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"REDUCTIVE ALKYLATION OF ALDEHYDE TOSYLHYDRAZONES WITH ORGANOLITHIUM REAGENTS"

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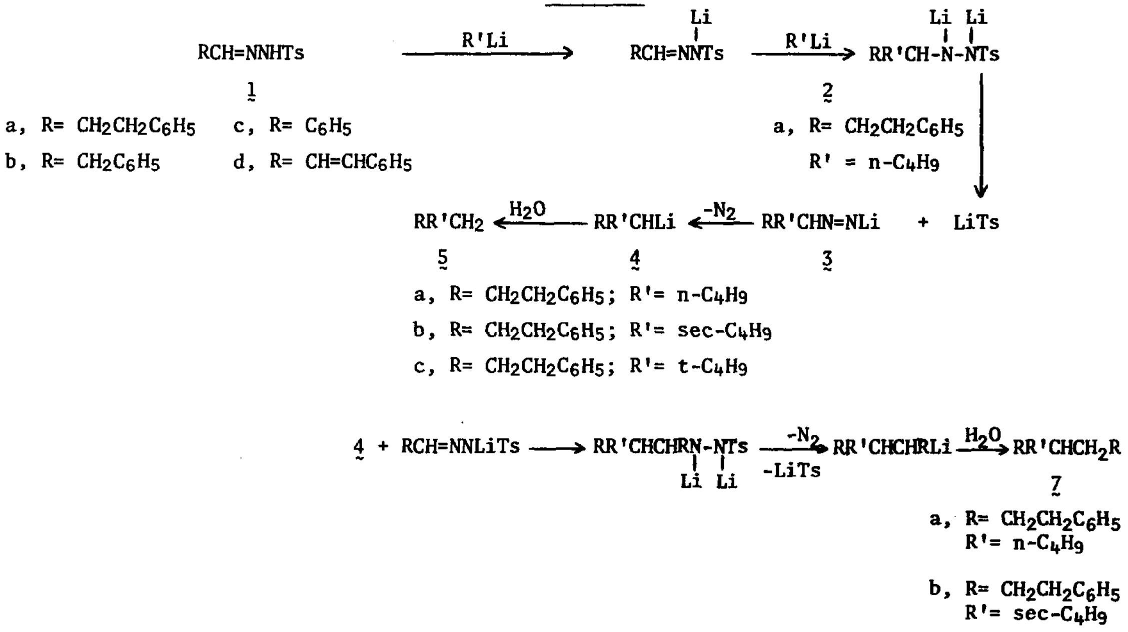
During unsuccessful attempts to generate dianions from aldehyde tosylhydrazones, we have observed that alkyllithium reagents add readily to the tosylhydrazone C=N linkage. The resulting adducts 2 fragment to organolithium species 4 and aqueous workup affords the reductive alkylation products 5. A similar process has been observed occasionally with ketone tosylhydrazones,[1-3] but dianion formation predominates in systems which have enolizable α-hydrogens.[2]

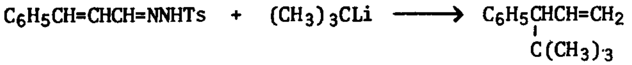
In a typical experiment, 1a is treated with 3 moles of n-butyllithium at -78°. The orange solution is warmed to -22° until nitrogen evolution ceases, and aqueous workup followed by chromatography over silica gel gives 1-phenylheptane 5a (49%) and the 2:1 adduct 7a (3%). The minor product is derived from attack of the organolithium intermediate 4a on the monoanion from 1a as shown in Scheme 1. If the experiment is performed at -22° instead of -78°, the yield of 7a (11%) increases at the expense of 1-phenylheptane (36%). Apparently, fragmentation of 2a is sufficiently rapid under these conditions to accumulate a substantial concentration of 4a in solution during introduction of n-butyllithium.

Scheme 1



Similar results are obtained with sec-butyllithium at -70° although relatively little of the 2:1 adduct **7b** is formed (Table 1). With tert-butyllithium the only significant hydrocarbon product is **5c** (61% at -22°), even when the experiment is performed at room temperature. None of the above reactions results in any detectable allylbenzene or isomeric olefins, the products expected from dianion formation.[2,3] Furthermore, the use of TMEDA as the solvent at 0° has no effect on the product distribution. These conditions have been reported to improve the yield of dianion-derived products from ketone tosylhydrazones and to inhibit the nucleophilic addition pathway.[2,4]

