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Hypervalent Iodine in Synthesis

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SYNTHETIC COMMUNICATIONS, 25(11), 1617-1626 (1995)

HYPERVALENT IODINE IN SYNTHESIS: XIX. OXIDATION OF ALDEHYDE HYDRAZONES WITH PHENYLIODINE DIACETATE: A NEW METHOD FOR THE GENERATION OF NITRILIMINES

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Abstract: Oxidation of aldehyde hydrazones with phenyliodine diacetate (PID) generated nitrilimines which were trapped by acrylonitrile to give 1,3-disubstituted 2-pyrazoline-5-carbonitriles in good yields.

Until recently, nitrilimines 1, like several other 1,3-dipoles, were considered reactive intermediates. Since their discovery by Huisgen et al. in 1959,[1] nitrilimines have been generated in situ and used in numerous 1,3-dipolar cycloaddition reactions for the formation of five membered heterocycles.[2]

$$RC\equiv\overset{+}{N}-\overset{-}{N}-R^1 \longleftrightarrow R\overset{+}{C}=N-\overset{-}{N}-R^1$$

1

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A number of methods have been reported for the preparation in situ of nitrilimines, e. g. , the base-induced dehydrochlorination of the hydrazononyl halides,[1,3] the thermal decomposition of 2,5-disubstituted tetrazoles[1,3a,4] or 3,5-disubstituted 3H-1,2,3,4-oxathiadiazole S-oxides[5] or 2,5-disubstituted $\triangle^2$-1,3,4-oxadiazolin-5-ones[6] or the sodium salt of α-nitrohydrazones,[7] the photolysis of 3,4-disubstituted sydnones[8] or 2,5-disubstituted tetrazoles,[9] the oxidation of aldehyde arylhydrazones with lead tetraacetate[10] or anodic oxidation.[11] Herein, we would like to report a new method for the preparation of nitrilimines by the reaction of aldehyde hydrazones with phenyliodine diacetate(PID). Trapping the nitrilimines with acrylonitrile, a series of 1,3-disubstituted 2-pyrazoline-5-carbonitriles were synthesized.

Hypervalent organoiodine oxidation of organic compounds has been successfully used in organic synthesis in many aspects. As an oxidant, phenyliodine diacetate(PID) is the most frequently used and easily availabe reagent in the family of hypervalent iodine compounds.[12] Recently, we reported that PID is an efficient reagent to oxidize tosylhydrazones[13] or semicarbazones[14] of ketones to parent ketones. In a continuation of our study on the application of hypervalent iodine compounds in organic synthesis, we investigated the reaction of aldehyde hydrazones with PID. Reaction of benzaldehyde p-nitrophenylhydrazone in methylene chloride resulted in the formation of a single product which was identified as N-acetyl-N'-benzoyl-p-nitrophenylhydrazine 3 ($R = C_6H_5$, $R^1 = p\text{-}NO_2C_6H_4$) on the basis of its m. p. 186—187℃ (lit[10], m. p. 186℃), IR spectrum and ^1H—NMR spectrum. However, when the reaction was carried out in acrylonitrile, the main product given was 1-(p-nitrophenyl)-3-phenyl-2-pyrazoline-5-carbonitrile 4a ($R = C_6H_5$, $R^1 = p\text{-}NO_2C_6H_4$) in 72% yield. It seems to be reasonable that the reactions involved the same intermediate, the nitrilimines 1, which un-

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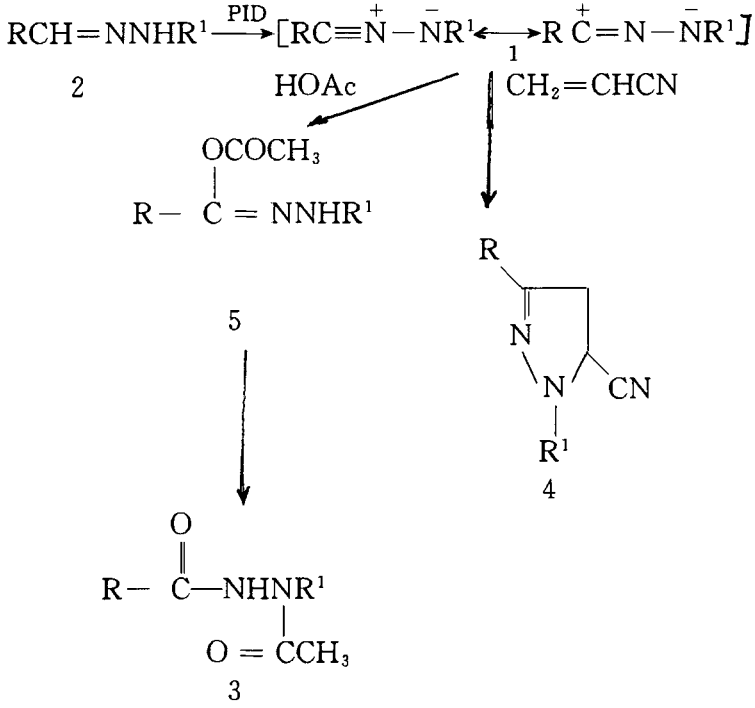
derwent the 1,3-electrophilic addition with acetic acid to form hydrazonyl acetate 5 and then coverted to 3 ($R = C_6H_5$, $R^1 = P\text{-}NO_2C_6H_4$) by the rearrangement of acyl group, or underwent the 1,3-cycloaddition with acrylonitrile to form 4a(Scheme l.)



