

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.

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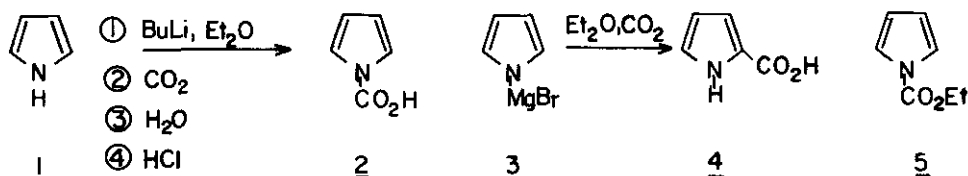
The preparation and reactions of such derivatives as esters, amides, and salts of N-carboxylic acids of pyrrole,^{1,2} indole,^{3,4} carbazole,^{5,6} imidazole,^{7,8} benzimidazole^{9,10}, triazole,^{11,12} and pyrazole^{13,14} are well known in the literature. However, many fewer reports concern the 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 CO₂ as a protecting and activating group, easily attached to and lost from heterocyclic nitrogen.

II. SYNTHESIS OF HETEROCYCLIC N-CARBOXYLIC ACIDS

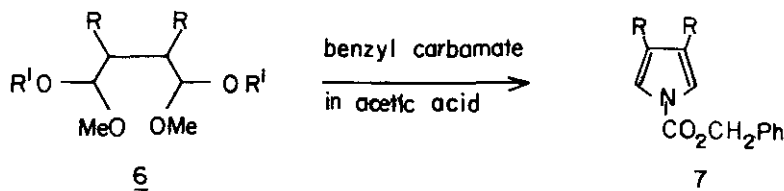
A. Pyrrole-1-carboxylic Acids

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



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 CO₂. 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).

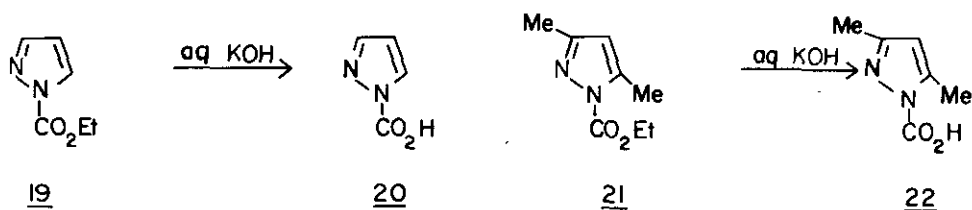


B. Indole-1-carboxylic Acids

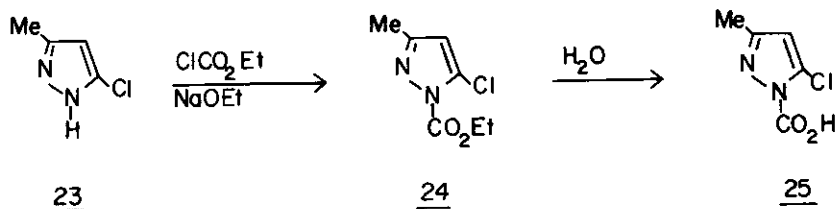
In 1911, Oddo and Sessa reported¹⁹ that 1-carboxyindole (9) was obtained by the carbonation of indole-1-magnesium iodide (8). However, Majima and Kotake²⁰ later described 3-carboxyindole (10) as being the only product of this reaction. Subsequently, other workers^{21,22} prepared 3-carboxyindole (10) by the method of Majima and Kotake. However, detailed investigation by Kasperek and Heacock²³ showed that both acids (9) and (10) are formed, in approximately equal quantities, during this reaction. Excess powdered CO₂ 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-

specific reaction at nitrogen might, in general, be possible. Carbazole readily reacts with MeMgI in Et₂O forming the Grignard compound (17), which in turn reacts with CO₂ to yield the *N*-carboxylic acid (18),²⁹ an unstable substance decomposing to CO₂ and carbazole even at -20°C. However, if the magnesium compound (17), free from Et₂O, is heated in CO₂ 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 CO₂ 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 CO₂ 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 CO₂ on a mixture of a hydroxycarbazole and alkali, have also been used as intermediates in making dyes and pharmaceutical products.³³

