THE N-CARBOXYLIC ACIDS OF NITROGEN HETEROCYCLES

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Abstract - Nitrogenous heterocyclic carbamic acids possess considerable stability and can frequently be isolated as free acids. A variety of synthetic methods are available and the expected range of derivatives is formed. Recently, such N-carboxylic acids have been demonstrated to form useful protecting/activating groups in metalation reactions.

I. INTRODUCTION

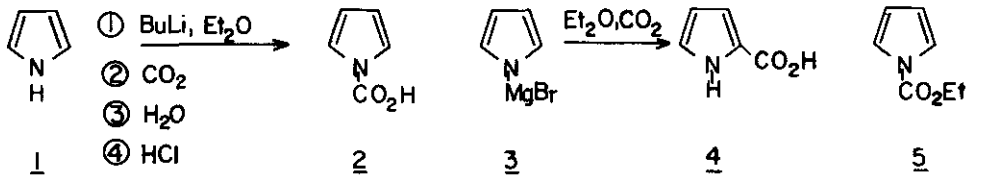
The preparation and reactions of such derivatives as esters, amides, and salts of N-carboxylic acids of pyrrole,[1,2] indole,[3,4] carbazole,[5,6] imidazole,[7,8] benzimidazole[9,10], triazole,[11,12] and pyrazole[13,14] are well known in the literature. However, many fewer reports concern the free acids, probably because of their instability when compared to that of their derivatives. This review, which covers the literature up to the middle of 1985, presents the available knowledge concerning the synthesis and properties of the free acids of this type.

As is discussed in Section IV, the importance of such heterocyclic N-carboxylic acids has recently *much increased with the discovery in our laboratory of the utility of* CO_2 as a protecting and activating group, easily attached to and lost from heterocyclic nitrogen.

II. SYNTHESIS OF HETEROCYCLIC N-CARBOXYLIC ACIDS

A. Pyrrole-1-carboxylic Acids

The preparation of pyrrole-1-carboxylic acids is readily achieved by the direct carbonation of the pyrrole anion. However, the gegenion is important; thus whereas the anion prepared using butyllithium is satisfactory for the synthesis of pyrrole-N-carboxylic acids (1 --> 2),[15] the use of Grignard reagents and hence a magnesium gegenion yields mainly pyrrole-2-carboxylic acids (3 --> 4).[16]



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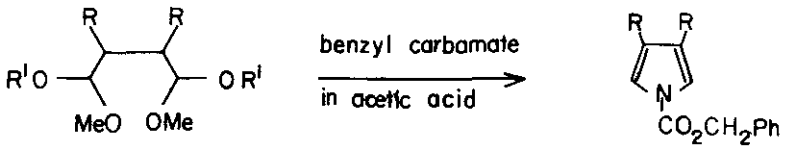
In the procedure (1 --> 2), n-butyllithium in ether was added slowly to pyrrole in ether. The reaction mixture was stirred and heated under reflux for 1 h and then poured onto solid CO_2. The mixture was treated with water, and the ether layer separated and extracted with several portions of water. The combined aqueous portions were acidified with HCl to give pyrrole-1-carboxylic acid as a white precipitate which could be recrystallised.[15] Pyrrole 1-carboxylic acid (2) has also been prepared by hydrolysis of the corresponding ethyl ester (5) (itself obtained from the reaction of ethyl chloroformate with pyrrole) in the presence of KOH.[17]

Recently,[18] the 1-carboxylic acids of some 3,4-dialkylpyrroles were prepared by the anodic oxidation of the alkenyl alkyl ethers (RCH = CHOR') to give the acetals (6) which were cyclised to the benzyl pyrrole-1-carboxylates (7). Hydrogenolysis over palladium of the latter gave the free 1-carboxylic acids (2).



