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Carbon Dioxide: A Reagent for the Simultaneous Protection of Nucleophilic Centres and the Activation of Alternative Locations to Electrophilic Attack. Part 8[1]. A Novel Synthetic Route to 4-Substituted-2-pyridones

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Abstract: 2-Pyridone, using the one-pot protection method, is lithiated specifically in the 4-position. In this way, a range of 4-substituted 2-pyridones was prepared. Their orientation of substitution was proved by X-ray analysis.

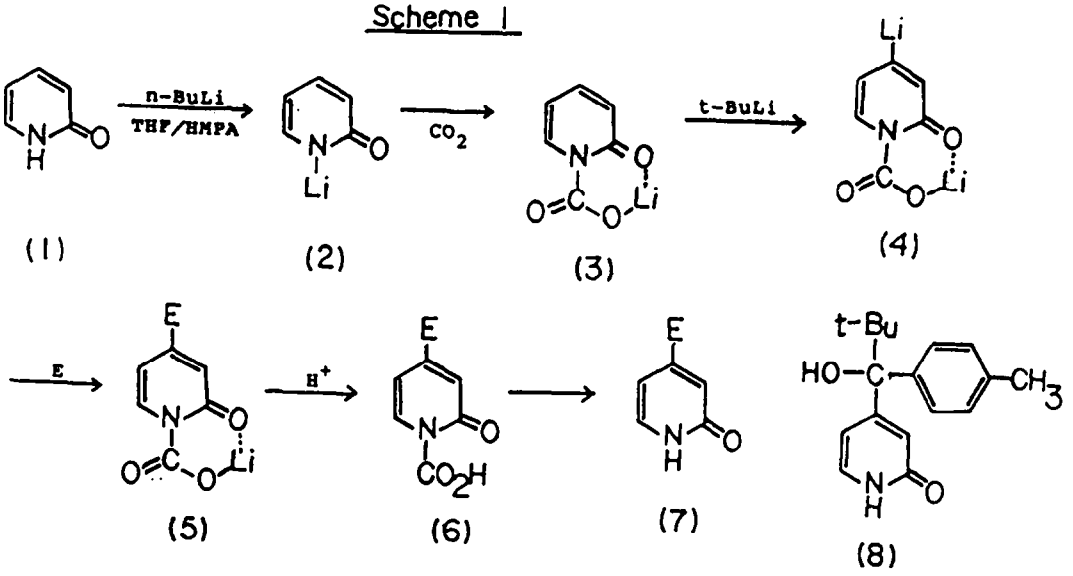
Pyridines are susceptible to ring deprotonation: strong base-catalyzed H-exchange[2] and lithiation[3] of many derivatives have been described. However, pyridones have received relatively little attention. Our group has reported[4] the preparative lithiation reaction of simple N-alkyl-2-pyridones with LDA, the resulting N-(lithioalkyl)pyridone reacted with electrophiles to give the expected products. Recently, Joule described[5] the formation of a stable 1-methyl-2-lithio-4-pyridone from 1-methyl-4-pyridone with n-butyllithium in THF, giving 2-substituted products with a range of alkylating and acylating agents, but they failed to lithiate 1-methyl-2-pyridone under these condition. No preparative C-lithiation has been described for an N-unsubstituted pyridone itself: the presence of an N-proton is expected to lead to an unreactive anion. We have now examined the protection of this NH group prior to the lithiation.

We have reported recently that carbon dioxide provides excellent protection for use during the functionalization of secondary amines,[6] of benzylamine and benzyl alcohol,[7] and of secondary amides[8] in each case via the corresponding lithio species. We speculated that an analogous reaction sequence could operate in the case of a pyridone and that this should provide a potentially novel method for the regioselective functionalization of pyridones.

Based on our results reported in this paper, with 2-pyridone as a substrate, a general approach to accomplish lithiation and substitution at the pyridone ring has been developed with carbon dioxide as the reagent used to protect the NH group. The procedure comprises four stages: (i) the protection of the NH group by lithiation and subsequent treatment with carbon dioxide to form the lithium carbamate; (ii) lithiation by t-butyllithium; (iii) introduction of a suitable substituent by reaction with an electrophile; (iv) removal of the N-protecting group in an acidic medium (Scheme 1).