Scheme 1

A plausible mechanism for the generation of nitrilimine 1 is analogous to the oxidation of the aldehyde hydrazones with lead tetracetate[10]and is illustrated in scheme 2.

First, the exchange of an acetoxy ligand of PID formed a hypervalent iodine intermediate 6. Subsequently, 6 generated a mitrilimine intermediate 1 along with the expulsion of a molecule of iodobenzene and acetic acid.

The generality of this methodology for the generation of the nitrilimine intermediates was established by treating other aldehyde

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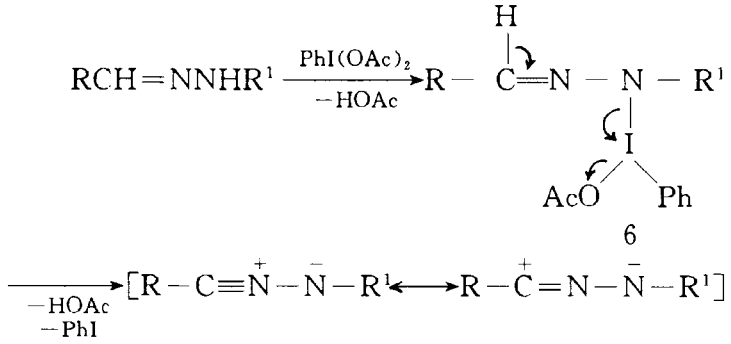
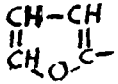


Scheme 2

hydrazones with PID.[15] Trapping these nitrilimines with acrylonitrile gave 1, 3-disubstituted 2-pyrazoline-5-carbonitriles 4 in good yields (Table 1). It is known that pyrazoline derivatives were useful compounds not only as intermediates in the synthesis of pyrazoles but also as effective chemical bleaching agents, and as luminescent and fluoroscent substances.[16]

Table 1 1. 3-Disubstituted 2-pyrazoline-5-carbonitriles 4 prepared

pyrazoline	R	R^1	Yield(%)[a]
4a	C_6H_5	p-$NO_2C_6H_4$	72
4b	C_6H_5	C_6H_5	60
4c	p-$CH_3C_6H_4$	C_6H_5	58
4d	p-$CH_3OC_6H_4$	C_6H_5	58
4e	p-$NO_2C_6H_4$	C_6H_5	70
4f	$C_6H_5CH=CH-$	C_6H_5	69
4g		C_6H_5	55
4h	n-C_3H_7	p-$NO_2C_6H_4$	30

a: Yield of isolated product based on 2.

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It was shown the hydrazones of not only aromatic aldehydes containing an electron-withdrawing substituent or electron-releasing substituent but also α,β-unsaturated aromatic aldehyde and heterocyclic aldehyde can react with PID smoothly in the presence of acrylonitrile to give the corresponding pyrazolines. It was, however, noted that in the case of n-butyaldehyde p-nitrophenylhydrazone the yield of expecting 1-(p-nitrophenyl)-3-propyl-2-pyrazoline-5-carbonitrile 4 ($R=Pr, R^1=p\text{-}NO_2C_6H_4$) was lower, only in 30%, and the main product was N-acetyl-N'-butyryl-p-nitrophenyl-hydrazine 3, ($R=Pr, R^1=p\text{-}NO_2C_6H_4$) in 63%.

1, 3-dipolar cycloaddition of nitrilimines to acrylonitrile is known to be regioselective yielding 5-cyano-2-pyrazolines exclusively. [17] The structures of the products 4a-h were confirmed by their elemental analyses and spectral data. For example, the cyano group absorption was either absent or very weak in the IR spectra of 4a-h. This is similar to the case of aliphatic nitriles activated by a nitrogen atom or an oxygen atom in the α-position. [18] In their ^1H-NMR spectra the cycloadducts 4a-h exhibited an AB_2 or AX_2 pattern.

