzilic acid rearrangement),[5] such as diphenyl triketone, which has been shown to decarbonylate with various reagents.[6] However, simple aromatic or heteroaromatic ketones have been observed to decarbonylate only rarely under mild conditions. Popp et al. have reported the ring contraction (decarbonylation) of dibenzo[*c*,*f*][1,2]diazepin-11-one (**1a**, R = H,[7] or **1b**, R = Cl) upon treatment with either sodium hydroxide in dioxane or modified Wittig reaction conditions to afford **2**.[7a] We herein report the decarbonylation of electron-poor heteroaromatic ketones under mild reaction conditions to generate the corresponding biheteroaryl.



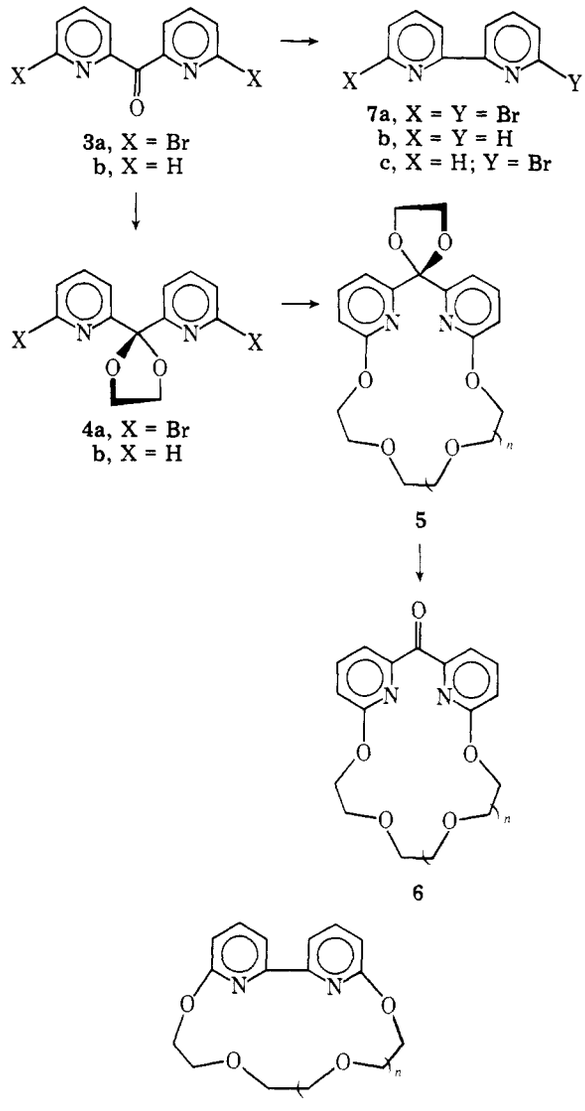
1



2

During the melding of ketonic[8] and polyethereal[9] macrocycles, ketal **4a**[10] was treated with a glycolate dianion, generated from the glycol and 2 equiv of oil-free sodium hydride in xylene at 140 °C to give **5** (n = 2–4,[11] 30%), which upon hydrolysis afforded **6** (n = 2–4) in near quantitative yield. In an effort to circumvent the ketal intermediate, **3a** was subjected to the same nucleophilic displacement procedure,[9] but rather than the anticipated macrocycle **6** (n = 2), **3a** underwent decarbonylation to afford **7a** (40%; mp 220–221 °C)[12] as well as traces of macrocycle **8** (n = 2; mp 90–92 °C)[13] (Scheme I).

Scheme I



Without the glycolate dianion, di(2-pyridyl) ketone (**3b**), when subjected to sodium hydride in anhydrous xylene at 140 °C, after 24 h afforded 2,2′-bipyridyl (**7b**; 35%, mp 72 °C) along with unchanged starting material (>50%). The overall conversion was not maximized, since with longer reaction times, increased yields can be realized. Either lithium or calcium hydride can be substituted for sodium hydride, but for comparable conversion longer reactions were deemed necessary for the less reactive hydride sources. Replacement of the hydride source with other better nucleophiles (e.g., NaOMe, NaOH) afforded only traces of the decarbonylated products along with starting ketone and numerous degradation products.[14] No reaction of **3** was observed (**3** recovered in toto) when either (a) the hydride source was eliminated or (b) benzoyl peroxide was substituted for sodium hydride. The intermolecularly coupled product **7c** was *not* isolated from an equimolar reaction mixture of **3a** and **3b**, only **7a** and **7b** were isolated in 35% yield each along with the starting ketones.

In order to extend this procedure to nonheterocyclic systems, 2-benzoylpyridine and 3,3′-dinitrobenzophenone were separately subjected to the above reaction conditions; both were recovered in near quantitative yield. To better reflect the electron-withdrawing character of the pyridine moiety, 4,4′-dinitrobenzophenone[15] (**9**) was prepared by oxidation of bis(4-nitrophenyl)methane. When **9** was subjected to the decarbonylation conditions for 12 h, 4,4′-dinitrobiphenyl[16] (mp 240 °C) was isolated (25%) along with starting ketone!