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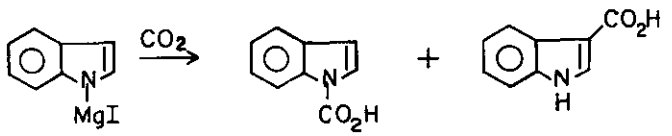
B. Indole-1-carboxylic Acids

In 1911, Oddo and Sessa reported[19] that 1-carboxyindole (9) was obtained by the carbonation of indole-1-magnesium iodide (8). However, Majima and Kotake[20] later described 3-carboxyindole (10) as being the only product of this reaction. Subsequently, other workers[21,22] prepared 3-carboxyindole (10) by the method of Majima and Kotake. However, detailed investigation by Kasparek and Heacock[23] showed that both acids (9) and (10) are formed, in approximately equal quantities, during this reaction. Excess powdered CO_2 was added to a stirred solution of indole magnesium iodide, and the products were decomposed by ice-water. The aqueous layer was acidified to pH 5.5-

6.0 with 2% acetic acid, repeatedly extracted with ether, cooled to 0°C, and acidified with concentrated HCl to pH 1.3. 1-Carboxyindole (9) separated as a chromatographically pure, colourless crystalline solid.[23]



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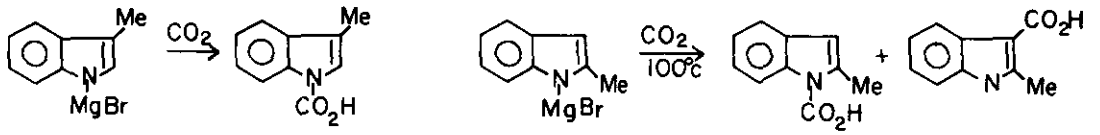
Similarly, carbonation of 3-methyl-1-magnesium bromide (11) with CO_2 at 20-100°C yielded 3-methylindole-1-carboxylic acid (12),[24,25] which occurs in beets.

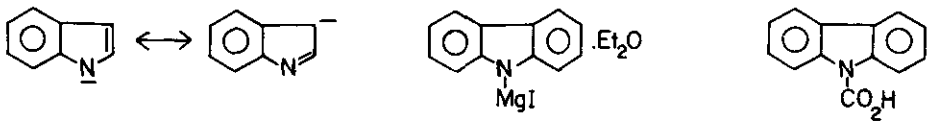


11 12 13 14 15

The formation of indole-1- or -3-carboxylic acids is temperature-dependent; carbonation of 2-methylindole-1-magnesium bromide (13) with CO_2 at 100°C yielded the 1-carboxylic acid (14) which is soluble in Na_2CO_3. However, if the reaction with CO_2 is conducted at 115°C in refluxing toluene, the 3-carboxylic acid (15) is formed, possibly via the 1-carboxylic acid (14), by migration of the CO_2H group.[24]

Shirley and Roussel later found that treatment of indole with a slight excess of n-butyllithium, and carbonation by pouring over solid CO_2 gave 1-indolecarboxylic acid (9) in 61% yield.[26] Typically, a solution of indole in ether was treated with excess n-butyllithium and heated under reflux for 2 h. The mixture was then poured over a slurry of excess crushed solid CO_2 in dry ether; treatment with hydrochloric acid liberated 1-indolecarboxylic acid (9).[26] A four-fold excess of n-butyllithium failed to produce a dilithioindole, even using temperatures up to 50°C and reaction times of up to 48 h. In no case was there any evidence of C-metalation, as indicated by carbonation of the intermediates.

The above is in sharp contrast to the behaviour of phenothiazine and carbazole[27,28] in which N-lithiation occurs, followed by metalation ortho to the nitrogen atom in good yield. The lack of reactivity of N-lithioindole towards n-butyllithium would appear to be due to stabilisation of the anion (16a-16b), a situation which would be less likely in N-lithiocarbazole, for example, since structures corresponding to (16b) would involve higher energy quinonoid forms in one of the benzene rings.



