

1,4-ADDITION OF REFORMATSKY REAGENT TO 1,3-DIAZA-1,3-BUTADIENES

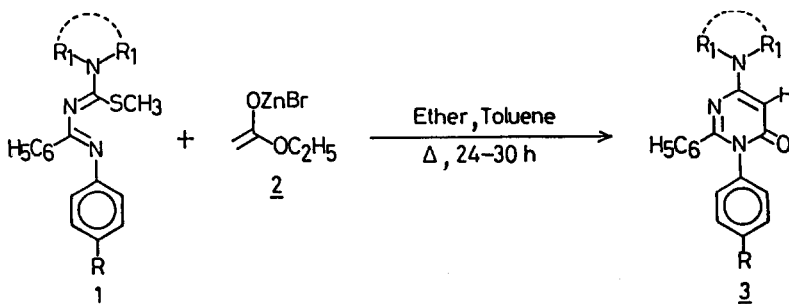
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Abstract: The 1,4-conjugated addition of the Reformatsky reagent from ethyl bromoacetate to 1-aryl-4-methylthio-4-sec.amino-2-phenyl-1,3-diaza-1,3-butadienes gives 1-aryl-2-phenyl-4-sec.amino-1,6-dihydropyrimidin-6-ones.

Reformatsky reagents have attracted much attention because of structural interest^{1,2} and their potential applicability in effective carbon-carbon bond formation on carbonyl³. They have been shown normally to undergo 1,2-addition across carbonyl group¹⁻⁴ and in limited cases, reported to add to α,β -unsaturated carbonyl compounds in a 1,4-manner^{3,5,6}. On the contrary, the reports concerning the 1,2-addition of Reformatsky reagents to carbon-nitrogen multiple bonds are less and they have been found to add to imines^{3,7-10} and nitriles^{3,10-13} yielding β -lactams and ketoesters, respectively. However, to our knowledge there are no such reports concerning the 1,4-addition of Reformatsky reagents to substrates having a carbon-nitrogen double bond. Hence in continuation of our work on cycloaddition reactions of 1,3-diaza-1,3-butadienes^{14,15}, we report here 1,4-conjugate addition of a Reformatsky reagent to 1,3-diaza-1,3-butadienes.

The treatment of 1-aryl-4-methylthio-2-phenyl-4-sec.amino-1,3-diaza-1,3-butadienes (1) with the Reformatsky reagent, prepared from ethyl bromoacetate, resulted in very good yields of the previously unknown 1-aryl-2-phenyl-4-sec.amino-1,6-dihydropyrimidin-6-ones (3).