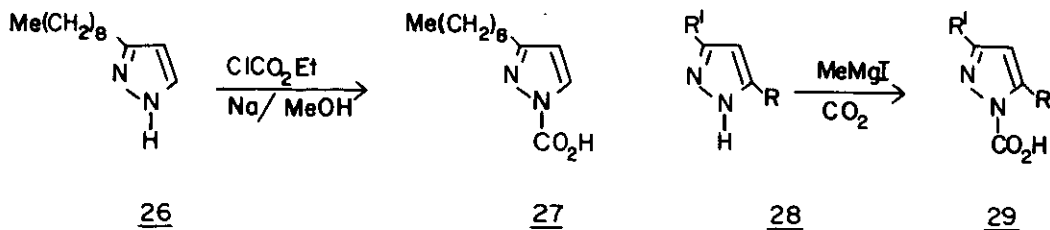
D. Pyrazole-1-carboxylic Acids



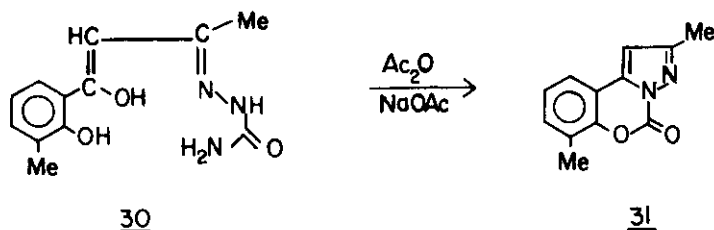
Pyrazole-1-carboxylic acids are prepared by hydrolysis of the corresponding esters. Thus, agitation of ethyl pyrazole-*N*-carboxylate (19) (obtained by the action of ethyl chloroformate on magnesium pyrazole) with aqueous KOH gave, after acidification, pyrazole-*N*-carboxylic acid (20).³⁴ Prolonged agitation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



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 CO₂.³⁶ 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 CO₂.³⁸

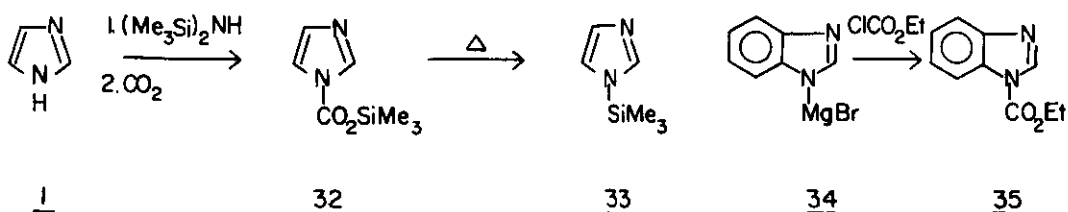


Lactonisation of derivatives of pyrazole-*N*-carboxylic acid can result in relatively thermally stable heterocycles, such as the pyrazole (31), obtained by heating the semicarbazone of 2-methyl-6-acetylacetophenol (30) with acetic anhydride and sodium acetate.³⁹

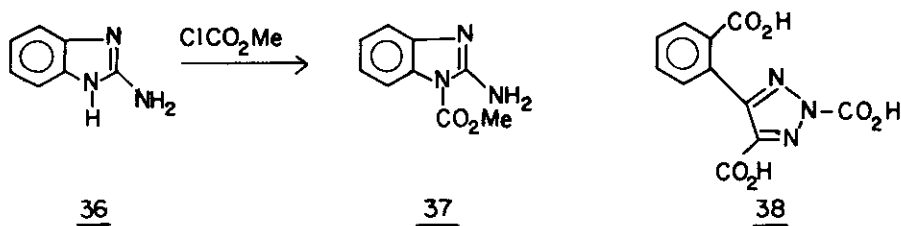


E. Imidazole- and Benzimidazole-1-carboxylic Acids

The reaction between imidazoliummagnesium bromide and ethyl chloroformate produces ethyl 1-imidazolecarboxylate. Ethyl 4-methyl-1-imidazolecarboxylate is similarly prepared from 4-methyl-1-imidazoliummagnesium bromide.⁴⁰ The interaction between imidazoliummagnesium bromide and ethyl chloroformate does not give ethyl imidazole-2-carboxylate, as has been claimed by Oddo and Mingoa.^{41,42} Imidazole-1-carboxylic acid is an unstable compound which loses CO₂ 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 ((CH₃)₃Si)₂NH and CO₂ gave the silyl ester (32), which upon heating lost CO₂ to give the *N*-silylated imidazole (33).⁴⁴

