SYNTHESIS OF N1-ALKYL AND N1-ALLYL OF PHENYLHYDRAZONES

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Abstract

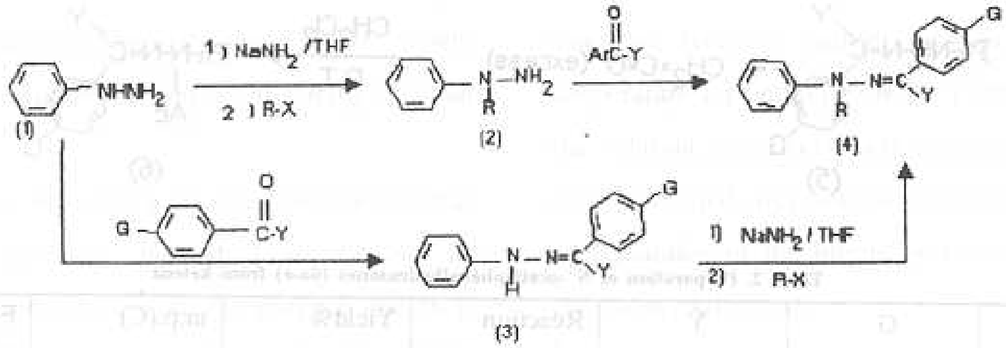
A general and convenient method for prepatation of N^1-alkyl and N^1-allylphenylhydrazones is described and their reactivity towards ketene is studied.

Introduction

In continuation of our interest on the reaction on imines with ketenes [1], we needed substantial amounts of N^1-substituted phenylhydrazones. In preparation of N^1-alkyl or N^1-allylphenylhadrazones, however, we found out that no convenient synthetic method is available. There are spread reports in the literature and in most cases two steps sequence(1 → 2 → 4)(schemel) is utilized for the synthesis of N^1-substituted phenylhydrazones [2,3]. The synthesis of N^1 alkylphenylhydrazones by this method is problematic for several reasons. First, since both hydrazine(1) and (2) are liquid with similar physical properties, separtion and purification of N^1-alkyphenylhydrazine from the reaction mixture is difficult and resulting in low yield. Another problem in the synthesis of (4) by this route is that condensation of N^1-alkylphenylhydrazine (2) with aldehydes and ketones, when comparing with simple non-alkylphenylhydrazine is rather difficult. Steric factor caused by substitution at N^1 position may be responsible for this low reactivity.

Results and Discussion

Alternative method, i. e. 1 → 3 → 4 is, to our knowledge, the simplest route for preparation of compounds (4). In 1990 Sherma *er. al.* reported the prepatation of only N-Methylphenylhydrazone by this method, claiming quantitative yield[4]. We repeated Sherma procedure several times, but the yields obtained were hardly more than 40 percent. By changing the reaction condition (see experimental section) we were able to alkylate phenylhydrazone (3) with various alkyl and allylhalide in good yields (table 1).



Scheme 1

Table 1. Perparation of phenylhydrazones 4a-h

No	R-X	G	Y	Yield	m.p.(C)	Molecular formula(m/z) or Lit.m.p.(C)
a	CH3I	H	H	90	103-104	103[3,5]
b	CH3I	4-Cl	H	88	105-106	Cl4H13N2(244.73)
c	CH3I	4-NO2	H	75	128-130	$C_{14}H_{13}N_3O_2$(255.28)
d	CH3I	4-(CH3)2N-	H	72	146-147	Cl6H19N3(253.35)
e	CH2=CH-CH2-Br	H	H	80	51-53	51-53[3,5]
f	n-C3H7I	H	H	80	63-65	63[3,5]
g	CH2=CH-CH2-Br	4-(CH3)2N	H	55	109-110	Cl8H2N3(279.52)
h	CH3I	H	C6H5	79	75-76	76-79[5]

In preparation of hydrazone (4a-h), (3a-h) were treated with sodium amide in tetrahydrofuran (THF) to give corresponding anions. When these anions allowed to react *in situ* with appropriate alkyl hakide, N^1-alkylated hydrazones (4a-h) were formed in good yied and good purity. No by - products were detected and work-up condition were straight forward. THF may be replaced by dimethoxyethane as solvent without appreciable loss in yield and purity. However, sodium amide proved to be superior to sodium hydride and n-buthylithium as deprotonationg agent. Alkyl iodide; bromide or chloride afforded comparable yields.

In pursuing our interest, the next step was to examine the reactivity of hydrazones with ketene. These reactions should be of interest, since they could lead either to β-lactam rings[1] or acetylhydrazones.

Addition of ketence, produced by pyrolysis of acetone at 700-750C, to phenylhdrazones (3a-e) gave N^1-acetyl phenylhydrazones (6a-e) in high yield (table 2).

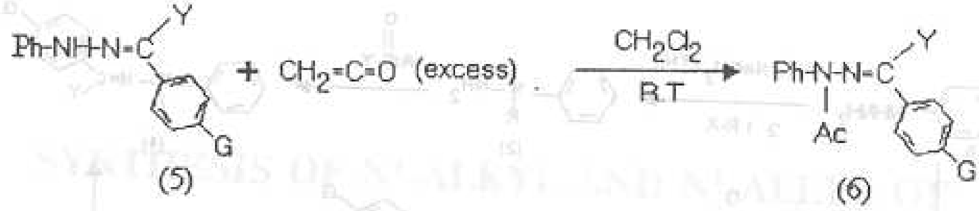


Table 2. Perparation of N¹-acetylphenylhydrazones (6a-e) from ketene

Compound (6)	G	Y	Reaction Time(hr)	Yield%	m.p.(C)	Formula or Lit.m.p.(C)
a	H	H	4	95	120-121	122[6]
b	4-Cl	H	8	91	87-8	C15H13ClN2O
c	4-NO2	H	8	90	164-5	C15H13N3O3
d	4-N(CH3)2	H	3	94	143-4	C17H19N3O
e	H	ph	7	90	88-9	90[7]

In order to ratigy the structure (6a-e), these compounds were prepared by the reaction actic anhdride with hydrazones (5) in acetic acids (table 3).

