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CARBON DIOXIDE: A REAGENT FOR THE PROTECTION OF NUCLEOPHILIC CENTRES AND THE SIMULTANEOUS ACTIVATION OF ALTERNATIVE LOCATIONS TO ELECTROPHILIC ATTACK. PART I. A NEW SYNTHETIC METHOD FOR THE 2-SUBSTITUTION OF 1-UNSUBSTITUTED INDOLES.

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Abstract: Indole was converted into several 2-substituted derivatives by using carbon dioxide both for N-protection and to give an intermediate carbanion stabilizing group. t-Butyllithium was used as a lithiating agent at the alpha-carbon atom of the indole enamino group. The resulting 2-substituted indole-1-carboxylic acids underwent smooth thermal decarboxylation under mild conditions. Alternatively, with longer reaction times the protecting group is lost during the reaction.

alpha-Aminovinylcarbanions, i.e. enamine alpha-carbanions, are of considerable interest. Acyclic derivatives are acylanion equivalents,[1] while cyclic analogs are important intermediates in the manipulation of heterocycle functionality. Selective introduction of functional substituents at an alpha-position of an enamine possessing a N-H proton is not easily performed. Based on the analogy of ketone dianions,[2] di-lithiation is expected at the beta-position of an enamine, should an enamine be treated with excess alkyllithium.

A general approach to accomplish alpha functionalization of an enamine comprises four stages. The first is appropriate protection of the amino group and the second is to replace an alpha-proton by a suitable metal, such as lithium, using a metallating agent, for example an alkyllithium, LDA, etc. Thirdly, the desired substituent is introduced by the reaction with a suitable electrophile and then finally the N-protecting group is removed.[3]

We now report a novel synthetic sequence of this type for the introduction of a substituent at the alpha-position of an enamine having a N-H proton. We have used indole[4] as a typical heterocyclic enamine and carbon dioxide both as the source of the protection and as an alpha-carbanion stabilizing group.

The reaction scheme involves the following manipulations for the conversion of 1 into 2:

(i) indole is treated with n-BuLi/THF, n-hexane, at -70 °C, for 0.5h, under N_2
(ii) CO_2 added at -70 °C and allowed to warm to 20 °C, N_2
(iii) t-BuLi/n-pentane, added at -70 °C, kept 1h, N_2
(iv) electrophile/THF, added at -70 °C, 2h, N_2
(v) H_2O, added at -70 °C allowed to warm to 20 °C, N_2
(vi) NH_4Cl/H_2O added
(vii) 5% H_2SO_4-H_2O added
(viii) gentle heat

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* Submitted in honor of Harry Wasserman's 65th birthday.

1 2

Table. 2-Substituted Indoles Prepared from Indole

Entry	2-Substituent	Electrophile	Yield[a] (%)	MP (°C)	Lit. MP (°C)
1[5]	D	D_2O	86, 85[6]	53.0 - 55.0	49.0 - 52.0[7]
2[8]	CH_3	CH_3I	68, 60[6]	58.0 - 60.0	60.0[9]
3[10]	COPh	PhCOCl	59	149.0 -150.0	151.0 -152.0[11]
4[10]	COPh	$PhCO_2Me$	52	149.0 -150.0	151.0 -152.0[11]
5[12]	COC_6H_4OMe-4	4-$MeOC_6H_4COCl$	64	190.0 -191.0	-
6[13]	$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$	72	103.0 -104.0	98.0 -100.0[4]
7[14]	CONHPh	PhNCO	55	197.0 -197.5	-
8[15]	CO_2H	CO_2	70	206.0 -208.0	206.0 -208.0[16]

