Michael Additions of Hydrazones for Carbon–Carbon Bond Formation

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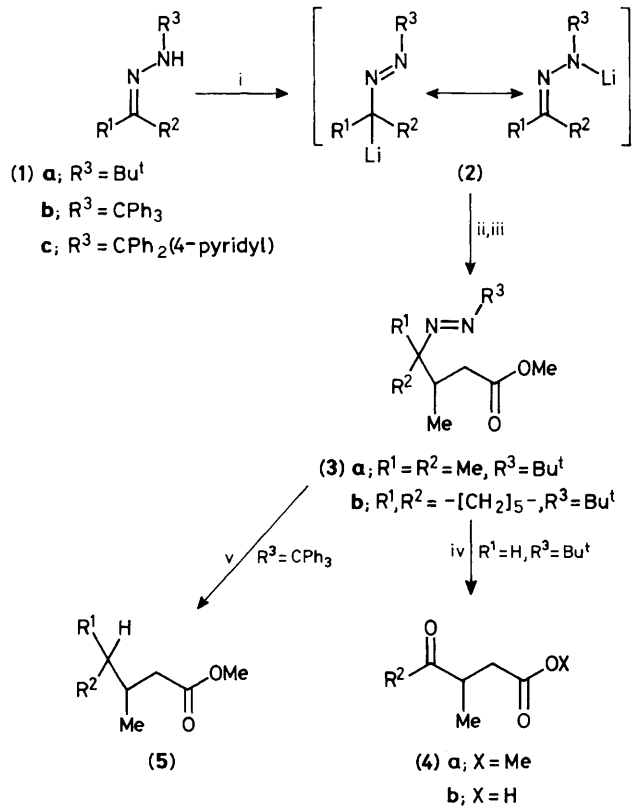
The lithium salts of t-butyl- and trityl-hydrazones react with methyl crotonate to form *C*-trapped azo-esters and similar products were observed from a thermal ene-reaction of aldehyde t-butylhydrazones with methyl acrylate or acrylonitrile, and aldehyde phenylhydrazones with methyl acrylate; these products can be diverted into synthetically useful γ-keto-esters, γ-keto-nitriles, saturated esters, γ-alkyl-2-pyrrolidones, and γ-amino-esters.

Recently we described the use of t-butylhydrazones (**1a**) as acyl anion equivalents,[1] and the use of trityl (**1b**) and diphenyl-4-pyridylmethyl (**1c**) hydrazones for reductive C–C bond formation from aldehydes and ketones.[2] Herein we report C–C bond forming reactions by the reaction of these hydrazones with Michael type electrophiles in both ionic (Scheme 1) and thermal (Schemes 2 and 3) type pathways.

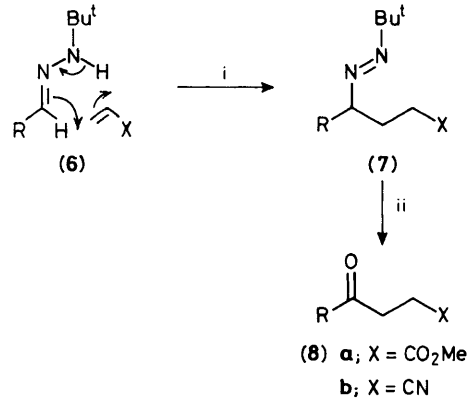
Thus treatment of the t-butylhydrazones (**1a**) with n-butyl-lithium (0.95 equiv.) in tetrahydrofuran (THF) at 0 °C gave the azo-anion (**2**) which was cooled to −78 °C and treated with methyl crotonate (1.0 equiv., −78 °C, 30 min) (Scheme 1). Acetic acid (1.0 equiv.) was added, and in the case of ketone t-butylhydrazones, the stable azo-esters [(**3a**), 58%; (**3b**), 53%] were isolated by chromatography.† The azo-esters (**3**) derived from aldehyde t-butylhydrazones were not isolated, but directly isomerised [trifluoroacetic acid (TFA), 5 h, 20 °C]



Scheme 1. *Reagents:* i, n-butyl-lithium (0.95 equiv., −78 or −50 °C); ii, methyl crotonate; iii, HOAc or TFA (1.0 equiv.); iv, TFA, 5 h, 20 °C; $(CO_2H)_2$–H_2O–diethyl ether, 12 h, 20 °C; v, EtSH.

