Azo Anions in Synthesis. t-Butylhydrazones as Acyl-anion Equivalents

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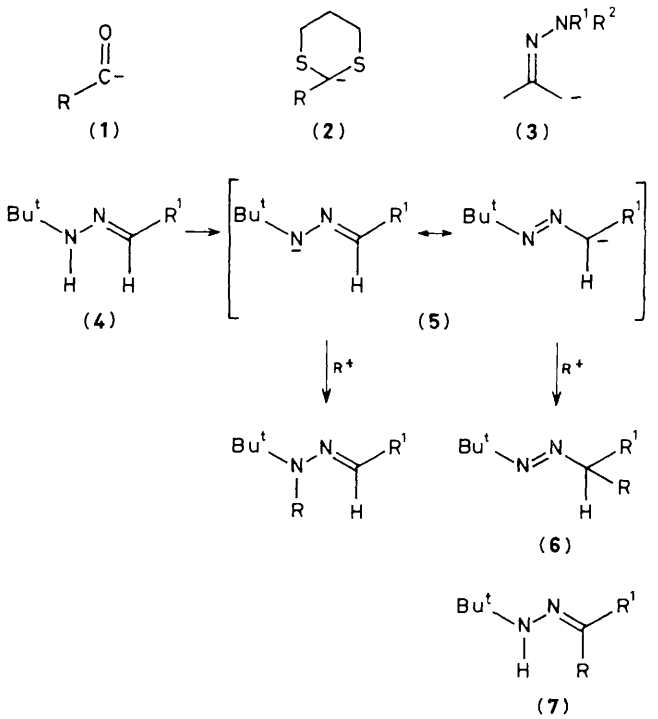
The lithium salts of aldehyde t-butylhydrazones react with electrophiles (aldehydes, ketones, alkyl halides) to form *C*-trapped t-butylazo compounds; isomerisation and hydrolysis gave α-hydroxy ketones and ketones in good yields, thereby providing a convenient new acyl-anion equivalent.

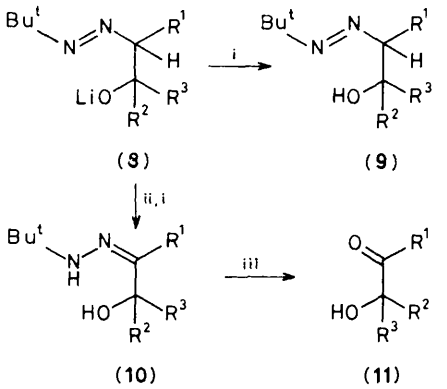
Operational equivalents of the acyl-anion (**1**) are widely used in organic synthesis although frequently difficulties arise during the removal of the anion stabilising auxiliary.[1] This is often a problem with the dithiane sequence, based on (**2**). As an alternative to the existing methods, which might avoid some of these problems, we have examined the chemistry of azo anions, which are readily obtained by deprotonation of hydrazones. Whilst the deprotonation of dialkyl-[2] and arylsulphonyl-hydrazones[3] at the α-carbon atom, as (**3**), is well known, the azo anions derived from alkylhydrazones have not been previously investigated for synthetic purposes.

As expected, in the case of methylhydrazones the anion reacted poorly on carbon. However, the sterically hindered t-butylhydrazones (**4**) directed the reaction along the desired carbon alkylation pathway, *via* the azo compound (**6**) and after tautomerisation of this intermediate yielded the ketone hydrazone (**7**), Scheme 1. Thus, treatment of t-butylhydrazones (**4**) [from aldehyde and t-butylhydrazine in acetic acid (68—85%)] with n-butyl-lithium (1.1 equiv.) in tetrahydrofuran at 0 °C (15 min) gave the azo anion (**5**) to which was added the aldehyde/ketone (1.1 equiv.) providing the alkoxide (**8**) which on protonation gave an unstable azo alcohol (**9**), slowly reverting at room temperature to the parent hydrazone and carbonyl compound. On reaction of alkoxide (**8**) with a further portion of n-butyl-lithium (1.4 equiv.) *in situ* followed by a quench with water the hydroxy hydrazones (**10**)† were cleanly obtained. These were smoothly hydrolysed to the α-hydroxy ketones (**11**) (40—95%, Table 1, Scheme 2).‡

Alternatively, for a ketone synthesis, the azo anion (**5**) could be directly alkylated with alkyl halides. When (**5**; R^1 = Pr^n) was allowed to react with methyl iodide (1 equiv.) there resulted predominantly *N*-alkylation to the isolated *N*-t-butyl-*N*-methylhydrazone (71%). However more bulky halides (*e.g.* RI, R ≠ Me; $PhCH_2Br$; Me_3SiCl) proceeded largely by *C*-alkylation§ to the stable azo compounds, (**12a**) 75, (**12b**) 90%,



Scheme 1



Scheme 2. *Reagents:* i, H_2O; ii, Bu^nLi (1.4 equiv.), 0 °C, 30—60 min; iii, $(CO_2H)_2$–H_2O–diethyl ether–N_2 or H_3PO_4–H_2O–diethyl ether–N_2, 1—6 h.

