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The Reaction of 1,1-Dimethyl-1-Phenacylhydrazinium Bromide with Aqueous Sodium Hydroxide

Kunio Kano[†] and Jean-Pierre Anselme*

Department of Chemistry, University of Massachusetts at Boston, Harbor Campus, Boston, Massachusetts 02125, U.S.A.

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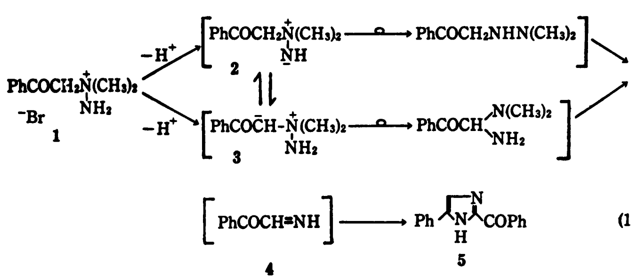
Synopsis. The reaction of 1,1-dimethyl-1-phenacylhydrazinium bromide with 1 M aqueous sodium hydroxide give benzoic acid, 3-phenyl-1-methylpyrazole, 5-benzoyl-3-phenyl-1-methylpyrazole, and benzonitrile as the major components; the expected product, 2-benzoyl-5-phenylimidazole was formed in only small amounts. Mechanisms to rationalize the formation of the major products are discussed.

In contrast to the vigorous conditions usually necessary,[1,2] the Wawzonek rearrangement of 1,1-dimethyl-1-phenacylhydrazinium bromide (**1**) proceeded smoothly upon heating in 1-propanol,[3] to afford 2-benzoyl-5-phenylimidazole (**5**).[4] It thus became of interest to investigate the behavior of **1** in the presence of aqueous alkali.



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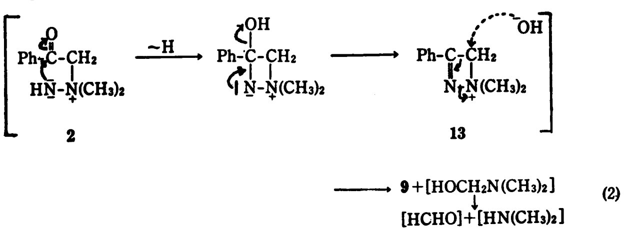
The treatment of 80 mmol of 1,1-dimethyl-1-phenacylhydrazinium bromide (**1**) with 1 M aqueous NaOH gave only trace amounts of 2-benzoyl-5-phenylimidazole (**5**); seven compounds were characterized: benzoic acid (**6**, 24.6 mmol), 3-phenyl-1-methylpyrazole (**7**, 12.2 mmol), 5-benzoyl-3-phenyl-1-methylpyrazole (**8**, 3.3 mmol), benzonitrile (**9**, 2.2 mmol), trace amounts of acetophenone (**10**), acetophenone dimethylhydrazone (**11**) and 3-phenyl-1-methyl-2-pyrazoline (**12**); dimethylamine and trimethylamine were subsequently characterized from the evolved gases.

The formation of benzonitrile can be rationalized *via* an internal nucleophilic attack of the negative nitrogen of the aminimide **2** on the carbonyl group to give the diazetinium ion **13**.[5] Fragmentation of **13** or attack of **13** by hydroxide ion (*vide infra*) yields benzonitrile. Support for this mechanism was obtained from the bromination of acetophenone dimethylhydrazone (**11**) with *N*-bromosuccinimide which afforded benzonitrile as one of the products;[6] presumably α-bromination followed by an internal nucleophilic displacement by the sp^3 nitrogen lead to **13**. A Stevens rearrangement of **13** (Eq. 3) can account for the formation of 3-phenyl-1-methyl-2-pyrazoline (**12**). The reaction of **1** with base in the presence of **12** did not result in an increase in the yield of **7** and thus rules **12** out as the source of **7**.[7] An alternate path to **7** involving the condensation of phenylglyoxaldimine (**4**), a probable intermediate in the rearrangement of **1** to **5**,[3] with 1,1-dimethylhydrazine at more reactive *imino* carbon followed by cyclization of the resulting phenylglyoxal dimethylhydrazone (**14**)[6,8] would lead to 4-phenyl-1-methylpyrazole (**15**) and not to **7**. On the other hand, attack of 1,1-dimethylhydrazine on **13** (*vide infra*) can lead to an intermediate **16** with the structural features required to undergo cyclization to yield 3-phenyl-1-methylpyrazole (**7**) (Eq. 5). A control experiment in which the reaction of **1** with hydroxide ion was carried out in the presence of added 1,1-dimethylhydrazine resulted in a seven-fold increase in the yield of **7** at the expense of benzonitrile.



