

SYNTHESIS OF N¹-ALKYL AND N¹-ALLYL OF PHENYLHYDRAZONES

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Abstract

A general and convenient method for preparation of N¹-alkyl and N¹-allylphenylhydrazones is described and their reactivity towards ketene is studied.

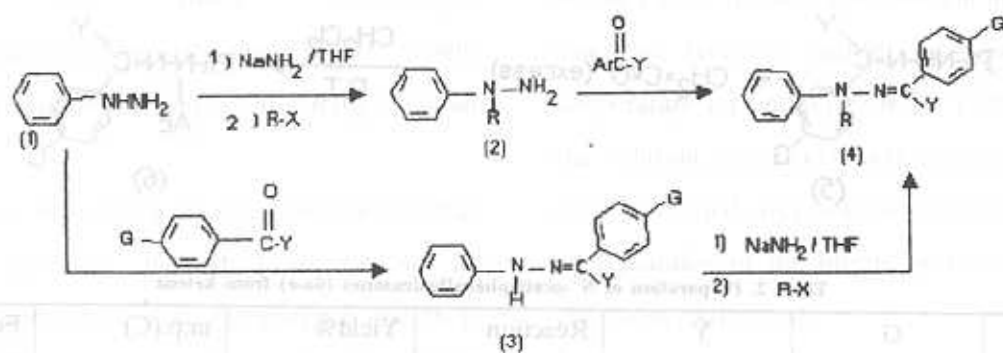
Introduction

In continuation of our interest on the reaction on imines with ketenes [1], we needed substantial amounts of N¹-substituted phenylhydrazones. In preparation of N¹-alkyl or N¹-allylphenylhydrazones, 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) (scheme 1) is utilized for the synthesis of N¹-substituted phenylhydrazones [2,3]. The synthesis of N¹-alkylphenylhydrazones by this method is problematic for several reasons. First, since both hydrazine (1) and (2) are liquid with similar physical properties, separation and purification of N¹-alkylphenylhydrazine

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 N¹-alkylphenylhydrazine (2) with aldehydes and ketones, when comparing with simple non-alkylphenylhydrazine is rather difficult. Steric factor caused by substitution at N¹ 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 *et al.* reported the preparation 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. Preparation of phenylhydrazones 4a-h

No	R-X	G	Y	Yield	m.p.(C)	Molecular formula(m/z) or Lit.m.p.(C)
a	CH ₃ I	H	H	90	103-104	103[3,5]
b	CH ₃ I	4-Cl	H	88	105-106	C ₁₄ H ₁₃ N ₂ (244.73)
c	CH ₃ I	4-NO ₂	H	75	128-130	C ₁₄ H ₁₃ N ₃ O ₂ (255.28)
d	CH ₃ I	4-(CH ₃) ₂ N-	H	72	146-147	C ₁₆ H ₁₉ N ₃ (253.35)
e	CH ₂ =CH-CH ₂ -Br	H	H	80	51-53	51-53[3,5]
f	n-C ₃ H ₇ I	H	H	80	63-65	63[3,5]
g	CH ₂ =CH-CH ₂ -Br	4-(CH ₃) ₂ N	H	55	109-110	C ₁₈ H ₂ N ₃ (279.52)
h	CH ₃ I	H	C ₆ H ₅	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 halide, N¹-alkylated hydrazones (4a-h) were formed in good yield 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-butyllithium as deprotonating 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 ketene, produced by pyrolysis of acetone at 700-750C, to phenylhydrazones (3a-e) gave N¹-acetyl phenylhydrazones (6a-e) in high yield (table 2).

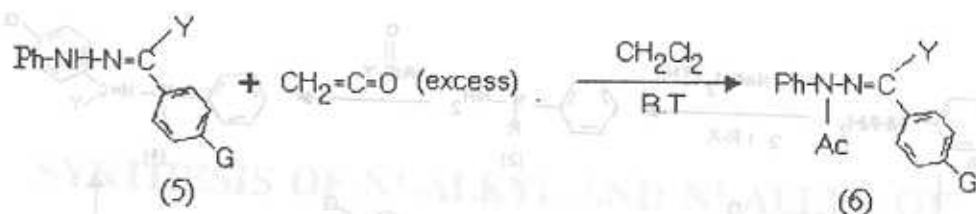


Table 2. Preparation of N¹-acetylphenylhydrazones (6a-e) from ketene

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	C ₁₅ H ₁₃ ClN ₂ O
c	4-NO ₂	H	8	90	164-5	C ₁₅ H ₁₃ N ₃ O ₃
d	4-N(CH ₃) ₂	H	3	94	143-4	C ₁₇ H ₁₉ N ₃ O
e	H	ph	7	90	88-9	90[7]

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

Table 3. Preparation of N¹-acetylphenylhydrazones (6a-e) from Ac₂O

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-NO ₂	H	5	75	164-5
d	4-(CH ₃) ₂ N	H	1	77	142-3
e	H	Ph	6	70	86-90

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

N¹-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. ¹H-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 Institute, 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.