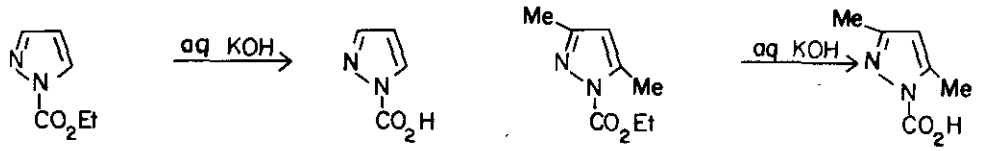
16a 16b 17 18

C. Carbazole-9-carboxylic Acids

The fact that pyrrolemagnesium salts with CO_2 yield 1-carboxylic acids, while the indolemagnesium compounds usually form mixtures of 1- and 3-carboxylic acids raised the question as to whether

specific reaction at nitrogen might, in general, be possible. Carbazole readily reacts with MeMgI in Et_2O forming the Grignard compound (17), which in turn reacts with CO_2 to yield the N-carboxylic acid (18),[29] an unstable substance decomposing to CO_2 and carbazole even at -20°C. However, if the magnesium compound (17), free from Et_2O, is heated in CO_2 at 265-270°C, a monocarboxylic acid of carbazole is formed, although the site of C-carboxylation was not reported.[30] Tetrahydrocarbazole-9-carboxylic acid, obtained by the action of CO_2 upon the magnesium derivative of tetrahydrocarbazole, is very unstable; however, the ethyl ester is quite stable and is formed by the action of ethyl chloroformate upon the appropriate Grignard reagent.[31] When carbazole potassium is heated under pressure with CO_2 to above 200°C a mixture of mono- and di-carboxylic acids of carbazole is obtained. Aqueous sodium hydrogen carbonate was used to isolate the carbazolemonocarboxylic acid (of unknown substitution) which has been used as a starting material in the manufacture of dyes.[32] Hydroxycarboxylic acids of carbazole, prepared by the action of CO_2 on a mixture of a hydroxycarbazole and alkali, have also been used as intermediates in making dyes and pharmaceutical products.[33]

D. Pyrazole-1-carboxylic Acids



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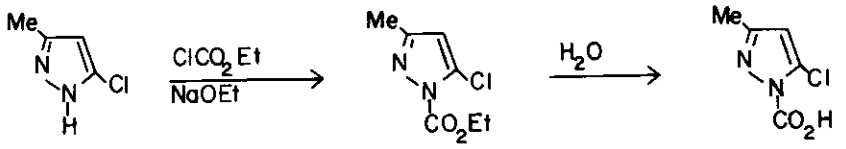
Pyrazole-1-carboxylic acids are prepared by hydrolysis of the corresponding esters. Thus, agitation of ethyl pyrazole-N-carboxylate (19) (obtained by the action of ethyl chloroformate on magnesium pyrazole) with aqueous KOH gave, after acidification, pyrazole-N-carboxylic acid (20).[34] Prolonged agitation of ethyl 3,5-dimethylpyrazole-1-carboxylate (21) with KOH gave after acidification, 3,5-dimethylpyrazole-1-carboxylic acid (22).[35]



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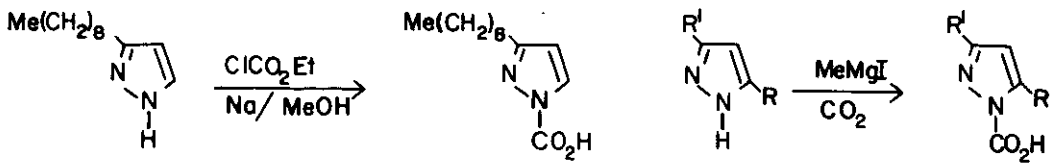
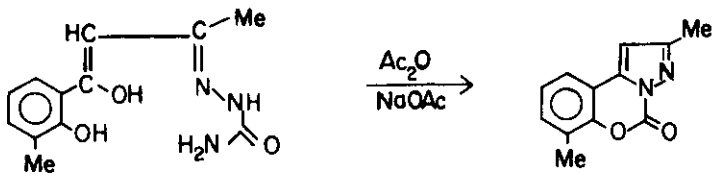
The reaction of the pyrazole (23) with ethyl chloroformate in the presence of NaOEt afforded ethyl 3-methyl-5-chloropyrazole-1-carboxylate (24), which was readily hydrolysed to the corresponding acid (25). The latter spontaneously decomposed to 3-methyl-5-chloropyrazole (23) and CO_2.[36] This would appear to be a useful method of protecting 1-unsubstituted pyrazoles. Heating 5-nonylpyrazole (26) with ethyl chloroformate and sodium in methanol gave 3-nonylpyrazole-1-carboxylic acid (27).[37] Pyrazole-N-carboxylic acids (29) have also been obtained by the carbonation of the pyrazolemagnesium derivatives with CO_2.[38]