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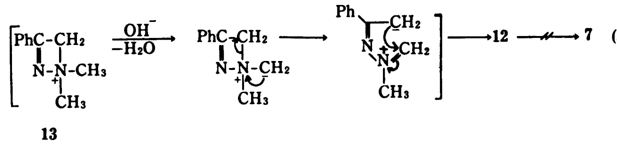

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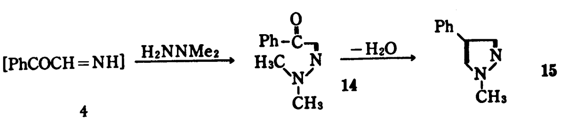

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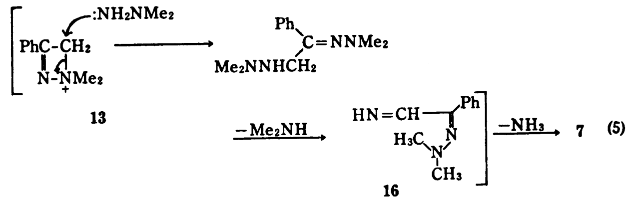

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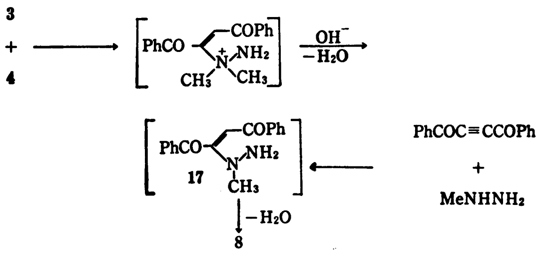
NMR experiments demonstrated that the CH$_2$ hydrogens also underwent deuterium exchange and make it likely that ylide **3**, derived from removal of a hydrogen from the CH$_2$, is also generated.[9] A mechanism proceeding *via* the same intermediate **17** presumably involved in the synthesis of **8** from dibenzoylacetylene and methylhydrazine,[10] explains the formation of **8** (Eq. 6). It is interesting to note that the reaction of **1** with water gave an approximately 1:1 mixture of **2** and **5**.



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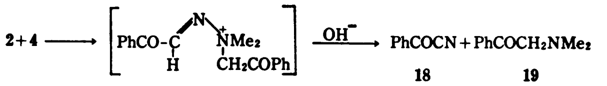
[†] Taken from the M. S. Thesis of Kunio Kano, University of Massachusetts at Boston, June 1980.

It was initially surmized that *in situ* hydrolysis[11] of benzoyl cyanide (**18**) perhaps generated by air oxidation of phenylglyoxaldimine (**4**), could help account for the formation of benzoic acid. However, the reaction of **1** with hydroxide under *oxygen-free* nitrogen left the yield of benzoic acid unaffected. The hydrazinium salt **1** or more likely the aminimide **2** could act as the oxidizing agent (Eq. 7).[12]



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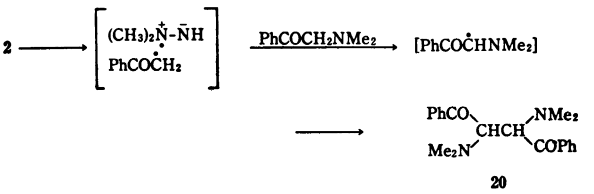
Apparent support for this path came from the reaction of benzaldehyde, *p*-chlorobenzaldehyde and *p*-bromophenylglyoxal with **1** under the same conditions, which gave benzonitrile, *p*-chlorobenzonitrile and *p*-bromobenzoic acid respectively. However, α-dimethylaminoacetophenone (**19**), the expected by-product (Eq. 7) could not be detected by TLC. The reaction of **19** with 1 M sodium hydroxide in the presence of oxygen gave sodium benzoate (60%); the reaction of **1** with hydroxide in the presence of **19** gave 2,3-bis(dimethylamino)-1,4-diphenyl-1,4-butanedione (**20**).[13,14]