Table 3. Perparation of N¹-acetylphenylhydrazones (6a-e) from Ac_2O

Compound	G	Y	Reaction time(hr)	Yield%	m.p.C[a]
a	H	H	3	85	119-120
b	4-Cl	H	1	81	87-8
c	4-NO2	H	5	75	164-5
d	4-(CH3)2N	H	1	77	142-3
e	H	Ph	6	70	86-90

a: To compare melting points with hydrazones obtained from the ketene reaction.

N^1-Alkylphenylhydrazones, however, were not reactive toward ketene. Prolong treatment of hydrazone (4a, b, c, e) with ketene led to almost pure starting material.

Experimental Section

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Varian T-60 spectrometer. Tetrahydrofuran was dried with sodium and distilled prior to use. Microanalysis were performed by Food Research Institue, Norwich-England. Infrared spectra were recorded using the nujol mull technique on a Beckmann Acculab 3 spectrometer. Mass spectra were taken by varian Mat 311 instrument.

Perparation of N^1-alkyl-1-phenylhydrazone(4a-h). Typical Procedure*

Benzaldehyde methyphenydrazone (4a).- To the solution of sodium amide (2g, 0.05mole) in 50ml) was added benzaldehyde lhydrazone(3a) (5.9g, 0.03 mole) in THF (20ml) -6C, whereupon a persistent orange colour ared.

he solution was stirred for one hour and the flue nitrogen gas was intensified to remove all onium formed in solution. The nitrogen flue, then, ped and methyl iodide (8.5g, 0.06mole) in THF (10ml) was added dropwise to the solution at 10-15C. At the end of the addition, solution became colourless and the reaction mixture was stirred at room temperature for one hour. Weter (50ml) was added to the solution and layers were sepatated. The organic layer was dried over sokium sulphate. Filtration and concentatuion of the filtrate by cooling gave a white crystals of (4a) (90%).

* For physical and spectral data see table 1 and 4.

Table4. Spectral data of new compounds(4)

	^{1}H-NMR(CDCl3/TMS)	M.S.(70ev)m/e
		244(M), 111, 77,51
b	3.29(s,3H,N-Ch3); 7.0-7.5(m,10H)	255(M+), 148,147,120,119,118
c	3.33(s,3H,N=CH3); 7.33-8.30(m,10H)	255(M+), 106,77,42
d	3.1(s,6H,N(CH3)$_2$); 3.45(s,3H,N-CH3); 6.7-7.9(m,10H)	279(M+), 238,222,77,41
g	2.95(s,6H,N(CH3)$_2$) 4.5(s,2H,N-CH2-); 5.1(m,1H,CH=CH2) 5.3(s,2H,C=CH2); 6.6-7.7(m,10H)	

Prepatation of 1-acetyl-1-phenylhydrazones(6a-e) by he reaction of ketene with hydrazones(5).

Typical Procedure*

Acetic acid benzylidene phenylhydrazide(6a). - Ketene gas (produced by pyrolysis of acetone at 700-730C) was passed through the solution of hydrazone (5a)(lg, 0.05mol) in dichloromethane (30ml) at room temperaturde for 4 hours. The solvent was evaporte in vaccue. The soild residue was crystallized in ether to give a pale yellow needles of (6a)(95%).

* For physical and spectral data for the new compounds (6) see table 3 and 4 respectively.

Table 5. Spectral data for the new compounds 6

Compound	^{1}HNMR(CDCl$_3$/TMS)	IR(V_{max}KBr)	MS(70ev) m/z
b	2.53(s,3H,N-COCH3),7.0-7.8(m,10H)	3020,1690,1610,1390	273(M$^+$),231,135,93,77,43,28.
c	2.6(s,H;N-COCH3); 7.21-8.22(m,10H)	3020,1690,1580,1385	285(M$^+$),194,135,92,77,43.
d	2.58(s,3H;N-COCH3); 2.97(s,6H,J=7Hz,N(CH3)$_2$);6.6-7.5(m,10H)	2900-3000,1690-1610	282(M$^+$),239,147,94,77,43,28

Perparation of 1-acetyl-l-phenylhydrazones(6a-e) by the reaction of acetic anhydride with hydrazones(5)

Typical Procedure*

Acetic acid benzylidene phenylhydrazide(6a).- To phenylhydrazone(5a) (1g, 0.005mol) in glacial acetic acid (10ml) was added acetic anhydride (1g, 0.01mole) at room temperature. The reaction mixture was heated under reflux for 3 hours. The solvent and excess acetic anhydride were evaporated in vaccuo and the residue was washed with distilled water (10ml). The solid was dissolved in ether (20ml) and sodium sulphate was then added and after stirring for few minutes the solution was collected by filtration. The filtrate was concentrated to 10 ml and cooled in an ice bath to give (6a) as a white crystalls (0.65g, 85%).

* For physical and spectral data see table 3 and 5.

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