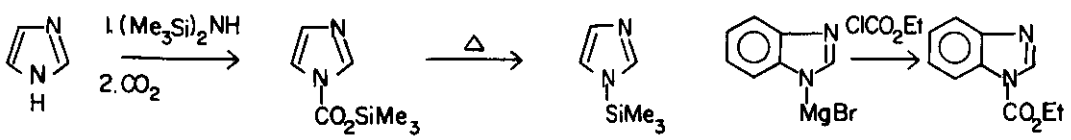


Lactonisation of derivatives of pyrazole-N-carboxylic acid can result in relatively thermally stable heterocycles, such as the pyrazole (31), obtained by heating the semicarbazone of 2-methyl-6-acetylacetophenol (30) with acetic anhydride and sodium acetate.[39]

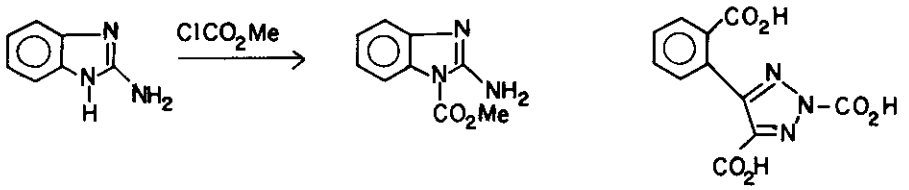


E. Imidazole- and Benzimidazole-1-carboxylic Acids

The reaction between imidazolemagnesium bromide and ethyl chloroformate produces ethyl 1-imidazolecarboxylate. Ethyl 4-methyl-1-imidazolecarboxylate is similarly prepared from 4-methyl-1-imidazolemagnesium bromide.[40] The interaction between imidazolemagnesium bromide and ethyl chloroformate does not give ethyl imidazole-2-carboxylate, as has been claimed by Oddo and Mingoia.[41,42] Imidazole-1-carboxylic acid is an unstable compound which loses CO_2 extremely readily, giving imidazole.[43] In contrast, the ethyl ester is a basic liquid which can be distilled unchanged, and which forms a crystalline picrate. Treatment of imidazole (1) with $((CH_3)_3Si)_2NH$ and CO_2 gave the silyl ester (32), which upon heating lost CO_2 to give the N-silylated imidazole (33).[44]



Ethyl benzimidazole-1-carboxylate (35) has been prepared by the reaction of benzimidazole magnesium (34) with ethyl chloroformate.[45] Methyl 2-aminobenzimidazole-1-carboxylate (37) can be prepared by the reaction of 2-aminobenzimidazole (36) with methyl chloroformate.[46]



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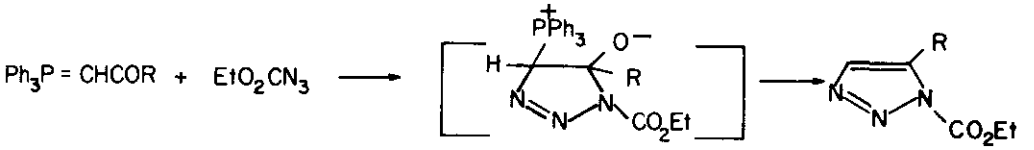
F. Triazole-N-carboxylic Acids

