Azo Anions in Synthesis. Use of Trityl- and Diphenyl-4-pyridylmethyl-hydrazones for Reductive C–C Bond Formation from Aldehydes and Ketones

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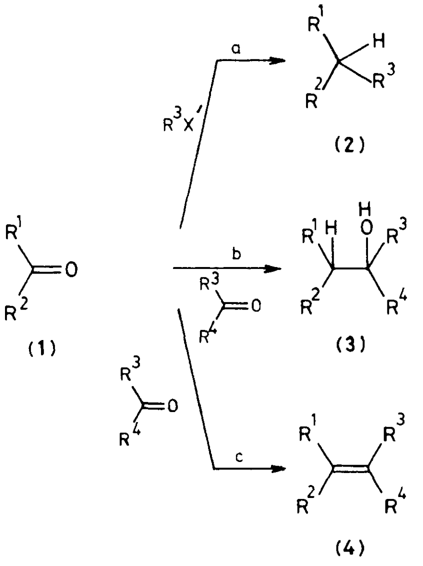
The lithium salts for trityl- and diphenyl-4-pyridylmethyl-hydrazones of both aldehydes and ketones react with electrophiles (alkyl halides, aldehydes, and ketones) at low temperature to form *C*-trapped azo compounds; these intermediates decompose homolytically with loss of nitrogen below room temperature and can be diverted in a synthetically useful way to alkanes, or alkenes, or alcohols.

Reductive couplings of carbonyl compounds (**1**) to alkanes [(**2**, path a], alcohols [(**3**), path b], and alkenes [(**4**), path c], Scheme 1, are not at present easily achieved without extensive functional manipulations. Since we recently demonstrated[1] that t-butylhydrazones, as their lithium salts, undergo reaction with electrophiles at carbon we decided to extend this reactivity to alternative hindered hydrazones (**5**) except that we selected groups (X) which would labilise the azo product (**7**) towards homolytic decomposition to a radical pair (**8**), Scheme 2.[2] Interception of this radical system (**8**) by various types of reagent would then enable, in principle, generation of a wide variety of different products, particularly those shown in Scheme 1.



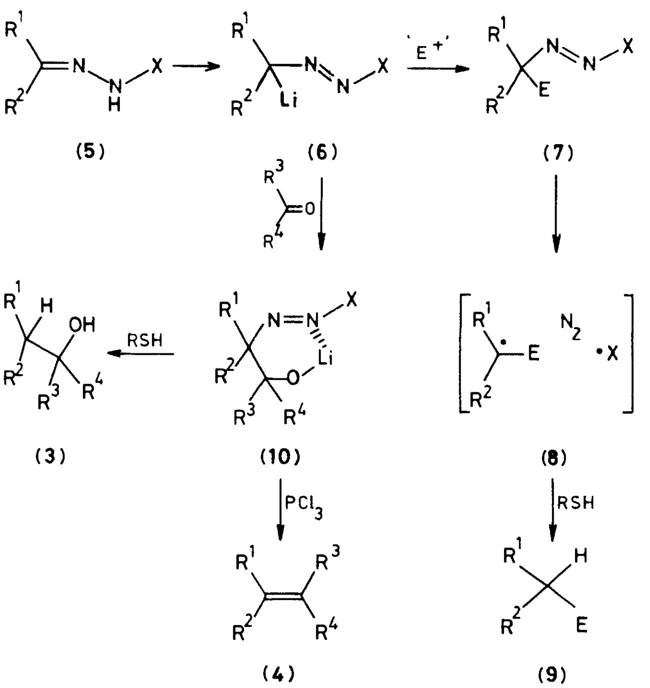
Scheme 1

In the first example, of reductive alkane synthesis, path a, Scheme 1, we alkylated the lithium hydrazone with alkyl halides and reduced the so formed radical pair with thiol to yield compounds of the type (**9**). Thus, treatment of tritylhydrazones (**5**, X = trityl) [from aldehyde/ketone and triphenylmethylhydrazine hydrochloride[3] (1 equiv.) in methanol–water–sodium formate (2.2 equiv.) in 85—90% yield] with methyl-lithium (1.1 equiv.) in tetrahydrofuran at −40 °C gave the azo-anion (**6**), to which was added the alkyl halide (1.5 equiv.). After 2 h at −30 °C the reaction was quenched (acetic acid, 1.1 equiv.) and treated with ethanethiol

Table 1

Compound (**1**)		Alkyl halide[a]		
R^1	R^2	R^3	X′	Yield of (**2**)[b]/%
-[CH$_2$]$_5$-		n-C_7H_{15}	I	67
-[CH$_2$]$_5$-		n-C_4H_9	I	43
-[CH$_2$]$_5$-		PhCH$_2$	Br	69
Me	Me	PhCH$_2$	Br	42
Me	Me	n-$C_{10}H_{21}$	I	60

[a] Path a, Scheme 1. [b] *via* the tritylhydrazone.



Scheme 2. X = CPh_2(4-pyridyl) or CPh_3.