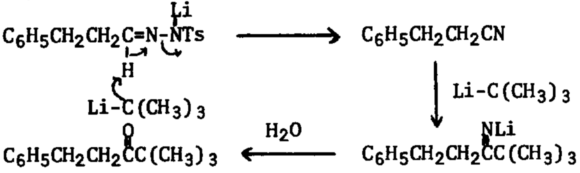
We have examined the addition of tert-butyllithium to several other aldehyde tosylhydrazones (Table 1). Reductive alkylation products have been isolated in every example studied although yields are variable. A notable special case is the reaction of cinnamaldehyde tosylhydrazone **1d** which undergoes exclusive 1,4-addition with tert-butyllithium to form a terminal olefin **8**. An analogous product is observed using n-butyllithium. Several unidentified hydrocarbons are also formed in the latter reaction, but none are present in greater than 2% yield.



$$C_6H_5CH{=}CHCH{=}NNHTs \;+\; (CH_3)_3CLi \longrightarrow C_6H_5\underset{\displaystyle C(CH_3)_3}{\underset{|}{C}}HCH{=}CH_2$$

1d **8** (58%)

The major competing process in all of the reactions described above appears to be the base-induced conversion of the mono-lithiated tosylhydrazone into a nitrile and a lithium salt of p-toluenesulfonamide.[5] In typical experiments the nitrile is attacked by excess alkyllithium reagent to give a ketone after hydrolysis. Occasionally, both the ketone and the nitrile can be isolated. Thus, the crude product after aqueous workup of the reaction of **1a** with tert-butyllithium contains the ketone **9** (7%) and 3-phenylpropionitrile (9%) in addition to the hydrocarbon mentioned previously.



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In summary, it is possible to convert aldehydes RCHO into reductive alkylation products RCH_2R' via the tosylhydrazones. Although yields are mediocre, the procedure is simple and appears well suited for the introduction of branched alkyl groups. In contrast to ketone tosylhydrazones, the aldehyde derivative **1a** does not form a dianion with alkyllithium reagents. This finding suggests that the Shapiro olefin synthesis is limited to ketone tosylhydrazones.[6]

Table 1. Reductive Alkylation of Aldehyde Tosylhydrazones

Starting hydrazone	Temperature	Solvent	RLi	Hydrocarbons isolated	
$C_6H_5CH_2CH_2CH{=}NNHTs$	-78°	THF	n-C_4H_9Li	$C_6H_5(CH_2)_6CH_3$ (49%)	$C_6H_5(CH_2)_2CH(n\text{-}C_4H_9)(CH_2)_3C_6H_5$ (3%)
$C_6H_5CH_2CH_2CH{=}NNHTs$	-22°	THF	n-C_4H_9Li	(36%)	(11%)
$C_6H_5CH_2CH_2CH{=}NNHTs$	-78°	THF	sec-C_4H_9Li	$C_6H_5(CH_2)_3CHCH_3C_2H_5$ (40%)	$C_6H_5(CH_2)_2CH(sec\text{-}C_4H_9)(CH_2)_3C_6H_5$ (1%)
$C_6H_5CH_2CH_2CH{=}NNHTs$	-22°	THF	tert-C_4H_9Li	$C_6H_5(CH_2)_3C(CH_3)_3$ (61%)	
$C_6H_5CH_2CH_2CH{=}NNHTs$	0°	TMEDA	tert-C_4H_9Li	(54%)	
$C_6H_5CH_2CH{=}NNHTs$	0°	TMEDA	tert-C_4H_9Li	$C_6H_5CH_2CH_2C(CH_3)_3$ (20%)	
$C_6H_5CH{=}NNHTs$	0°	TMEDA	tert-C_4H_9Li	$C_6H_5C(CH_3)_3$ (38%)	
$C_6H_5CH{=}CHCH{=}NNHTs$	-22°	THF	tert-C_4H_9Li	$C_6H_5CH(tert\text{-}C_4H_9)CH{=}CH_2$ (58%)	
$C_6H_5CH{=}CHCH{=}NNHTs$	-78°	THF	n-C_4H_9Li	$C_6H_5CH(n\text{-}C_4H_9)CH{=}CH_2$ (20%)	

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2. R. H. Shapiro, M. F. Lipton, K. J. Kolonko, R. L. Buswell, and L. A. Capuano, Tetrahedron Lett., 1811 (1975).
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4. J. E. Stemke and F. T. Bond, Tetrahedron Lett., 1815 (1975).
5. Nitriles are formed somewhat more cleanly using the non-nucleophilic base lithium diisopropylamide (LDA). This reagent converts **1c** into benzonitrile (76%) and p-toluenesulfonamide (78%) after water workup. Other aldehyde tosylhydrazones give more complex product mixtures due to nitrile deprotonation by excess LDA. In the case of **1b**, LDA causes efficient formation of a dianion at -78°, as evidenced by dianion trapping by sulfenylation.
6. The failure of typical aldehyde tosylhydrazones to form stable dianions at low temperatures is consistent with the strong preference for deprotonation syn to the N-SO_2·Ar group observed by Shapiro with the ketone analogs.[2] The aldehyde tosyl hydrazones presumably have E geometry, and stabilization of the dianion by chelation effects is not possible.