Triazole-N-carboxylic acids are unknown, with the apparent exception of 4-o-carboxyphenyl-5-carboxy-1,2,3-triazolic acid (38), which has reportedly been prepared[47] by the oxidation of a naphthotriazole with $KMnO_4$. However, many esters of triazole-N-carboxylic acids are stable. For example, L'abbe and Bestmann prepared 5-substituted-1-ethoxycarbonyl-1,2,3-triazoles (42) by the *reaction of ethyl azidoformate (40) with alpha-ketophosphorus ylides (39).*[48]



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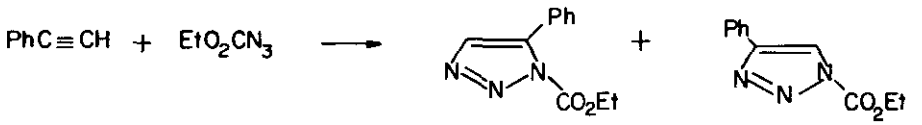

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Huisgen and Blaschke prepared the 4-(45) and 5-(44) phenyl derivatives of 1-ethoxycarbonyl-1,2,3-triazole by the addition of ethyl azidoformate (40) to phenylacetylene (43).[49]

III. PROPERTIES AND REACTIONS OF N-CARBOXYLIC ACIDS

A. Decarboxylation

The N-carboxylic acids of pyrrole and indole are rather unstable solids which easily lose CO_2 when boiled with water, treated with alkali or NH_3, or even kept at room temperature. Pyrrole-N-carboxylic acid immediately decomposes to pyrrole and CO_2 on heating. This decomposition proceeds without any resinification and gives pure pyrrole almost quantitatively.[17] Even in sealed vessels, pyrrole N-carboxylic acid (2) becomes light pink and begins to smell of pyrrole. The acid is also decomposed slowly by water at 20°C, the evolution of CO_2 increasing as the temperature is raised. Indole- and 3-methylindole-N-carboxylic acids are decomposed by boiling water into the corresponding indoles and CO_2.[19,24] However, when 2-methylindole-N-carboxylic acid is treated with Na_2CO_3, it loses CO_2 at room temperature and forms 2-methylindole. Rearrangement of 2-methylindole

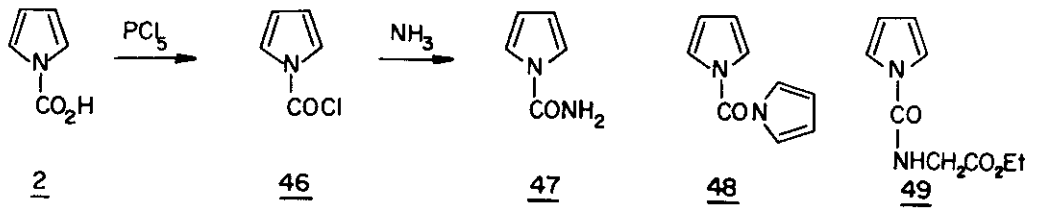
N-carboxylic acid to the 3-carboxylic acid occurs on heating in toluene.[24] Carbazole-N-carboxylic acid is very unstable; even at -20°C it decomposes into carbazole and CO_2. Pyrazole-N-carboxylic acids are also unstable and decompose to the original pyrazole and CO_2 when boiled with water, heated alone, or treated with NH_3 or acids.[34-36] Again, imidazole-1-carboxylic acid easily loses CO_2.[43] Ethyl 1-imidazolecarboxylate also loses CO_2 when heated at 250-260°C, and is converted into 1-ethylimidazole. Under similar conditions ethyl 4-methyl-1-imidazolecarboxylate affords a mixture of 1-ethyl-4-methylimidazole and 4-(or 5-) methylimidazole.[40]