This reaction sequence was found to provide a novel one-pot synthetic sequence for the functionalization of 2-pyridone at the 4-position. The following operations are involved in the conversion of 2-pyridone (1) to a 4-substituted 2-pyridone (2):

Scheme I



(i) **Protection:** 2-pyridone was converted into the corresponding lithium carbamate (3) by reaction with n-butyllithium in THF and 5% (V/V) HMPA solvent mixture (1 -- 2), followed by quenching with carbon dioxide (2 -- 3).

(ii) **Lithiation:** lithiation of intermediate (3) was accomplished by the addition of 1.2 equivalent of t-butyllithium in THF-HMPA solvent at ca. -20°C to give (4).

(iii) **Carbon-carbon bond formation:** intermediate (4) was converted into (5) by adding 1.1 equivalent of the electrophile at ca. -70°C and then allowing the mixture to warm to 25°C overnight.

(iv) **Deprotection:** aqueous 2N hydrochloric acid was slowly added to the reaction mixture at 0°C and the whole kept for 15 minutes at this temperature to convert (5) into (7) via (6).

As shown in Table 1, a wide range of electrophiles was employed, and the yields of the products are moderate to good. Groups introduced in this way into the 4-position of 2-pyridone include an alkyl group from an alkyl halide; secondary and tertiary alcohols from aldehydes and ketones; carbonyl derivatives from an acyl halide and an isocyanate; and the carboxylic acid from carbon dioxide as electrophile. D-Incorporation resulted from the reaction with D_2O. However, when ethyl p-methylbenzoate was used as the electrophile, the product (8) isolated in 35% yield contained a t-butyl group, presumably it was formed *via* addition of t-butyllithium to 4-(p-methylbenzoyl)-2-pyridone. The new derivatives were characterized analytically, and by their ^1H and ^{13}C NMR spectra (see Experimental Section).

Unexpectedly and interestingly, the substituent was introduced at the 4-position, and not at 3- or 6-position as had been anticipated. The evidence of functionalization on the 4-position comes from: (i) the physical properties (e.g., mp.) of some known compounds (7e and 7f) are consistent with those reported in the literature (see Table 1); (ii) in the ^1H NMR spectra of some products (cf. 7b and 7c), a singlet appears at δ 6.60 (7b) or 6.45 (7c) which is easily assigned to C-3 proton of 4-substituted 2-pyridone (see Table 1); and conclusively, (iii) the X-ray structure determination of the product (7a) from benzophenone.

Table 1. Preparation of 4-Substituted 2-Pyridones

Cpd. No.	electrophile	substituent	yield (%)	mp (°C)	lit. mp (°C)	δ_H(Py-C3-H)
7a	Ph_2CO	$C(OH)Ph_2$	60	260-262	---	6.70[c]
7b	p-$CH_3C_6H_4CHO$	$CH(OH)C_6H_4CH_3$-p	52	266-268	---	6.60(s)
7c	p-$CH_3OC_6H_4CHO$	$CH(OH)C_6H_4OCH_3$-p	57	226-228	---	6.45(s)
7d	D_2O	D	85[a]	103-105	105-107	6.55
7e	CH_3I	CH_3	53	127-128	130[9]	6.40(s)
7f	CO_2	CO_2H	62	330(dec)	325(dec)[10]	--
7g	PhNCO	PhNHCO	58	153-155	---	6.50[c]
7h	p-$CH_3OC_6H_4COPh$	$C(OH)PhC_6H_4OCH_3$-p	49	227-230	---	6.50[c]
7i	$PhCH_2COCl$	$PhCH_2CO$	51	198-201	---	6.80[c]
8	p-$CH_3C_6H_4CO_2Et$	b	35	180-182	---	6.75[c]

a. ^1H NMR yield.

b. product (8) was obtained

c. overlapped with other pyridone or phenyl proton signals.