† All known compounds were characterised by comparison to literature data. All new compounds were characterised by full spectral and analytical data. Yields refer to isolated and purified products from the hydrazone starting material.

to their hydrazone forms. Thereafter hydrolysis [$(CO_2H)_2$–H_2O–diethyl ether, 12 h, 20 °C] and chromatography gave the γ-keto-esters (**4a**) (50—60%, Table 1). With trityl (**1b**) or diphenyl-4-pyridylmethyl (**1c**) hydrazones a lower yielding *C*-addition pathway *via* the azo-anion (**2**) was observed. Thus treatment of the tritylhydrazone (**1b**) with n-butyl-lithium (0.95 equiv.) in dimethoxyethane at −78 °C gave the azo-anion (**2**) which was warmed to −50 °C and treated with methyl crotonate (2.0 equiv. added over 1 h, −50 °C). TFA (1.0 equiv.) and ethanethiol (5 equiv.) were added in sequence and the solution warmed to 20 °C. Purification by chromatography gave the saturated esters (**5**) (20—35%, Table 1).‡



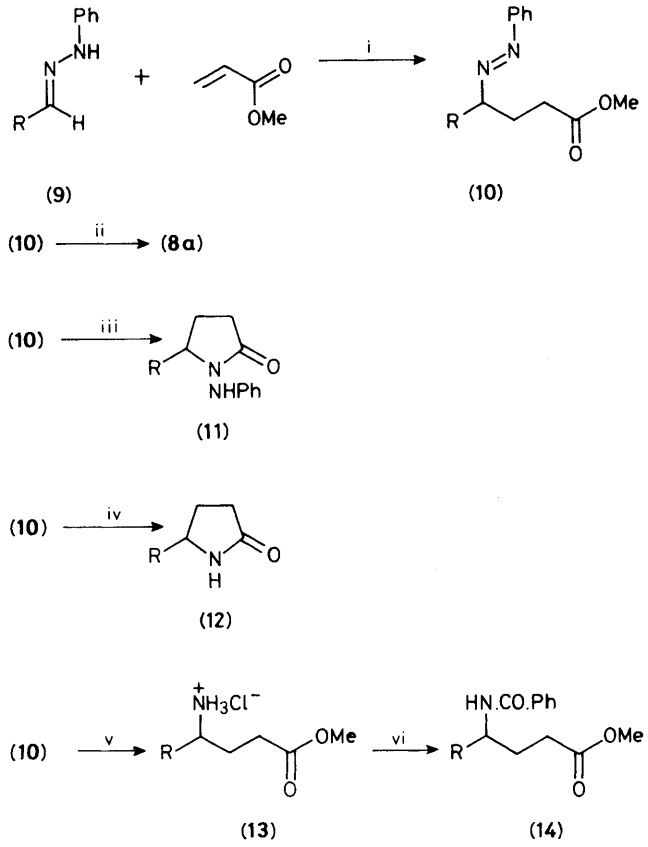
Scheme 2. *Reagents:* i, methyl acrylate or acrylonitrile (2–3 equiv.), toluene or xylene, reflux, 24 h; ii, TFA, 1.5 h, 20 °C; $(CO_2H)_2$–H_2O–diethyl ether, 20 °C, 12 h (X = CO_2Me) or 3 h (X = CN).

Table 1

Hydrazone (**1**)			Product, %			
R^1	R^2	R^3				
Me	Me	But	(**3a**)	58		
	-$[CH_2]_5$-	But	(**3b**)	53		
H	Me	But	(**4a**)	58		
H	Bun	But	(**4a**)	60[a]		
H	Bui	But	(**3**)	55	(**4b**)	47[b]
H	n-C_7H_{15}	But	(**4a**)	50		
H	Ph	But	(**3**)	68	(**4b**)	47[b]
	-$[CH_2]_5$-	$C(Ph)_3$	(**5**)	35		
H	Bun	$C(Ph)_3$	(**5**)	20		
H	Bui	$C(Ph)_3$	(**5**)	23		

[a] If a deficiency of methyl crotonate (0.5 equiv.) was used in this reaction, then the yield of (**4a**) was 76% based upon methyl crotonate. [b] These hydrazones proved resistant to hydrolysis at 20 °C. γ-Keto-acids were isolated after more forcing hydrolysis [2 M HCl in H_2O: THF (1 : 1), reflux, 15 h].

‡ The major pathway in these examples appears to be a basic deprotonation of methyl crotonate by the azo-anion (**2**) to give a recovered hydrazone (**1b**).



Scheme 3. *Reagents:* i, xylene, reflux, 24 h; ii, TFA, 20 °C, 5 h then $(CO_2H)_2$–H_2O–diethyl ether, 20 °C, 12 h; iii, Zn, HOAc, 60 °C, 1.5 h; iv, Pd/C, H_2 (1 atm), 50 °C, 12—24 h; v, PtO_2, H_2 (1 atm), 20 °C, 24 h, MeOH–HCl; vi, C_5H_5N, PhCOCl.