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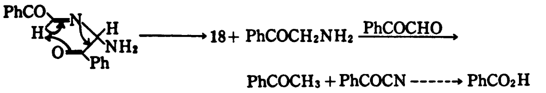
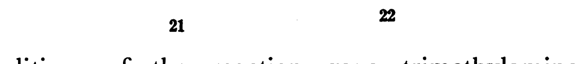
The self-condensation product of **4** which cyclized to **5**,[3] could collapse in an alternate fashion to give benzoyl cyanide and phenacylamine (Eq. 9). Condensation of the latter compound with phenylglyoxal hydrate was shown to yield benzoid acid and acetophenone, presumably *via* fragmentation of the intermediate imine, in a fashion analogous to the formation of **18** from phenylglyoxaldoxime with acetyl chloride.[15] Phenacyl alcohol, which might have arisen from attack of hydroxide ion on **1**, was not converted to benzoic acid as expected.[16] Furthermore, the addition of phenacyl alcohol to a reaction of **1** with base resulted in a *decrease* in the yield of benzoic acid.



(9)

In view of the failure of these mechanisms, the path involving the direct attack of the hydroxide ion at the carbonyl carbon was reluctantly considered (Eq. 10). Indeed, trimethylhydrazinium iodide under the conditions of the reaction gave trimethylamine.[17] Nucleophilic displacement on the methyl group of trimethylhydrazinium ion can lead to methanol and 1,1-dimethylhydrazine, necessary to account for the formation of acetophenone dimethylhydrazone and of the pyrazoles.



(10)

Experimental

Elemental analysis were carried out at the Microanalysis Laboratories of the University of Massachusetts at Amherst. Mass spectra were taken at Chemical Spectrometry Laboratory of Massachusetts Institute of Technology and obtained on a Varian Mat 44 mass spectrometer. The infrared spectra were recorded on a Perkin-Elmer model 137B Infrared spectrophotometer and the NMR spectra were determined on a Hitachi Perkin-Elmer R-24 (60 MHz) in deuteriochloroform unless otherwise noted, using tetramethylsilane as internal standard. The vapor phase chromatograms were obtained on a Perkin-Elmer Vapor Fractometer 154D (column: silicone grease).

Reaction of 1,1-Dimethyl-1-phenacylhydrazinium Bromide (1) with 1 M Aqueous Sodium Hydroxide. To 80 mmol of **1** was added 120 ml of 1 M aqueous NaOH, previously degassed for 1 h with purified nitrogen. The reaction mixture was stirred for 24 h at ambient temperature and the reaction flask was protected from light. The reaction mixture was extracted with ether and the ethereal layer was washed with water until it was neutral. The ethereal solution was dried over $MgSO_4$ and evaporated *in vacuo*. The aqueous layer was neutralized with conc. hydrochloric acid, the resulting precipitate was collected, and the filtrate was extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated *in vacuo*; the residue and the precipitate obtained from neutralization of the aqueous phase were combined and crystallized from water to give 3.0 g (24.6 mmol) of benzoic acid, mp 121—122 °C.

The IR, NMR, and VPC of the residue obtained from the original ethereal phase were determined. VPC showed a 5.1:1 ratio of 3-phenyl-1-methylpyrazole (**7**)[18] to benzonitrile and trace amounts of acetophenone, acetophenone dimethylhydrazone (**11**) and 3-phenyl-1-methyl-2-pyrazoline (**12**).[19] The mixture was then chromatographed on 50 g of neutral aluminum oxide (powder) using benzene as eluent. The first fraction gave 0.73 g (2.7 mmol) of 5-benzoyl-3-phenyl-1-methylpyrazole (**5**), the second fraction gave 1.9 g of a mixture of **8** and **7** in a ratio of 1:12.1, the third fraction gave 0.175 g (1.07 mmol) of **7**. The total yields of **7** and **8** were 12.2 mmol and 3.3 mmol respectively. The purity and identity of each fraction was checked by TLC and NMR.

In a separate experiment, three picric acid–ethanol traps were attached to the outlet of the reaction vessel; 1.2 g of a mixture of the picrates of dimethylamine and trimethylamine was collected, and its NMR indicated it to be composed of 4 mmol of trimethylamine picrate and 0.7 mmol of dimethylamine picrate.