B. Reactions at the N-Carboxyl Group

The N-(t-butoxycarbonyl) substituent has been used as a protecting group. It can be removed rapidly and in high yield from pyrrole derivatives under basic conditions. From indole derivatives, the protecting group can be removed using either acidic or basic conditions.[50] Pyrrole N-carboxylic acid (2) reacts with PCl_5 to form the acid chloride (46) from which pyrrole-1-carboxamide (47) can be obtained by reaction with NH_3.[17] The acid chloride of pyrrole-N-carboxylic acid (46) reacts with potassium pyrrole to give pyrrolide (48), and with ethyl glycinate to give ethyl N-pyrrolylglycinate (49). The reaction[51] of pyrrole-N-carboxylic acid (2) with tetramethyl-alpha-chlorogenoenamine (50) yielded the acid chloride (46).[52]

Table 1. Decomposition Temperatures of N-Carboxylic Acids

N-Carboxylic acid	Temp. Decomp. (°C)	Ref.	Products
Pyrrole-1-	20 (slow) vigorous at 70	17	pyrrole, CO_2
Indole-1-	106	19	indole, CO_2
3-Methylindole-1-	129	25	3-methylindole, CO_2
Carbazole-9-	-20	29	carbazole, CO_2
Pyrazole-1-	102	34	no products isolated; (in boiling water pyrazole, CO_2)
3,5-Dimethylpyrazole-1-	90	35	no products isolated; (in boiling water 3,5-dimethylpyrazole, CO_2)
5-Chloro-3-methylpyrazole-1-carboxylic acid	20	36	5-chloro-3-methylpyrazole, CO_2
4-o-Carboxyphenyl-1,2,3-triazole-2-	160-170	47	4-phenyl-5-carboxy-1,2,3-triazole, CO_2 and H_2O



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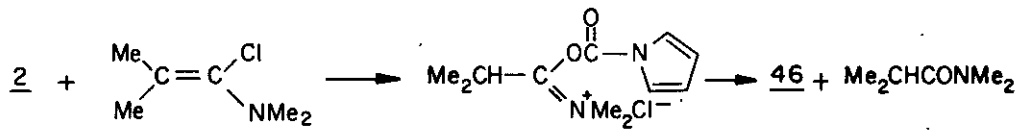

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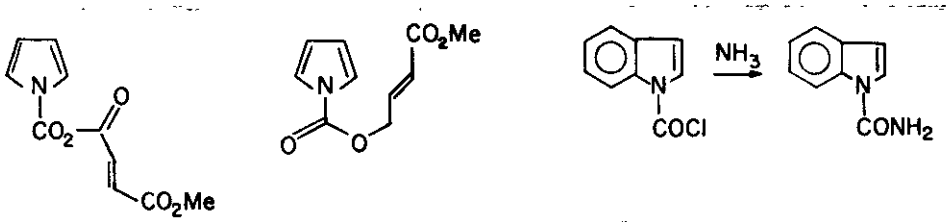
Pyrrole-N-carboxylic acid (2) condensed with trans-3-(methoxycarbonyl)acryloyl chloride in the presence of Et_3N to give the anhydride (53).[52] The acid chloride (46) on esterification with methyl trans-3-hydroxycrotonate[53] yielded the ester (54).[52]



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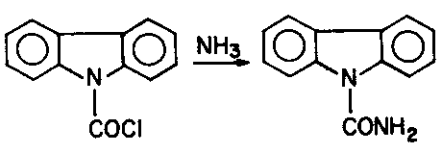
Reaction of indole-N-carboxylic acid (9) with PCl_5 gave the acid chloride (55) which with NH_3 afforded indole-N-carboxamide (56).[54]

The sites of reactivity of carbazole-N-carboxylic acid (11) have been correlated with LCAO MO calculations.[55] The acid chloride (57), prepared by the reaction of phosgene with carbazole in pyridine, yielded the carbazole N-carboxamide (58) upon treatment with NH_3.[56]



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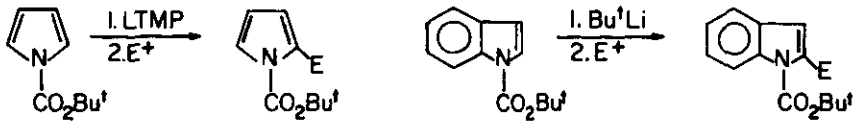
C. Reactions of the Heterocyclic Ring