In summary we have presented a new, simple, and general method for the generated in situ of nitrilimines by the reaction of aldehyde hydrazones with PID. It has some advantages over the existing ones such as accesssible starting materals, mild reaction conditions, simple procedure, and avoiding the using of hazardous and toxic reagents. Furthermore, a practicable method for the synthesis of 1,3-disubstituted 2-pyrazoline-5-carbonitriles has been providied and the range of useful applications of PID in organic chemistry has been extended.

EXPERIMENT SECTION

Aldehyde hydrazones 2 were prepared according to reported method[19] by refluxing aldehyde with hydrazine in ethanol in the

presence of some acetic acid and water. PID was purchased from Aldrich. All melting points are uncorrected. ^{1}H-NMR spectra were recorded at 60MHz on a Varian EM－360 spectrometer from a solution in $CDCl_3$ or d_6-DMSO of the product. Infrared spectra were recorded on a perkin Elmer 683 spectrophotoameter in KBr with absorptions in cm^{-1}. UV spectra were recorded on a Shimadzu UV 265 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 instrument.

A general procedure for preparation of 1,3-disubstituted 2-pyrazoline-5-carbonitriles 4 is as follows: 1mmol of PID in 2ml $CH_2Cl_2$was added dropwise at -10℃to a stirred suspension of 1mmol of aldehyde hydrazone 2 in 5ml acrylonitrile under an N_2 atmosphere. The starting material disappearance (monitored by TLC) was abouut 3hr. The reaction mixture was then concentrated under vacuum. To the residue was added 20ml CH_2Cl_2 and the organic layer was washed with 5% aq. Na_2CO_3 solution (10ml), H_2O (10ml), and dried over $MgSO_4$. The crude material, after evaporation of the solvent, was purified by column chromatograph on silica gel using CH_2Cl_2－petroleum ether as eluent. The product was further purified by recrystallization.

4a: Yellow solid; m. p. 216－218℃ (acetone) (lit.,[10] 206－208℃; lit.,[17] 216－217); ^{1}H－NMR (d_6－DMSO) δ: 8.4－7.3 (m, 9H, ArH), 5.90 (q, J_{AB} 8.7Hz, 1H, 5-H), 3.94 (t, J_{AB} 8.7Hz, 2H, 4-H); IR (KBr) ν(cm^{-1}): 2240 (w, C≡N), 1613 (C=N); UV (CH_2Cl_2) λ_{max}nm (logε): 386.8 (4.49), 300.4 (3.82), 230.8 (4.22), 200.0 (3.90); λ_{min}nm (logε): 310.0 (3.79), 274.0 (3.52); Microanalysis: $C_{16}H_{12}N_4O_2$ (292.30), Required: C, 65.74, H, 4.14, N, 19.17; Found: C, 65.74, H, 4.00, N, 19.08.

4b: White solid; m. p. 145－147℃ (MeOH) (lit.,[3a] 138－140) ^{1}H－NMR ($CDCl_3$) δ: 7.83－7.30 (m, 10H, ArH), 4.97 (t, J

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8Hz, 5-H), 3.65(d, J 8Hz, 2H, 4-H); IR(KBr)ν(cm^{-1}): 2240(w, C≡N), 1608(C=N); UV(EtOH)λ_{max}nm(logε)335.6(4.24), 238.0(4.25), 204.2(4.36); λ_{min}nm(logε): 257.0 (3.63), 204.0(4.04); Microanalysis: $C_{16}H_{13}N_3$(247.3), Required: C, 77.71, H, 5.30, N, 17.00; Found: C, 77.66, H, 5.33, N, 17.00.

4c: White solid; m.p. 127－129℃(MeOH); ^{1}H－NMR($CDCl_3$) δ: 7.8－7.1(m, 9H, ArH), 4.87(t, J 8Hz, 1H, 5-H), 3.53 (d, J 8Hz, 2H, 4-H), 2.33(S, 3H, CH_3); IR(KBr)ν(cm^{-1}): 2240(w, C≡N), 1605(C=N); UV(EtOH)λ_{max}nm(logε): 335.0(4.27), 241.0(4.26), 205.6(4.38); λ_{min}nm(logε): 269.7(3.71), 215.9(4.04); Microanalysis: $C_{17}H_{15}N_3$(261.3), Required: C, 78.13, H, 5.79, N, 16.08; Found: C, 78.31, H, 6.03, N, 15.50.