Reaction of 1 with 1 M NaOH in the Presence of 1,1-Dimethylhydrazine. The reaction of **1** (20 mmol) with 30 ml of 1 M NaOH under nitrogen was carried out and analyzed as described previously, except that 20 mmol of 1,1-dimethylhydrazine was added to the reaction mixture. There was a seven-fold increase in the yield of 3-phenyl-1-methylpyrazole (**7**).

Reaction of 1 in Water. A solution of 5.18 g (20 mmol) of **1** in 100 ml of distilled water was stirred for 5 d at ambient temperature. The precipitate was filtered to give 2 g of a mixture of **5**, **7**, **8**, and the filtrate was extracted with ether. The ethereal layer was dried over $MgSO_4$ and the ether was evaporated to give 0.19 g of a mixture of **5**, **7**, **8**, and other minor products. The aqueous layer was acidified with concd hydrochloric acid and then was extracted with ether. The ethereal solution was dried over $MgSO_4$ and the ether was evaporated to yield 0.10 g (8%) of benzoic acid.

5-Benzoyl-3-phenyl-1-methylpyrazole (**8**) (0.8 g, 31%), mp 65.5—67 °C, was obtained as white crystals from the precipitate after three recrystallizations from ether–pet. ether followed by column chromatography (silica gel).

*Reaction of **1** with* p*-Bromophenylglyoxal.* To **1** (1.04 g, 4 mmol) and *p*-bromophenylglyoxal monohydrate (0.92 g, 4 mmol) was added 6 ml of previously degassed 1 M aqueous NaOH and stirred for 24 h. The reaction mixture was acidified with concd HCl; the precipitate was filtered and washed with water. Its IR showed it to be a mixture (0.19 g) of benzoic acid and *p*-bromobenzoic acid.

Reaction of Phenylglyoxal with Phenacylamine. To a suspension of phenylglyoxal monohydrate (2.13 g, 14 mmol) and phenacylamine hydrochloride (2.4 g, 14 mmol)[20] in THF (40 ml) was added triethylamine (1.4 g, 14 mmol) in THF (15 ml); the solution was stirred overnight at room temperature. Triethylamine hydrochloride was filtered and THF was evaporated from the filtrate. The residue was dissolved in 50 ml of ether, then the solution was washed with water, dried over anhydrous $MgSO_4$ and the ether was evaporated. A solution of the residue in toluene (100 ml) was heated to reflux overnight. The cooled reaction mixture was washed with aqueous $NaHCO_3$ and water, dried and the toluene was evaporated. To the residue was added 2,4-dinitrophenylhydrazine solution. The R_f value (silica gel, chloroform) and the IR spectrum of the product were identical with that of authentic acetophenone 2,4-dinitrophenylhydrazone. The sodium bicarbonate solution was neutralized with concd hydrochloric acid to give 0.63 g (37%) of benzoic acid, mp 120—121.5 °C.

Reaction of Trimethylhydrazinium Iodide with 1 M Sodium Hydroxide. To 16.2 g (80 mmol) of trimethylhylhydrazinium iodide in 250 ml three-necked round bottom flask equipped with a 250 ml addition funnel, a nitrogen gas inlet and reflux condenser was added 120 ml of 1 M aqueous NaOH; the condenser was connected to a trap containing 50 ml of a saturated ethanolic solution of picric acid. After the addition, nitrogen gas was bubbled through the reaction flask for 3 d at ambient temperature, The solid which precipitated in the trap was collected, dried and shown to be trimethylamine picrate, mp 221—223 °C, by comparison with an authentic sample.

*2,3-Bis(dimethylamino)-1,4-diphenyl-1,4-butanedione (**20**).* A mixture of 2.70 g (12.5 mmol) of α-dimethylaminoacetophenone in 30 ml of 1 M aqueous NaOH was degassed for 30 min, then added to **1** (5.18 g, 20 mmol). The reaction mixture was treated as described previously in the general procedure. The solid present in the viscous residue which had been left standing, was filtered recrystallized from ether–pet. ether to give pale yellow crystals, mp 136—138 °C. Mass spectrum: *m/e* 324, 162, 105, 77; NMR($CDCl_3$): δ 7.80 (ArH, m, 5H), 4.92 (CH, s, 1H), 2.26 (CH_3, s, 6H); IR: 1680 cm^{-1}.

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