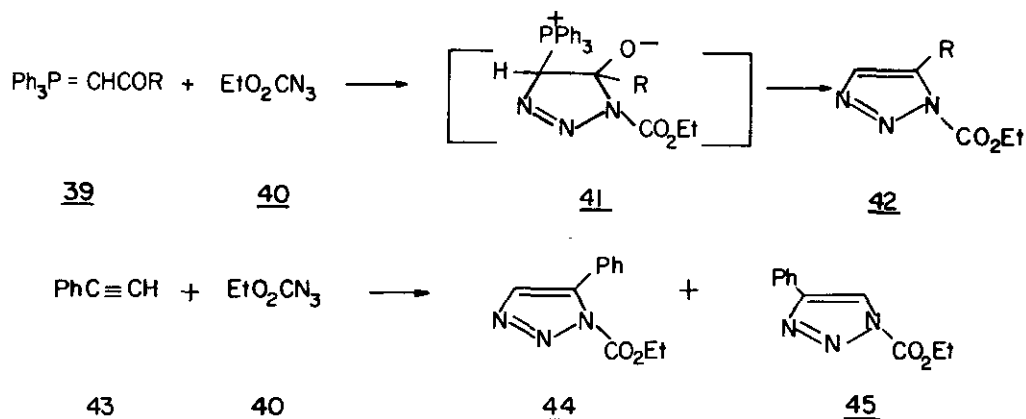


Ethyl benzimidazole-1-carboxylate (35) has been prepared by the reaction of benzimidazole magnesium (34) with ethyl chloroformate.⁴⁵ Methyl 2-aminobenzimidazole-1-carboxylate (37) can be prepared by the reaction of 2-aminobenzimidazole (36) with methyl chloroformate.⁴⁶



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 prepared⁴⁷ 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



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 CO₂. Pyrazole-N-carboxylic acids are also unstable and decompose to the original pyrazole and CO₂ when boiled with water, heated alone, or treated with NH₃ or acids.³⁴⁻³⁶ Again, imidazole-1-carboxylic acid easily loses CO₂.⁴³ Ethyl 1-imidazolecarboxylate also loses CO₂ 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

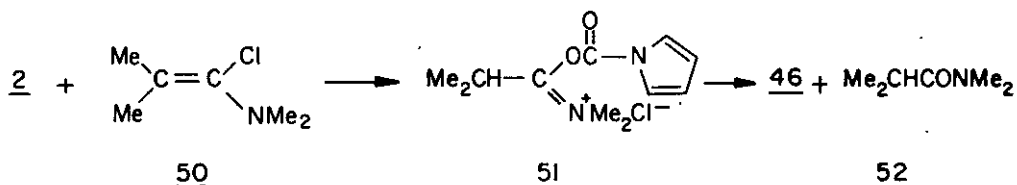
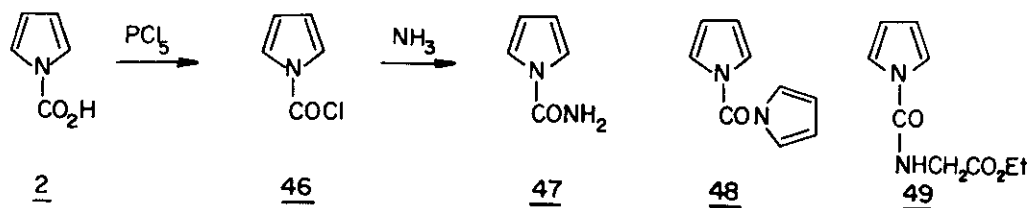
B. Reactions at the N-Carboxyl Group