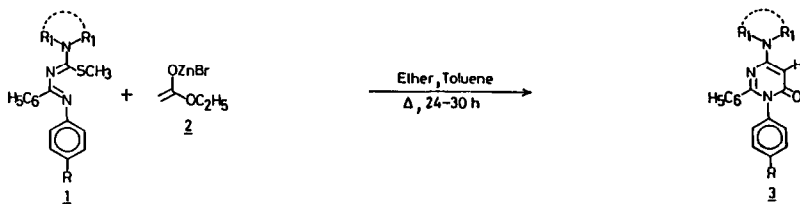


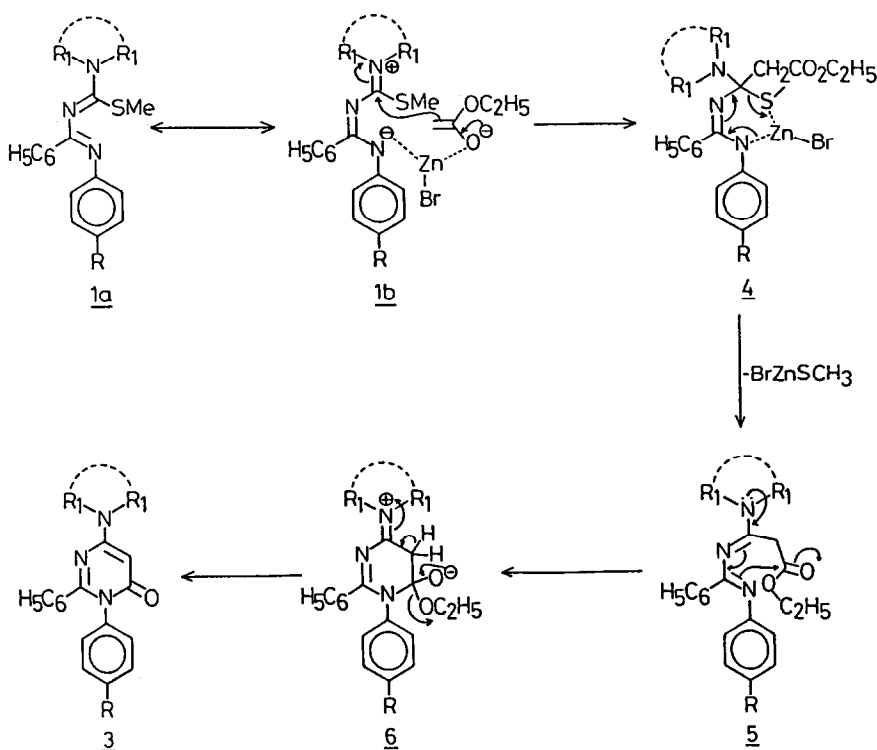
Table-1

Compound	R	R ¹	R ¹	Yield (%)	mp. (°C)
3a	H	-(CH ₂) ₂ -O-(CH ₂) ₂ -		90	198-9
b	H	-(CH ₂) ₂ -CH ₂ -(CH ₂) ₂ -		90	162
c	H	-CH ₂ -CH ₂ -CH ₂ -		86	178-9
d	H	-CH ₃	-CH ₃	86	173-4
e	CH ₃	-(CH ₂) ₂ -O-(CH ₂) ₂ -		86	225
f	CH ₃	-(CH ₂) ₂ -CH ₂ -(CH ₂) ₂ -		84	232
g	CH ₃	-CH ₂ -CH ₂ -CH ₂ -		83	186
h	CH ₃	-CH ₃	-CH ₃	83	193-4
i	Cl	-(CH ₂) ₂ -CH ₂ -(CH ₂) ₂ -		85	235
j	Cl	-CH ₂ -CH ₂ -CH ₂ -		70	220
k	Cl	-CH ₃	-CH ₃	80	194

A solution of 1,3-diaza-1,3-butadienes (1) ¹⁶ (2 mmole) in dry toluene (30 ml) was added slowly, over a period of 45 minutes to the ether solution of Reformatsky reagent (2) (4.4 mmole). The reaction mixture was refluxed for 24-30 hours and poured over an ice cold 5% sulphuric acid (50 ml) solution. The organic layer was separated and the aqueous layer was extracted with chloroform (2x50 ml). The combined extract was washed with saturated sodium hydrogen carbonate solution, water and finally dried over anhydrous sodium sulphate. The removal of solvent under reduced pressure yielded crude pyrimidones (3), which were recrystallised from a mixture of (1:1) benzene and petroleum ether (Table-1).

The products were characterised on the basis of analytical and spectral evidence¹⁷. Their i.r. spectra (KBr) showed a strong absorption peak at ca. 1670 cm⁻¹ due to α,β-unsaturated carbonyl group and ¹H n.m.r. spectra (CDCl₃) showed the absence of signals due to -SCH₃ and -OCH₂CH₃ protons, and the presence of a singlet at ca. δ 5.5 for the olefinic proton of 1,6-

dihydropyrimidin-6-ones (3). The probable mechanism for the formation of 3 is outlined in Scheme-1. In this mechanism, it is presumed that the Reformatsky reagent initially attacks at the position 4 of the zwitterionic form of the 1,3-diaza-1,3-butadienes (1b) leading to the formation of an organo-zinc intermediate 4. The intermediate 4 then undergoes elimination of methylthiozinc bromide to result in another intermediate 5. This intermediate, 5 inturn undergoes nitrogen lone pair assisted cyclisation to the desired pyrimidones (3). The absence of any 1,2-addition product and preferred 1,4-mode of addition of Reformatsky reagent, in this case, may be due to the presence of a polarising secondary amino group at position 4 of 1,3-diaza-1,3-butadiene.



Scheme 1

It may be worthwhile to mention here that the Reformatsky reagent generated from ethyl bromoacetate, in this case, may be considered equivalent to simple ketene, because the pyrimidones (3) may also be obtained by the cyclo-addition reaction of 1 with simple ketene. However, the facile synthesis of 3 by this method is advantageous because of the apparent difficulties encountered in getting simple ketene in free monomeric state. Further investigations concerning the reactions of Reformatsky reagent with various carbon-nitrogen double bonded substrates is being undertaken.

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1-Aryl-4-methylthio-2-sec.amino(morpholino/piperidino/pyrrolidino/dimethylamino)-1,3-diaza-1,3-butadienes (1) were prepared by the thiomethylation of corresponding N'-(N-arylbenzimidoyl)-N,N-sec.amino thio-ureas (0.1 mole) in dry acetone by methyl iodide (0.22 mole). The basification of the hydroiodide salt of 1 with 3N potassium hydroxide (50 ml) solution, followed by extraction with chloroform (200 ml), resulted in almost quantitative yield of 1.
- Elemental analysis and spectral data for compound 3a: Found: C, 70.86; H, 5.73; N, 12.58. C₂₀H₁₉N₃O₂ requires C, 70.07; H, 5.71; N, 12.61. max (KBr): 1670 cm⁻¹ (α,β-unsaturated carbonyl). δ_H (CDCl₃): 3.50-3.63 (t, 4H, CH₂-N-CH₂); 3.72-3.83 (t, 4H, CH₂-O-CH₂); 5.53 (s, 1H, olefinic) and 7.00-7.36 (m, 10H, arom). M⁺ 333.

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