Reactions of Hydrazides and Hydrazones with n-Butyl-lithium

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Aromatic hydrazides give indazol-3(2*H*)-ones in good yield when treated with 3 equivalents of n-butyl-lithium; aliphatic and heterocyclic hydrazides afford the corresponding aldehydes under the same conditions.

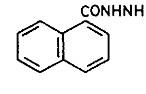
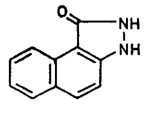
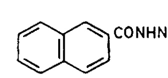
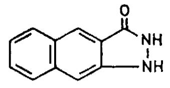
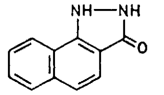
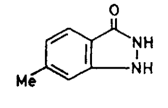
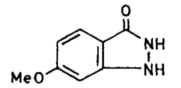
Little is known about the reactions of the polyanions of acid hydrazides and of hydrazones.[1] We suspected that such anions would be at a high level of energy and might show interesting chemical behaviour.

When benzoylhydrazine (**1**) in tetrahydrofuran (THF) was treated with n-butyl-lithium (3 equiv.) in hexane under a nitrogen atmosphere at −78 °C for 1.5 h and allowed to come to room temperature overnight indazol-3(2*H*)-one (**2**) was isolated in 80% yield. Various alkyl- and alkoxy-substituted benzoylhydrazines led in the same way to the corresponding indazol-3(2*H*)-ones in good yields (Table 1). The structures of the various indazolones were confirmed by ^{1}H n.m.r. evidence and by their transformations in the presence of zinc and hydrochloric acid into the corresponding known *ortho*-amino aromatic acids. However, *N*-benzoyl-*N'*-methylhydrazine afforded under the given reaction conditions 1-methylindazol-3(2*H*)-one with only 8% yield. *N*-benzoyl-*N'*-phenyl- and *N*-benzoyl-*N'*-benzyl-hydrazine, as well as benzohydroxamic acid, failed to react. When n-butyl-lithium was replaced by sodium or potassium hydride and a catalytic amount of imidazole was used, under the same experimental conditions (**2**) was obtained from (**1**) in 49 and 54% yields respectively. Scheme 1 gives the proposed mechanism.

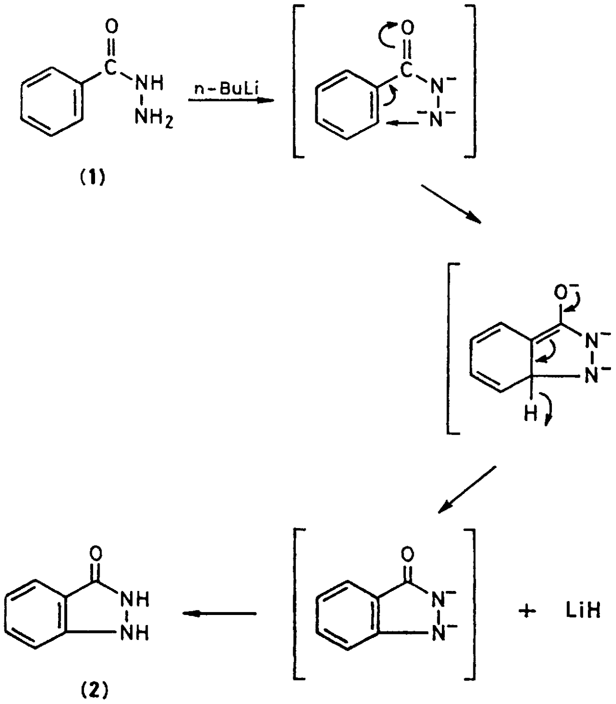
Hydrazones were also found to react with Bu^{n}Li. Thus benzophenone hydrazone when treated with Bu^{n}Li (2 equiv.) at −78 °C for 2 h and the temperature allowed to come to room temperature overnight gave a mixture of products from which 3-phenylindazole (**3**) was isolated by chromatography in 39% yield. Acetophenone hydrazone led to 3-methylindazole (**4**) in 26% yield. As a consequence of the interesting results obtained in the case of aromatic hydrazides and hydrazones, a study of the action of Bu^{n}Li on aliphatic and heterocyclic hydrazides was undertaken. In a typical experiment, pivaloyl hydrazide (**5**) in THF was treated with Bu^{n}Li (2 equiv.) under a nitrogen atmosphere for 2 h at −78 °C and allowed to return to room temperature overnight. From the reaction mixture chromatography permitted the isolation of the aldehyde (**6**) as its 2,4-dinitrophenylhydrazone (59%). Various hydrazides (isobutyryl, hexanoyl, mesitoyl) afforded the corresponding aldehydes in yields of 43—56% (Table 2). In the presence of 3 equiv. of Bu^{n}Li the yield of (**6**) from (**5**) was only 53%. The mechanism of this reaction is outlined in Scheme 2.

The attack by H$^+$ on the intermediate (a) was proved by carrying out the reaction in the presence of methyl iodide. Thus the hydrazide (**5**), when treated with Bu^{n}Li at −78 °C for 15 min and then with an excess of methyl iodide at −78 °C

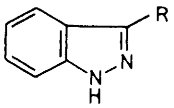
Table 1

Hydrazide	Indazol-3(2*H*)-one	Yield / %
PhCONHNH$_2$ (1)	(2)	80
		69^a
		27^b
		11^c
p-Me–C$_6$H$_4$CONHNH$_2$		61^d
p-MeO–C$_6$H$_4$CONHNH$_2$		79

[a] m.p. 227 °C, characterised by reduction to 2-amino-1-naphthoic acid. [b] m.p. 235 °C, characterised by reduction to 3-amino-2-naphthoic acid. [c] m.p. 249 °C, characterised by reduction to 1-amino-2-naphthoic acid. [d] m.p. 258—260 °C.

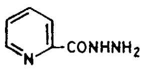
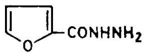
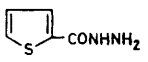
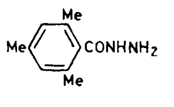


Scheme 1

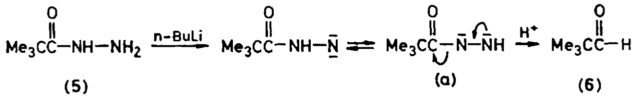

(3) R = Ph

(4) R = Me

Table 2

Hydrazide	Aldehyde^a yield / %
Me$_3$CCONHNH$_2$	59
n–C$_5$H$_{11}$–CONHNH$_2$	56
Me$_2$CHCONHNH$_2$	43
	51
	47
	43
	52

[a] Isolated as the 2,4-dinitrophenylhydrazone.



Scheme 2

and allowed to come to room temperature, gave pinacolone (13%) and **(6)** (9%).

Heterocyclic hydrazides such as picolinoyl hydrazide, 2-furoyl hydrazide, and 2-thenoyl hydrazide reacted with Bu^nLi under the usual conditions to give the corresponding aldehydes in yields of 51, 47, and 43% respectively, isolated as their 2,4-dinitrophenylhydrazones.

The two new reactions presented in this communication permit syntheses of *ortho*-amino aromatic acids and of aldehydes in reasonable yields from the hydrazides of aromatic acids and of aliphatic and heterocyclic acids, respectively.

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References

1 B. C. Challis and J. A. Challis, 'Comprehensive Organic Chemistry,' eds. D. H. R. Barton, W. D. Ollis, and I. O. Sutherland, Pergamon Press, Oxford, 1979, Vol. 2, p. 1046.