Striking differences in mass spectral fragmentation patterns for benzophenone [$M^{+\cdot} - CO \rightarrow m/e$ 154 (1–2%)][17] vs. di(2-pyridyl) ketone [$M^{+\cdot} - CO \rightarrow m/e$ 156 (40%)][18] further demonstrate an enhanced ease for decarbonylation of ketones which possess electron-withdrawing aryl groups. Recently, formation of bipyridyl by a facile dephosphorylation of di(2-

0022-3263/79/1944-1362$01.00/0

pyridyl)phenylphosphine *P*-oxide[13] was suggested to proceed via a benzilic acid rearrangement; a similar mechanistic course can be tentatively considered plausible for this decarbonylation reaction.

In conclusion, it appears that ketones which possess two electron-withdrawing aryl groups will undergo decarbonylation under mild reaction conditions. Work is continuing in order to ascertain the breadth of this reaction and to gain further insight into the mechanistic rationale.

Acknowledgment. Supported in part by the National Institutes of Health (GM 20985).

References and Notes

(1) Part 38 in the Chemistry in Heterocyclic Compounds Series. Presented in part at the Organic Reactions Mechanisms Symposium at the 34th Southwest Regional Meeting of the American Chemical Society, Corpus Christi, Texas, Dec., 1978.
(2) Schubert, W. M. "The Chemistry of the Carbonyl Group", Vol. 1, S. Patai, Ed.; Interscience: New York, 1966; p 695.
(3) (a) McMillan, G. R.; Calvert, J. G.; Pitts, Jr., J. N. *J. Am. Chem. Soc.* **1964,** *86,* 3602. (b) Srinivasan, R. *ibid.* **1959,** *81,* 5061. (c) *ibid.* **1962,** *84,* 2475. (d) Kan, R. O. "Organic Photochemistry", McGraw-Hill: New York, 1966. (e) Coxonand, J. M.; Halton, B. "Organic Photochemistry", Cambridge University Press: London, 1974.
(4) (a) Steacie, E. W. R. "Atomic and Free Radical Reactions", 2nd ed., Vol. 1; Reinhold: New York, 1954; pp 205–229. (b) Rice, F. O.; Herzfeld, K. F. *J. Am. Chem. Soc.* **1958,** *80,* 3289. (c) McNesly, J. R.; Gordon, A. S. *ibid.* **1954,** *76,* 1416. (d) Cesare, F. C. Ph.D. Thesis, University of Maryland, **1961.** (e) Daignault, L. G.; Walters, W. D. *J. Am. Chem. Soc.* **1958,** *80,* 541. (f) Bailey, W. J.; Cesare, F. C. *J. Org. Chem.* **1978,** *43,* 1421.
(5) Review: Salman, S. S.; Eastham, J. F. *Q. Rev., Chem. Soc.* **1960,** *14,* 211.
(6) Roberts, J. D.; Smith, D. R.; Lee, C. C. *J. Am. Chem. Soc.* **1951,** *73,* 618.
(7) (a) Dubois, R. J.; Popp, F. D. *Chem. Commun.* **1968,** 675. (b) *Chem. Ind. (London)* **1969,** 620. (c) Casey, A. C.; Popp, F. D. *Org. Prep. Proced.* **1970,** *2,* 29.
(8) (a) Newkome, G. R.; Sauer, J. D.; Mattschei, P. K.; Nayak, A. *Heterocycles,* **1978,** *9,* 1555. (b) Newkome, G. R.; Nayak, A.; Sauer, J. D.; Mattschei, P. K.; Watkins, S. F.; Fronczek, F.; Benton, W. H. submitted for publication.
(9) Newkome, G. R.; Danesh-Khoshboo, F.; Nayak, A.; Benton, W. H. *J. Org. Chem.* **1977,** *42,* 1500. Newkome, G. R.; Nayak, A.; Otemaa, J.; Van, D. A.; Benton, W. H. *J. Org. Chem.* **1978,** *43,* 3362. Newkome, G. R.; Danesh-Khoshboo, F.; Nayak, A.; Benton, W. H. *J. Org. Chem.* **1978,** *43,* 2685. Newkome, G. R.; Nayak, A. *J. Org. Chem.* **1978,** *43,* 409.
(10) Newkome, G. R.; Sauer, J. D.; McClure, G. L. *Tetrahedron Lett.* **1973,** 1599.
(11) Taylor, H. C. R., unpublished results.
(12) Parks, J. E.; Wagner, B. E.; Holm, R. H. *J. Organomet. Chem.* **1973,** *56,* 53.
(13) Newkome, G. R.; Hager, D. C. *J. Am. Chem. Soc.* **1978,** *100,* 5567.
(14) Degradation products were not investigated further.
(15) Kochergin and Karpov's procedure [*Byul. Izobret. Tovarnykh. Znakov,* **1964,** 11] for the transformation of diphenylmethanol to **9** was unsuccessfully attempted; 3,3′-dinitrobenzophenone was isolated in high yield. Oxidation of di(4-nitrophenyl)methane with sodium dichromate gave **9** [Rieveschl, Jr., G. *Org. Synth.* **1950,** *3,* 420].
(16) DeTar, D. F.; Kazimi, A. A. *J. Am. Chem. Soc.* **1955,** *71,* 3842.
(17) Natalis, P.; Franklin, J. L. *J. Phys. Chem.* **1965,** *69,* 2943. Eland, J. H. D.; Danby, C. J. *J. Chem. Soc.* **1965,** 5935.
(18) Keats, N. G.; Summers, L. A. *J. Heterocycl. Chem.* **1976,** *13,* 1289.