Table 1

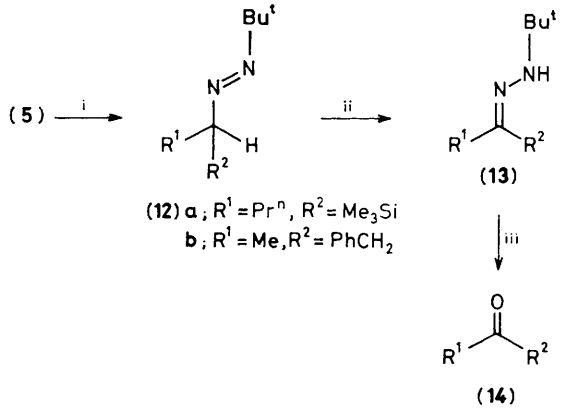
Hydrazone (**4**) R^1	Electrophile R^2	R^2·CO·R^3 R^3	α-Hydroxy ketone (**11**), % yield
Me	H	n-C_7H_{15}	60
Me	H	Ph	55
Me	Me	n-C_6H_{13}	44[a]
Me	Me	Ph	43[b]
Et	–[CH_2]$_5$–		56
Et	H	Ph	66
Pr^n	H	Pr^n	62
Pr^n	Me	Me	45
Pr^n	H	Ph	80
Pr^i	–[CH_2]$_5$–		40
Pr^i	H	Ph	95
Ph	Me	Me	—

[a] Octan-2-one (23%) recovered. [b] Acetophenone (32%) recovered.

† The isomerisation and quenching, (**8**) to (**10**), were essentially quantitative as judged by the 300 MHz ^{1}H n.m.r. spectra of (**10**; R^1 = Me, R^2, R^3 = H, Ph).

‡ Compounds (**4**), (**11**), (**12**), and (**14**) were characterised by spectral and analytical data, and where appropriate by comparison to literature data. Compound (**9**) was not isolated in pure form.

§ The ratio of *C*:*N* alkylation of anion (**5**; R^1 = n-C_7H_{15}) with MeI (13:87), EtI (80:20), and Pr^nI (87:13) was estimated from the 300 MHz ^{1}H n.m.r. spectra of the initial alkylation reaction product.



Scheme 3. *Reagents:* i, −78 °C, R^2X, −78 → 20 °C, 1—2 days; ii, TFA, 20 °C, 6 h; iii, $(CO_2H)_2$–H_2O–diethyl ether–N_2, 14 h.

which were isomerised [trifluoroacetic acid (TFA)] to the hydrazones (**13**). Thereafter hydrolysis [$(CO_2H)_2$–H_2O–diethyl ether] and chromatography gave the ketones (**14**) (15—83%, Table 2, Scheme 3).

In conclusion, the above results indicate that azo anions, derived from t-butylhydrazones represent useful and convenient alternatives to currently used acyl-anion equivalents.

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Table 2

(**4**) R^1	Alkyl halide R^2X	Ketone (**14**), % yield
Me	n-$C_{10}H_{21}I$	68
Me	$PhCH_2Br$	67
Pr^n	n-$C_7H_{15}I$	48
Pr^n	$PhCH_2Br$	71
Pr^i	n-$C_7H_{15}I$	15
Pr^i	$PhCH_2Br$	74
Ph	n-$C_7H_{15}I$	83
Ph	$PhCH_2Br$	72
n-C_7H_{15}	MeI	<5[a]
n-C_7H_{15}	EtI	41[a]
n-C_7H_{15}	Pr^nI	53[a]
n-C_7H_{15}	Pr^iI	24
n-C_7H_{15}	Bu^nI	39

[a] See footnote § in text.

References

1 Reviewed by O. W. Lever, Jr., *Tetrahedron*, 1976, 1943.
2 D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 549; *Tetrahedron Lett.*, 1977, 191.
3 R. M. Adlington and A. G .M. Barrett, *Acc. Chem. Res.*, 1983, **16**, 55 and references therein.