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

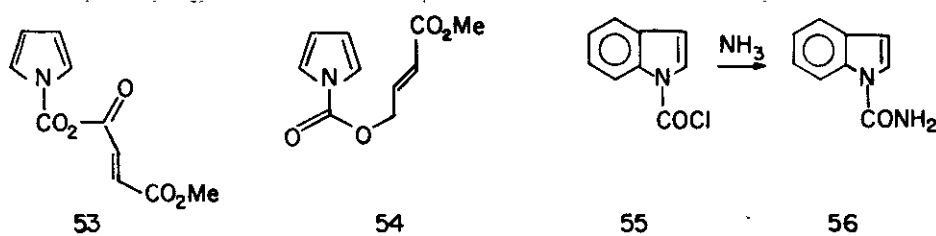
Pyrrole N-carboxylic acid (2) reacts with PCl₅ to form the acid chloride (46) from which pyrrole-1-carboxamide (47) can be obtained by reaction with NH₃.¹⁷ The acid chloride of pyrrole-N-carboxylic acid (46) reacts with potassium pyrrole to give pyrrolide (48), and with ethyl glycinate to give ethyl N-pyrrolylglycinate (49). The reaction⁵¹ of pyrrole-N-carboxylic acid (2) with tetramethyl- α -chlorogenoamine (50) yielded the acid chloride (46).⁵²

Table 1. Decomposition Temperatures of N-Carboxylic Acids

<u>N</u> -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- <u>o</u> -Carboxyphenyl-1,2,3- triazole-2-	160-170	47	4-phenyl-5-carboxy-1,2,3-triazole, CO ₂ and H ₂ O

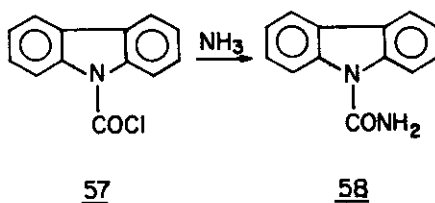


Pyrrole-*N*-carboxylic acid (2) condensed with *trans*-3-(methoxycarbonyl)acryloyl chloride in the presence of Et_3N to give the anhydride (53).⁵² The acid chloride (46) on esterification with methyl *trans*-3-hydroxycrotonate⁵³ yielded the ester (54).⁵²



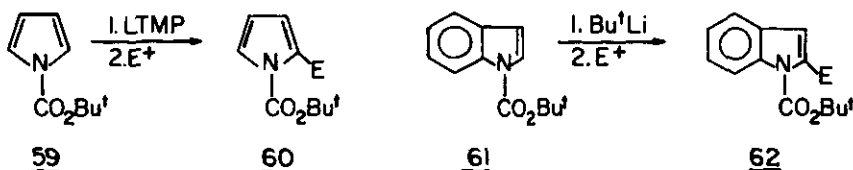
Reaction of indole-*N*-carboxylic acid (9) with PCl_5 gave the acid chloride (55) which with NH_3 afforded indole-*N*-carboxamide (56).⁵⁴

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

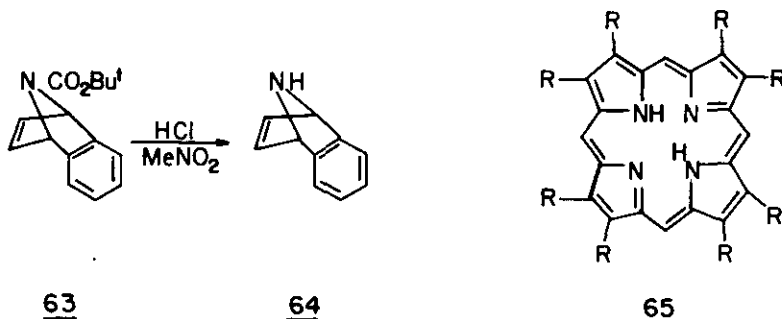


C. Reactions of the Heterocyclic Ring

N-(*t*-Butoxycarbonyl)pyrrole (59) and *N*-(*t*-butoxycarbonyl)indole (61) (prepared by the reaction of pyrrole⁵⁷ and indole⁵⁰ 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).



