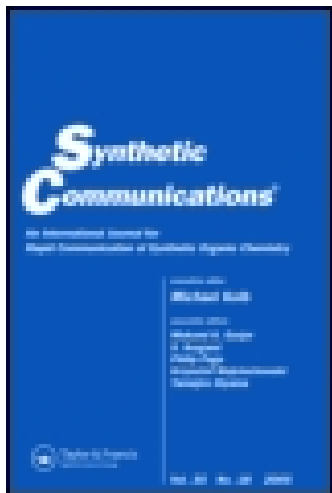


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Ethanollic or Aqueous Formic Acid (1:1) - A New Efficient Reagent for the Regeneration of Ketones from Phenylhydrazones

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**ETHANOLIC OR AQUEOUS FORMIC ACID (1:1) - A NEW
EFFICIENT REAGENT FOR THE REGENERATION OF
KETONES FROM PHENYLHYDRAZONES**

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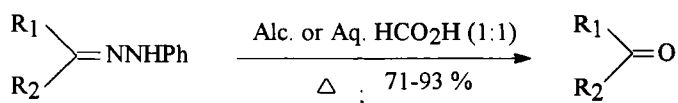
Abstract : 50% Ethanolic or aqueous formic acid has been found to be extremely efficacious for the regeneration of aliphatic and aromatic ketones from phenylhydrazones.

2,4-Dinitrophenylhydrazones (DNP's) of aldehydes and ketones find extensive applications in organic chemistry for the characterisation of the parent carbonyl compounds¹. Their use as protective groups in multistep organic syntheses is, however, limited because the methods available for their deprotection² pose a variety of problems, the major difficulty stemming from their stability towards acid hydrolysis. This difficulty can be largely overcome by

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the use of phenylhydrazones instead of DNP's, specially in the case of ketones. But, even all the methods reported³ for the deprotection of phenylhydrazones have certain limitations. For example, an old method⁴ requires the use of excess acetylacetone along with upto five mol% of a mineral acid (2N HCl), still giving poor yields in some cases, e.g. 29% for benzophenone. A later method⁵ employs excess (five times by wt.) of 'active MnO₂' in dry benzene or toluene, regenerating the ketones in only (40-60)% yields, that too requiring purification by column chromatography (CC) from biphenyl or bi-*o*-tolyl, a constant by-product (25-34)% of the reaction. A third method⁶, citing cyclohexanone phenylhydrazone as the lone example of a ketone, required 100 hours of heating with acetone in a sealed tube resulting in only 60% recovery of the ketone. In a very recent method⁷, the cleavage of phenylhydrazones was achieved by using the specialised reagent, 3-carboxypyridinium chlorochromate.

Evidently, there exists a need for the development of more effective reagents for the deprotection of ketone phenylhydrazones. We report herein such a simple and high-yielding reagent which is 50% ethanolic or aqueous formic acid. Refluxing the phenylhydrazones with this reagent for a few hours, followed by appropriate work-up (Experimental), regenerated the parent ketones in very good to excellent yields (Table 1) and additionally furnished in each case *N*-formylphenylhydrazine (1)⁸. The ¹H and ¹³C NMR data of 1 (vide Experimental),



$\text{R}_1, \text{R}_2 = \text{Me, Me ; isoBu, Me ; - (CH}_2\text{)}_4\text{- ; - (CH}_2\text{)}_5\text{- ; - (CH}_2\text{)}_6\text{- ;$
 $\text{Me, CH}_2\text{CH}_2\text{COMe ; Ph, Me ; } o\text{-C}_6\text{H}_4\text{-(CH}_2\text{)}_3\text{- ;}$
 $\text{(CH}_3\text{)}_2\text{C=CH-, Me ; Ph, Ph ; C}_6\text{H}_5\text{-CH(OH)-, Ph}$

not reported earlier, demonstrated for the first time that it exists as a (3:2) mixture of the *Z* and *E* rotamers⁹.

Because of the inherent tendency of most of the aldehydes to undergo oxidation, the reagent was tried with only one aldehyde, viz. vanillin, but without success. The only osazone and DNP tried were those of benzil and acetophenone, respectively, but the reagent proved abortive in these cases as well. The reagent thus appears to be selective for ketone phenylhydrazones.

The formation of **1** suggested that a cleavage of the phenylhydrazone had taken place and the regenerated phenylhydrazine underwent formylation by formic acid to produce **1**. This observation triggered the exploration of the use of formic acid as *N*-formylating agent for various types of amines, and the preliminary results are encouraging.