The crystals of (pyrid-2-on-4-yl)diphenylcarbinol are monoclinic, $P2_1/c$, with unit cell parameters a = 7.961(1), b = 14.493(2), c = 12.396(2)Å, β = 94.04(1)°, V = 1426.6(4)Å^3 and Z = 4. A crystal of 0.14 x 0.14 x 0.22 mm was used for measurements of the diffraction intensities on a Syntex P1 diffractometer with Ni-filtered Cu Kα radiation. Within the 2θ range of 1.5 to 112.5°, 2189 reflections were measured. The Lorentz and polarization corrections were applied to the data but none for the absorption [μ(Cu Kα) = 6.9 cm^{-1}]. The structure was solved by direct methods using all 1616 unique observed reflections with $F_o \geq 2\sigma(F_o)$. Least squares refinement of positional and anisotropic thermal parameters for non-hydrogen atoms gave final values of R = 0.056 and R_w = 0.040; the weighting scheme was $w = 1/\sigma^2(F)$. The H-atoms were found unambiguously in the difference map and were included, with fixed parameters, in the structure-factor calculations. In the final cycle of the refinement the maximum shift was 0.003σ. The final difference map showed residual peaks in the range -0.26 to 0.19 eÅ^{-3}. All calculations were carried out on a DG Desktop 30 computer using the SHELXTL system[11]. Molecular conformation, atom numbering and selected bond distances are given in Fig. 1[12].

Table 2 Atomic coordinates (x 10^4) and isotropic thermal parameters (Å^2)

	x	y	z	U
N(1)	-3758(3)	69(2)	1431(2)	0.056(1)
C(1)	-2697(3)	449(2)	741(2)	0.046(1)
O(1)	-3255(2)	674(1)	-195(1)	0.056(1)
C(2)	-990(3)	557(2)	1157(2)	0.043(1)
C(3)	-458(3)	274(2)	2179(2)	0.041(1)
C(4)	-1625(4)	-132(2)	2845(2)	0.053(1)
C(5)	-3265(4)	-225(2)	2446(2)	0.064(1)
C(6)	1391(3)	388(2)	2573(2)	0.041(1)
O(2)	2381(2)	531(1)	1664(1)	0.048(1)
C(11)	1644(3)	1252(2)	3280(2)	0.046(1)
C(12)	631(4)	1433(2)	4124(3)	0.067(1)
C(13)	935(4)	2204(3)	4782(3)	0.082(2)
C(14)	2268(5)	2780(2)	4632(3)	0.078(1)
C(15)	3265(4)	2609(2)	3776(3)	0.071(1)
C(16)	2949(4)	1850(2)	3111(2)	0.057(1)
C(21)	2050(3)	-494(2)	3155(2)	0.044(1)
C(22)	2958(4)	-478(2)	4154(2)	0.052(1)
C(23)	3633(4)	-1283(3)	4592(3)	0.068(1)
C(24)	3451(4)	-2109(3)	4048(3)	0.076(1)
C(25)	2550(5)	-2129(2)	3047(3)	0.075(2)
C(26)	1841(4)	-1334(2)	2611(2)	0.059(1)

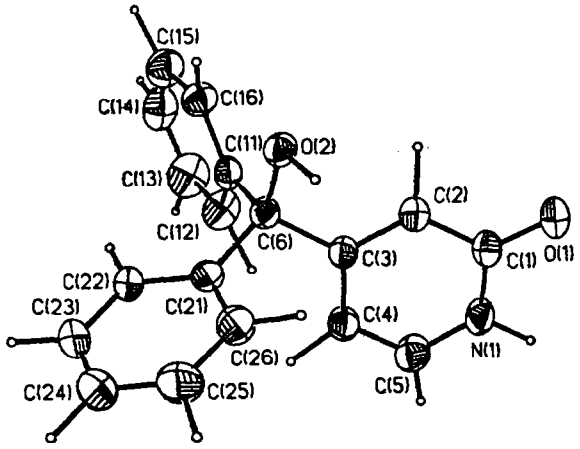


Fig. 1. The perspective view of the molecule and atomic labeling. Bond lengths (Å) within the 2-pyridone ring and around the C(6) atom are: N(1)-C(1) 1.361(4), N(1)-C(5) 1.359(4), C(1)-O(1) 1.256(3), C(1)-C(2) 1.427(4), C(2)-C(3) 1.370(4), C(3)-C(4) 1.414(4), C(3)-C(6) 1.527(3), C(4)-C(5) 1.369(4), C(6)-O(2) 1.434(3), C(6)-C(11) 1.533(4), C(6)-C(21) 1.541(4).