Table 2

Hydrazone (**6**) R	Product, %			
Me	(**8a**)	80[a]	—	
Bu[t]	(**8a**)	77[b]	(**8b**)	20[b]
Bu[n]	(**8a**)	75[b]	(**8b**)	47[b]
n-C_7H_{15}	(**8a**)	90[b]	(**8b**)	60[b]

[a] Thermal reaction in toluene solvent. [b] Thermal reaction in xylene solvent.

Under these ionic conditions with either t-butyl (**1a**) or trityl (**1b**) hydrazones, substitution of methyl crotonate by methyl acrylate, methyl β,β-dimethylacrylate, or acrylonitrile gave negligible *C*-addition to the azo-anions (**2**). However under thermal conditions (reflux in toluene or xylene) the aldehyde t-butylhydrazones (**6**) reacted with methyl acrylate (2 equiv.) or acrylonitrile (3 equiv.) in high yield *via* *C*-addition to yield the t-butyl-azo compounds (**7**) in an ene-type reaction. These azo-species (**7**) were not isolated but were directly isomerised (TFA, 5 h, 20 °C) and subsequently hydrolysed [$(CO_2H)_2$–H_2O–diethyl ether, 20 °C]. Work up and chromatography gave the γ-keto-esters and γ-keto-nitriles (**8**) (20—90%, Scheme 2, Table 2). The thermal reaction of aldehyde t-butylhydrazones with methyl crotonate or methyl β,β-dimethylacrylate gave negligible *C*-addition to azo-esters (**7**), as did a reaction of cyclohexanone t-butylhydrazone with methyl acrylate.

Table 3

Phenyl hydrazone (**9**) R	Product (%) from (**9**) (**10**)	(**8a**)	(**11**)	(**12**)	(**14**)
H	60	—	48	51	33
Me	56	41	45	48	34
Et	57	44	45	46	34
Pr[i]	56	52	52	45	38

Unfortunately these azo-adducts (**3**) and (**7**) derived from t-butylhydrazones could not be reductively cleaved to yield the potentially valuable amino functions. However the reported[3] thermal reaction of aldehyde phenylhydrazones (**9**) with methyl acrylate to yield the phenylazo-esters (**10**) offered a solution to this problem and provides thereby a convenient route to protected γ-amino-acids.§ Thus treatment of the aldehyde phenylhydrazones (**9**) with methyl acrylate (2.0 equiv.) under reflux in xylene gave the γ-phenylazo-esters (**10**) in reasonable yields (55—60%). As before these azo-esters (**10**) could be isomerised (TFA, 20 °C, 5 h) and hydrolysed [$(CO_2H)_2$–H_2O–diethyl ether, 20 °C, 12 h] to the γ-keto-esters (**8a**) (41—52%). Alternatively the azo-esters (**10**) were reduced under mild conditions (Zn, HOAc, 60 °C, 1.5 h) to hydrazo-esters, which upon work up cyclised to the 5-alkyl-1-(phenylamino)-2-pyrrolidones (**11**) (45—52%). Under more forcing conditions [Pd/C, H_2 (1 atm), 50 °C, 12—24 h] the azo-esters (**10**) gave the 5-alkyl-2-pyrrolidones (**12**) (45—51%) arising from reductive cleavage of the azo function. With Adam's catalyst [PtO_2, H_2 (1 atm), 20 °C , 24 h, MeOH–HCl] in the presence of hydrochloric acid, the azo-esters (**10**) gave the hydrochloride salts of γ-amino-esters (**13**)¶ which were isolated as their *N*-benzoyl derivatives (**14**) (Scheme 3, Table 3).

In summary, the azo-anions have now been extended to conjugate additions to α,β-unsaturated systems. Similar types of product may be reached more economically by a purely thermal ene reaction of aldehyde t-butyl- or phenylhydrazones. The derived phenylazo-esters (**10**) allow reductive azo-bond cleavage and thus offer an operational equivalent of an α-aminocarbanion.

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§ Although the thermal ene reaction of aliphatic aldehyde phenylhydrazones with methyl acrylate or acrylonitrile to give phenylazoalkanes has been described,[3] the potential to use such adducts as amine synthons was not exploited.

¶ This reduction gave a mixture (*ca.* 1 : 1) of the hydrochloride salts of γ-amino-esters (**13**) and cyclohexylamine in high yield (>90%) from the azo-esters (**10**).