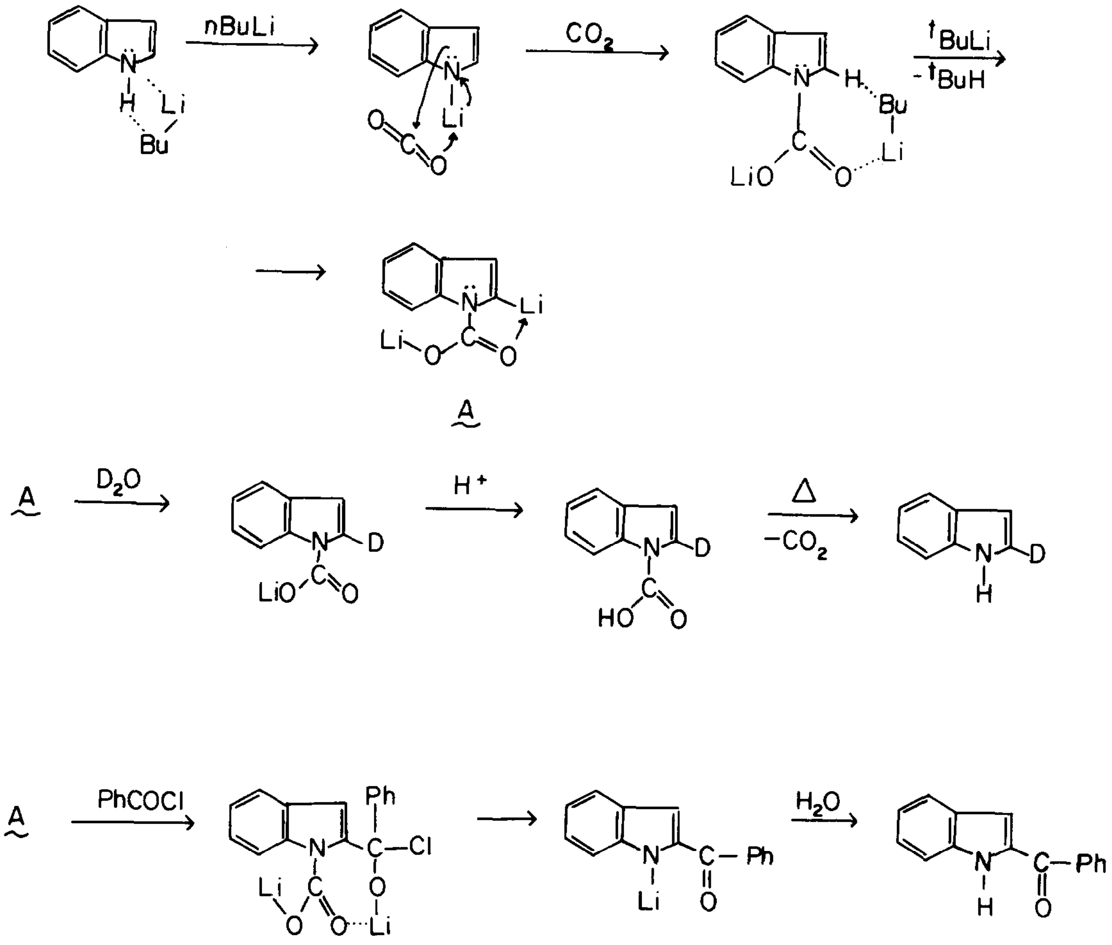
[a] isolated yield after purifying by column chromatography (silica gel-chloroform)

Typically, (i) The solution of indole (1.0 g in 15.0 ml THF) was cooled to -70 °C and *n*-butyllithium (3.5 ml of 2.5 M, *n*-hexane solution) was slowly added dropwise. (ii) The solution was kept at -70 °C for 30 min, and then added to excess of carbon dioxide (dry ice) in THF (30.0 ml). The solution was allowed to rise to room temperature. Solvent was evaporated under vacuum to remove excess carbon dioxide to give a residue of a colorless solid: the lithium salt of indole-1-carboxylic acid. (iii) THF (15.0 ml) was added to the solid and the solution was cooled to -70 °C. *t*-Butyllithium (5.5 ml, 1.6 M *n*-pentane solution) was carefully added to avoid increasing the solution temperature. (iv) The solution was kept at -70 °C for 1 hr, and then the whole was added to an electrophile dissolved in THF at -70 °C as shown in the Table. (v) The solution was kept at -70 °C for 2 h and then H_2O (1.0 ml) was added slowly at -70 °C. (vi) The reaction mixture was allowed to reach room temperature, and then poured into aqueous ammonium chloride. The aqueous phase was poured into 5% aqueous sulfuric acid (100 ml) at 0 °C. A colorless precipitate formed. (viii) The precipitate was collected by vacuum filtration and dried under vacuum at room temperature. The solid was heated (E=D: 150 °C, 5 min; E=CH_3: 190 °C, 1 min). Purification was carried out by column chromatography (silica gel-chloroform).