The molecule is clearly a 4-substituted derivative of 2-pyridone. The two phenyl rings are planar and have normal bond lengths (mean values are 1.384 and 1.385 Å). The 2-pyridone system is also planar: the bond lengths in the 6-membered ring indicate partially double character of the C(2)-C(3) and C(4)-C(5) bonds, while the C(1)-C(2) and C(3)-C(4) bonds are longer than an aromatic C-C bond. These values are closer to the calculated bond distances for the 2-pyridone ring[13] than values found in the crystal structure of a 2-pyridone complex[14]. The ketone O(1) atom is double acceptor of hydrogen bonds {O(1)...H-N(1)[-1-X,$\bar{Y}$,$\bar{Z}$] and O(1)...H-O(2)[$\bar{X}$,$\bar{Y}$,$\bar{Z}$]} and the N(1) is a donor, which can influence the pattern of the electron distribution in the system.

The reason that the substituent enters into 4-position instead of 6-position is not yet clear. A possible rationalization is that the lithium carbamate intermediate (3) coordinates with co-solvent HMPA which was used to enhance the solubility of (3), hindering the attack of the electrophile at the 6-position. The detailed mechanism is under investigation.

In summary, 4-substituted 2-pyridones were synthesized in a one-pot sequence by the use of carbon dioxide as the protecting agent in good yield. The particular ease of introduction and of removal, which characterize our use of carbon dioxide as a protecting group, thus provide a novel method to prepare 4-substituted 2-pyridones.

Experimental Section

General: Melting points of the products were measured by a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM 360L using TMS as internal standard. ^{13}C NMR spectra were obtained on a Model FX100 spectrometer. Elemental analyses were carried out under the supervision of Dr. R. King of this Department. Processes (i) to (iii) were carried out under dry argon. 2-Pyridone was purified by recrystallization from benzene twice.

General Procedure: The interior of a Schlenk type reactor was flushed with argon and 2-pyridone (0.95 g, 10 mmol) was introduced. Tetrahydrofuran (28.5 ml) and HMPA (1.5 ml) was then added. The reaction solution was cooled to -70°C and n-butyllithium (4.0 ml, 2.6 M n-hexane solution) was added dropwise. The temperature of the resulting solution was allowed to rise to 25°C. Carbon dioxide gas was passed through the solution for 5 minutes. The solvent was evaporated under reduced pressure and a pale solid was obtained. The atmosphere was replaced with argon. Tetrahydrofuran (28.5 ml) was added. The whole was cooled to ca. -70°C. t-Butyllithium (7.0 ml, 1.7 M n-pentane solution) was added slowly. The cooling bath was replaced by an ice-salt bath, and the solution was kept at ca. -20°C for 1h. The electrophile in THF was added at -70°C. The reaction was allowed to regain room temperature overnight. Aqueous hydrochloric acid (2N) was added slowly at 0°C. Gas was evolved immediately, then the solution was neutralized and extracted with chloroform, washed with water, and dried with anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure gave the product. Purification was carried out by recrystallization from ethanol. For yields and physical data, see Table 1.

(Pyrid-2-on-4-yl)diphenylcarbinol (7a): $C_{18}H_{15}NO_2$, ^{1}H NMR(DMSO-d_6) 11.65 (brs, 1H, NH), 7.40 (s, 11H, Ph-H and Py-H), 6.2-6.7 (m, 3H, OH and Py-H); ^{13}C NMR 161.8 (Py-C2), 159.1 (Py-C6), 144.1 (Py-C4), 131.7, 126.3, 126.1, 125.6, 117.0 (Py-C5), 104.8 (Py-C3), 78.8 (C-OH); Anal. calcd. C, 77.98, H, 5.42, N, 5.05%; Found C, 78.15, H, 5.25, N, 4.91%.

α-(Pyrid-2-on-4-yl)-4-methylbenzyl alcohol (7b): $C_{13}H_{13}NO_2$, ^{1}H NMR(DMSO-d_6) 7.25 (d, 2H, Ar-H), 7.46 (d, 1H, Py-C6-H), 7.38 (d, 2H, Ar-H), 6.60 (s, 1H, Py-C3-H), 6.30 (d, 1H, Py-C5-H), 5.70 (s, 1H, CH), 2.50 (s, 3H, CH_3); ^{13}C NMR 162.8 (Py-C2), 158.7 (Py-C6), 140.7 (Py-C4), 136.4, 134.6, 128.8, 126.5, 115.1 (Py-C3), 103.9 (Py-C5), 73.0 (CHOH), 20.7 (CH_3); Anal. calcd. C, 72.56, H, 6.05, N, 6.51%; Found C, 72.33, H, 6.28, N, 6.31%.