Table 2

Compound (1) R¹	R²	Electrophile[a] R³	R⁴	Yield of (3)/%
$-[CH_2]_5-$[b]		$-[CH_2]_5-$		35
Me	H[b]	Ph	H	74
Me	Me[b]	Ph	H	85[c]
$-[CH_2]_5-$[d]		Me_2CH	H	70
$-[CH_2[_5-$[d]		Ph	H	80

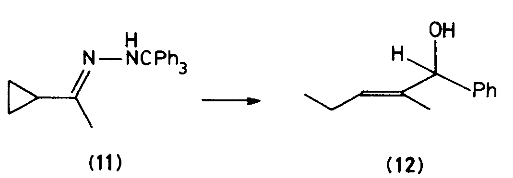
[a] Path b, Scheme 1. [b] *via* the tritylhydrazone. [c] In this case, the alcohol (**3**) ($R^1 = R^2$ = Me, R^3,R^4 = H, Ph) was contaminated by 2-methylene-1-phenylpropan-1-ol (**14**), *ca.* 5%. With acetone DPP-hydrazone the ratio of (**3**):(**14**) was (85:15). However with the DPP-hydrazone, in the absence of an ethanethiol work-up, the ratio of (**3**):(**14**) changed dramatically to (<5:>95), and the isolated alcohol yield dropped to *ca.* 40%. [d] *via* the DPP-hydrazone.

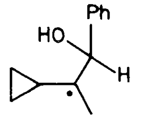
Table 3

Compound (1) R¹	R²	Electrophile[a] R³	R⁴	Yield of (4)/%
Me	Me[b]	Ph	H	45
$-[CH_2]_5-$[b]		$-[CH_2]_5-$		24
$-[CH_2]_5-$[b]		Ph	H	47
n-C_6H_{13}	Me[c]	H	n-C_7H_{15}	55(*E*:*Z* 60:40)
n-C_6H_{13}	Me[c]	Ph	H	60(*E*:*Z* 65:35)

[a] Path c, Scheme 1. [b] *via* the tritylhydrazone. [c] *via* the DPP-hydrazone.

(5 equiv.) and the solution warmed to 20 °C.† Evaporation of solvents and purification by chromatography–distillation gave the alkanes‡ (42—67%), Table 1.





$CH_2=C(Me)-C(H)(Ph)OH$
(**14**)

For reductive coupling of carbonyls to yield alcohols, path b, Scheme 1, the azo-anion (**6**, X = trityl) was treated with an aldehyde or ketone ($R^3{\cdot}CO{\cdot}R^4$, 1.1 equiv.) at −40 to −25 °C followed by addition of acetic acid (1.1 equiv.) and ethanethiol (5 equiv., at −25 °C) which on warming to 20 °C was worked-up, as before, after nitrogen evolution ceased, to yield the alcohols (**3**) (35—90%), Table 2. In this table the last two entries show the use of the diphenyl-4-pyridylmethylhydrazones (**5**, X = diphenyl-4-pyridylmethyl) (referred to as DPP-hydrazones) as reagents.§ These hydrazones enable facile removal of the basic residue after the reaction is complete by a dilute acid wash of the product. In general for alcohol synthesis this is the preferred reagent. Direct evidence for the free radical intermediate postulated in these reactions was obtained by reaction of the tritylhydrazone (**11**) of cyclopropyl methyl ketone with benzaldehyde as above, which gave the ring opened alcohol (**12**) (*E*:*Z* 93:7 by nuclear Overhauser enhancement experiments, 52%). The intermediate radical (**13**) would, as is known,[4] be expected to undergo rapid ring opening to the isomeric homoallylic radical, which is then trapped by thiol to yield (**12**).

The intermediate lithium salts (**10**) from condensation of the hydrazones with carbonyl compounds can also be converted into olefins by reaction with PCl_3. Thus addition at −78 °C to the adducts (**10**), formed as before, of triethylamine (3 equiv.) and phosphorus trichloride (1.2 equiv.) gave upon warming to 20 °C and standard isolation procedures, alkenes (**4**) (24—60%), Table 3. This reaction, whose mechanism is as yet unknown, operationally enables the discriminated coupling of two different carbonyl compounds as opposed to the usual pinacol related processes[5] which necessarily yields both symmetrically coupled and cross-over products. The coupling of two ketones to give a tetrasubstituted double bond is also noteworthy.

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† Nitrogen evolution was observed from −10 to +20 °C.

‡ All known compounds were characterised by comparison with literature data. All new compounds were fully characterised by full spectral and analytical data. Yields refer to isolated and purified products.

§ Diphenyl-4-pyridylmethylhydrazones were prepared by the same method as the trityl derivatives. Diphenyl-4-pyridylmethylhydrazine dihydrochloride, m.p. 184 °C (decomp.), was prepared from diphenyl-4-pyridylmethyl chloride and hydrazine, followed by salt formation with hydrogen chloride in diethyl ether.