N-(t-Butoxycarbonyl)pyrrole (59) and N-(t-butoxycarbonyl)indole (61) (prepared by the reaction of pyrrole[57] and indole[50] with t-butoxycarbonylazide) may be lithiated at the 2-position with lithium 2,2,6,6-tetramethylpiperidide (LTMP) and t-butyllithium, respectively. These lithium reagents react with a variety of electrophiles to give the 2-substituted N-(t-butoxycarbonyl) pyrroles (60) and N-(t-butoxycarbonyl)indoles (62).



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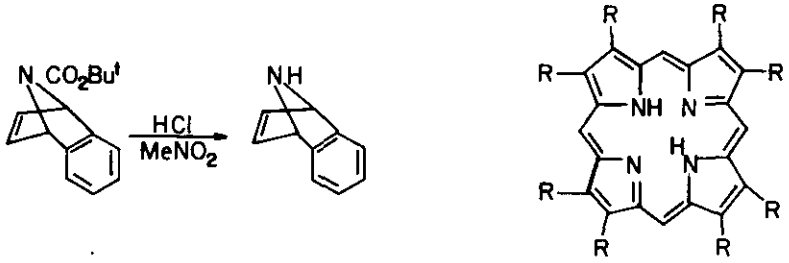
A Diels-Alder addition of benzyne to t-butyl pyrrole-N-carboxylate (59) followed by subsequent cleavage of the protective group by HCl in nitromethane yielded the 7-azabenzonorbornadiene (64).[57]



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Reaction of 3,4-dialkylpyrrole-N-carboxylic acids with formaldehyde in the presence of air yields octaalkylporphyrins (65),[18] which are simple and useful models for natural porphyrins.

IV. UTILITY OF NITROGEN HETEROCYCLE N-CARBOXYLIC ACIDS IN SYNTHESIS

Our group has recently discovered[58,59] that indole N-carboxylic acids can be employed as intermediates in some most useful synthetic sequences:

A. The 2-Lithiation of Indole-1-carboxylic Salts[58]

Indole was converted into several 2-substituted derivatives by using carbon dioxide both to provide 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.

The reaction scheme involved the following manipulations for the conversion of (66) into (67):

(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 mixture allowed to warm to 20°C, under N_2

(iii) t-BuLi/n-pentane added at -70°C, kept 1h, under N_2

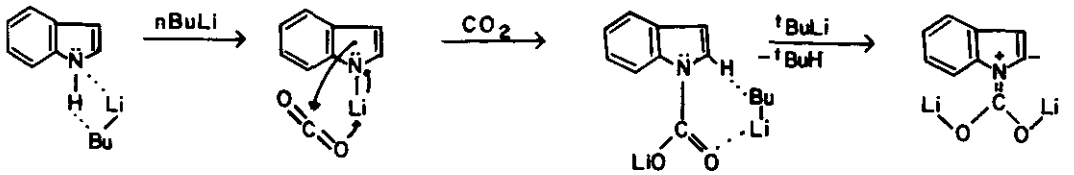
(iv) electrophile/THF added at -70°C, 2h, under N_2

(v) H_2O added at -70°C and mixture allowed to warm to 20°C, under N_2

(vi) NH_4Cl/H_2O added

(vii) 5% H_2SO_4/H_2O added

(viii) gentle heating[60]



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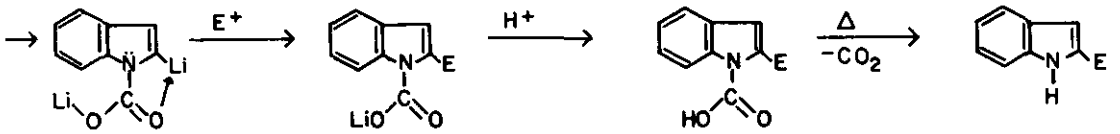