α-(Pyrid-2-on-4-yl)]-4-methoxylbenzyl alcohol (7c): $C_{13}H_{13}NO_3$, ^{1}H NMR(DMSO-d_6) 7.35 (d, 2H, Ar-H), 7.30 (d, 1H, Py-C6-H), 6.92 (d, 2H, Ar-H), 6.45 (s, 1H, Py-C3-H), 6.10 (d, 1H, Py-C5-H), 5.45 (s, 1H, CHOH), 3.70 (s, 3H, OCH_3), 3.50 (brs, 1H, OH); ^{13}C NMR 162.6 (Py-C2), 158.4 (Py-C6), 135.7 (Py-C4), 134.5, 127.7, 126.8, 126.7, 115.0 (Py-C3), 106.7 (Py-C5), 72.6 (CHOH), 55.0 (OCH_3); Anal. calcd. C, 67.53, H, 5.63, N, 6.06%; Found C, 67.24, H, 5.75, N, 5.87%.

4-Methyl-2-pyridone (7e): C_6H_7NO, ^{1}H NMR($CDCl_3$) 7.30 (d, 1H, Py-C6-H), 6.40 (s, 1H, Py-C3-H), 6.15 (d, 1H, Py-C5-H), 2.25 (s, 3H, CH_3).

4-(N-Phenylcarbamoyl)-2-pyridone (7g): $C_{12}H_{10}N_2O_2$, ^{1}H NMR(DMSO-d_6) 10.40 (brs, 2H, NH), 6.5-8.1 (m, 8H, Ph-H and Py-H); ^{13}C NMR 163.9 (CONH), 161.9 (Py-C2), 143.5 (Py-C6), 138.2 (py-C4), 135.4, 128.7, 123.9, 120.5, 118.8 (Py-C3), 103.3 (Py-C5); Anal. calcd. C, 67.29, H, 4.67, N, 13.08%; Found C, 67.99, H, 4.73, N, 12.66.

α-(Pyrid-2-on-4-yl)-α-(4-methoxyphenyl)benzyl alcohol (7h): $C_{19}H_{17}NO_3$, ^{1}H NMR(DMSO-d_6) 7.05-7.70 (m, 9H), 6.50-6.90 (m, 3H), 3.70(s, 3H, CH_3), 3.50 (brs, 1H, OH); ^{13}C NMR 166.6 (Py-C2), 157.9 (Py-C6), 139.0 (Py-C4), 132.1, 130.8, 128.8, 128.6, 127.4, 127.2, 126.8, 117.2 (Py-C3), 107.4, 106.6 (Py-C5), 73.0 (COH), 54.8 (OCH_3); Anal. calcd. C, 74.27, H, 5.54, N, 4.56%; Found C, 73.89, h, 5.69, N, 4.32%.

4-Phenylacetyl-2-pyridone (7i): $C_{13}H_{11}NO_2$, ^1H NMR(DMSO-d_6) 7.4 (s, 5H, Ph), 6.8-7.3 (m, 3H, Py-H), 3.57 (s, 2H, CH_2); Anal. cald. C, 73.24, H, 5.16, N, 6.56%; Found C, 73.71, H, 5.27, N, 6.29%.

α-(Pyrid-2-on-4-yl)-α-t-butyl-p-methylbenzyl alcohol (8): $C_{17}H_{21}NO_2$, ^1H NMR ($CDCl_3$) 7.58 (d, 2H, Ar-H), 7.30 (d, 2H, Ar-H), 6.3-6.75 (m, 2H, Py-H), 5.5 (m, 1H, Py-H), 3.90 (brs, 1H, OH), 2.48 (s, 3H, CH_3), 1.05 (s, 9H, t-Bu). ^{13}C NMR 171.8 (Py-C2), 168.0 (Py-C6), 140.1 (Py-C4), 132.0, 128.8, 128.7, 124.1, 115.9 (Py-C3), 98.4 (Py-C5), 63.7 (COH), 37.0, 25.3, 21.4. Anal. cald. C, 75.28, H, 7.75, N, 5.17%; Found C, 75.69, H, 7.55, N, 5.31%.

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