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



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 Salts⁵⁸

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 N₂
- (ii) CO₂ added at -70°C and mixture allowed to warm to 20°C, under N₂
- (iii) *t*-BuLi/*n*-pentane added at -70°C, kept 1h, under N₂
- (iv) electrophile/THF added at -70°C, 2h, under N₂
- (v) H₂O added at -70°C and mixture allowed to warm to 20°C, under N₂
- (vi) NH₄Cl/H₂O added

(vii) 5% H₂SO₄/H₂O added

(viii) gentle heating⁶⁰

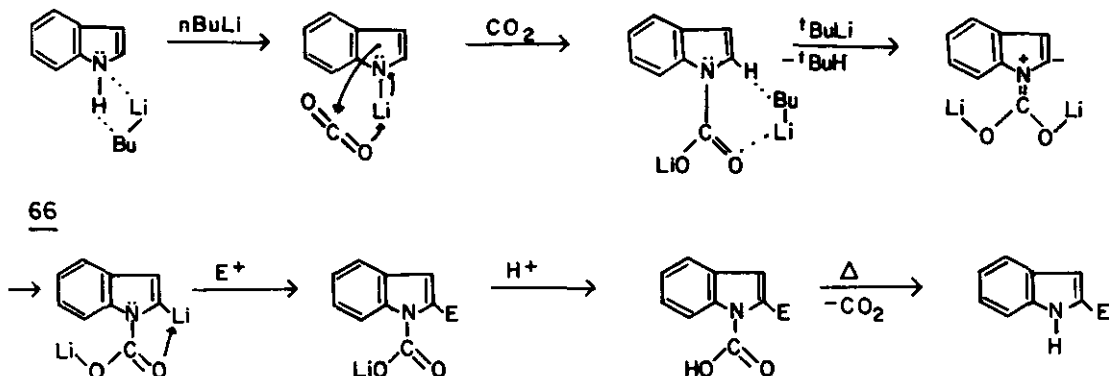


Table 2. 2-Substituted Indoles Prepared from Indole by Lithiation

2-Substituent	Electrophile	Yield (%)	m.p. (°C)
D	D ₂ O	86	53-55
Me	Me	68	58-60
COPh	PhCOCl	59	149-150
COPh	PhCO ₂ Me	52	149-150
COC ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ COCl	64	190-191
CH(OH)C ₆ H ₄ OMe-4	4-MeOC ₆ H ₄ CHO	72	103-104
CONHPh	PhNCO	55	197-197
CO ₂ H	CO ₂	70	206-208

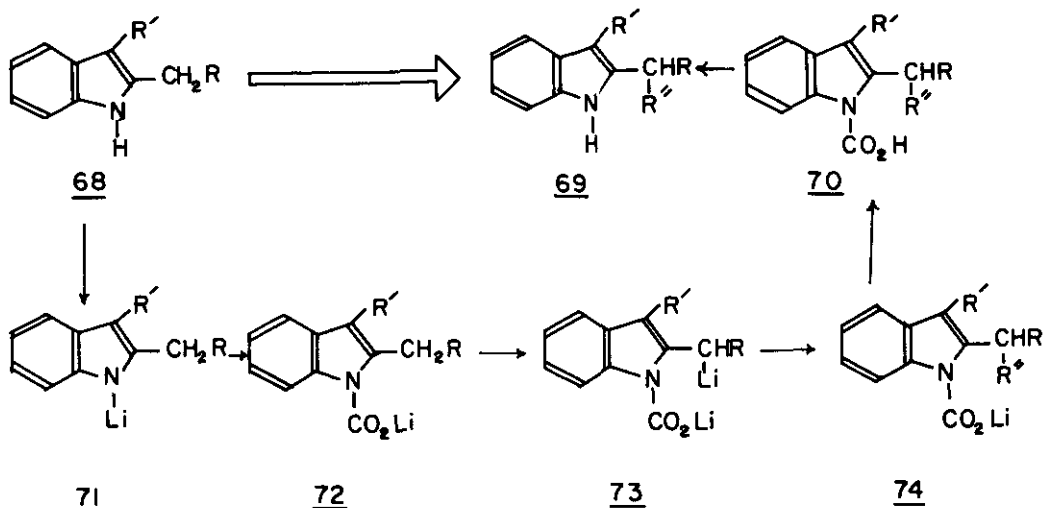
B. The Lithiation of a 2-Alkyl Group in Indole-1-carboxylate Salts⁵⁹

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 CO₂ 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: D₂O, RI, R₂CO, RNCO, CO₂ 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.



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 CO₂ group activates both ring and adjacent alpha-alkyl protons with respect to metalation, but is also easily introduced and eliminated.

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