4d: White solid; m.p. 145－147℃(MeOH); ^{1}H－NMR($CDCl_3$) δ: 7.8－6.8(m, 9H, ArH), 4.85(t, J 8Hz, 1H, 5-H), 3.78 (S, 3H, O-CH_3), 3.53(d, J 8Hz, 2H, 4-H); IR(KBr)ν (cm^{-1}): 2240(w, C≡N), 1610(C=N); UV(EtOH)λ_{max}nm (logε): 335.4(4.18), 247.2(4.13), 205.0(4.35); λ_{min}nm (logε): 273.7(3.87), 225.5(4.03); Microanalysis: $C_{17}H_{15}N_3O$ (277.3), Required: C, 73.62, H, 5.45, N, 15.16; Found: C, 72.92, H, 5.29, N, 15.10.

4e: Yellow solid; m.p. 209－211℃(acetone); ^{1}H－NMR(d_6－DMSO) δ: 8.38(d, J8Hz, 2H, ArH), 8.07(d, J8Hz, 2H, ArH), 7.48－7.03(m, 5H, ArH), 5.83(q, J_{AB} 8.7Hz, 1H, 5-H), 3.90(t, J_{AB} 8.7Hz, 2H, 4-H); IR(KBr)ν(cm^{-1}): 1605 (C=N); UV(EtOH)λ_{max}nm(logε): 403.4(4.28), 256.0(4.24), 203.8(4.43); λ_{min}nm(logε): 320.8(3.42), 221.8(3.89); Microanalysis: $C_{16}H_{12}N_4O_2$(292.3), Required: C, 65.74, H, 4.14, N, 19.17; Found: C, 65.46, H, 3.91, N, 18.80.

4f: Greenish solid; m.p. 154－156℃(MeOH); (lit.,[17] 139－140) ^{1}H－NMR($CDCl_3$) δ: 7.80－6.50(m, 12H, ArH, －CH

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=CH−, 4.85(t,J 8Hz,1H,5-H),3.43(d,J 8Hz,2H,4-H); IR(KBr)ν(cm^{-1}): 2240(w,C≡N),1612(C=N); UV(EtOH)λ_{max}nm(logε):356.6(4.50),255.0(4.20),204.0(4.33),λ_{min}nm(logε): 304.0(3.95),263.7(3.92), microanalysis: $C_{18}H_{15}N_3$(273.3), Required: C,79.09,H,5.53,N,15.38; Found: C,78.61,H,5.36,N,15.41.

4g: Yellowish solid; m.p. 134−136℃(MeOH); ^{1}H−NMR($CDCl_3$)δ:7.7−6.4(m,8H,ArH), 4.88(t,J 8Hz,1H,5-H), 3.52(d,J 8Hz,2H,4-H); IR(KBr)ν(cm^{-1}): 2240(w,C≡N), 1608(C=N); UV(EtOH)λ_{max}nm(logε):336.4(4.28),244.0(4.03),202.8(4.11),λ_{min}nm(logε): 271.7(3.76),217.9(3.91), microanalysis: $C_{14}H_{11}N_3O$(273.3), Required: C,70.87, H,4.67,N,17.71; Found: C,69.66,H,4.46,N,17.78.

4h: Yellow oil; ^{1}H−NMR($CDCl_3$)δ:8.2(d,J 10Hz,2H,ArH), 7.1(d,J 10Hz,2H,ArH), 4.88(t,J 9Hz,1Hz,5-H),3.30(d, J 9Hz,2H,4-H),2.57−2.30(t,J 8Hz,2H,CH_2), 1.87−0.87(m,5H,CH_3CH_2); IR(neat)ν(cm^{-1}): 2240(w,C≡N), 1608(C=N); UV(EtOH)λ_{max}nm(logε):369.2(3.80),223.0(3.59),202.4(3.84),λ_{min}nm(logε): 279.7(3.25).

N-Acetyl-N^1-butyryl-p-Nitrophenylhydrazine(3,R=n−C_3H_7,R_1=p-$NO_2C_6H_4$). (It was obtained by silica gel column chromatography after eluting 4h.) Yellowish solid; Yield:63%; m.p. 138−140℃(CH_2Cl_2−Petroleum ether); ^{1}H−NMR($CDCl_3$)δ:8.9(S, 1H,N−H), 8.1(d,J 10Hz,2H,ArH), 7.5(d,J 10Hz,2H, ArH), 2.13(S,3H,CH_3), 2.4−0.67(m,7H,C_3H_7); IR(KBr)ν(cm^{-1}): 3280(N−H),1725(>C=O), 1690(>C=O); UV(EtOH)λ_{max}nm(logε),303.4(4.04),218.6(4.01), 203.0(4.16), λ_{min}nm(logε), 247.8(3.44), 211.9(4.00); Microanalysis: $C_{12}H_{15}N_3O_4$(265.3), required, C,54.3, H,5.70, N,15.84, Found: C, 54.32, H,5.90, N,15.69.

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