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Table 2. 2-Substituted Indoles Prepared from Indole by Lithiation

2-Substituent	Electrophile	Yield (%)	m.p. (°C)
D	D_2O	86	53-55
Me	Me	68	58-60
COPh	PhCOCl	59	149-150
COPh	$PhCO_2Me$	52	149-150
COC_6H_4OMe-4	4-$MeOC_6H_4COCl$	64	190-191
$CH(OH)C_6H_4OMe$-4	4-$MeOC_6H_4CHO$	72	103-104
CONHPh	PhNCO	55	197-197
CO_2H	CO_2	70	206-208

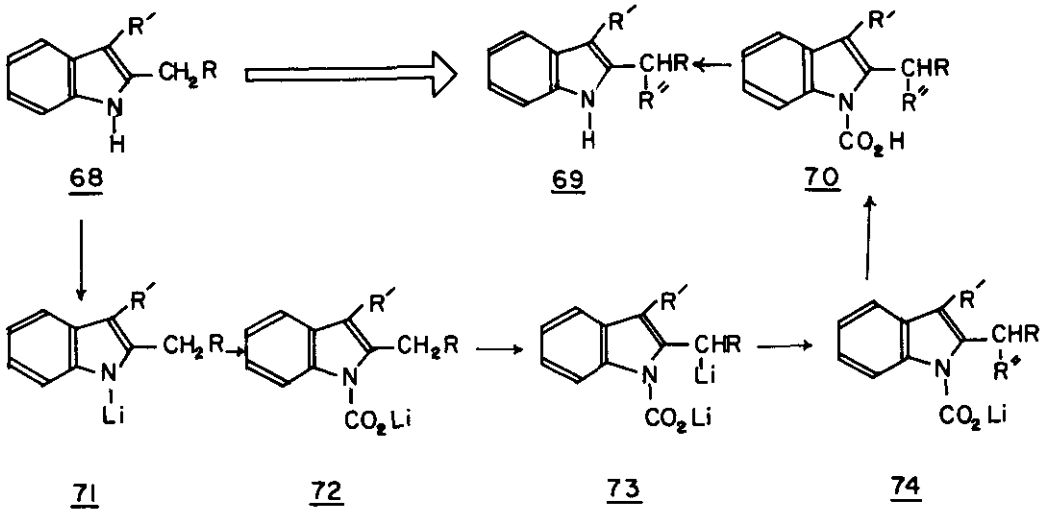
B. The Lithiation of a 2-Alkyl Group in Indole-1-carboxylate Salts[59]

Proton loss from C-methyl groups in pyrroles and indoles is difficult, and few procedures are available for their functionalization *via* carbanion formation. Recently we have discovered that the 2-alkyl groups of N-unsubstituted 2-alkylindoles can be activated towards proton loss by using carbon dioxide both to protect the N-H position and to enable lithiation at the methyl group 68 --> 71 --> 72. Subsequent reaction with an electrophile 73 --> 74 affords the corresponding 2-(substituted alkyl)indole-1-carboxylic acid and easy loss of CO_2 then occurs (70 --> 69) to reform the NH group. The whole sequence can be carried out in the usual one-pot procedure.

A wide variety of electrophiles were employed to give the corresponding 2-(substituted alkyl)indoles: D_2O, RI, R_2CO, RNCO, CO_2 all gave the expected products.

C. The Lithiation of the 1-Position Methylene Group in 1,2,3,4-Tetrahydroisoquinoline-2-carboxylate Salts

A rather similar sequence has been used to introduce functionality at the 1-position of tetrahydroisoquinoline: for details see Ref. 61.



68 69 70

71 72 73 74

V. CONCLUSIONS AND OUTLOOK

The N-carboxylic acids of pyrrole and indole are surprisingly stable compounds. Moreover, they have been shown to possess considerable synthetic potential, since the CO_2 group activates both ring and adjacent alpha-alkyl protons with respect to metalation, but is also easily introduced and eliminated.

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