In conclusion, ethanolic or aq. formic acid (1:1) under reflux has been demonstrated to be an efficient reagent for the deprotection of phenylhydrazones to ketones. The advantage of this reagent over the extant ones is that it is

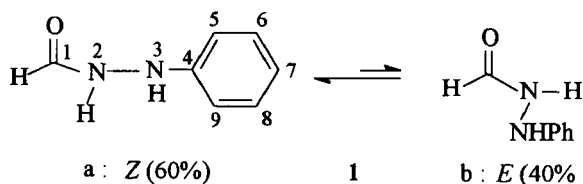
Table 1. Regeneration of ketones from phenylhydrazones
using 50 % ethanolic formic acid

Entry	Phenylhydrazones of ketones	Yields (%) of	
		1	ketone ^a
1	Acetone	90 ^b	93 ^b
2	Isobutyl methyl ketone	81	77
3	Cyclopentanone	74	76
4	Cyclohexanone	92	87
5	Cycloheptanone	93	87
6	Acetylacetone	75	80
7	Acetophenone	77	82
8	α -Tetralone	84	81
9	Mesityl oxide	72	71
10	Benzophenone	76	82
11	Benzoin	76	83
12	Benzil	--	--
13	Vanillin	--	--

a : Identified by TLC, IR and MS.

b : Using aq. HCO₂ H (1:1) .

More importantly, the conditions are moderate enough not to affect most other functionalities which might be present in a ketone, except the chiral ones where the conditions used might lead to the loss of chirality. All considered, although offering no advantage over only one other reagent, viz. Baker's yeast, used¹⁰ for



inexpensive, the isolation procedure simple and the yields are consistently high. this purpose, our reagent appears to be superior to the rest of the reagents available for the deprotection of ketone phenylhydrazones.

Experimental: Melting points were recorded on a Toshniwal melting point apparatus and are uncorrected. The IR spectra (KBr) were recorded on a Perkin Elmer model 1600 FT-IR spectrophotometer, the UV spectrum (EtOH) on a Shimadzu UV-160 spectrophotometer, the mass spectra (EIMS) on a Finnigan MAT TSQ 700 mass spectrometer and the ^1H (400 MHz) and ^{13}C (100 MHz) NMR spectra (d_6 -DMSO) on a Unity 400 NMR spectrometer. Only the D_2O -exchange ^1H NMR spectrum (100 MHz) was recorded separately on a GEOL FX-100 NMR spectrometer. CC was performed on silica gel (60-120 mesh ;Qualigens, India) and TLC on silica gel G (E. Merck, India) plates. The phenylhydrazones, prepared conventionally¹¹, were identified by comparing their m.p.s with those reported in the literature¹².

A typical experiment.- The phenylhydrazone (2 mM) was refluxed with 50% ethanolic formic acid (6 ml) for 5 hours (only benzoin required 14 hours), after

which ethanol was boiled off. For water-immiscible liquid ketones (entries 2, 5, 7, 8), the solution was allowed to cool and the resulting crystals of **1** were collected by filtration. The mother liquor, and in the case of solid ketones (entries 10,11,12), the reaction mixture itself (sans EtOH) was poured into water, neutralised with solid NaHCO₃ (care must be taken not to make the solution alkaline, since **1** is soluble in such a medium) and extracted with EtOAc. The residue from the dried (Na₂SO₄) EtOAc extract was chromatographed (CC) over a silica gel column. For ketones miscible with water (entries 3,4,9), except acetone, the solution (from which ethanol was boiled off) was cooled to room temperature, neutralised (NaHCO₃), diluted somewhat with EtOAc, dried (Na₂SO₄) and the residue obtained therefrom was subjected to CC. In all the cases, the ketones and **1** were eluted in (5-8)% and 25% EtOAc/petroleum eluates, respectively. For acetone, 50% aqueous formic acid was used, and after the completion of the reaction, acetone was collected by distillation. The remaining solution on cooling afforded **1**.

1 : m.p. 142°C (Lit.⁹ m.p. 142-143°C); UV : 233 nm; IR : 3230 (NH), 1680, 1655 (CO) cm⁻¹ ; ¹H NMR : δ 9.7, 1H, br, NH_a-2; 9.41, 1H, d, *J* 11.4 Hz, NH_b-2; 8.11, 1H, s, H_a-1; 8.09, 1H, d, *J* 11.4 Hz, H_b-1; 7.94, 1H, s, NH_b-3; 7.78, 1H, ill-resolved d, NH_a-3; 7.1-7.23, 4H, m, H_a, b-6 & -8; 6.81-6.68, 6H, m, H_a, b -5, -7 & -9; +D₂ O (*d*₆-DMSO) : all NH signals disappeared and δ 8.09 changed from d to s; ¹³C NMR; multiplicities by DEPT 135 experiment) : δ

167.6, d, C_b -1; 160.5, d, C_a -1; 149.4, s, C_b -4; 148.7, s, C_a -4; 128.9 (2x), d, C_b -6, -8; 128.7 (2x), d, C_a -6, -8; 119.4, d, C_b -7; 118.6, d, C_a -7; 112.3 (2x), d, C_b -5, -9; 112.1 (2x), d, C_a -5, -9; MS : *m/z* 136 (M⁺ ; 100%), 108 (13), 107 (79), 92 (10), 77 (30).

The regenerated ketones were identified by usual comparisons, viz. m.p.s (for solid ketones), TLC, IR and EIMS with those of standard samples.

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