In the initial stage of the reaction in step (v), 2-substituted 1-indolecarboxylic acids were isolated in the case of the Table Entries 1 and 2.[6] These 1-indolecarboxylic acids were converted into the corresponding indole by pyrolysis. Steps (vii) and (viii) were not needed for runs (3) - (8) because the protecting group was automatically removed during the reaction.

The following control experiments were carried out. 1-Indolecarboxylic acid was prepared in 90% yield.[17] 1-Indolecarboxylic acid when heated just above its melting point at 120 °C lost CO_2 quantitatively to give unsubstituted indole quantitatively. The reaction of 1-indolecarboxylic acid with 2 moles of t-butyllithium, followed by the reaction with deuterium oxide and by pyrolysis produced the corresponding 2-deuterated N-H indole in 90% yield.

We have no evidence to support the mechanism of this reaction. However, the following reaction scheme appears likely:



Hence, we have demonstrated that commercially easily available, cheap carbon dioxide is a most convenient reagent as both a source of an N-protecting group and an alpha-carbanion stabilizing group for accomplishing the introduction of a substituent at the alpha-position of an enamine having a N-H proton, and it has the advantage of being easily removable.

Further applications of this method to other acyclic, cyclic, and heterocyclic enamine systems and to enolate systems are now under active investigation in our research group.

References and notes

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4. R. J. Sundberg and H. F. Russell, J. Org. Chem., 38, 3324 (1973).
5. Entry 1: ^{1}H NMR ($CDCl_3$) 6.47 (1H, s, 3-H), 7.10 (3H, m, 5-H, 6-H, and 7-H), 7.13 (1H, s, 4-H), and 7.63 ppm (1H, m, 1-H).
6. Alternatively with longer reaction times the protecting group was lost during the reaction.
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10. Entries 3,4: ^{1}H NMR ($CDCl_3$) 7.07-8.00 (10H, m, 3-H, 4-H, 5-H, 6-H, 7-H, and $-C_6H_5$, and 9.80 ppm (1H, s, 1-H).
11. R. J. Sundberg, J. Org. Chem., 30, 3604 (1965).
12. Entry 5: ^{1}H NMR ($CDCl_3$) 3.87 (3H, s, $-C_6H_4OCH_3$), 6.87-8.03 (9H, m, 3-H, 4-H, 5-H, 6-H, 7-H, and $-C_6H_4OCH_3$), and 9.63 ppm (1H, s, 1-H); elemental analysis requires C: 76.48, H: 5.21, N: 5.57%, Found C: 76.57, H: 5.35, N: 5.39%.
13. Entry 6: ^{1}H NMR ($CDCl_3$) 2.40 (1H, s, -OH), 3.77 (3H, s, $-C_6H_4-OCH_3$), 5.90 (1H, s, -CH(OH)-), 6.23 (1H, s, 3-H), 6.73-7.50 (8H, m, 4-H, 5-H, 6-H, 7-H, and $-C_6H_4-OCH_3$), and 8.27 ppm (1H, s, 1-H).
14. Entry 7: ^{1}H NMR (CD_3COCD_3) 6.37-7.27 (10H, m, 3-H, 4-H, 5-H, 6-H, 7-H, and $-C_6H_5$), 8.87 (1H, s, $-NHC_6H_5$), and 10.27 ppm (1H, s, 1-H); elemental analysis requires C: 76.25, H: 5.12, N: 11.86%, Found C: 76.04, H: 5.09, N: 11.64%.
15. Entry 8: ^{1}H NMR (CD_3COCD_3) 6.33-7.13 (5H, m, 3-H, 4-H, 5-H, 6-H, and 7-H), 8.83 (1H, s, $-CO_2H$), and 10.17 ppm (1H, s, 1-H).
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