George R. Newkome,* Hellen C. R. Taylor
Department of Chemistry
Louisiana State University
Baton Rouge, Louisiana 70803
Received October 17, 1978

Diisobutylaluminum 2,6-Di-*tert*-butyl-4-methylphenoxide. Novel Stereoselective Reducing Agent for Prostaglandin Synthesis

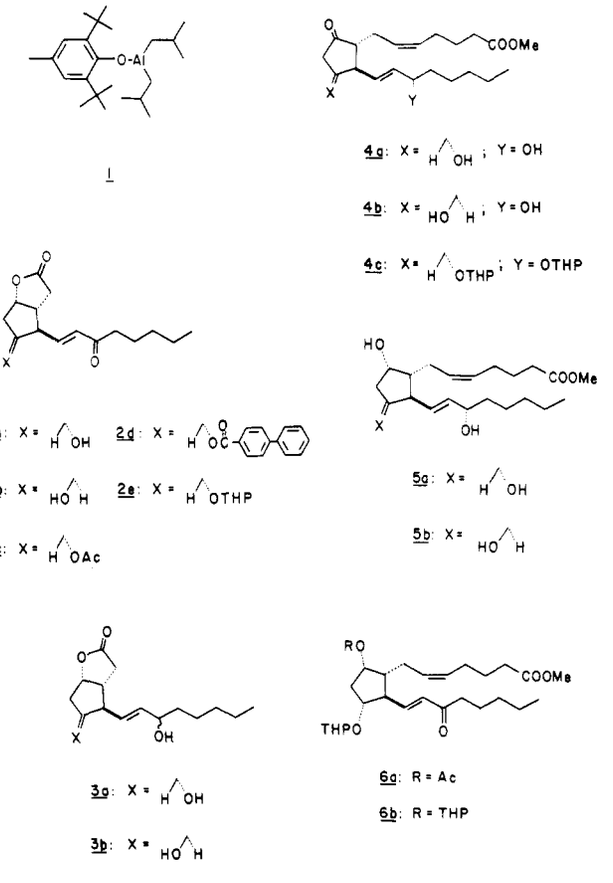
Summary: In an effort to explore the selective reducing agents suitable for prostaglandin synthesis, diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (**1**) is found to be among the best. Reduction of the C-15 ketone **2a** with **1** in toluene at −78 °C produced the desired α-alcohol **3a** in 95% yield with 92% stereoselectivity. The procedure is suitable for the synthesis of prostaglandin derivatives and related polyfunctional natural products.

Sir: At the heart of almost any prostaglandin synthesis[1] whose ultimate goal is the stereoselective approach must lie a methodology which controls stereochemistry at C-15.[2] In consonance with this fact we have been interested for many years in devising an efficient approach to the stereocontrolled reduction of the C-15 ketone. The present method utilizes the title compound as the key reagent for a *simple* and *practical* solution to this problem.

A solution of diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (**1**)[3,4] can be prepared from diisobutylaluminum hydride (1.76 M solution in toluene) and 2,6-di-*tert*-butyl-4-methylphenol (molar ratio 1:1 to 1:2)[5] in toluene at 0 °C for 1 h. Reaction of **1** (10 equiv) with the enone **2a** in toluene (~0.2 M reagent) first at −78 °C for 2 h was complete after warming to −20 to −40 °C for 1 h. The reaction was terminated by addition of hydrochloric acid (~1 M) and the product was extracted with ethyl acetate. Short-path chromatographic separation to remove the recovered phenol gave the allylic alcohol **3a** in 95% yield. The ratio of 15*S* to 15*R* (prostanoic acid numbering) isomers in several runs was 92:8 by high-pressure liquid chromatographic analysis.[6]

Starting from the C-11 isomeric **2b** and using the same procedure as applied for the synthesis of **3a,** there was produced in 94% isolated yield the alcohol **3b** (15*S*/15*R* = 85:15).[6] Similarly starting from PGE_2 methyl ester (**4a**) there was obtained $PGF_{2\alpha}$ methyl ester (**5a**) in 95% yield and 100% selectivity.[7] Furthermore, reaction of **1** with the C-11 epimeric PGE_2 methyl ester **4b** again furnished the C-11 epimeric $PGF_{2\alpha}$ methyl ester (**5b**) exclusively and efficiently (92% yield).[8]

In contrast to the highly selective reduction of hydroxy ketones, the acetate **2c** afforded the corresponding allylic alcohols without any stereoselectivity (15*S*/15*R* = ~1:1).[6] Analogously, no stereoselectivity could be observed using



0022-3263/79/1944-1363$01.00/0