Preparation of N¹-alkyl-1-phenylhydrazone(4a-h).

Typical Procedure*

Benzaldehyde methoxyphenylhydrazone (4a). To the

solution of sodium amide (2g, 0.05mole) in (50ml) was added benzaldehyde hydrazone(3a) (5.9g, 0.03 mole) in THF (20ml) at 0-6°C, whereupon a persistent orange colour appeared.

The solution was stirred for one hour and the blue nitrogen gas was intensified to remove all ammonium formed in solution. The nitrogen flue, then, was added and methyl iodide (8.5g, 0.06mole) in THF

(10ml) was added dropwise to the solution at 10-15°C. At the end of the addition, solution became colourless and the reaction mixture was stirred at room temperature for one hour. Water (50ml) was added to the solution and layers were separated. The organic layer was dried over sodium sulphate. Filtration and concentration of the filtrate by cooling gave a white crystals of (4a) (90%).

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

Table 4. Spectral data of new compounds(4)

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

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

Typical Procedure*

Acetic acid benzylidene phenylhydrazide(6a) - Ketene gas (produced by pyrolysis of acetone at 700-730°C) was passed through the solution of

hydrazone (5a)(1g, 0.05mol) in dichloromethane (30ml) at room temperature for 4 hours. The solvent was evaporated in vacuo. The solid 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 H-NMR(CDCI ₃ /TMS)	IR(V _{max} KBr)	MS(70ev) m/z
b	2.53(s,3H,N-COCH ₃),7.0-7.8(m,10H)	3020,1690,1610,1390	273(M ⁺),231,135,93,77,43,28.
c	2.6(s,H;N-COCH ₃); 7.21-8.22(m,10H)	3020,1690,1580,1385	285(M ⁺),194,135,92,77,43.
d	2.58(s,3H;N-COCH ₃); 2.97(s,6H,J=7Hz,N(CH ₃) ₂);6.6-7.5(m,10H)	2900-3000,1690-1610	282(M ⁺),239,147,94,77,43,28

Preparation of 1-acetyl-1-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 vacuo 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 crystals (0.65g, 85%).

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

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Table 3: Spectral data for the new compounds

Compound	¹ H NMR (CDCl ₃ /TMS)	IR (KBr)
1	7.2(m, 1H), 6.8(m, 1H), 6.5(m, 1H), 6.2(m, 1H), 5.8(m, 1H), 5.5(m, 1H), 5.2(m, 1H), 4.8(m, 1H), 4.5(m, 1H), 4.2(m, 1H), 3.8(m, 1H), 3.5(m, 1H), 3.2(m, 1H), 2.8(m, 1H), 2.5(m, 1H), 2.2(m, 1H), 1.8(m, 1H), 1.5(m, 1H), 1.2(m, 1H), 0.8(m, 1H), 0.5(m, 1H)	1650, 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100
2	7.2(m, 1H), 6.8(m, 1H), 6.5(m, 1H), 6.2(m, 1H), 5.8(m, 1H), 5.5(m, 1H), 5.2(m, 1H), 4.8(m, 1H), 4.5(m, 1H), 4.2(m, 1H), 3.8(m, 1H), 3.5(m, 1H), 3.2(m, 1H), 2.8(m, 1H), 2.5(m, 1H), 2.2(m, 1H), 1.8(m, 1H), 1.5(m, 1H), 1.2(m, 1H), 0.8(m, 1H), 0.5(m, 1H)	1650, 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100
3	7.2(m, 1H), 6.8(m, 1H), 6.5(m, 1H), 6.2(m, 1H), 5.8(m, 1H), 5.5(m, 1H), 5.2(m, 1H), 4.8(m, 1H), 4.5(m, 1H), 4.2(m, 1H), 3.8(m, 1H), 3.5(m, 1H), 3.2(m, 1H), 2.8(m, 1H), 2.5(m, 1H), 2.2(m, 1H), 1.8(m, 1H), 1.5(m, 1H), 1.2(m, 1H), 0.8(m, 1H), 0.5(m, 1H)	1650, 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100
4	7.2(m, 1H), 6.8(m, 1H), 6.5(m, 1H), 6.2(m, 1H), 5.8(m, 1H), 5.5(m, 1H), 5.2(m, 1H), 4.8(m, 1H), 4.5(m, 1H), 4.2(m, 1H), 3.8(m, 1H), 3.5(m, 1H), 3.2(m, 1H), 2.8(m, 1H), 2.5(m, 1H), 2.2(m, 1H), 1.8(m, 1H), 1.5(m, 1H), 1.2(m, 1H), 0.8(m, 1H), 0.5(m, 1H)	1650, 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100